Chapter 13

Hepatobiliary Agents

Primary Author

Victoria Chernyak Montefiore Medical Center

Contributing Authors

Kathryn J. Fowler UC San Diego
Jay P. Heiken Mayo Clinic of Rochester
Claude B. Sirlin UC San Diego

Illustrators & figure contributors

Victoria Chernyak Montefiore Medical Center
Claude B. Sirlin UC San Diego

Editors

Victoria Chernyak Montefiore Medical Center
Claude B. Sirlin UC San Diego

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Hepatobiliary Agents

Introduction

Hepatobiliary agents (HBA) are gadolinium-based intravenous contrast agents with sufficient hepatobiliary excretion to enable hepatobiliary phase (HBP) imaging in addition to dynamic postcontrast phases.

Two agents have sufficient hepatobiliary excretion to be considered HBA:

- Gadoxetate disodium or Gd-EOB-DTPA, a.k.a. gadoxetic acid (Eovist®, Primovist®, Bayer Healthcare)
  - Hepatobiliary excretion: approximately 50% administered dose.
  - Window for HBP imaging: approximately 10 minutes - several hours (typically 15-20 minutes)
- Gadobenate dimeglumine (Multihance®, Bracco)
  - Hepatobiliary excretion: approximately 5% of the administered dose.
  - Window for HBP imaging: approximately 1-3 hours (typically 1 hour)

This chapter focuses on gadoxetate disodium.

- Gadoxetate disodium is a more widely used HBA for HCC imaging. It has higher hepatobiliary excretion, a relatively short delay, and has been widely studied in the setting of HCC imaging.
- By comparison, the relatively long delay, low hepatobiliary excretion, and relative paucity of literature evaluating gadobenate compared to gadoxetate in the setting of background liver dysfunction make it a less frequently used HBA for HCC imaging.

Other liver-specific agents are not considered HBA by LI-RADS:

- Mangafodipir trisodium is a manganese based contrast agent that is taken up by hepatocytes and excreted into the bile. It is no longer commercially available.
- Superparamagnetic iron oxides are taken by Kupffer cells of the liver, not hepatocytes. The T1 shortening of these agents is due iron, not gadolinium.

The enhancement of liver, observations, and other tissue in the HBP reflects many biological factors.

Key biological factors: presence and density of hepatocytes, the expression and function of uptake and excretion transporters, the patency of the biliary system, the relative volume of the interstitial compartment, and renal function (affects renal clearance rate). Other factors include hepatic steatosis and iron overload, which may affect the intensity of liver on MR images.

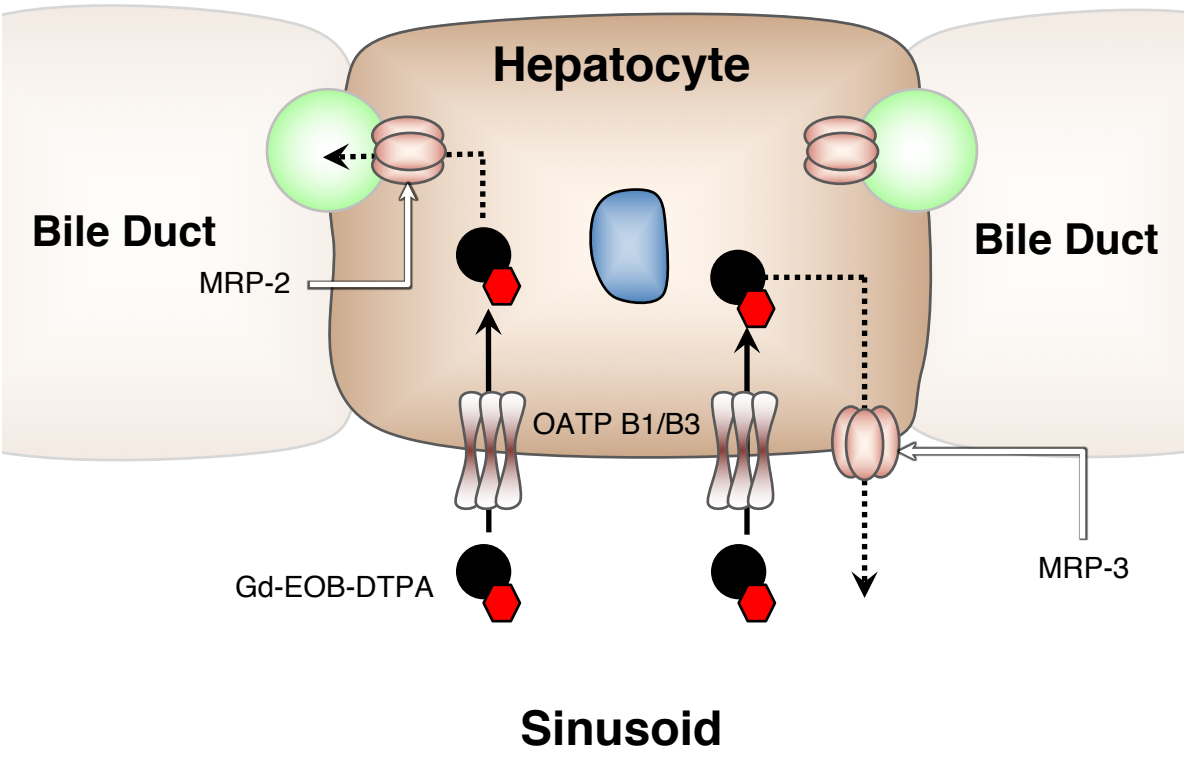
The presence or absence of expression of transporters for HBAs and the resultant HBP enhancement properties provide important diagnostic information for characterizing hepatic observations. See *page 13-2*.

