HCC-to-Liver Contrast in Arterial-Dominant Phase of EOB-Enhanced MRI: Comparison with Dynamic CT and CTHA

Poster No.: C-0559
Congress: ECR 2011
Type: Scientific Exhibit
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Keywords: Abdomen, MR, CT, Catheter arteriography, Contrast agent-intravenous, Neoplasia, Liver
DOI: 10.1594/ecr2011/C-0559

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Purpose

Hepatocellular carcinoma (HCC) is causing approximately 600,000 to 700,000 deaths annually worldwide. It is highly prevalent in the Asia-Pacific region and Africa, and is on the increase in western countries, so that early detection, accurate diagnosis, and proper management are urgently required on a global scale. The evaluation of arterial blood supply (i.e. vascularity or vascular pattern) in tumor is an essential step for both diagnosis and management of HCC [1-4], and it is usually performed by means of multiphasic contrast-enhanced dynamic computed tomography (CT) and magnetic resonance imaging (MRI) with intravenous bolus injection of contrast medium.

A recently available liver-specific contrast medium, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (EOB), reportedly has a high diagnostic capability for detection of malignant liver tumors [5, 6]. It works as both an extracellular and hepatocyte-specific contrast agent and provides both dynamic and hepatocyte-specific imaging. However, its diagnostic capability for HCC is reportedly only slightly better or equal to that of dynamic CT [7 - 13]. Possible reasons for this are that the administrated volume of EOB is smaller than that of extracellular gadolinium contrast media and its concentration of gadolinium is only about half. Therefore, HCC-to-liver contrast can be assumed to be lower on arterial phase images of EOB-enhanced MRI than that on arterial phase images of dynamic CT or MRI using extracellular gadolinium contrast media, thus resulting in a lower detection rate of HCC and lower ability to assess hypervascularity. However, no objective studies dealing with this issue have been reported.

Some investigators have suggested that CT during hepatic arteriography (CTHA) is useful for evaluation of arterial blood supply in HCC [14, 15], but no comparative studies of CTHA and EOB-enhanced MRI have been reported.

The purpose of the this study was thus to assess the efficacy of EOB-enhanced MRI for evaluation of arterial blood supply in HCC in comparison with that of multiphasic dynamic CT and CT during hepatic arteriography (CTHA).
Methods and Materials

Patients

A total of 45 patients prospectively underwent all three examinations of Gd-EOB-DTPA-enhanced MRI, contrast-enhanced multiphasic dynamic CT of the liver, and CTHA for preoperative assessment between January 2010 and November 2010. Fifteen patients whose diagnosis of HCC was not confirmed histopathologically were excluded from the study population, so that 30 patients (22 males, 8 females; mean age: 68.0 yrs) were considered eligible for this study. Twenty-five patients were diagnosed with chronic hepatitis virus infection (8 with hepatitis B and 17 with hepatitis C). Three patients had ethanol-induced and one had nonalcoholic steatohepatitis. Liver cirrhosis was surgically diagnosed in 4 patients and chronic hepatitis in 23 patients. All patients were classified as Child-Pugh A. None of them had previously undergone hepato-biliary surgery or trans-arterial chemo-embolization (TACE). All patients underwent the three examinations and hepatectomy within one month.

Consequently, this study included 40 histopathologically proven HCCs (well-differentiated: 3, moderately differentiated: 30, poorly differentiated: 7). The diameters of the tumors ranged from 13 to 130 mm with a mean of 45.1 ± 29.8 mm.

This study was approved by the local ethics committee of our institution and informed consent was obtained from all participating patients.

