Natural Course of Hypovascular Nodules Detected on Gadoxetic Acid-enhanced MR Imaging: Presence of Fat is a Risk Factor for Hypervascularization

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Purpose: Hypovascular nodules that exhibit hypointensity in hepatocyte-phase images of gadoxetic acid-enhanced magnetic resonance (MR) imaging are frequently encountered in clinical practice. We investigated risk factors for the development of these nodules into hypervascular hepatocellular carcinoma (HCC).

Methods: We retrospectively reviewed our institutional database and identified 302 patients who underwent gadoxetic acid-enhanced MR imaging for suspected or confirmed HCC from February 1, 2008 to January 30, 2011. We excluded patients who were examined for metastasis of other malignancies or for other hepatic tumors, such as focal nodular hyperplasia. We identified hypovascular nodules that were hypointense in hepatocyte-phase images, recorded their characteristics, and calculated the cumulative hypervascularization rate for nodules that were followed up.

Results: Of the 302 patients, 82 had hypovascular nodules (178 nodules; mean size, 9.3 mm). Sixty nodules were followed up for over 6 months, and eight progressed to hypervascular HCC. Hypervascularization occurred more frequently in nodules with fat than those without ($P < 0.01$). The cumulative hypervascularization rate was 5.1% over a year.

Conclusion: The presence of intralesional fat was found to be a risk factor for hypervascularization of hypovascular nodules that exhibited hypointensity in the hepatocyte-phase images of gadoxetic acid-enhanced MR imaging.

Keywords: gadoxetic acid, hepatocellular carcinoma, liver, magnetic resonance imaging

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related deaths.1–3 The prognosis for patients with this disease remains dismal because of its aggressive nature and frequent association with underlying cirrhosis. To improve the possibility of therapeutic intervention and patient survival, early detection of HCC is vital.4–6 However, despite efforts to improve the diagnostic accuracy of noninvasive imaging methods, the sensitivity and specificity of dynamic multidetector computed tomography (CT) and magnetic resonance (MR) imaging for detecting HCCs smaller than 2 cm remain unsatisfactory.7,8 The limitations of these modalities are mainly because of the difficulty in detecting hypovascular and isovascular lesions that occur during the early stages of multistep hepatocarcinogenesis.9

Gadoxetic acid is a recently developed MR contrast agent that is specifically taken up by hepatocytes and provides a better lesion-liver contrast, which is not achievable with extracellular gadolinium-based agents.10–12 Gadoxetic acid-enhanced MR imaging is known to have a higher sensitivity than dynamic CT for detecting HCC, especially le-
sions smaller than 2 cm in diameter.\(^{13-15}\) Therefore, this technique may more readily detect early-stage lesions than CT arterial portography,\(^ {16}\) which was believed to have the highest sensitivity for this purpose.\(^ {9}\)

The increased use of gadoxetic acid for routine examination may lead to the more frequent detection of hypovascular nodules that are hypointense on hepatocyte-phase (15 to 20 min after administration of gadoxetic acid) images of gadoxetic acid-enhanced MR imaging. However, the management of these nodules is a contentious issue. Several recent studies have reported the detection of hypovascular nodules by gadoxetic acid-enhanced MR imaging,\(^ {17-21}\) though the occurrence of hypervascular HCC varied. For this reason, we believe that results from different groups of patients are important to identify a treatment or surveillance strategy for these small hypovascular nodules.

The purpose of the present study was to investigate the risk factors for hypovascular nodules developing into hypervascular HCC.

**Methods**

**Patients**

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by our institutional review board. The need for written informed consent was waived because of the retrospective design of the study.

We retrospectively reviewed our institutional database and identified 302 patients who underwent gadoxetic acid-enhanced MR imaging for suspected or confirmed HCC from February 1, 2008 to January 30, 2011. We excluded patients examined for metastasis of other malignancies or for other hepatic tumors, such as focal nodular hyperplasia. For all cases, we documented patient age, sex, etiology of chronic liver disease, Child-Pugh classification, tumor markers (alpha-fetoprotein [AFP] and protein induced by vitamin K absence or antagonist II [PIVKA II]), presence of other hypervascular HCCs, and history of interventional treatment.

