Hypointense lesions on Gd-EOB-DTPA-enhanced magnetic resonance imaging changing into hypervascular hepatocellular carcinoma; how frequent is it?

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Purpose

The purpose of the present study is to investigate how frequent hypointense lesions on Gd-EOB-DTPA-enhanced magnetic resonance imaging (MRI) develops into hypervascular hepatocellular carcinoma (HCC) by performing a longitudinal study retrospectively in patients who showed hypointense lesions in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI.
Methods and Materials

Subjects

The present study was approved by the institutional review board of our institution. The institutional review board did not require informed consent for medical records or imaging examinations. The patient inclusion criteria were (a) patients who underwent surgical resection for HCC at our institution from June 2008 to May 2009, (b) patients who underwent Gd-EOB-DTPA-enhanced MRI prior to surgery and (c) patients who underwent follow-up studies on computed tomography (CT) or MRI after the operation. We identified 42 consecutive patients who met these criteria. Of these, two patients were excluded. One patient had an injection of iodized oil (Lipiodol) prior to the MRI study, and this patient was excluded because the signal intensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI might have been affected by the oil. Another patient displayed extremely inhomogeneous liver intensity in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, and this patient was excluded because the imaging quality was not good enough to evaluate the presence of hypointense lesions. Thus, 40 patients with 58 HCCs were enrolled in the present study.

Imaging techniques

All MRIs were performed using a 1.5 T system (Signa HDX 1.5 T; GE Medical Systems, Milwaukee, WI, USA). For all patients, unenhanced MRI, including T1-weighted imaging (fast spoiled gradient recall sequence, repetition time (TR)/echo time (TE) 120 ms/2.2, 4.4 ms, number of excitations 1, field of view 35-40 cm, matrix 256 × 192, slice thickness 6 mm, bandwidth 488.3 Hz/pixel, scan time 15 × 2 s), and T2-weighted imaging with fat suppression (fast spin echo sequence, TE 80 ms, number of excitations 2, echo train length 12, field of view 35-40 cm, matrix 320 × 256, slice thickness 6 mm, bandwidth 122.1 Hz/pixel, asset factor 2, scan time 15 × 2 s) was obtained before the dynamic study. The dynamic study was performed using the Liver Acquisition with Volume Acceleration (LAVA) sequence (TR/TE: 3.8-3.6 ms/1.9-1.8 ms; number of excitations: 1; flip angle: 15°; FOV: 35-40 cm; matrix size: 320×160; slice thickness: 5 mm, bandwidth: 390.6 Hz/pixel, asset factor: 2, scan time: 9 s), which is a three-dimensional (3-D) T1-weighted fast spoiled gradient-echo pulse sequence with fat suppression. During the dynamic study, each patient was administered 25 µmol/kg (0.1 ml/kg) of Gd-EOB-DTPA as an intravenous bolus using a power injector (Spectris Solaris EP; Nihon Medrad, Osaka, Japan) at a rate of 2 ml/s followed by a saline flush. Dynamic contrast-enhanced MRI was initiated at 20, 30, and 60 s after the start of the bolus injection to obtain multiphasic (early arterial, late arterial, and portal venous) images. After the dynamic study, hepatobiliary phase imaging was obtained 20 min after the injection using the LAVA sequence without a parallel imaging technique at a slice thickness of 3mm.
Image analysis

All images were interpreted independently by two experienced board-certified abdominal radiologists who knew that the patients were at risk for HCC but had no other clinical information. First, we recorded all hypointense lesions found in the hepatobiliary phase of the initial Gd-EOB-DTPA-enhanced MRI. The exclusion criteria for hypointense lesions were as follows: (a) lesions that showed hypervascularity on initial dynamic MRI (i.e., exclusion of classical HCC and other hypervascular tumors); (b) lesions that showed delayed enhancement on initial dynamic MRI (i.e., exclusion of slow-filling hemangiomas); (c) lesions that showed strong high intensity on T2WI (i.e., excluding cysts); and (d) lesions <5 mm (since the slice thickness of hepatobiliary phase of Gd-EOB-DTPA enhanced MRI was 3mm). For lesions meeting the above-mentioned criteria, the location, size were recorded. If there were any discordance between two interpreters, the lesion was checked by consensus reading of the two interpreters.

Follow-up study

After the surgery, enhanced CT or enhanced MRI was applied for follow-up studies, which ended in November 2011. The median follow-up period was 886 days (range, 144-1289 days) for all patients. For the follow up MRI studies, not only Gd-EOB-DTPA but nonspecific extracellular gadolinium chelates was also used. The primary endpoint based on lesions was the time when the hypointense lesion developed into classical HCC on follow-up dynamic CT or MRI. If the lesion was resected in the course of follow up, it was considered as right censored data at the time final CT or MRI scan was performed before the treatment, even though the pathological study revealed that the lesion was early HCC. Time schedule of this study is shown on Fig. 1 on page 6.

For the endpoint based on patients, we set two endpoints. Endpoint 1 was the time when classical HCC occurred from the hypointense lesions. We set this endpoint to investigate the clinical implication of the hypointense lesions. Endpoint 2 was the time when classical HCC occurred anywhere in the liver, which is the usual endpoint for disease-free survival.

