Detectability of liver metastases: comparison between Gd-EOB-DTPA-enhanced MRI and contrast-enhanced multi-detector CT

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Aims and objectives

The metastasis of gastrointestinal carcinomas to the liver is a frequent and critical problem [1]. In particular, liver metastasis is an important prognostic factor in colorectal cancer [2]. Further, in breast cancer, the development of liver metastases is an indication of advanced disease and a poor prognosis [3]. The early detection and precise characterization of liver metastasis are important liver imaging factors for ensuring appropriate treatment.

Contrast enhanced computed tomography (CT) has been widely used as a primary imaging procedure in the assessment of liver metastasis. As well, the recent development of multidetector computed tomography (MDCT) has allowed for detailed imaging of the liver, because it offers improved spatial and temporal resolution. However, reports on diagnostic studies of the liver using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) as a hepatocyte-specific magnetic resonance imaging (MRI) contrast agent have been increasing. Unlike existing contrast agents, Gd-EOB-DTPA allows combined dynamic imaging and hepatocyte-specific imaging in a single examination [4].

Prior studies have reported that Gd-EOB-DTPA-MRI (EOB-MRI) is useful for the detection and characterization of focal hepatic lesions [5, 6], and that lesion detectability using EOB-MRI is higher than that of dynamic enhanced CT [7, 8]. As well, previous studies have indicated that EOB-MRI was more accurate than contrast-enhanced MDCT (CEMDCT) for the detection of liver metastases [9, 10]. Although these studies were well designed and documented the improved detectability of liver metastases by EOB-MRI, most of the prior studies involved small populations or were single-center trials.

The purpose of the current study was to conduct a systematic literature review and meta-analysis to compare the sensitivity of EOB-MRI and CEMDCT for detecting liver metastases lesions from malignant tumors. A second objective was to determine whether the results would provide evidence that EOB-MRI is effective for the detection of liver metastasis.
Methods and materials

Search for published data

The PubMed Medline database and the Cochrane Library were searched for eligible studies. Articles published from January 2000 to September 2014 were searched. In a manual search, references in the eligible articles and reviews were also scanned and retrieved. The search terms were as follows:

Gadolinium-EOB-DTPA OR gadoxetic acid OR Gd-EOB-DTPA OR eovist OR primovist and (Liver metastases OR hepatic metastases OR liver lesions) and (computed tomography or MDCT)

Inclusion and exclusion criteria

Studies were included in the analysis if they met the following criteria:

1) Articles that included a comparison between EOB-MRI and CT for detectability of liver metastases in malignant tumors in the same subjects.

2) Articles that provided primary data on lesion detectability (sensitivity) using EOB-MRI and CT.

3) CT examination was performed exclusively using MDCT.

4) Full peer-reviewed journal papers.

5) The study population included at least 10 patients.

Studies were excluded if they met the following criteria:

1) Articles with duplicate or overlapping data.

2) Meeting abstracts (did not provide adequately detailed data).

3) Review articles without original data and case reports.

After an initial search, two investigators applied the inclusion and exclusion criteria and selected articles for data extraction. The selection was carried out independently, and disagreements were resolved by consensus.

Data extraction
Two investigators (K.I. and T.M.), independently reviewed the full text of each potentially eligible study and abstracted the data. The investigators were not blinded to the authors, journal name, or year of publication. Disagreements were resolved by consensus. The following data were recorded for each article:

1. Author and year of publication.
2. Sample size (number of patients and metastases).
3. Location of primary tumor.
4. Imaging technique for EOB-MRI (field strength, injection rate and total dose of Gd-EOB-DTPA, delay time of hepato-biliary phase).
5. Imaging technique for CEMDCT (scanner type, injection rate and total dose of contrast media, scan timing.
6. Sensitivity data including all lesion and tumor sizes up to or less than 1 cm.

Lesion detectability (sensitivity) of EOB-MRI and CEMDCT was recorded on a lesion by lesion basis. Sensitivity data was based on "true positive" and "false negative" datasets.

Methodological quality assessment

Methodological quality assessment was performed independently by two reviewers, using the Quality Assessment of Diagnostic Studies (QUADAS)-2 tool. Disagreements were resolved by consensus. The QUADAS-2 tool was designed specifically for studies of diagnostic accuracy. The tool is divided into four key domains that cover participant selection, index test, reference standard, and the flow of patients through the study (including the timing of tests). Each domain is rated for risk of bias (low, high or unclear), and the tool provides signaling questions in each domain to aid reviewers in reaching a decision.