**MR imaging protocol**

MR imaging in this study was performed with a 1.5- (Signa ES version 11.1, Signa HD TS version 12, GE Healthcare, Waukesha, WI, USA) or 3-tesla (Discovery MR750, GE Healthcare) scanner using either an 8- (1.5T) or 32-channel (3T) body-array surface coil. First, a T\(_1\)-weighted fast spoiled gradient echo (T\(_1\)W-FSPGR) sequence was obtained using in- and opposed-phase imaging. Next, noncontrast images with fat-suppressed T\(_1\)-weighted gradient echo imaging with a 3D acquisition sequence (liver acquisition with volume acceleration [LAVA]) were obtained with a parallel imaging technique (array spatial sensitivity encoding technique [ASSET]; factor = 2); scanning time was 16 to 20 s. For dynamic scans, the contrast agent (0.025 mmol/kg; 0.1 mL/kg) was administered over 4 seconds followed by a 30-mL saline flush using a power injector (Sonic Shot GX, Nemoto-Kyorindo, Tokyo, Japan). Fluoroscopic triggering was used to determine the timing of the arterial-phase image. After administration of 0.025 mmol/kg gadoxetic acid, arterial-, portal venous- (60 s after injection), and late-phase (120 to 180 s after injection) images were sequentially obtained. Between the late phase and final hepatocyte phase (15 to 20 min), T\(_2\)-weighted single-shot fast spin-echo sequence, fat-suppressed T\(_2\)-weighted fast spin-echo sequence, and diffusion-weighted images (DWIs) were obtained.

**CT protocol**

CT was performed with 64-multidetector-row scanners—LightSpeed VCT (GE Healthcare), Discovery 750 HD (GE Healthcare), or Aquilion 64 (Toshiba Medical Systems, Otawara, Japan). After acquisition of precontrast CT images, 2 mL/kg of a nonionic contrast medium was administered intravenously for 30 s using a power injector (Dual Shot Type-D, NemotoKyorindo). Arterial-phase images were obtained after a scan delay of 40 s, portal venous-phase images after 80 s, and equilibrium-phase images after 180 s. The slice thickness of precontrast images was 5.0 mm, and that of postcontrast images was 1.25 mm.

**Nodules**

We included nodules that demonstrated (1) round or oval shape and hypointense appearance on hepatocyte-phase images in both the axial and coronal planes; (2) no hypervascularity on arterial-phase images obtained using dynamic CT or gadoxetic acid-enhanced MR imaging; and (3) no distinct high signal intensity on T\(_2\)-weighted images (T\(_2\)WIs) that suggested hemangioma and cyst and nodules that were (4) detected before interventional treatment. In the case of follow-up assessment, we included those monitored longer than 6 months.

**Assessment of nodule hypervascularization**

We assessed hypervascularization using gadoxetic acid-enhanced MR imaging or dynamic CT. Hypervascular HCC was defined when a nodule showed hyperintensity in arterial-phase images and...
hypointensity in hepatocyte-phase images of gad- 
oxetic acid-enhanced MR imaging or in portal 
venous- or equilibrium-phase images of dynamic 
CT. A lesion that was isointense in arterial-phase 
images and hypointense in precontrast images was 
also deemed hypervascular HCC.

**Image interpretation**

Together, 2 radiologists (D.J. and A.U., with 8 
and 11 years’ experience in hepatobiliary imaging) 
evaluated the gadoxetic acid-enhanced MR imaging 
and dynamic CT using a picture archiving and com- 
munication systems (PACS). Any disagreement be- 
tween the 2 readers was solved in conference with a 
third radiologist (A.T., 30 years’ experience).

Nodule size was evaluated on axial-plane hepato- 
cyte-phase images. The major and minor axes were 
measured on the monitor. Measurements were 
repeated 3 times, and the median size was recorded. 
Nodules were evaluated for the presence of fat and 
signal changes on T1-weighted images (T1WIs), 
T2WIs, and DWIs. The presence of fat was consid- 
ered positive if the signal intensity of the nodules 
was decreased on opposed-phase T1WIs, which 
suggests the existence of an intracellular lipid com- 
ponent. In T1WIs and DWIs, the signal intensity of 
the nodule was visually classified as high if it ex- 
ceeded that of the liver parenchyma. On T1WIs, the 
nodule intensity was categorized as low if it was 
lower than that of the background liver on the 
precontrast LAVA images.

For patients who underwent gadoxetic acid-en- 
hanced MR imaging 6 months or more after initial 
assessment, the follow-up interval and follow-up 
period (total follow-up time) were ascertained.

**Statistical analysis**

We performed statistical analysis using IBM 
SPSS statistics version 19.0.0 (IBM Co., Armonk, 
NY, USA). We used Mann-Whitney U test to com- 
pare 2 continuous values, Kruskal-Wallis one-way 
analysis of variance to compare 3 continuous 
values, and Fisher’s exact test to compare propor- 
tions. Multivariate analysis of nodule imaging find- 
ings was performed using logistic regression analy- 
sis. Kaplan-Meier time-to-event curves were used to 
estimate the cumulative rate of hypervasculariza- 
tion and were compared using the log-rank test. A 
2-sided P value < 0.05 was considered significant in 
all analyses.