Diagnosis of classical HCC

For the diagnosis of classical HCC, lesions that showed hypervascularity on arterial phase and a washout pattern on delayed phase were considered as classical HCC. In addition, hypervascular lesions that showed hypointensity on the hepatobiliary phase were considered as classical HCC. If a lesion showed a typical enhancement pattern on the dynamic study, the lesion was considered as classical HCC even though the lesion was isointense or hyperintense relative to surrounding liver parenchyma on the hepatobiliary phase.

Statistical analysis
Based on lesions, the cumulative risk of a hypointense lesion turning into classical HCC was calculated according to the Kaplan-Meier method. We calculated hazard ratios (HRs) for the size using Cox proportional hazard regression.

Based on patients, recurrence curves were constructed according to the Kaplan-Meier method using the above-mentioned two endpoints, and the log rank test was used for statistical comparison. Values of p<0.05 were considered to denote statistically significant differences. All calculations were performed using JMP version 8.0.1 software (SAS Institute, Cary, NC, USA).
Fig. 1: Dotted lines represent for follow up studies. X represents for occurrence of HCC from hypointensity lesion, triangle represents for occurrence of HCC from different area from hypointensity lesion, and circle represents for non occurrence of HCC from hypointensity lesion. Thick lines represent for time to event (occurrence of HCC) or follow up period without occurrence of HCC for each lesion. Lesion C represents for lesion which was resected simultaneously with the HCC occurred from different area. If the lesion was not resected at 2nd or more operation (lesion D, E), time to event was calculated as usual (lesion A, B) lesions.
Results

Of 40 patients, nine patients showed no hypointense lesion in the hepatobiliary phase of the initial Gd-EOB-DTPA-enhanced MRI. Among the remaining patients (i.e., 31 patients), 130 hypointense nodules (size range, 5-23 mm; mean size, 8.1 mm) were found.

Among the 130 hypointense lesions on MRI, 17 lesions (13.1%) developed into classical HCC. The cumulative rates for the hypointensity lesions that developed into classical HCC were 1 year, 11.1% at 2 years and 15.9% at 3 years (Fig. 2 on page 8).

Hazard ratios for lesions 10-15 mm and ≥15 mm were higher compared to lesions 5-10 mm, but no significant difference was observed (p=0.064, 0.094 for each size group; table).

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Number of nodules</th>
<th>Number of occurrence of HCC</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5 mm and &lt;10 mm</td>
<td>97</td>
<td>8</td>
<td>1.0</td>
</tr>
<tr>
<td>≥10 mm and &lt;15 mm</td>
<td>24</td>
<td>6</td>
<td>2.86(0.94-8.23)</td>
</tr>
<tr>
<td>≤15 mm</td>
<td>9</td>
<td>3</td>
<td>3.55(0.79-12.3)</td>
</tr>
</tbody>
</table>

Hazard ratio for occurrence of classical HCC with increasing nodule size.

The occurrence curves of classical HCC for 31 patients who showed hypointense lesions in the hepatobiliary phase of the initial Gd-EOB-DTPA-enhanced MRI using two endpoints are shown in Fig. 3 on page 8. Among these 31 patients, first occurrence of classical HCC was seen at hypointense lesions in 8 patients, at different area from that of the hypointense lesions in 10 patients, and at both hypointense lesions and in a different area from that of the hypointense lesions in 2 patients. Eleven patients had no occurrence of classical HCC. The total occurrence rates were 25.8% at 1 year, 52.6% at 2 years and 76.4% at 3 years and the occurrence rates concerning only the occurrence from the followed site (i.e., the hypointense lesions in the hepatobiliary phase) were 10.0% at 1 year, 35.6% at 2 years and 44.6% at 3 years, with no significant difference (p=0.073).
Fig. 2: Cumulative rates for hypointense lesions that became classical HCC is shown. The cumulative rates for hypointense lesions that became classical HCC were 3.2% at 1 year, 11.1% at 2 years and 15.9% at 3 years.

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Fig. 3: The total occurrence rate of classical HCC (red line) and that concerning only the occurrence from the followed site (blue line) are shown. Although the total occurrence rate was higher, no significant difference was observed.

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Conclusion

The present study showed that hypointense lesions depicted in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI >5 mm developed into classical HCC with frequencies of 3.2% at 1 year, 11.1% at 2 years and 15.9% at 3 years.

Although, hypervascular HCC frequently occurred from different areas from that of the lesions being followed. So whether the lesions should be treated is questionable. Although not achieving statistical significant difference, larger nodules had higher hazard ratios for occurrence of classical HCC, so the size might be a criteria for the selection of treatment.

The major limitation of this study is that the number of cases and lesions in our study was small. Future research using a larger number of subjects is recommended to confirm and extend our results. Another limitation is that we only included preoperative patients, so the liver function of our patients were not severely damaged. Usually, uptake of Gd-EOB-DTPA to liver parenchyma is decreased or inhomogeneous in patients with severe liver dysfunction; thus, interpretation of the hepatobiliary phase might be difficult in those patients, resulting in over- or underestimation of hypointensity nodules.

In conclusion, hypointense lesions that are detected in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI have some malignant potential.
References