Magnetic Resonance Imaging

EOB-enhanced MR examination was performed with a superconducting imager operating at 1.5 Tesla (Achieva; Philips Medical Systems, Best, the Netherlands) and using a 4-element phase-array body coil. Pre-contrast axial T1-weighted gradient-echo images were obtained with fat suppression (TR/TE: 210/4.6 msec; FA: 75°) and without it (TR/TE: 235/4.6 and 2.3 msec; FA = 75°). A multiphasic dual-arterial dynamic study was performed using three-dimensional T1-weighted gradient-echo (TR/TE/FA: 2.25-3.09 msec/0.8-1.5 msec/10-15°; matrix size: 224´168; field of view: 380 - 400 mm; number of excitations: 1; slice thickness: 8 mm; transverse slices: 22-30; for fat saturation: spectral presaturation with inversion recovery (SPIR); parallel imaging factor: 2.0; scan time: 7 sec) with intravenous bolus injection of 25µmol/kg (0.1 ml/kg) of Gd-EOB-DTPA (Primovist; Bayer Healthcare, Osaka, Japan) by means of a power injector (Sonic Shot 50; Nemoto Kyorindo Co. Ltd., Tokyo, Japan) at a rate of 2 ml/sec, followed by 30 ml of saline chaser at the same rate during breath holding. The scan delays were set at 20 seconds after the start of injection and dual-arterial dynamic images were obtained serially during a single breathhold. Portal- and delayed-phase images were also obtained 60 and 90 seconds after injection.
Twenty minutes after injection, T1-weighted images with fat suppression were repeated as hepatobiliary phase images and breath-hold T2-weighted fast spin-echo images (TR/TE=2800 msec/90msec) were obtained. A slice thickness was set at 7-8 mm for all the sequences.

**Multiphasic Dynamic Computed Tomography**

CT examination was performed by using a 64-detector row CT systems (Aquilion 64; Toshiba Medical System, Ohtawara, Japan) with the following parameters: 64 × 0.5 mm detector collimation, reconstructed to axial slices with a thickness of 5mm, 0.5 sec/gantry rotation, 120 kVp, and 0.94 beam pitch. The tube current was set by automated exposure control (noise level: 10). Each subject was first examined with unenhanced CT, and this was followed by the injection of iodinated contrast medium (Iomeron 350; Eisai Co. Ltd., Tokyo, Japan) with a power injector (Dual Shot GX; Nemoto Kyorindo). Injection dose was 600 mg iodine per kg of body weight and since duration was fixed at 25 seconds, the injection rate depended on the patient's body weight. No saline chaser was administered.

A bolus tracking program was used to optimize the scanning delay for dual-arterial dynamic scans. The trigger point was placed at the abdominal aorta at the level of the celiac axis and the trigger threshold was set at an increase in CT number of more than 200 HU over the baseline value. The scan delays were set at 5 seconds after the trigger and dual-arterial dynamic images were obtained serially during a single breathhold. Portal- and delayed-phase images were also obtained 70 and 150 seconds after injection.

**CT During Hepatic Arteriography (CTHA)**

CT during arterio-portography via the superior mesenteric artery (CTAP) and CTHA were performed with the aid of an interventional CT unit (Aquilion LB; Toshiba Medical System, Ohtawara, Japan). Catheter angiography was performed via the right femoral artery with the Seldinger technique and a 3 or 4-Fr catheter. Prior to CTHA, CTAP and the selective celiac and common hepatic arteriograms were obtained. A total of 65-75 ml of iodinated contrast medium at a concentration of 300 mgI/ml was used for these procedures.

Dual-phasic CTHA was performed via the common hepatic artery approximately 5 min after prior administrations during breathholding with the injection of 20-30 ml of iodated contrast medium (diluted with saline to 100 mgI/ml) at a rate of 2-3 ml/sec with a power injector (Zone Master; Sheen Man Co. Ltd., Osaka, Japan) with the following parameters: 16 × 0.5 mm detector collimation, reconstruction to axial slices with a thickness of 5mm, 0.5 - 0.75 sec/gantry rotation, 120 kVp, 240 - 440 mA, and 0.94 beam pitch. Scanning delays were 10 and 30 seconds after the start of injection. The injection duration was set at 10 seconds, and the injection volume and rate were set according to the size of the largest tumor (e.g., 30 ml and 3 ml/sec were used for a patient with a tumor more than 5cm in diameter).
**Image Analysis**

*Image and phase selections*

Two experienced abdominal radiologists (T. K., T. Y.) with 8 and 17 years’ experience, respectively, independently reviewed the axial images from the three examinations of all 30 patients at a picture archiving and communication system (PACS) workstation (ShadeQuest; Yokogawa Electric Corporation, Musashino, Japan), while blinded to the histopathological diagnosis. First, the observers were asked to select the images with HCCs shown at their maximal diameter. Second, the observers were also asked to select the phase with the higher HCC-to-liver contrast from the first and second arterial-dominant phase images of dynamic CT and EOB-enhanced MRI and from the first and second phase images of CTHA for each patient. The selected phases and images were then used for further analyses.