**Results**

**Detected nodules**

In 82 of the 302 patients, 178 hypovascular nod- 
ules were detected on gadoxetic acid-enhanced MR 
imaging. The mean number of nodules per patient 
was 2.2 ± 1.9, ranging from one to 11. Eighty-one 
nodules in 48 patients were examined by gadoxetic 
acid-enhanced MR imaging only once, and 37 nod- 
ules in 12 patients were examined at least twice with 
a follow-up time of less than 6 months. The re- 
mainding 32 patients with 60 nodules underwent 
gadoxetic acid-enhanced MR imaging twice or 
more and were followed up after 6 months (Fig. 1). 
Ten patients had at least one nodule that was fol- 
lowed up and one that was examined only once.

**Followed-up nodules**

The median follow-up interval for the 60 nodules 
followed up longer than 6 months was 188 days 
(range, 76 to 823 days), and the median follow-up 
period was 492 days (range, 199 to 1002 days). The 
mean initial size of the nodules was 7.8 ± 3.1 mm 
(range, 4 to 17 mm); 47 were smaller than 10 mm 
(47/60, 78%) and 58 were smaller than 15 mm 
(58/60, 97%). The mean number of nodules per 
patient was 1.9 ± 1.3 (range, one to 5). No reduc- 
tion in lesion size was found during the follow-up 
period. Thirty-one nodules increased in size—eight 
progressed to hypervascular HCC (hypervascula- 
rized nodules), and 23 remained hypovascular 
(grown nodules). Twenty-nine nodules remained 
stable in size (stable nodules) during the follow-up 

![Image](image_url)

**Fig. 1.** Flow chart used in this study
period. The median time for the nodules to become hypervascularized was 463 days (range, 196 to 853 days).

No significant differences in age, sex, etiology of liver disease, Child-Pugh classification, tumor markers, presence of other hypervascular HCC, past history of intervention, follow-up interval, or follow-up period were found among patients with only stable nodules, grown nodules, or a combination of grown and stable nodules or with hypervascularized nodules. The presence of fat was most frequently seen in the hypervascularized nodules (Fig. 2), as determined by univariate and multivariate analyses ($P < 0.01$ for both). No statistically significant differences in initial nodule size, nodule signal intensity, follow-up interval, or follow-up period were observed among the stable, grown, or hypervascularized nodules (Table 1).

**Cumulative hypervascularization rate**

The cumulative hypervascularization rates for the followed-up nodules were $5.1\% \pm 2.9\%$ at one year, $13.1\% \pm 5.2\%$ at 2 years, and $37.6\% \pm 15.9\%$ at 3 years. Here, we considered 1002 days as 3 years in calculating the 3-year cumulative rate. Comparative analysis of nodules with and without fat showed that hypervascularization occurred earlier in those with fat ($P = 0.012$, Fig. 3). The curves of nodules larger than 10 mm and those smaller than or equal to 10 mm did not differ significantly.

**Discussion**

Gadoxetic acid-enhanced MR imaging can enable dynamic contrast and liver-specific imaging. A higher lesion-to-liver contrast in the hepatocyte phase may improve the sensitivity of the detection of hepatocellular lesions, especially early HCC. In our study, we observed hypovascular nodules that were hypointense in the hepatocyte-phase images in $27.2\%$ ($82/302$) of the patients who underwent gadoxetic acid-enhanced MR imaging for suspected or confirmed HCC.

Recent studies have shown that OATP8 is the most probable uptake transporter and that its expression gradually decreases during multistep
Table 1. Comparison of stable, grown, and hypervascularized nodules per patient and nodule