Hepatobiliary Agents

Molecular transporters

Gadoxetate disodium uptake and excretion is mediated by three molecular transporters:

- Organic anion transporting polypeptide (OATP) B1/B3, located on the sinusoidal surface membrane of hepatocytes, mediates uptake by hepatocytes.
  - This transporter is unique to hepatocytes.
  - Only liver parenchyma and liver lesions composed of functional hepatocytes take up gadoxetate and enhance on HBP images
  - Organs other than liver, lesions lacking functional hepatocytes, and lesions composed of cells other than hepatocytes do not take up gadoxetate and do not enhance on HBP images
- Multidrug-resistance-associated protein (MRP)-2, located on the canalicular surface, mediates excretion into the biliary system.
- MRP-3, located on the sinusoidal surface membrane, mediates excretion back into the sinusoidal space.



Phases of Enhancement

Phases of enhancement with gadoxetate disodium

Gadoxetate disodium initially distributes in and enhances the vascular and interstitial (extracellular) spaces, similar to extracellular agents during the AP and early PVP.

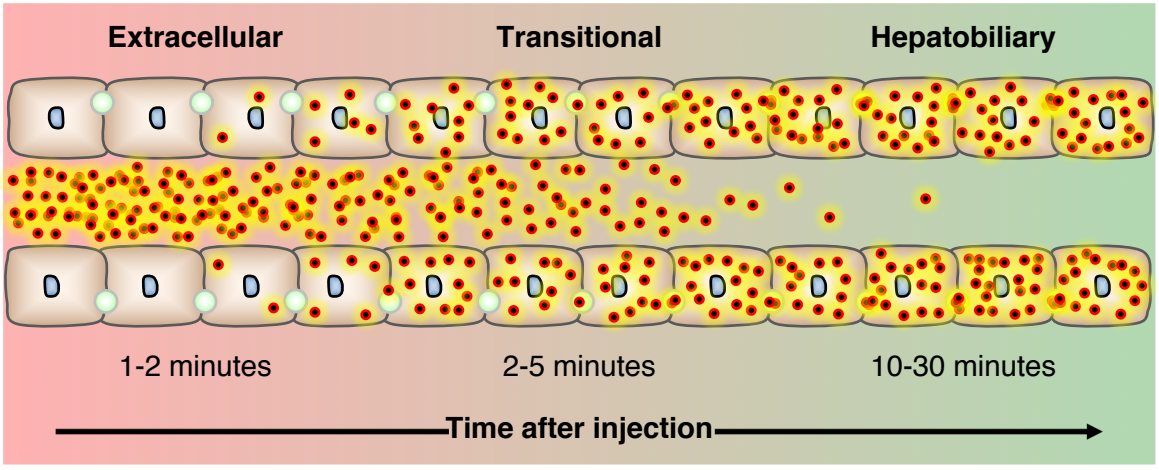
In normal liver, uptake of gadoxetate by hepatocytes begins as early as the first pass through the hepatic circulation and parenchymal enhancement due to hepatocyte uptake may be visible as early as the PVP.

