Paradoxical uptake of Gd-EOB-DTPA of focal hepatic nodule in the hepatobiliary phase

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Learning objectives

I. Introduction:

- About hepatocyte specific contrast agent, Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA, Primovist)
- Purpose of this exhibition

II. Typical and atypical paradoxical uptake of hepatic nodules in GD-EOB-DTPA enhanced MRI:

1. Hepatocellular carcinoma
2. Cholangiocarcinoma
3. Metastasis
4. Focal Nodular Hyperplasia
5. Regenerative Nodules

III. Pattern analysis according to dynamic phases with Gd-EOB-DTPA uptake in hepatic metastasis

Background

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA, Primovist) [1]:

- New liver-specific contrast agent with combined effects of ECF specific agent & hepatobiliary agent
- Distributed in the extracellular fluid (ECF) at arterial phase
- Taken up in functional hepatocytes & Excreted into biliary system at hepatobiliary phase after 20 minutes of injection
- Enables evaluation of vascularity from classic dynamic study with visualization of bile duct
- Malignant lesions without normal hepatocytes appear hypointense

Purpose:

- In clinical practice, HCC, metastatic lesions from different organs, such as stomach, pancreas, breast or colon cancers, FNH or regenerative nodules sometimes show paradoxical uptake of Gd-EOB-DTPA on hepatobiliary phase of Gd-EOB-DTPA enhanced MRI
• Show different image findings with paradoxical high SI in different focal liver lesions
• Literature review of this mechanism

Imaging findings OR Procedure details

I. Hepatocellular Carcinoma:

- Gd-EOB-DTPA enhanced MR images show early uptake at arterial phase, washout patterns at equilibrium phase, and a lower SI defect at the hepatobiliary phase
  - Transported via hepatocyte sodium-independent organic anion transporters (OATPs)
  - Excreted into bile canaliculi via multidrug resistance-associated protein (MRP2)
  - Sometimes we observe a paradoxical high SI in hepatobiliary phase

I. Hepatocellular Carcinoma-Mechanism of accumulation of gadoxetic acid in tumors [2]:

1. Expression of OATPs determines uptake of contrast
2. Expression of MRP2 on canalicular side determines whether tumor cells secrete gadoxetic acid into few bile ducts in tumor tissue
3. MRP3, an export transporter on sinusoidal side of hepatocyte, increased in hyperintense HCC, meaning excretion from HCC cells into tumor blood space is enhanced, causing persistent high SI in tumor
4. Impairment of bile excretion by compression effects of tumors
5. High preservation of hepatocyte function or transportation system such as OATPs and MRP2.

II. Cholangiocarcinoma [3]:

- Second most common form of primary hepatic malignancy from biliary epithelium
- On unenhanced T1-weighted MR image, low to hypointense SI
- Mild to moderately high SI on T2WI depending on its fibrous tissue & mucin content
  - Lower signal intensity from fibrous content
  - High signal intensity from mucin content
- Shows irregular, peripheral rim enhancement in early arterial phase with Gd-EOB-DTPA with progressive central enhancement in the later phases
- Commonly appears hypointense on hepatobiliary phase with Gd-EOB-DTPA due to surrounding liver parenchyma
• Sometimes cholangiocarcinoma shows paradoxical persistent uptake of Gd-EOB-DTPA, probably due to its fibrous content

III. Liver Metastasis [3][4]:

• Most common site for metastases from gastrointestinal tract, pancreas, breast, and lung
• Unenhanced T1-weighted MR appears hypointense
• Moderately hyperintense on T2-weighted images
• After contrast injection, peripheral ring enhancement in arterial phase with central progression of enhancement with washout pattern is a sign specific for malignancy
• On hepatocyte phase images, no uptake of contrast agent can be seen due to lack of normal functioning hepatocytes or OATP1 transport systems
• Low SI rim around tumor or purely hypointense mass in strongly enhancing background improve detection of metastasis
• Most of our metastases show a "target" appearance composed of central round strong enhancing portion & peripheral low-signal rim on hepatobiliary phases
• From our experience, we observed more than 50% of colon & breast liver metastasis show this "target" appearance
• Hypothesis for persistent enhancement on hepatocyte phase may be due to large fibrotic component with large interstitial space that contains contrast agent for long time
• For conventional gadolinium chelates, abundant fibrous stroma reveal persistent enhancement up to 4 h