<table>
<thead>
<tr>
<th>Per patient</th>
<th>Patients with only stable nodules</th>
<th>Patients with grown nodules</th>
<th>Patients with hypervascularized nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td>Patients with hypervascularized nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>11</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Number of nodules</td>
<td>29</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Age (mean ± SD) [y]</td>
<td>66.7 ± 8.5</td>
<td>67.0 ± 7.4</td>
<td>69.0 ± 8.2</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>7/4</td>
<td>10/4</td>
<td>6/1</td>
</tr>
<tr>
<td>Etiologya</td>
<td>A/B/C</td>
<td>0/2/10</td>
<td>3/2/9</td>
</tr>
<tr>
<td>Child-Pugh A/B, C</td>
<td>10/1</td>
<td>12/2</td>
<td>6/1</td>
</tr>
<tr>
<td>AFP (ng/mL)b</td>
<td>≤ 20/&gt; 20</td>
<td>5/1</td>
<td>9/5</td>
</tr>
<tr>
<td>PIVKA II (mAU/mL)b</td>
<td>≤ 40/&gt; 40</td>
<td>8/2</td>
<td>11/3</td>
</tr>
<tr>
<td>POHH+/−</td>
<td>4/7</td>
<td>7/7</td>
<td>4/3</td>
</tr>
<tr>
<td>Past history of intervention+/−</td>
<td>1/10</td>
<td>5/9</td>
<td>2/5</td>
</tr>
<tr>
<td>Number of patients</td>
<td>12</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Number of nodules</td>
<td>31</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Initial size (mean ± SD) [mm]</td>
<td>8.0 ± 3.8</td>
<td>8.2 ± 3.8</td>
<td>8.0 ± 3.8</td>
</tr>
<tr>
<td>Follow-up interval median (range) (days)</td>
<td>199 (102–351)</td>
<td>151 (76–693)</td>
<td>232 (85–823)</td>
</tr>
<tr>
<td>Total follow-up time median (range) (days)</td>
<td>538 (199–887)</td>
<td>466 (301–871)</td>
<td>460 (231–853)</td>
</tr>
<tr>
<td>Mean (range) (days)</td>
<td>245 (102–285)</td>
<td>145 (75–285)</td>
<td>231 (231–853)</td>
</tr>
<tr>
<td>Follow-up interval</td>
<td>0.078</td>
<td>N.A.</td>
<td>0.012</td>
</tr>
<tr>
<td>Total follow-up time</td>
<td>N.A.</td>
<td>0.415</td>
<td>0.285</td>
</tr>
</tbody>
</table>

a A, alcoholic; B, hepatitis B virus; C, hepatitis C virus. b Thirty-one cases in which alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA II) were assayed. c Patients with grown nodules but without hypervascularized nodules.

Fig. 3. Cumulative hypervascularization rate for hypovascular nodules that appeared hypointense on the hepatocyte-phase images of gadoxetic acid-enhanced magnetic resonance (MR) imaging, depending on the presence of fat.
Table 2. Summary of the results of 6 studies

<table>
<thead>
<tr>
<th></th>
<th>Number of nodules</th>
<th>Initial size of the nodule mean ± SD (range) (mm)</th>
<th>Number of hypervascularized nodules</th>
<th>One-year cumulative rate of hypervascularization</th>
<th>Risk factor of hypervascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>60</td>
<td>7.8 ± 3.1 (4 to 17)</td>
<td>8 (11.7%)</td>
<td>5.1% ± 2.9%</td>
<td>Presence of fat</td>
</tr>
<tr>
<td>Motosugi et al. (17)</td>
<td>135</td>
<td>8.4 ± 3.6 (3 to 26)</td>
<td>16 (11.9%)</td>
<td>15.6% ± 4.2%</td>
<td>&gt; 10 mm</td>
</tr>
<tr>
<td>Kumada et al. (18)</td>
<td>49</td>
<td>Hypervascularized 20 (4 to 40)</td>
<td>13 (26.5%)</td>
<td>43.5%</td>
<td>Presence of fat</td>
</tr>
<tr>
<td>Akai et al. (19)</td>
<td>130</td>
<td>8.1 (5–23)</td>
<td>17 (13.1%)</td>
<td>3.2%</td>
<td>&gt; 15 mm</td>
</tr>
<tr>
<td>Takayama et al. (20)</td>
<td>103</td>
<td>8.4 (5–30)</td>
<td>31 (30.1%)</td>
<td>18.4% ± 6.8%</td>
<td>(not significant)</td>
</tr>
<tr>
<td>Takechi et al. (21)</td>
<td>112</td>
<td>Hypervascularized 10.9 ± 3.5</td>
<td>27 (24.1%)</td>
<td>30.4% (&gt; 10 mm)</td>
<td>&gt; 9 mm</td>
</tr>
</tbody>
</table>

vascular before nodules with fat. Their initial sizes ranged between 5 to 8 mm, and all had synchronous or previous hypervascular HCC. Hence, we suspected them as intrahepatic metastatic nodules in which the pattern of progression differed from that of the typical early stage lesion of multistep hepatocarcinogenesis.

Our study has several limitations. First, we obtained pathologic confirmation in only a few cases. However, radiological findings obtained using gadoxetic acid-enhanced MR imaging are probably adequately informative for routine clinical use. Second, the follow-up interval was not fixed because of the retrospective study design. Third, because there were many small lesions, some measurement errors associated with nodular size may have occurred; however, we carefully repeated the measurements and magnified the images on the PACS monitor to minimize errors. Lastly, we did not include hyperintense nodules in the hepatocyte phase.

In conclusion, the presence of intralesional fat was found to be a risk factor for hypervascularization of hypovascular nodules that exhibited hypointensity in the hepatocyte-phase images of gad-oxetic acid-enhanced MR imaging.

Acknowledgements

We wish to thank Dr. Takayuki Abe for his kind advice regarding statistical analysis.

References