Data synthesis and statistical analysis

Individual and weighted sensitivity as well as 95% confidence intervals (CIs) for the detection of liver metastases were calculated for each study. Weighted sensitivity was calculated for the following:

1. All lesions.
2. Small lesions (Size of tumor is less than or equal to 1 cm).
3. Primary Cancer site was colorectal cancer.
The method of calculating the weighted sensitivity was determined based on homogeneity using a Q statistic. To assess the heterogeneity of the included studies, the Q statistic test and \( I^2 \)-statistic test were performed. When the p value was lower than 0.05 or the \( I^2 \) statistic test revealed a value greater than 50%, the heterogeneity was considered substantial. For data synthesis, the individual study results were analyzed using a fixed-effects model (if homogeneity could not be rejected) or a random-effects model (if homogeneity could be rejected).

**Comparison of EOB-MRI and CEMDCT**

The weighted sensitivity of EOB-MRI and CEMDCT for all lesions, small lesions, and primary colorectal cancer sites were compared. Absence of an overlap in 95% CIs was considered a statistically significant difference (p < 0.05).

**Assessment of publication bias**

Publication bias toward the weighted sensitivity was determined using data extracted from each of the articles, and was assessed by The Egger's regression test to examine the asymmetry of the funnel plot. A p value less than 0.05 was considered statistically significant.

All statistical analyses were performed using R (V.3.1.1 package: meta).
Results

Search results

The search process and results are shown in the Fig. 1 on page 8 flowchart. Seven studies [9-15] fulfilled all inclusion criteria and were eligible for meta-analysis. All eligible studies were published in peer-reviewed journals between 2011 and 2013.

Characteristics of the included studies

The seven studies included 306 patients with 638 target lesions ( Table 1 on page 8 ). In one of the studies, the number of hepatic metastasis was different following EOB-MRI (59) and CEMDCT (112) [10]. Two of the studies were prospective studies [11, 14], and five studies were retrospective studies [9, 10, 12, 13, 15]. In the primary cancer site, four studies were colorectal cancer [9-11, 14], one study was pancreatic cancer [13], and two studies were various forms (colorectal, stomach, breast, lung, pancreas and gall bladder) [12,15]. Two studies were based only on pathological examination as a reference test [11, 14]. Other studies involved pathologic examination as well as multimodality assessments (e.g. intraoperative ultrasound, follow-up imaging) as a reference test [9, 10, 12, 13, 15]. Methodological quality assessment by QUADAS-2 is shown in Fig. 2 on page 9.

EOB-MRI detectability of liver metastases of (All lesions)

Table 2 on page 9 shows imaging techniques and individual sensitivity in each EOB-MRI study. In contrast-enhance scanning, six studies involved dynamic scanning after an injection dose of 0.025 mmol/Kg, while one study was performed following a 10ml injection dose. Four studies used a bolus-timing program. The weighted sensitivity was 92.0% (95% CI, 89.3% to 94.0%). The test for heterogeneity was not significant (Q = 10.73, p = 0.09), and the I² value was 44.1%. In the assessment of publication bias, there was no evidence of a significant publication bias (t = - 1.48, p = 0.20).

CEMDCT detectability of liver metastases (All lesions)

Table 3 on page 9 details the imaging techniques and individual sensitivity for each CEMDCT study. In the CT scanning, four studies involved an automatic dose modulation technique. In addition, three CE scanning studies used a bolus-tracking program. For image interpretation, three studies utilized combined reconstructed multiplanar images. The weighted sensitivity was 70.2% (95% CI, 61.3% to 77.8%). The test for heterogeneity was significant (Q = 30.76, p < 0.0001). The I² value was 80.5%. In the assessment of publication bias, no evidence of a significant publication bias existed (t = -0.26, p = 0.80).
EOB-MRI and CEMDCT detectability of liver metastases (Size of tumor: equal to or less than 1 cm)

Five of the studies assessed the EOB-MRI and CEMDCT detectability of liver metastases for tumors with a size equal to or less than 1 cm (Table 4 on page 10) [10, 11, 13-15]. The studies included a total of 209 patients, and 422 target lesions for EOB-MRI and 475 lesions for CEMDCT.

Using EOB-MRI, the weighted sensitivity was 84.1% (95% CI, 78.3% to 88.6%). The test for heterogeneity was not significant (Q = 4.68, p = 0.32), and the $I^2$ value was 14.5%. In the assessment of publication bias, no evidence of significant publication bias was detected (t = -2.73, p = 0.07).