IV. Focal Nodular Hyperplasia [3]:

• Second most common benign liver tumor
• A congenital vascular malformation resulting in hyperplastic response
  • Normal hepatic parenchyma but with abnormal biliary drainage
  • Nodular lesion with a central stellate scar with radiating fibrous septa
• Isointense to minimally hypointense to normal liver with a hypointense central scar on T1WI
• Isointense to hyperintense with a hyperintense central scar on T2WI
• With Gd-EOB-DTPA, vivid enhancement resembling a spoked wheel because of its central scar & fibrous septa
  • Accumulation of Gd-EOB-DTPA with poor biliary drainage
  • Expressed higher levels of OATP8 & export transporters in hyperplastic cells
• Central scar is hypointense on Gd-EOB-DTPA enhanced image

V. Regenerative Nodule [5]:

• Focal hepatocellular proliferation with one or more portal tracts surrounded by fibrous septa
• In hepatocyte phase of Gd-EOB-DTPA, regenerative nodule shows contrast uptake & excretion because of preserved hepatocellular function & intact organic ion transporters
• Dysplastic nodules develop from regenerative nodules
• In hepatocyte phase of Gd-EOB-DTPA, dysplastic nodules that have ability to take up contrast, but not excrete it, appears homogeneously or heterogeneously hyperintense

Images for this section:

Fig. 1: Schematic of transporter expression & mechanism of gadoxetic acid dynamics in HCC: Between hypointense and iso-, or hypointense HCCs, the most significant differences were observed in OATPS8 and MRP3 expression. That is, in iso-, or hyperintense HCCs, a larger amount of gadoxetic acid would be taken up from the tumor blood sinusoid s into HCC cells by OATP8 and be excreted again into blood sinusoids by
MRP3 very gradually, probably because of depletion of bile ducts in HCCs. In contrast, in hypointense HCCs, the uptake of gadoxetic acid might be blocked or reduced because of lower expression of OATP8.

Fig. 2: Hypothetical mechanism of gadoxetic acid accumulation in HCC: (a). Diagram shows that OATP1B1 and/or -1B3 mediates uptake of gadoxetic acid from sinusoid to tumor cells, whereas MRP2 mediates secretion of gadoxetic acid from tumor cell to lumen (*) of canaliculus or (/) pseudoglands. (b). Flow chart illustrates relationship between transporter expression pattern and accumulation pattern of gadoxetic acid. Tumors without OATP1B1 and/or -1B3 expression do not accumulate gadoxetic acid, whereas tumors with OATP1B1 and/or -1B3 expression accumulate gadoxetic acid in cytoplasm, canaliculi, or pseudoglandular lumina depending on MRP2 expression pattern.
**Fig. 3:** A 70-year old man with pathologically proven G1 HCC in liver segment 7: (A-E) The lesion shows low SI on pre-contrast T1 weighted images (A), enhancement in the lateral portion (red arrow) and slight enhancement in the medial portion (blue arrow) during the arterial phase of the Gd-EOB-DTPA enhance T1WI (B), and wash-out in the both portions during the portal (C), and delayed phase (D).