Following the PVP, contrast agent is progressively taken up by hepatocytes and excreted into the biliary system. This results in progressively increasing enhancement of the liver parenchyma and rapid clearance from the vascular/interstitial space by both renal and hepatobiliary excretion.

- Visually, the liver parenchyma peaks in signal intensity by the HBP, and there is relatively little remaining contrast material within the blood vessels and other organs/tissues.

The period between the PVP and HBP is the transitional phase (TP)--the distribution of contrast *transitions* from predominantly extracellular to predominantly hepatobiliary.

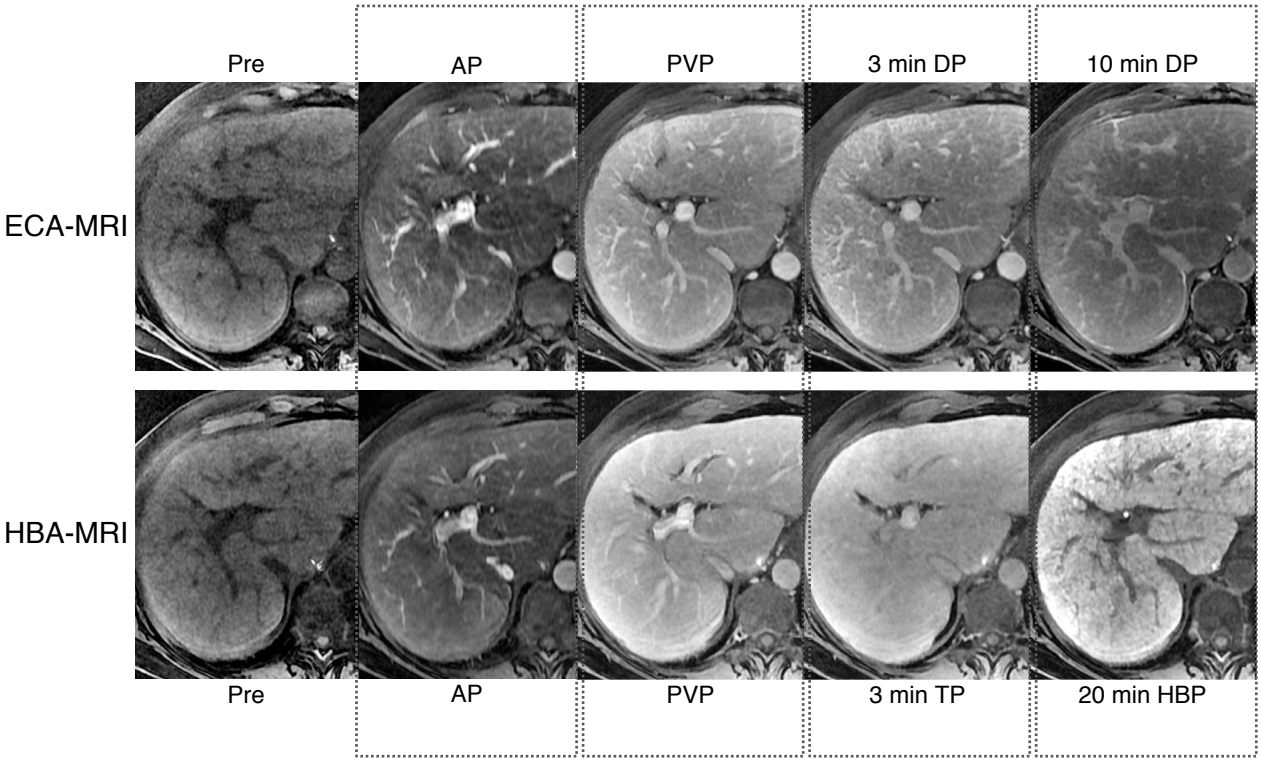
As shown below, the phases overlap and have gradual transitions.



The timing of the phases varies between patients. Generally, TP and HBP are delayed in cirrhotic patients with reduced hepatic function.

