Enhancements in Hepatobiliary Imaging:

Novel Uses of Gadolinium EOB DTPA in Hepatobiliary Magnetic Resonance Imaging

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Learning Objectives

- Update the reader on the novel uses of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) in hepatobiliary MR imaging

- Familiarize the reader with MR protocols that will optimize Gd-EOB-DTPA usage

- Inform the reader of the diagnostic challenges associated with Gd-EOB-DTPA
Hepatobiliary lesions are not only common, but their accurate characterization also directly affects clinical management.

Gd-EOB-DTPA is an emerging hepatobiliary-specific MR contrast agent.

Familiarity with its various uses is essential for accurate imaging interpretation and clinical consultation.
Distributes into the extracellular compartment, which allows for dynamic imaging

Later taken up by functioning hepatocytes via an organic anion transport system, which allows for hepatobiliary phase imaging 10-20 minutes post-injection

It is excreted into the biliary system by an ATP dependent glutathione S-transferase

Has 50:50 renal: biliary excretion

Hepatocellular uptake and biliary excretion of Gd-EOB-DTPA depend on hepatocellular expression of the organic anion transporting polypeptide (OATP1) and multidrug resistant protein (MRP2) systems, respectively
Hepatobiliary Imaging

- Hepatic evaluation
  - HCC
  - Cirrhotic nodules
  - Hepatic fibrosis
  - Metastases
  - Focal nodular hyperplasia (FNH)
  - Hepatic adenoma
  - Hemangioma
  - Hepatic cysts

- Biliary evaluation
  - Biliary cysts
  - Bile duct obstruction
  - Patent bile duct stent
  - Abscess vs Biloma
  - Cholangiocarcinoma
62 year old male with nonalcoholic fatty liver disease. Segment 2 liver mass demonstrates (A) enhancement on the arterial phase, (B) washout on the portal venous phase, and (C) no gadolinium EOB DTPA uptake on the hepatobiliary phase. The findings from this biopsy disclosed a well–differentiated hepatocellular carcinoma.

Hepatocellular Carcinoma

- HCC shows no uptake of Gd-EOB-DTPA on the hepatocyte phase given lack of functional hepatocyte
- Tumor margins are most clearly delineated in the hepatocyte phase, potentially improving detection of HCCs not readily visible in dynamic imaging phases
- When “EOB Criteria” (defined as arterial enhancement, venous washout, and a lack of uptake on hepatobiliary phase imaging) was compared with the AASLD and Barcelona Criteria, EOB criteria was more sensitive and accurate for diagnosing HCC
- Challenges include detection of very small lesions (<1 cm) and distinguishing premalignant dysplastic nodules from HCC
Low vs High Grade HCC

62 year old female with a segment 6 liver mass that enhances on the (A) arterial phase, and appears isointense on the (B) portal venous phase. On the (C) delayed phase, the mass appears hypointense, which persist to the (D) hepatobiliary phase. 71 year old female with segment 8 mass with enhancement on the (E) arterial phase and drop out on the (F) portal venous phase, and becomes pronounced on the (G) delayed and (H) hepatobiliary phases. The graph illustrates the slope of the signal intensity change, which shows that the high grade lesion has a steeper negative slope compared to low grade lesion.

Low vs High grade HCC can be distinguished by comparing:

- Enhancement trend on Gd-EOB-enhanced MR imaging, with higher grade lesions washing out sooner
- Lesion–to-liver contrast enhancement ratio: \( \frac{(\text{Lesion} - \text{Liver})}{\text{Liver}} \times 100 \) can be calculated, with high grade lesions having a significantly lower ratio compared to low grade.
## Cirrhotic Nodules

<table>
<thead>
<tr>
<th>Type of Cirrhotic Nodule</th>
<th>Dynamic Imaging</th>
<th>Hepatobiliary phase</th>
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<tbody>
<tr>
<td>Regenerative nodule</td>
<td>Enhances in portal venous phase, becoming iso-or hyperintense</td>
<td>Iso- to hyperintense</td>
</tr>
<tr>
<td>Dysplastic nodule</td>
<td>Enhances in portal venous phase, becoming iso-or hyperintense</td>
<td>Enhances</td>
</tr>
<tr>
<td><strong>Well differentiated</strong></td>
<td>May enhance in arterial phase</td>
<td>May or may not enhance</td>
</tr>
<tr>
<td><strong>Poorly differentiated</strong></td>
<td>May enhance in arterial phase</td>
<td>May or may not enhance</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>May enhance in arterial phase</td>
<td>May or may not enhance</td>
</tr>
<tr>
<td><strong>Well differentiated</strong></td>
<td>May enhance in arterial phase</td>
<td>May or may not enhance</td>
</tr>
<tr>
<td><strong>Moderately to poorly differentiated</strong></td>
<td>80-90% enhance in arterial phase</td>
<td>No enhancement</td>
</tr>
</tbody>
</table>

- The major differential diagnoses of HCC in the setting of cirrhosis are regenerative nodules/low grade dysplastic nodules and high grade dysplastic nodules.