**Fig. 4:** continued: However, a high SI focus (red arrow) and low SI portion (blue arrow) were detected at hepatobiliary phase (20min). (F-H) On the cut surface of tumor, a greenish portion and a yellowish portion of the mass were well matched with the lateral white and medial black portion of the images at hepatobiliary phase of MRI (F). On pathological examination, the mass confirmed as G1 HCC without distinction between lateral and medial aspect. The lateral portion showed prominent bile staining (arrow) and prominent cytoplasm (G), whereas the medial portion did not (H).
Fig. 5: A 54-year-old man pathologically proven G1 HCC in liver segment 5: MRI showed high SI mass in Segment 5 of the liver on T2WI (A), low SI on pre-enhanced T1WI (B). The lesion demonstrated enhancement on the arterial phase (C), and washout on portal (D) and the equilibrium (2 min) phase (E). However, a half of the mass showed low SI and the other half of the mass showed high SI (arrow) on the hepatobiliary phase (F).
**Fig. 6:** Pathologically confirmed HCC patient at Segment 7:  
A. Slightly high SI on T2WI at Segment 7  
B. Low SI on T1WI  
C. Arterial enhancement in early phase  
D. Wash-out pattern in equilibrium phase (2 min)  
E. Partially high SI focus on hepatobiliary phase (20 min)
**Fig. 7:** Pathologically confirmed HCC patient: A. Heterogeneous SI on T2WI B. Heterogeneous SI on pre-enhanced T1WI C. Early arterial enhancement pattern. D. Wash-out pattern on equilibrium phase (2min) E. High SI focus on hepatobiliary phase is noted (20 min)
Fig. 8: Pathologically confirmed HCC patient, a 7cm sized, lobulated mass lesion in hepatic angle: A. High SI on T2WI B. Heterogeneous SI on pre-enhanced T1WI C. Early arterial enhancement pattern D. Washout pattern on equilibrium phase (2min) E. Paradoxical enhancement on hepatobiliary phase (20 min)
**Fig. 9:** A patient with pathologically confirmed cholangiocarcinoma: A. High SI on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial enhancement pattern D. Central irregular enhancement on equilibrium phase (2min) E. Paradoxical enhancement on hepatobiliary phase (20 min)
**Fig. 10:** A patient with pathologically confirmed cholangiocarcinoma at Segment 6 subcapsular portion: A. High SI on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial subtle enhancement pattern D. Wash out pattern on equilibrium phase (2min) E. Paradoxical enhancement on hepatobiliary phase (20 min)

**II. Cholangiocarcinoma**

**Fig. 11:** A patient with pathologically confirmed adenocarcinoma: A. Heterogeneous SI on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial enhancement pattern D. Central irregular enhancement on equilibrium phase (2min) E. Paradoxical enhancement on hepatobiliary phase (20 min)
Fig. 12: A patient with pathologically confirmed cholangiocarcinoma: A. High SI on T2WI with cirrhotic liver B. Low SI on pre-enhanced T1WI C. Early arterial enhancement pattern D. Wash out pattern on equilibrium phase (2min) E. Paradoxical enhancement on hepatobiliary phase (20 min)

Fig. 12. A colon cancer patient with liver metastasis using Primovist shows ring enhancement in arterial phase & hypointense compared to well-enhancing surrounding liver, with paradoxical uptake in the central portion.
**Fig. 13:** (ABOVE) A colon-cancer patient with liver metastasis using Primovist shows ring enhancement in arterial phase & hypointense compared to well-enhancing surrounding liver, with paradoxical uptake in the central portion (BELOW) A colon-cancer patient with liver metastasis using Gadovist shows ring enhancement in arterial phase & persistent enhancement in delayed phase (20 minute)

![III. Metastasis](image)

**Fig. 14:** Suspicious multiple metastasis in gastric cancer patient: A, B. Multiple, High SI lesions on T2WI at Segment 4 & 7 C. Low SI on pre-enhanced T1WI D. Early arterial subtle enhancement pattern E. Wash-out pattern on equilibrium phase (2min) F. Paradoxical enhancement on hepatobiliary phase at Segment 7 and
Fig. 15: Suspicious single metastatic lesion on segment 4 from GB cancer patient: A. Single High SI lesions on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial peripheral ring enhancement pattern D. Wash-out pattern on equilibrium phase (2min) E. Reversed target appearance on hepatobiliary phase (20 min)