Phases of Enhancement

Example: Phases of enhancement with ECA (top row) vs. gadoxetate (bottom row) in the same patient



AP: Very similar to ECA if no motion artifact

PVP: HBA may begin to enter ICS in normal functioning livers

TP: HBA in ECS and ICS

Blood vessels isointense to parenchyma

HBP: HBA mainly in ICS and bile

Blood vessels hypointense to parenchyma

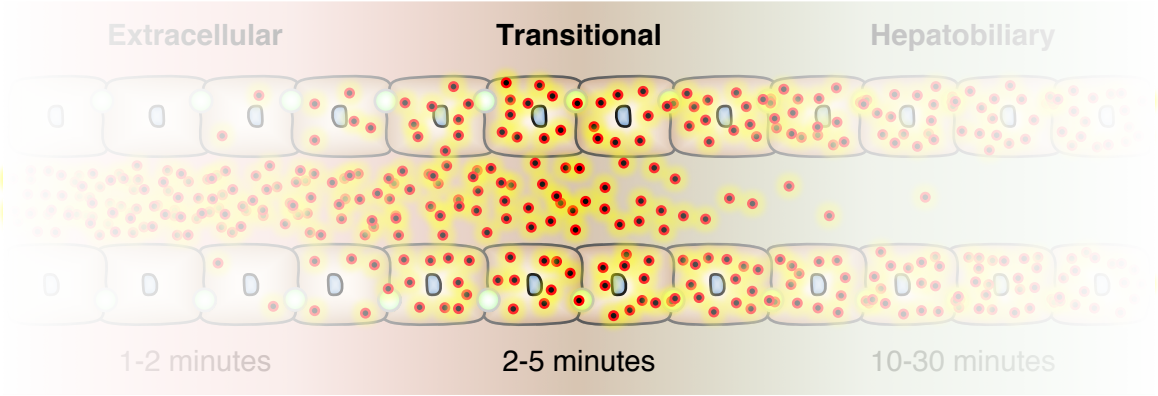
Abbreviations: ECS = extracellular space; ICS: intracellular space

Transitional Phase

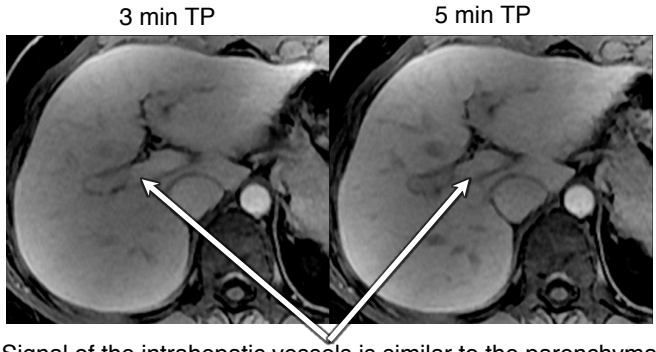
Transitional phase (TP)

TP is a phase after the PVP and before the HBP in which both the hepatocellular and extracellular pools of gadoxetate contribute substantially to parenchymal enhancement.

- Typically starts 2-5 min after injection and lasts until the HBP (15-20 minutes), may be delayed in cirrhotic patients with decreased liver function.
- Intrahepatic vessels and hepatic parenchyma are of similar intensity.



Example: Transitional phase with gadoxetate disodium



Signal of the intrahepatic vessels is similar to the parenchyma

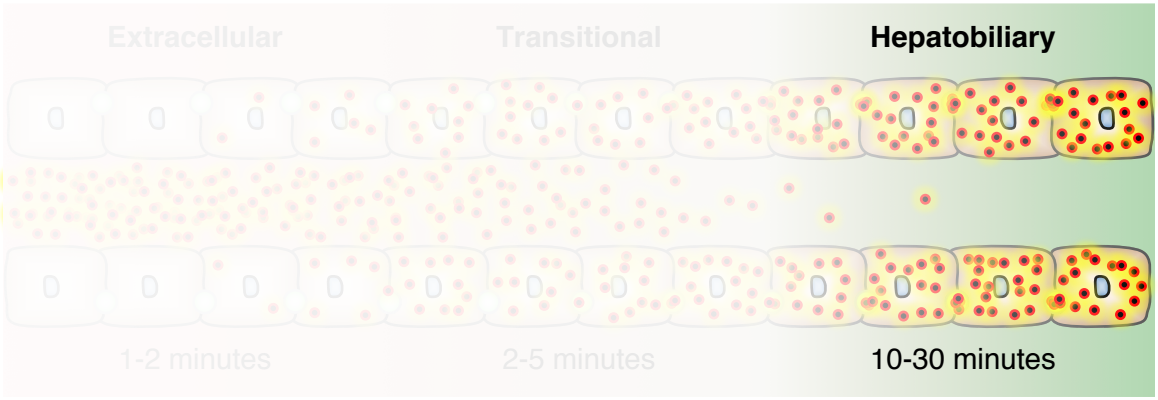
TP applies only to HBA-enhanced MRI, not ECA-enhanced MRI or ECA-enhanced CT