Using CEMDCT, the weighted summary sensitivity was 42.5% (95% CI, 26.7% to 59.9%). The test for heterogeneity was significant (Q =24.72, p < 0.0001), and the $I^2$ value was 83.8%. In the assessment of publication bias, no evidence of significant publication bias was noted (t = 2.03, p =0.14).

EOB-MRI and CEMDCT detectability of liver metastases (Primary cancer: colorectal cancer)

Four studies assessed the EOB-MRI and CEMDCT detectability of liver metastases when the primary cancer was colorectal cancer (Table 5 on page 10) [9-11,14]. The studies included a total of 134 patients, and 276 target EOB-MRI lesions and 329 CEMDCT lesions.

Using EOB-MRI, the weighted sensitivity was 93.9% (95% CI, 90.3% to 96.2%). The test for heterogeneity was not significant (Q =1.76, p = 0.63), and the $I^2$ value was 0%. In the assessment of publication bias, no evidence of significant publication bias was noted (t = -1.13, p = 0.38).

Using CEMDCT, the weighted sensitivity was 71.1% (95% CI, 62.8% to 78.2%). The test for heterogeneity was not significant (Q =7.04, p = 0.07), and the $I^2$ value was 57.4%. In the assessment of publication bias, no evidence of significant publication bias was detected (t = -0.58, p = 0.62).

Comparison of EOB-MRI and CEMDCT

Using the weighted sensitivity, EOB-MRI and CEMDCT for all lesions, small lesions, and primary colorectal cancer sites were compared. In all cases, the pooled sensitivity of EOB-MRI was significantly higher than the sensitivity of CEMDCT, based on no apparent overlap in the 95% CIs [Tables 2-5].
Fig. 1: Flow chart of the search process and results. N: number

Table 1: Characteristics of the studies included. Various: Various primary cancer sites: (e.g.: colorectal, stomach, breast, lung, pancreas, gall bladder, and so on)

<table>
<thead>
<tr>
<th>First Author</th>
<th>Ref.</th>
<th>Year</th>
<th>Total patient Populations</th>
<th>Number of Metastases</th>
<th>Study Design</th>
<th>Primary Cancer Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan VO</td>
<td>9</td>
<td>2012</td>
<td>30</td>
<td>53</td>
<td>Retrospective</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Muhi A</td>
<td>10</td>
<td>2011</td>
<td>46</td>
<td>*112(59)</td>
<td>Retrospective</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Berger-Kulemann V</td>
<td>11</td>
<td>2012</td>
<td>23</td>
<td>68</td>
<td>Prospective</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Kim YK</td>
<td>12</td>
<td>2012</td>
<td>67</td>
<td>110</td>
<td>Retrospective</td>
<td>Various</td>
</tr>
<tr>
<td>Motosugi U</td>
<td>13</td>
<td>2011</td>
<td>54</td>
<td>62</td>
<td>Retrospective</td>
<td>Pancreas cancer</td>
</tr>
<tr>
<td>Scharitzer M</td>
<td>14</td>
<td>2013</td>
<td>35</td>
<td>96</td>
<td>Prospective</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Lee KH</td>
<td>15</td>
<td>2013</td>
<td>51</td>
<td>137</td>
<td>Retrospective</td>
<td>Various</td>
</tr>
</tbody>
</table>

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Fig. 2: Methodological quality assessment (using QUADAS-2 tool).

Table 2: EOB-MRI all lesions. CI: Confidence interval N.A: Not available
Table 3: CEMDCT-all lesions. CI: Confidence interval N.A: Not available *Scan timing A: Arterial phase, PP: Pancreatic parenchymal phase, P: Portal venous phase, D: Delayed phase B/W: depend on the patients’ body weight CI: Confidence interval Various: 4, 16, 64, and other (40× 2)

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<table>
<thead>
<tr>
<th>First Author</th>
<th>Ref.</th>
<th>EOB-MRI Sensitivity (%) (95% CI)</th>
<th>CEMDCT Sensitivity (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muhi A</td>
<td>10</td>
<td>91.7 (73.0-99.0)</td>
<td>26.0 (14.6-40.3)</td>
</tr>
<tr>
<td>Berger-Kulemann V</td>
<td>11</td>
<td>90.3 (74.3-98.0)</td>
<td>38.7 (21.9-57.8)</td>
</tr>
<tr>
<td>Motosugi U</td>
<td>13</td>
<td>90.5 (77.4-97.3)</td>
<td>61.9 (45.6-76.4)</td>
</tr>
<tr>
<td>Scharitzer M</td>
<td>14</td>
<td>77.4 (59.0-90.4)</td>
<td>64.5 (45.3-80.8)</td>
</tr>
<tr>
<td>Lee KH</td>
<td>15</td>
<td>81.0 (70.6-89.0)</td>
<td>26.6 (17.3-37.7)</td>
</tr>
</tbody>
</table>