- High grade dysplastic nodules are considered premalignant.

- Gd-EOB-DTPA MR imaging can help distinguish the different types of cirrhotic nodules.
Innumerable hepatic nodules show (A) mild arterial enhancement with persistent hyperintensity in the (B) portal venous phase. (C) In the hepatobiliary phase, these nodules appear hyperintense and more conspicuous. Biopsy results revealed these to be regenerative nodules.

• In contrast to HCC, regenerative nodules generally do not enhance on hepatic arterial phase images because they derive their blood supply largely from the portal vein.
Nodular cirrhotic liver in a patient with known history of primary sclerosing cholangitis with marked enlarged regenerative macro-nodules showing enhancement in the (A) arterial, (B) portal venous, and (C) hepatobiliary phase.

• However, regenerative nodules may also grow up to 5 cm and show arterial enhancement, thereby mimicking HCC
Gd EOB DTPA MR imaging has been found to be useful for differentiation of a dysplastic nodule from early HCC, with an accuracy of up to 93%.

Low grade dysplastic nodule (arrow) appears to enhance in the (A) arterial phase but appears to enhance similar to the liver on (B) portal venous and (C) hepatobiliary phases. On the other hand, the high grade dysplastic nodule below is only seen on (D) T1W imaging (arrow), and not well seen on (E) arterial and (F) portal venous phases, but lacks Gd EOB DTPA uptake (arrowhead) on the (G) hepatobiliary phase.

• Gd EOB DTPA MR imaging has been found to be useful for differentiation of a dysplastic nodule from early HCC, with an accuracy of up to 93%.
Hepatic Fibrosis

• Gd–EOB-DTPA MR imaging has been shown to be more reliable for staging hepatic fibrosis than diffusion-weighted MR imaging, hematologic, and clinical parameters.
• Decreases in enhancement on hepatocyte-phase images suggest that Gd-EOB-DTPA uptake by the liver is impaired.
• Contrast enhancement index has been shown to be significantly lower in advanced fibrosis.
  • This is in contrast to dynamic imaging, where hepatic fibrosis would be hyperintense in signal on delayed post-contrast scans.

(A) Axial TW1 hepatocyte-phase image obtained after injection of Gd-EOB-DTPA in a 68-year-old man with fibrosis stage F1 and a liver contrast enhancement index of 1.61. (B) Axial T1-weighted hepatocyte-phase image obtained after injection of Gd-EOB-DTPA in a 71-year-old man with fibrosis stage F4 and a liver contrast enhancement index of 1.05.
Resection of hepatic metastases from colorectal cancer has been shown to improve survival compared to other treatment methods.

On hepatocyte phase images, no uptake of contrast agent can be seen in hepatic metastases because these lesions do not contain hepatocytes.

Segment 1 liver mass (arrow) demonstrates minimal enhancement within the (A) arterial phase without much change in the (B) portal venous phase in a patient with rectal cancer metastases. No gadolinium EOB-DTPA uptake on the (C) hepatobiliary phase. Similar findings were seen in a patient with lung cancer metastases on the (D) arterial, (E) portal venous, and (F) hepatobiliary phase.
Metastases

- Gd-EOB-DTPA has been shown to **reliably detect small metastases less than 1 cm in size**
- Gd-EOB-DTPA may improve lesion characterization and diagnostic confidence

42 year old male with metastatic neuroendocrine tumor. (A) On the portal venous phase, the multiple hypointense liver lesions are poorly visualized. (B) On the hepatobiliary phase, these lesions lack Gd EOB DTPA uptake and are better seen.
Lobulated mass with a central scar involving segments 7 and 8 of the liver with enhancement in the (A) arterial and portal venous (not shown) phase. (B) The mass enhances to a greater extent than the surrounding liver on the hepatobiliary phase with Gd EOB DTPA. Biopsy of this lesion confirmed the diagnosis of FNH.

- Confident diagnosis of focal nodular hyperplasia (FNH) at imaging allows for conservative management
- FNH contains densely packed functional hepatocytes and abnormal blind-ending bile ductules that do not communicate with larger bile ducts, hence biliary excretion is slow
- Will retain Gd-EOB-DTPA more than normal liver parenchyma on the hepatocyte phase
34 year old female with history of L-transposition of the great arteries with hypoplastic left heart status post Fontan operation at 7 years of age. Patient had a lobulated segment 7 mass that appears hyperintense in (A) T1W imaging, and (B) isointense to liver on T2W imaging. The mass appears to enhances in the (C) arterial phase and shows some enhancement in the (D) hepatobiliary phase. This patient was able to avoid a biopsy given the FNH-like appearance of this mass.