*Quantitative Analysis*

The quantitative analysis was conducted by the two observers on the images obtained with all the examinations using the operator-defined region-of-interest (ROI) measurements of mean signal intensity or CT value of HCC and surrounding normal liver parenchyma. The oval ROI was placed within HCC and made as large as possible to include necrotic areas and the visually selected maximal enhancement area (5 to 10% of the total tumor area). The ROI for surrounding normal liver parenchyma was at least 5 cm² and located adjacent to the target lesion, while vessels were avoided as much as possible. The ROIs were placed in the same locations among all the examinations as far as possible.

The definition of contrast used in this study is known as Michelson’s contrast ($C_M$) [16] and is defined as:

$$C_M = \frac{(S_{HCC} - S_{Liver})}{(S_{HCC} + S_{Liver})}$$

Where $S_{HCC}$ is the signal intensity or CT value of the HCC and $S_{Liver}$ is the signal intensity or CT value of the surrounding normal liver parenchyma. The mean HCC-to-liver contrasts and mean maximal HCC-to-liver contrasts obtained with the three examinations were then calculated and compared.

*Qualitative Analysis*

For each patient, the observers subjectively scored the degree of HCC-to-liver contrast according to the following five-point scale: 1, signal intensities or CT values of HCC are lower than those of surrounding normal liver; 2, signal intensities or CT values of HCC are equal to those of surrounding normal liver; 3, signal intensities or CT values of HCC are slightly higher than those of surrounding normal liver; 4, signal intensities or CT values of
HCC are noticeably higher than those of surrounding normal liver; signal intensities or CT values of HCC are markedly higher than those of surrounding normal liver. The mean visual scores for HCC-to-liver contrast for the three modalities were then calculated and compared.

**Statistical analysis**

Statistical analysis of the mean HCC-to-liver contrast \( (C_M) \) was performed with the aid of one-way analysis of variance (ANOVA) and the Scheffé criterion. For statistical analysis of the mean visual scores for HCC-to-liver contrast, the Kruskal-Wallis test and Scheffé criterion were used. All of the quantitative and qualitative values were expressed as mean ± SD. For all tests, a p value of less than 0.05 was considered statistically significant.

For the qualitative analysis, interobserver agreements were analyzed by means of Kappa statistics. Positive correlation was considered to be indicated by a k value greater than 0, poor correlation by values of 0.00-0.01, low correlation by values of 0.01-0.20, moderate correlation by values of 0.21-0.40, good correlation by values of 0.41-0.60, substantial correlation by values of 0.61-0.80, and almost perfect agreement by values greater than 0.81 [17].
Results

HCC-to-liver contrasts were visually higher on the second arterial-dominant phase images of both EOB-enhanced MRI and dynamic CT for all patients, so that only these images were used for further analyses. On the other hand, since HCC-to-liver contrasts were visually higher on the first phase images of CTHA, only these images were used for further analyses.

For one observer, the mean $C_M$ of CTHA was significantly higher than that of EOB-enhanced MRI (Fig. 1). For both observers, the mean maximal $C_M$s of dynamic CT were significantly higher than those of EOB-enhanced MRI. For one observer, the mean maximal $C_M$ of CTHA was significantly higher than that of EOB-enhanced MRI (Fig. 2). Finally, for both observers the mean visual scores of dynamic CT and CTHA were significantly higher than those of EOB-enhanced MRI (Fig. 3). Typical cases are shown in Figures 4 and 5.

The $k$ values for the two observers were 0.80 for dynamic CT, 0.80 for EOB-enhanced MRI, 0.74 for the CTHA, indicating that substantial to almost perfect agreements were obtained.
### Mean HCC-to-Liver Contrasts of the three Modalities*

<table>
<thead>
<tr>
<th></th>
<th>Dynamic CT</th>
<th>EOB-MRI</th>
<th>CTHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer1</td>
<td>0.19±0.11</td>
<td>0.13±0.13</td>
<td>0.20±0.15a</td>
</tr>
<tr>
<td>Observer2</td>
<td>0.19±0.10</td>
<td>0.13±0.14</td>
<td>0.18±0.19</td>
</tr>
</tbody>
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**Fig. 0:** *Michelson's contrast: \( CM = \frac{(S \text{ Tumor} - S \text{ Liver})}{(S \text{ Tumor} + S \text{ Liver})} \), a: \( p < 0.05 \)