Table 4: Table 4 EOB-MRI and CEMDCT detectability of liver metastases (Size of tumor: equal to or less than 1 cm) CI: Confidence interval

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<table>
<thead>
<tr>
<th>First Author</th>
<th>Ref.</th>
<th>EOB-MRI Sensitivity (%) (95% CI)</th>
<th>CEMDCT Sensitivity (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan VO</td>
<td>9</td>
<td>96.2 (87.0-99.5)</td>
<td>71.7 (57.7-83.2)</td>
</tr>
<tr>
<td>Muhi A</td>
<td>10</td>
<td>94.9 (85.9-98.9)</td>
<td>63.4 (53.8-72.3)</td>
</tr>
<tr>
<td>Berger-Kulemann V</td>
<td>11</td>
<td>95.6 (87.6-99.1)</td>
<td>69.1 (56.7-79.8)</td>
</tr>
<tr>
<td>Scharitzer M</td>
<td>14</td>
<td>91.7 (84.2-96.3)</td>
<td>80.2 (70.8-87.6)</td>
</tr>
</tbody>
</table>

Table 5: EOB-MRI and CEMDCT detectability of liver metastases (Primary tumor: colorectal cancer) CI: Confidence interval

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Conclusion

The results suggested that EOB-MRI was suitable for the detection of liver metastases. Also, in comparison with CEMDCT, the results indicated that EOB-MRI might be significantly more accurate in the detection of liver metastases. When the size of the tumor was equal to or less than 1 cm, the difference in weighted sensitivity between CEMDCT and EOB-MRI became larger. Moreover, the results supported past studies that indicated EOB-MRI lesion detectability was higher than CEMDCT.

In a prior study included in the current systematic review and meta-analysis, Niekel et al. [16] reported that the estimated sensitivity of MRI (non-enhanced, extracellular and intracellular contrast agent enhanced) and contrast enhanced CT on a per-lesion basis were 80.3% (95% CI, 74.6 to 85.0%) and 74.4% (95% CI, 68.7 to 79.3%) for detection of liver metastases from colorectal cancer, respectively. As well, Floriani et al. [17] reported that the overall sensitivity of MRI (extracellular and intracellular contrast agent enhanced) and contrast enhanced CT (included CT arterial portography) on a per-lesion basis were 86.3% (95% CI, 84.5 to 88.2%) and 82.6% (95% CI, 80.9 to 84.4%) for detection of liver metastases from colorectal cancer, respectively. Our results suggested that the weighted sensitivity of EOB-MRI was significantly higher than the sensitivity of MRI and CT for detection of liver metastases from colorectal cancer (Table 5). Chen et al. [18] reported that pooled sensitivity of EOB-MRI on a per-lesion basis was 93% (95% CI, 90.0 to 95.0%) for detection of liver metastases, which was similar to the current results. As well, the pooled sensitivity of EOB-MRI on a per-lesion basis was 79% (95% CI, 72.0 to 85.0%) for lesions less than 1 cm in size, which was not significantly different from the current results.

Currently, evaluation of liver metastasis by CEMDCT is performed during screening for other distant metastases as a primary imaging procedure. However, the technical development of MDCT has made fast scanning with improved image quality and resolution possible. Further, the current results suggested that CEMDCT lesion detectability, in particular small lesions less than 50%, was insufficient. In preoperative examinations, early detection and precise characterization of liver metastasis are important factors for establishing the appropriate treatment. Accordingly, when local findings indicate a patient has a high pretest prevalence of liver metastases, EOB-MRI should be performed, regardless of CEMDCT findings.

In conclusion, the systematic review demonstrated that EOB-MRI was suitable for the detection of metastatic liver tumor lesions. In particular, the sensitivity of EOB-MRI was significantly higher than that of CEMDCT. Thus, in preoperative examinations for the evaluation of liver metastases, the performance of EOB-MRI should be given priority if patients are expected to have increased prevalence of liver metastases. In addition, the results could provide evidence regarding the utility of EOB-MRI.
Potential conflicts of interest: The authors declare no conflicts of interest.
References


16. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010;257:674-684.