Focal Nodular Hyperplasia-like nodule

FNH-like nodules are macroscopically, microscopically, and immunohistochemically identical to FNH seen in the noncirrhotic liver.

FNH-like nodules in the cirrhotic liver are usually hypervascular, and they can mimic HCC.

Gd-EOB-DTPA can be used to help distinguish FNH-like nodules from HCC.
Hepatic Adenoma

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Sex distribution</th>
<th>Frequency</th>
<th>Imaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCA with TCF1 gene mutation</td>
<td>Exclusively in women</td>
<td>35-50</td>
<td>Moderate enhancement is seen in the arterial phase without persistent enhancement in the portal venous and hepatobiliary phases.</td>
</tr>
<tr>
<td>HCA with β-catenin activation</td>
<td>Men and women</td>
<td>10-18</td>
<td>Intense arterial enhancement is seen, which may or may not persist into the hepatobiliary phase</td>
</tr>
<tr>
<td>HCA with inflammatory infiltrates (IL6ST mutations)</td>
<td>Most frequent in women, but also found in men</td>
<td>40-55</td>
<td>Hypervascular masses with persistent enhancement on portal venous and hepatobiliary phase images</td>
</tr>
<tr>
<td>Unclassified</td>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

- Hepatic adenoma (HCA) can be divided into four different subgroups according to genotypic and phenotypic characteristics and clinical features.
- Malignant transformation to HCC is estimated to occur in about 5%.
- Hepatic adenomas are characterized by benign proliferation of hepatocytes separated by dilated sinusoids and enclosed by a pseudocapsule.
- Hepatic adenomas do not contain bile ducts, resulting in blocked bilirubin excretion.
HCA with b-catenin activation

Top images; 55 year old male with HCA with b-catenin activation, with adenoma showing intense arterial uptake, and decreased uptake in the portal venous and hepatobiliary phases. Bottom images; 45 year old woman with HCA with IL6ST mutation, with large hypervascular mass within the inferior hepatic lobe demonstrating predominant peripheral enhancement.

HCA with IL6ST mutation
Most common benign liver tumors and can be found in up to 20% of the general population

Composed of vascular sinusoids separated by fibrous septa

During the dynamic phase, peripheral discontinuous nodular enhancement can be appreciated

Hemangiomas will appear iso- or hypointense to the liver in the late dynamic phase and hepatocyte phase, for the following reasons:
  • There is marked hepatocyte uptake of Gd-EOB-DTPA in the surrounding liver
  • The overall administered dose of Gd-EOB -TPA is substantially lower
  • The plasma half-life of Gd EOB DTPA is substantially shorter

46 year old female with liver hemangiomas. (A) Large hypoenhancing masses are seen within the liver in the arterial phase. (B) In the hepatobiliary phase, these masses appear to heterogeneously enhance.
Hepatic Cysts

- Cysts are fluid-filled cavities, and are typically hypointense on T1W imaging and hyperintense on T2W imaging, and do not enhance.

- Contrast-to-noise ratio (CNR) increases significantly with contrast administration.

- Cysts appear markedly hypointense on hepatobiliary phase imaging.

(Left images) Patient with polycystic liver disease with massive liver and multiple cysts, and (Right images) patient with single large cyst without enhancement in the (A,D) arterial, (B, E) portal venous, or (C,F) hepatobiliary phase, respectively.
Multiseptated cystic lesion within the right hepatic lobe appears hyperintense on (A) T2W images, and without enhancement in the (B) arterial, (C) portal venous, or (D) hepatobiliary phases. Pathology results revealed biliary cysts.

- Unilocular; single or multiple; when multiple usually a component of adult polycystic kidney disease
- Usually age 40+ years; prevalence increases with age
- No malignant potential
- Subcapsular, and not connected to biliary tree, as opposed to *Caroli disease* which would show Gd-EOB-DTPA uptake due to its connection with the biliary tree
55 year old male with history of primary sclerosing cholangitis, status post orthotopic liver transplant with moderately dilated intrahepatic ducts followed by stricturing, which appear most conspicuous on T2W images and the hepatobiliary phase, since contrast cannot be effectively excreted into the biliary system due to the strictures.