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**Mean Maximal HCC-to-Liver Contrasts of the three Modalities**

<table>
<thead>
<tr>
<th>Dynamic CT</th>
<th>EOB-MRI</th>
<th>CTHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1</td>
<td>0.29 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.19 ± 0.12</td>
</tr>
<tr>
<td>Observer 2</td>
<td>0.30 ± 0.09&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.20 ± 0.14</td>
</tr>
</tbody>
</table>

**Fig. 0:** *Michelson’s contrast: CM = (S Tumor - S Liver) / ( S Tumor + S Liver), a: p < 0.005, b: p < 0.05, c: p < 0.05*

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Mean Visual Scores for HCC-to-liver contrast of the three Modalities

<table>
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<tr>
<th></th>
<th>Dynamic CT</th>
<th>EOB-MRI</th>
<th>CTHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer1</td>
<td>3.5±1.1(a)</td>
<td>2.5±0.9</td>
<td>3.2±1.4(b)</td>
</tr>
<tr>
<td>Observer2</td>
<td>3.7±1.1(c)</td>
<td>2.6±1.0</td>
<td>3.2±1.3(d)</td>
</tr>
</tbody>
</table>

**Fig. 0:** a: \(p < 0.001\), b: \(p < 0.05\), c: \(p < 0.0005\), d: \(p < 0.05\)

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Fig. 0: A 78-year-old man with hepatocellular carcinoma (HCC) in the right posterior segment. Second arterial-dominant phase image of EOB-enhanced MRI (a) shows heterogeneous and slight enhancement of the lesion. The visual score was 3. Second arterial-dominant phase image of contrast-enhanced dynamic CT (b) and first phase image of CT during hepatic arteriography (CTHA) (c) demonstrate heterogeneous and noticeable enhancement of the lesion. The visual score was 4 for both images. The regions-of-interest (ROI) were placed within HCC and made as large as possible to include necrotic areas, the visually selected maximal enhancement area, and the surrounding normal liver parenchyma. Signal intensity and CT value were measured and HCC-to-liver contrasts calculated. The latter were 0.20 for EOB-enhanced MRI, 0.29 for dynamic CT, and 0.29 for CTHA. Maximal HCC-to-liver contrasts were also calculated and were 0.33 for EOB-enhanced MRI, 0.37 for dynamic CT, and 0.37 for CTHA.

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Fig. 0: An 81-year-old man with hepatocellular carcinoma (HCC) in the left medial segment. Second arterial-dominant phase image of EOB-enhanced MRI (a) shows heterogeneous enhancement in the lesion approximately equal to the normal parenchyma. The visual score was 2. Second arterial-dominant phase image of contrast-enhanced dynamic CT (b) and first phase image of CT during hepatic arteriography (CTHA) (c) demonstrate heterogeneous and slight enhancement of the lesion. The visual score was 3 for both. HCC-to-liver contrasts were calculated and were 0.03 for EOB-enhanced MRI, 0.07 for dynamic CT, and 0.07 for CTHA. Maximal HCC-to-liver contrasts were also calculated and were 0.10 for EOB-enhanced MRI, 0.10 for dynamic CT, and 0.09 for CTHA.

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Conclusion

DISCUSSION

For early detection, accurate diagnosis, and proper management of HCC, the evaluation of arterial blood supply in tumor is essential. This evaluation is commonly performed using either multiphasic dynamic CT or MRI with intravenous bolus injection of contrast medium [1-4]. Recently, Gd-EOB-DTPA has come to play a major role in diagnosis of HCC, because it functions as both an extracellular and hepatocyte-specific contrast agent and provides both dynamic and hepatocyte-specific information. The addition of hepatobiliary phase imaging makes it possible to detect very early stages of HCC.