- ECAs remain within the extracellular spaces and equilibrate between vascular/interstitium (sometimes called equilibrium phase or interstitial phase).
  - There is no transition to hepatocellular space
- A prolonged TP occurs with gadobenate, beginning tens of minutes after contrast injection, but this phase is not routinely acquired with this agent

Hepatobiliary Phase

Hepatobiliary phase

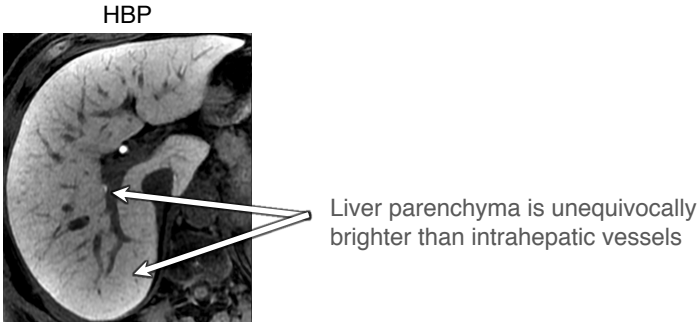
The HBP is defined by the peak of hepatic parenchymal enhancement due to transporter mediated hepatocyte uptake of contrast material. During this phase there is excretion of contrast material by hepatocytes into the biliary system. Since contrast material localizes to hepatocytes and bile ducts, the phase is called hepatobiliary.



Visually, during the HBP, the following characteristics are observed:

- The hepatic parenchyma reaches peak enhancement
- The hepatic parenchyma is hyperintense to the hepatic blood vessels and spleen
- There may be excretion of contrast into the biliary system

Example: Hepatobiliary phase with gadoxetate disodium



HBP applies only to HBA-enhanced MRI, not ECA-enhanced MRI or ECA-enhanced CT

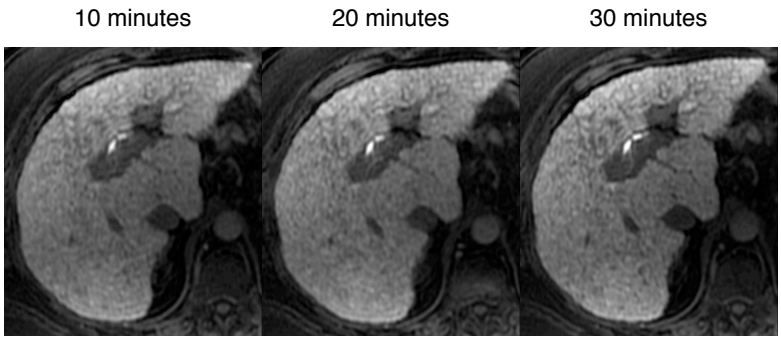
- ECAs remain in extracellular spaces and are not take up by hepatocytes or excreted in the bile.

Hepatobiliary Phase

HBP typically occurs about 20 minutes after injection of gadoxetate disodium, but may be as early as 10 minutes in normal liver or as late as 60 minutes in cirrhosis.

If obtained, HBP is typically acquired 1-3 hours after injection with gadobenate dimeglumine.

Example: Hepatobiliary phase with gadoxetate disodium achieved as early as 10 minutes



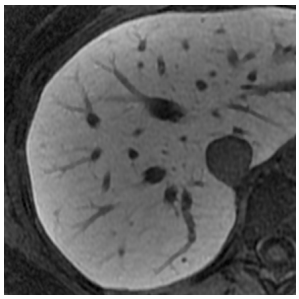
For both gadoxetate and gadobenate, the HBP is not defined primarily by the timing delay. Rather it is characterized by the enhancement of the hepatic parenchyma and clearance of contrast from the vasculature.

Hepatobiliary Phase

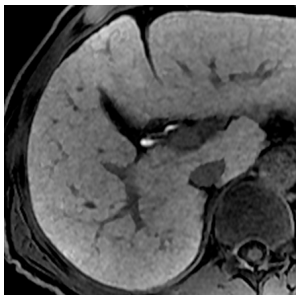
The normal liver appears homogenously hyperintense on HBP images.

The cirrhotic liver has variable appearance on HBP images, depending on the degree of function and the visibility, size, shape, and density of parenchymal nodules and fibrotic scars.

