Hepatobiliary Contrast Agents

1. Unenhanced (signal on T1w, T2w images; morphology)
2. With contrast agents:
   • specific enhancement pattern in the early dynamic acquisition (during bolus administration)
   • tissue-specificity: reticular endothelial system, hepatocytes

Characterization with unenhanced MRI

Hemangioma  Metastasis  FNH

Wrong timing
Wrong conclusion

Pitfalls in Hypervascular Metastasis

Missed metastases  DDX: FNH

MR contrast agents for liver imaging

Pre-contrast liver MRI (T1w, T2w, morphology)

Extracellular contrast agents
- Gd-chelates
- good safety profile (> 30ml/min clearance)
- dynamic enhancement characteristics

Liver-specific contrast agents
- SPIO (Iron Particles)
- Hepato-biliary agents

http://www.ma.uni-heidelberg.de/inst/ifr/RSNA2007/Livercontrastmedia
Liver-specific Contrast Agents

Hepatocyte-selective agents (signal-rise in T1w)
- Multihance® (Gd-BOPTA)
- Teslascan® (Mn-DPDP)
- Gd-EOB® (Gd-EOB-DTPA)

RES-selectivity (signal-loss in T2w)
- Endorem® (SPIO)
- Resovist® (SHU 555 A)
- Sinerem® (USPIO)

Kupffer-Cell

Gd-EOB - Primovist®
- hydrophilic, ionic, highly water soluble Gd-DTPA-derivate with lipophilic ethoxybenzyl (EOB)
- high liver-specific uptake, bolus injectable
- uptake via the organic anion-transporting polypeptide 1 (OATP1), a membrane transport system
- active hepatobiliary excretion via canalicular multispecific organic anion transporter (cMOAT)
- Elimination by:
  - excretion into bile and feces (50%)
  - renal pathway via glomerular filtration into urine (50%)

Gd-EOB - Chemistry

(4S)-4-(4-EthOxyBenzyl)-3,6,9-tris(carboxylato-methyl) -3,6,9-triaza-undecandioic acid

Gd-EOB - Primovist®

CM Entrapment → FNH

Examination Protocol Gd-EOB

bolus injection
recommended dose: 0.025 mmol/kg

T1w pre arterial, portal-venous equilibrium, dynamic studies
T2w + MRCP liver-specific phase

Hirohashi S et al., ISMRM 2003

Safety Profile of Gd-EOB

Most frequent adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatation</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>0.7</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.5</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.3</td>
</tr>
<tr>
<td>Injection site reaction (pain edema)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Total number of patients: 1404
Patients with at least one AE related to the drug: 48 (3.4%)
Gd-BOPTA (Multihance®)

- Gd-DTPA
- Magnevist®
- Gd-BOPTA
- MultiHance®

benzyloxymethyl group

Safety profile of Gd-BOPTA

  - No significant difference between two study agents
  - No serious AEs
  - 14 non-serious AEs reported for each agent (~9%)
  - 1 each withdrew due to AE (contrast extravasation at injection site)
- Phase 3 liver study gadobutrol vs. Gd-BOPTA
  - No significant difference between two study agents

Examination Protocol Gd-BOPTA

- bolus injection
- recommended dose: 0.05-0.1 mmol/kg
- T1w pre
- arterial, portal-venous equilibrium
- liver-specific phase
- ~ 10 min
- ~ 4-5 min
- ~40-60 min

Examination Protocol Mn-DPDP (Teslascan®)

- slow iv infusion
- (2-3 mL/min, 10-20 min)
- recommended dose: 0.005 mmol/kg
- liver-specific phase
- ~ 10 min
- ~ 5-10 min
- ~ 20 min
- 120 min

MnDPDP Contrast Administration

- T1W-spoiled-GRE sequences are preferred
- TE must be as shortest as possible, out-of-phase favorable
- Flip angle between 60-80°
- Fat suppression improves small lesion-to-liver contrast
- T2W images are not influence by MnDPDP at the usual dose

Safety profile of Mn-DPDP

- From a large series of patients, only 7% showed adverse events.
- Adverse events are mild in most patients, being quite rare the severe adverse events.
- They consist mainly in nausea, vomiting, urticaria, rash and generalized anaphylactic reactions. Serious life threatening reactions are extremely rare.
- Administration as a bolus injection (1 ml/s) is feasible but related to increase rate of minor adverse events like warm sensation and hot flushes in the face.