Degree of bile duct obstruction can be classified with delayed Gd-EOB-DTPA–enhanced bile flow dynamics (>30 minutes after intravenous injection of Gd-EOB-DTPA):

**Partial obstruction** - passage of contrast agent beyond the apparent stricture or obstructive lesion

**Near-complete obstruction** - significantly delayed contrast agent filling only in the proximal part of the stricture or obstructive lesion

**Complete obstruction** - absence of contrast agent filling in the distal and even proximal parts of the stricture or obstructive lesion
63 year old man with history of pancreatic cancer with an extrahepatic metallic stent is seen. Contrast is seen flowing through the stent on the hepatobiliary phase, suggesting patency.
77 year old woman who had radiofrequency ablation to a liver mass within the right posterior liver. On follow up exam, she was found to have a fluid collection with an air-fluid level, that appeared to fistulize to her skin (arrow). This was favored to be an abscess as a biloma would have more intense signal on the hepatobiliary phase due to biliary excretion of contrast.
65 year old female with irregular appearing mass (arrow) adjacent to the gallbladder with minimal enhancement on (A) arterial and (B) delayed phases. (C) The hepatobiliary phase more clearly depicts the margins of the mass, which proved to be an intrahepatic cholangiocarcinoma.

Cholangiocarcinoma

- Second most common form of primary hepatobiliary malignancy

- Derives from the biliary epithelium, arising as adenocarcinoma, papillary carcinoma, or mucinous carcinoma

- Can be classified as either intra- or extrahepatic

- Hypointense appearance of cholangiocarcinoma on the hepatobiliary phase allows for better lesion demarcation, which can be rather difficult in the presence of extracellular agents

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- Hypointense appearance of cholangiocarcinoma on the hepatobiliary phase allows for better lesion demarcation, which can be rather difficult in the presence of extracellular agents
47 year old male with bile duct adenocarcinoma. The mass abuts and narrows the confluence of the right and left hepatic ducts, and shows minimal enhancement on the (A) arterial phase. The mass appears more conspicuous on (B) delayed and (C) hepatobiliary phases, with irregular peripheral rim enhancement.

- Decreased uptake of Gd-EOB-DTPA in the parenchyma surrounding the tumor is indicative of decreased hepatocyte function
- Irregular peripheral rim enhancement during the arterial phase may be appreciated after injection of Gd-EOB-DTPA
# Suggested Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Gd EOB DTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precontrast imaging</td>
<td>T1W in- and opposed-phase GRE*</td>
</tr>
<tr>
<td></td>
<td>T2W fat suppressed fast spin echo**</td>
</tr>
<tr>
<td></td>
<td>T2W MRCP***</td>
</tr>
<tr>
<td>Contrast agent injection</td>
<td>0.025 mmol/kg bolus (2 mL/sec)</td>
</tr>
<tr>
<td>Dynamic imaging</td>
<td>2D or 3D T1W fat suppressed GRE</td>
</tr>
<tr>
<td>Hepatobiliary phase imaging:</td>
<td></td>
</tr>
<tr>
<td>time of imaging</td>
<td>10-60 min</td>
</tr>
<tr>
<td>parenchymal assessment and lesion detection/characterization</td>
<td>axial and/or coronal 2D or 3D T1W fat suppressed spoiled GRE****</td>
</tr>
<tr>
<td>T1W contrast enhanced MR cholangiography</td>
<td>axial and oblique coronal 2D or 3D T1W fat suppressed GRE</td>
</tr>
</tbody>
</table>

*Axial images (150–200/4.2 [repetition time msec/echo time (TE) msec]; second TE, 1.8–2.1 msec; flip angle, 60°–80°; section thickness, 5–8 mm).

**Axial images (4000–6000/102–135; echo train length, 16; section thickness, 5–8 mm).

***Oblique coronal heavily T2-weighted thick-slab turbo SE (2800–3300/900–1100; section thickness, 60 mm).

****Performed at 15, 60, and 180 seconds after the start of contrast agent injection (hepatic arterial, portal venous, and hepatic venous phases).
When hepatocyte function is impaired, the uptake of Gd-EOB-DTPA in the hepatobiliary phase may be compromised, which results in decreased distinction between the liver and the lesion.

Between 10% and 27% of HCCs may remain iso- to hyperintense on hepatocyte phase images, also known as “Green HCC.”

Hepatocytes in well-differentiated HCC may retain enough hepatocellular function to take Gd-EOB-DTPA, may appear iso- or hyperintense to liver at delayed imaging, and hence may appear similar to a dysplastic nodule.

Poor mixing of Gd-EOB-DTPA and preexisting bile can result in pseudo-filling defects.

Benign lesions such as hemangiomas and hepatic fibrosis may be mistaken for malignancy due to their hypointense signal on the hepatobiliary phase.

The delayed enhancement seen in cholangiocarcinomas on dynamic phase imaging is not present with hepatobiliary imaging, and may mislead the reader.
Conclusions

- Familiarity with the novel uses of Gd-EOB-DTPA will allow radiologists to optimize its use.
- Within the liver, Gd-EOB-DTPA can improve lesion detection and provide clues in terms of malignancy.
- Biliary excretion of Gd-EOB-DTPA can be used to evaluate the anatomic structure and patency of the biliary system.