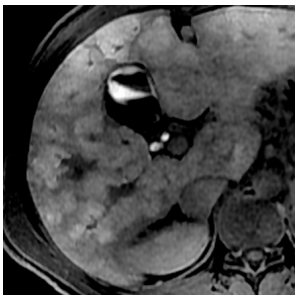
Example: Spectrum of hepatic parenchymal appearance in HBP



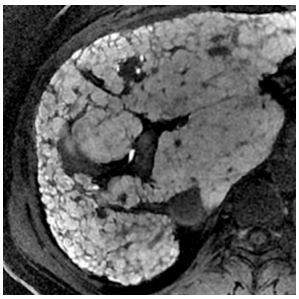
Normal liver



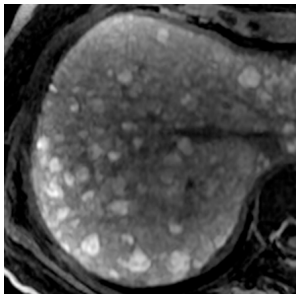
Hepatitis C cirrhosis



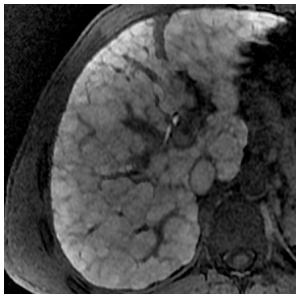
PSC/PBC overlap syndrome



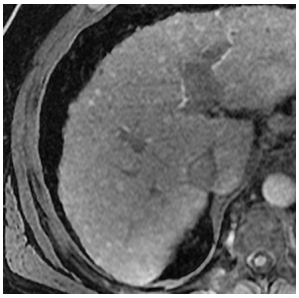
Autoimmune hepatitis



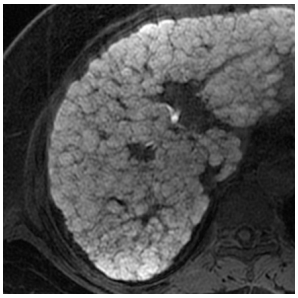
Hepatitis C cirrhosis



Wilson's disease



Alcoholic cirrhosis with poor liver function



Hepatitis B cirrhosis

Hepatobiliary Phase

HBP images may be suboptimal in some patients.

- Suboptimal HBP: hepatic parenchyma is ***not*** unequivocally hyperintense relative to the intrahepatic blood vessels.
- If suboptimal, interpretation of HBP intensity of liver observations (particularly if iso- or hyperintense to the background) may be unreliable.

Presence of biliary excretion ***does not*** mean that HBP is adequate, as excretion can be preserved despite poor hepatocyte uptake

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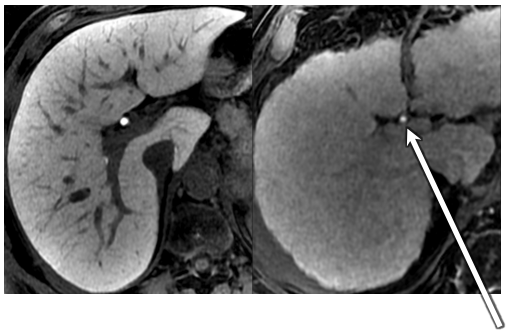
Adequate HBP: Liver is much brighter than intrahepatic vessels



Suboptimal HBP: Liver is NOT much brighter than intrahepatic vessels

Notice biliary excretion despite suboptimal HBP

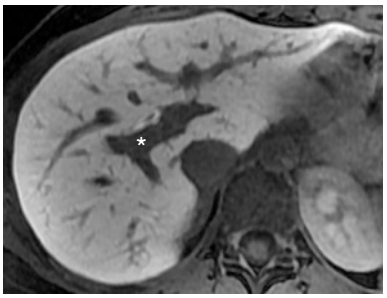
Causes of suboptimal HBP:

- Advanced cirrhosis with severe hepatic dysfunction (most common)
  - Thought to reflect reduced number of functional hepatocytes or dysfunctional cellular transport mechanisms.
- Cholestasis
- Reduced signal of liver parenchyma despite adequate uptake of HBA
  - Severe iron overload: T2* shortening causes the liver to appear dark even if there is hepatocellular uptake of HBA.
  - Severe steatosis: causes signal loss of liver parenchyma due to fat-water signal interference on out-of-phase images, fat suppression of fat-suppressed images, or both.