Wang C. Acta Radiol Suppl 1998;415:1
Value of liver specific contrast agents

• Detection, multifocality
• Lesion characterization: benign vs. malignant
• Grading
• Comprehensive protocols
• Intervention / operability

Metastasis of Renal Cell Carcinoma @ 3T

T1w in phase T2w T1w Gd-EOB portal venous T1w Gd-EOB liver specific 20 min

2D vs 3D post Gd-EOB

2D GRE 40min 3D GRE (VIBE) F5 30min

T1w pre

Potential for ultra-high resolution 3D-sequences under steady state conditions with liver specific agents

Multifocality

3D GRE 20 min post Gd-EOB

Multiple metastases of rectal CA

Detection of Small Lesions @ 3T

Gd-EOB

T2 FSE F5
T1w VIBE pv Gd-EOB
T1w F5 20 min post contrast

Metastasis of Klatskin’s tumor

Ruling Out Lesions on MSCT?

CT pv 3mm SL
T2w HASTE pre

VIBE pv Gd-EOB
VIBE 20min Gd-EOB
Multifocal HCC in liver cirrhosis (Child B)

- Arterial enhancement, rapid wash-out
- Hepatocyte-selective uptake, isointense with homogeneous enhancement in the liver-specific phase

Multifocal hepatocellular carcinoma with SPIO

- Detection, multifocality
- Lesion characterization: benign vs. malignant
- Grading
- Comprehensive protocols
- Intervention / operability

Gd-BOPTA for MRI of liver metastases

- Peripheral wash-out in late phase

Triphasic 3D liver imaging with Gd-BOPTA

MnDPDP: detection of metastasis

- Rim enhancement in metastases: composed of compressed liver parenchyma due to an expansive lesion → characteristic but non-specific
Focal nodular hyperplasia (FNH)

- Early arterial enhancement
- Heterogeneously hyperintense in the hepatocyte-selective phase
- Non-enhancing central regions and septae corresponding to a fibrous scar
- Delayed wash-out

Signal characteristics of FNH (n=59) in different sequences

<table>
<thead>
<tr>
<th></th>
<th>Hyperintense</th>
<th>Isointense</th>
<th>Hypointense</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-w pre-contrast</td>
<td>4%</td>
<td>14%</td>
<td>76%</td>
<td>6%</td>
</tr>
<tr>
<td>T2-w pre-contrast</td>
<td>71%</td>
<td>17%</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td>Hepatocyte phase 10 min</td>
<td>29%</td>
<td>33%</td>
<td>2%</td>
<td>37%</td>
</tr>
<tr>
<td>Hepatocyte phase 20 min</td>
<td>38%</td>
<td>32%</td>
<td>2%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Zech CJ, et al. submitted

Adenoma

Heterogeneous hyperintensity with central hypointense spots in the hepatocyte-selective phase

Metastasis of Renal Cell Carcinoma?

Typical / atypical adenoma with Gd-EOB

Gd-BOPTA: adenoma versus FNH

After 1–3 hours 96.9% of FNHs hyper- or isointense, 100% of HA and LA hypointense  
sensitivity / specificity: 96.9% / 100%

Liver MR imaging with Gd-EOB

<table>
<thead>
<tr>
<th>Literature Gd-EOB</th>
<th>Number of Lesions</th>
<th>Detection Rate</th>
<th>Correct Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huppertz et al. 2004, Radiology</td>
<td>302 lesions</td>
<td>MRI plain: 80.8%</td>
<td>MRI EOB: 87.4%</td>
</tr>
<tr>
<td>Bluemke et al. 2005, Radiology</td>
<td>316 lesions</td>
<td>Biphasic CT: 65.9%</td>
<td>MRI plain: 62.7%</td>
</tr>
<tr>
<td>Halavaara et al. 2006, JCAT</td>
<td>250 lesions (3 blinded readers)</td>
<td>No detection data</td>
<td>Biph. CT: 58% 64% 55%</td>
</tr>
<tr>
<td>Jung et al. 2006, Acta Radiologica</td>
<td>41 HCCs</td>
<td>No detection data</td>
<td>Biph. CT: 77.5%</td>
</tr>
<tr>
<td>Zech et al. 2006, ISMRM Proc.</td>
<td>59 FNHs</td>
<td>No detection data</td>
<td>Biph. CT: 84.7%</td>
</tr>
</tbody>
</table>