However, the overall diagnostic capability of Gd-EOB-DTPA for HCC is reportedly only slightly better than or equal to dynamic CT [7 - 13] - except for the evaluation in one recently published report [18] - in spite of the use of hepatobiliary phase images, which were found to improve the diagnostic ability of EOB-enhanced MRI [19 - 22]. Possible reasons for this are that the administrated volume of EOB (0.025mmol/kg) is smaller than that of extracellular gadolinium contrast media (0.05mmol/kg) and its concentration of gadolinium is only about half. Although this is partially compensated for by the higher T1 relaxivity of Gd-EOB-DTPA, enhancement of HCC in the arterial-dominant phase decreases, resulting in lower HCC-to-liver contrast on arterial phase images. Akai et al. visually compared the arterial phase images of EOB-enhanced MRI with those obtained with dynamic CT and reported that the former was slightly inferior to the latter for evaluation of vascularity in HCC although the difference was not significant. However, this study covered only a small patient population and used subjective assessment. As for enhancement of the liver parenchyma, Tamada et al. reported that signal intensity ratio of the liver on EOB-enhanced arterial phase image was significantly lower than that of Gd-DTPA for normal subjects [23] and Filippone et al. reported reduced enhancement of EOB for both cirrhotic and non-cirrhotic liver compared to Gd-DTPA [24].

On the other hand, dynamic CT techniques have rapidly improved and become optimized in recent years [25]. We therefore hypothesized that dynamic CT was superior to EOB-enhanced MRI for evaluation of arterial blood supply in HCC. In addition, some investigators have suggested that CTHA is highly effective for detection of arterial blood supply in HCC [14, 15], although it involves invasive procedures. No studies comparing CTHA and EOB-enhanced MRI have been reported.

In addition, previous relevant reports mainly used subjective methods of assessment. A comparative study using both subjective and objective methods for assessment across the various modalities was therefore needed. However, direct comparison of the degree of tumor enhancement by the various modalities is impossible because the mechanisms for image reconstruction and contrast enhancement are completely different. To overcome this problem, we introduced an index known as Michelson's
contrast \((C_M)\), which has already been used in the field of radiology [16]. With this index, we can compare tumor-to-normal tissue contrasts on images obtained with the modalities, and this contrast is the most important factor for detection of HCC and evaluation of its vascular pattern for routine image interpretations.

Our results showed that both observers in our study rated the mean \(C_M\) of dynamic CT as significantly higher than that of EOB-enhanced MRI when using maximal HCC-to-liver contrast was used. This was confirmed by our qualitative analysis, thus indicating that EOB-enhanced MRI is not a suitable modality for evaluation of arterial blood supply in HCC. This should be taken into account for diagnosis and management of HCC, and when using EOB-enhanced MRI, injection techniques should be optimized or administration doses should be reviewed [23, 26]. The results of quantitative and qualitative analyses showed good correlation, indicating that the use of \(C_M\) for this purpose is satisfactory.

Interobserver agreement analysis in our study showed substantial to almost perfect agreements among the observers for all three modalities, although agreement for CTHA was slightly lower. A possible reason for this discrepancy may be the difference in the observers’ experience. One of them had ample experience in the fields of both diagnostic and interventional radiology, while the experience of the other observer was limited to the field of diagnostic radiology.

The imaging and contrast enhancement techniques used in this study were somewhat different for the different modalities. Saline chaser was not used for dynamic CT, which have resulted in underestimation of the efficacy of dynamic CT. Moreover, we did not use a bolus tracking technique for EOB-enhanced MRI and the scan timing of arterial phase images may not have been appropriate. However, the latter is not a major limitation because we used a dual-arterial phasic protocol which is reportedly quite adequate for scan timing. Administration of a large volume of contrast medium before CTHA probably increased the baseline CT values in the liver and resulted in underestimation of the diagnostic capability of CTHA. However, CTHA is usually performed in combination with conventional angiography and CTAP and after them. Nevertheless, CTHA still showed the best performance among our results.

There are some limitations to this study. First, the number of patients involved was rather small, so that further studies with larger populations are needed to verify our results. Second, HCCs in our study were rather large, resulting in insufficient data for smaller lesions. However, quantitative assessment of small lesions can be adversely affected by partial volume averaging. In addition, it is difficult to obtain accurate pathological diagnosis for small lesions because biopsy is often difficult and it is often interpreted as intrahepatic metastasis which prevents the patient from benefiting from curative surgery.

In conclusion, EOB-enhanced MRI is not a suitable modality for evaluation of arterial blood supply in HCC. This should be taken into account for diagnosis and management of HCC.
References


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