Fig. 16: A patient with a colon cancer metastasis in liver Segment 8: A. Single High SI lesions on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial enhancement
Fig. 17: A patient with colon cancer metastasis, an irregular marginated bulky tumor at Segment 1 & 6 with capsular retraction: A. Heterogeneous high SI on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial irregular tumor enhancement in periphery & central portions D. Centripetal enhancement pattern on equilibrium phase (2min) E. Paradoxical uptake of contrast on hepatobiliary phase (20 min)
**Fig. 18:** A patient with breast cancer metastasis, confluent segmental: A. Heterogeneous high SI on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial tumor enhancement in periphery D. Paradoxical uptake of contrast on hepatobiliary phase (20 min)
Fig. 19: A patient with breast cancer metastasis, Miliary: A. Heterogeneous high SI on T2WI B. Low SI on pre-enhanced T1WI C. Early arterial tumor enhancement in periphery D. Paradoxical uptake of contrast on hepatobiliary phase (20 min)

Fig. 20: A patient with breast cancer metastasis: A. Target appearance, central high SI on T2WI B. Low SI on pre-enhanced T1WI C, D. Early arterial tumor enhancement in periphery and centripetal pattern. E. Paradoxical uptake of contrast on hepatobiliary phase (20 min)
Fig. 21: A patient with suspicious FNH at Segment 5 on Gd-EOB-DTPA enhance MR: A. Faintly hyperintense on T2WI B. Faintly hyperintense on pre-enhanced T1WI C. Early arterial homogeneous enhancement pattern D. Persistent enhancement pattern on equilibrium phase (2min) E. Isointense on hepatobiliary phase (20 min)

Fig. 22: A patient with suspicious FNH at Segment 4 on Gd-EOB-DTPA enhance MR: A. Slightly heterogeneous hyperintensity on T2WI B. Isointense on pre-enhanced T1WI C. Early strong arterial homogeneous enhancement pattern D, E. Slightly higher intensity
than normal parenchyma on portal, delayed phases. F, G. Heterogeneous high SI with hypointense central scar on hepatobiliary phase (20 min)

**Fig. 23:** A patient with suspicious regenerative nodule seen only on hepatobiliary phase on Gd-EOB-DTPA enhance MR & no interval change in size on 1 year follow up studies:
A. Isointense on T2WI B. Isointense on pre-enhanced T1WI C. No arterial enhancement
D, E. Subtle enhancement on hepatobiliary phase only (20 min)
Fig. 24: A patient with suspicious regenerative nodule seen only on hepatobiliary phase on Gd-EOB-DTPA enhance MR & no interval change in size on 1 year follow up studies: A. Isointense on T2WI B. Isointense on pre-enhanced T1WI C. No arterial enhancement D, E. Subtle enhancement on hepatobiliary phase only (20 min)
Conclusion

- We sometimes see paradoxical high SI of HCC in hepatobiliary phase on Gd-EOB-DTPA MR.
- Aside from HCC, we see many focal liver lesions such as cholangiocarcinoma, focal nodular hyperplasia, regenerative nodules, metastasis from other solid organs, such as breast, colon, stomach and gallbladder, with paradoxical uptake of Gd-EOB-DTPA in 20 minute delayed hepatobiliary phases.
- Moreover, metastasis show a ring enhancement on early arterial phase with washout pattern in delayed phase, and a "target" appearance with a central round high SI with a low SI rim in hepatobiliary phase.
- We need to investigate about the mechanism of this persistent paradoxical uptake on 20 minute delayed hepatobiliary phase on Gd-EOB-DTPA enhanced MR in benign and malignant focal liver lesions.
- There may be shared mechanisms that needs to be clarified.
- Metastasis showing a "ring" enhancement on early arterial phase and washout in delayed phase, and a "target" appearance on hepatobiliary phase rather than hypointensity is a distinctive feature that may be an additional value for detection and differentiation from other focal liver lesions in the future.

Personal Information

References