Liver MR imaging with Gd-BOPTA

<table>
<thead>
<tr>
<th>Literature Gd-BOPTA</th>
<th>Number of Lesions</th>
<th>Detection Rate</th>
<th>Correct Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. 2004, AJR</td>
<td>35 HCCs</td>
<td>MRI Gd-BOPTA: 91.4%</td>
<td>MRI Gd-BOPTA: 91.9%</td>
</tr>
<tr>
<td>Del Frate et al. 2002, Radiology</td>
<td>37 Metastases</td>
<td>MRI Gd-BOPTA: 81%</td>
<td>MRI Gd-BOPTA: 91.9%</td>
</tr>
<tr>
<td>Pirovano et al. 2000, AJR</td>
<td>107 / 149 lesions</td>
<td>MRI Gd-BOPTA: 76.5%</td>
<td>MRI Gd-BOPTA: 74.5%</td>
</tr>
</tbody>
</table>

Liver MR imaging with Mn-DPDP

<table>
<thead>
<tr>
<th>Literature Mn-DPDP</th>
<th>Number of Lesions</th>
<th>Detection Rate</th>
<th>Correct Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartlozzi et al. 2004, Eur Radiol</td>
<td>128 lesions</td>
<td>Biph. CT: 71%</td>
<td>MRI Mn-DPDP: 90%</td>
</tr>
<tr>
<td>Kim et al. 2006, AJR</td>
<td>53 metastases</td>
<td>MRI Mn-DPDP: 82%</td>
<td>MRI Mn-DPDP: 81.4%</td>
</tr>
<tr>
<td>Sahani et al. 2005, AJR</td>
<td>79 metastases</td>
<td>MRI Mn-DPDP: 82%</td>
<td>PET-CT: 67.0%</td>
</tr>
</tbody>
</table>

Added Value of Delayed Imaging

- For Gd-BOPTA the number of detected metastases increased from 18/37 (non-enhanced), 20/37 (dynamic phase) to 30/37 (BOPTA delayed)
- Up to now there is no data in the literature with regard to the added value of the hepato-biliary phase of Gd-EOB-DTPA compared to early dynamic imaging - based on personal experience an increase of 5-10% can be expected
- For Mn-DPDP only delayed imaging is possible, compared to standard Gd-chelates equal to increased detection rates are published (missing dynamic imaging phase)
Value of liver specific contrast agents

- Detection, multifocality
- Lesion characterization: benign vs. malignant
- Grading
- Comprehensive protocols
- Intervention / operability

Characterization of HCC with hepatocyte-specific agents

- Perfusion
- Dynamic imaging with Gd-EOB

Characterization of HCC with hepatocyte-specific agents

Tumor perfusion  Hepatobiliary excretion

Grading of HCC with hepatocyte-specific agents


HCC (WHO G1 versus G2/3) – Gd-EOB

Huppertz A, Harayda S, Kraus A, Zech CJ et al., Radiology 2005

Grading of HCC with Mn-DPDP

Well differentiated HCC

Undifferentiated HCC

Courtesy of L. Marti-Bonmati, Valencia, Spain
Value of liver specific contrast agents

- Detection, multifocality
- Lesion characterization: benign vs. malignant
- Grading
- Comprehensive protocols
- Intervention / operability

Gd-EOB-enhanced MRC 3Tesla

- T1w 3D GRE 2mm; 384 Matrix; Gd-EOB liver-specific phase

Central cholangiocarcinoma

- EOB-enhanced MRC using 3D-GRE (VIBE)

Value of liver specific contrast agents

- Detection, multifocality
- Lesion characterization: benign vs. malignant
- Grading
- Comprehensive protocols
- Intervention / operability

Indication for stent replacement

- Absent excretion of Gd-EOB, ↑ renal excretion
  - significant obstruction vs. chronic dilatation of biliary tree

VIBE – Liver specific phase post Gd-EOB

- 1.5T: 4 x 1.9 x 1.4mm
- 3T: 2 x 2.6 x 1.1mm
  - Metastases of sigmoid-CA; additional benign lesion
High quality reformats feasible at 3T

<table>
<thead>
<tr>
<th>1.5 T</th>
<th>3 T</th>
</tr>
</thead>
</table>

Coronal MPR from a transversal acquired dataset

Value of liver specific contrast agents

- Detection better than CT, probably equal for all 3 hepatobiliary agents
- Gd-EOB and Gd-BOPTA advantage of dynamic information → superior results
- Only Gd-EOB EMEA-approved for lesion characterization, superior results compared to CT
- CE MRC reserved for special indications → dynamic information: e.g. obstruction
- 3D GRE sequences + higher field strength → isotropic resolution > CT

http://www.ma.uni-heidelberg.de/inst/ikr/RSNA2007/Livercontrastmedia

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- Imaging Science Institute Charité-Siemens: Alexander Huppertz MD

http://www.ma.uni-heidelberg.de/inst/ikr/RSNA2007/Livercontrastmedia