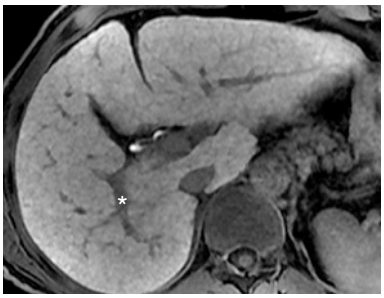
Hepatobiliary Phase

Example: Adequate HBP

Normal liver



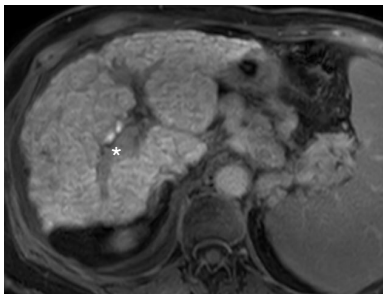
Compensated cirrhosis



✓ Liver is unequivocally brighter than intrahepatic vessels (*)

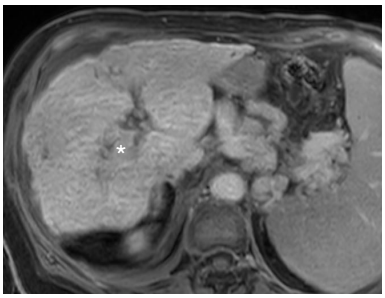
Example: Suboptimal HBP in decompensated cirrhosis

Adequate HBP on initial MRI



✓ Liver is unequivocally brighter than intrahepatic vessels (*)

Suboptimal HBP on 3-month follow-up

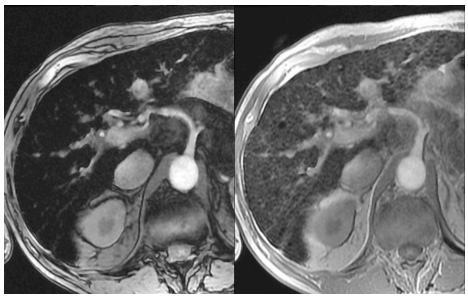


✗ Liver is NOT unequivocally brighter than intrahepatic vessels (*)

Hepatobiliary Phase

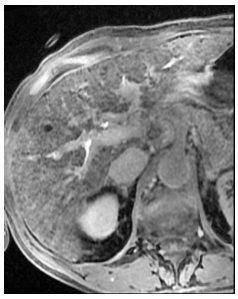
Example: Suboptimal HBP in iron overload

TE=5.8 ms TE=2.3 ms



Hepatic signal loss on longer echo indicates iron overload

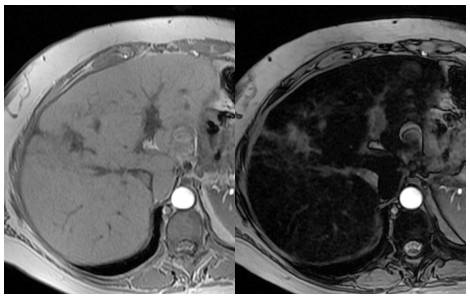
HBP



Suboptimal HBP:
Liver is DARKER
than intrahepatic vessels

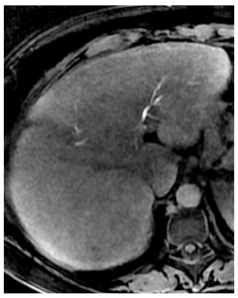
Example: Suboptimal HBP in severe steatosis

IP OP



Hepatic signal loss on OP compared to IP indicates steatosis

HBP



Suboptimal HBP:
Liver is NOT brighter
than intrahepatic vessels

Imaging Features Unique to Hepatobiliary Agents

Gadoxetate disodium (and to a lesser extent gadobenate) provides unique imaging features

Imaging features unique to gadoxetate (and gadobenate):

One LR-M feature:	• TP/HBP targetoid appearance (*Chapter 1, page 227*)
Two ancillary features favoring malignancy:	• TP hypointensity (*Chapter 16, page 295*) • HBP hypointensity (*Chapter 16, page 300*)
One ancillary feature favoring benignity:	• HBP isointensity (*Chapter 16, page 366*)

In addition to its unique imaging features, gadoxetate disodium can affect the ability to characterize major features

Arterial phase hyperenhancement (APHE) (*page 13-14*)

- APHE may be more difficult to detect on HBA-MRI than ECA-MRI.

Washout appearance (*page 13-15*)

- Washout appearance may be more difficult to detect on HBA-MRI than ECA-MRI.

Capsule appearance (*page 13-20*)

- Enhancing “capsule” may be more difficult to detect on HBA-MRI than ECA-MRI.

These effects are discussed on next several pages.

Effect of Gadoxetate on Major Features

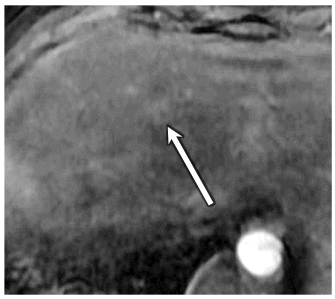
Effect of gadoxetate on major features

Arterial phase hyperenhancement (APHE)

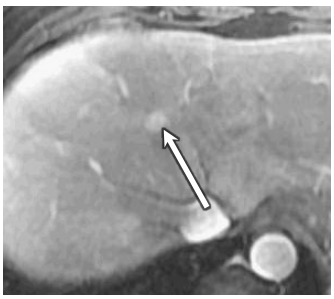
Gadoxetate is associated with motion artifacts on AP (*page 13-30*), which may reduce reduce AP quality and visibility of APHE.

Example: Motion artifact reduces sensitivity for APHE on gadoxetate disodium enhanced MRI

AP: HBA-MRI



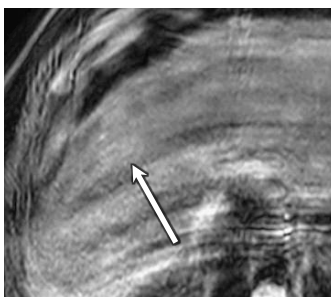
AP: ECA-MRI 3 months prior



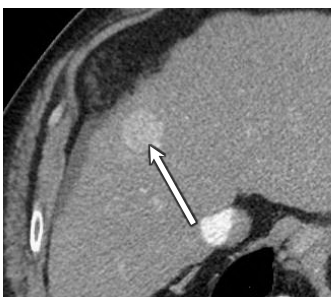
APHE is not well seen on HBA-MRI compared with ECA-MRI

Example: Severe motion may degrade arterial phase completely

AP: HBA-MRI



AP: CT 6 weeks later



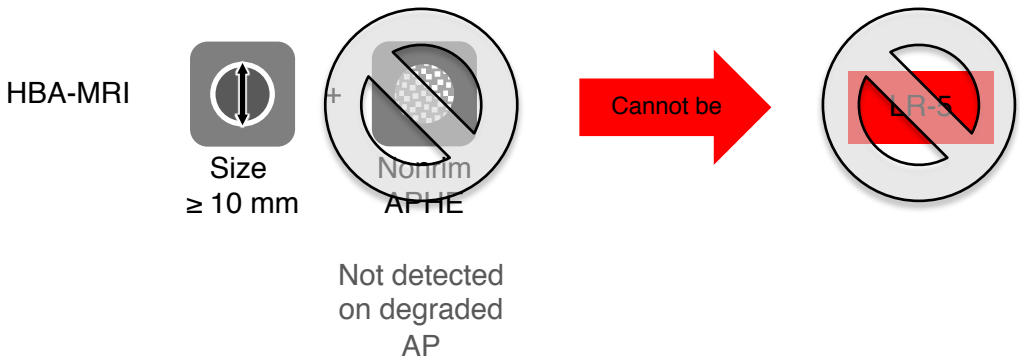
Extensive respiratory motion artifact may degrade AP, rendering it nondiagnostic for detection of observations or APHE

Effect of Gadoxetate on APHE

The suboptimal depiction of APHE can affect the categorization of observations.

For example: a ≥ 10 mm observations with nonrim APHE may be LR-5 (depending on other features):

If APHE is not seen, the same observation cannot be LR-5:



Effect of Gadoxetate on “Washout”

Washout appearance applies only to PVP on HBA MRI

“Washout” should only be characterized on extracellular phase images.

For gadoxetate disodium enhanced MRI, ***PVP only*** can be used to characterize “washout”.

- TP hypointensity is not “washout” for purposes of LI-RADS categorization.

Rationale

TP hypointensity is not specific for HCC. It can be seen in any of the following:

- HCC
- Non-HCC malignancy: iCCA, cHCC-CCA, metastases
- Some dysplastic nodules
- Some hemangiomas
- Confluent fibrosis

Allowing TP hypointensity to count as “washout” may lower the specificity for HCC. Based on current literature:

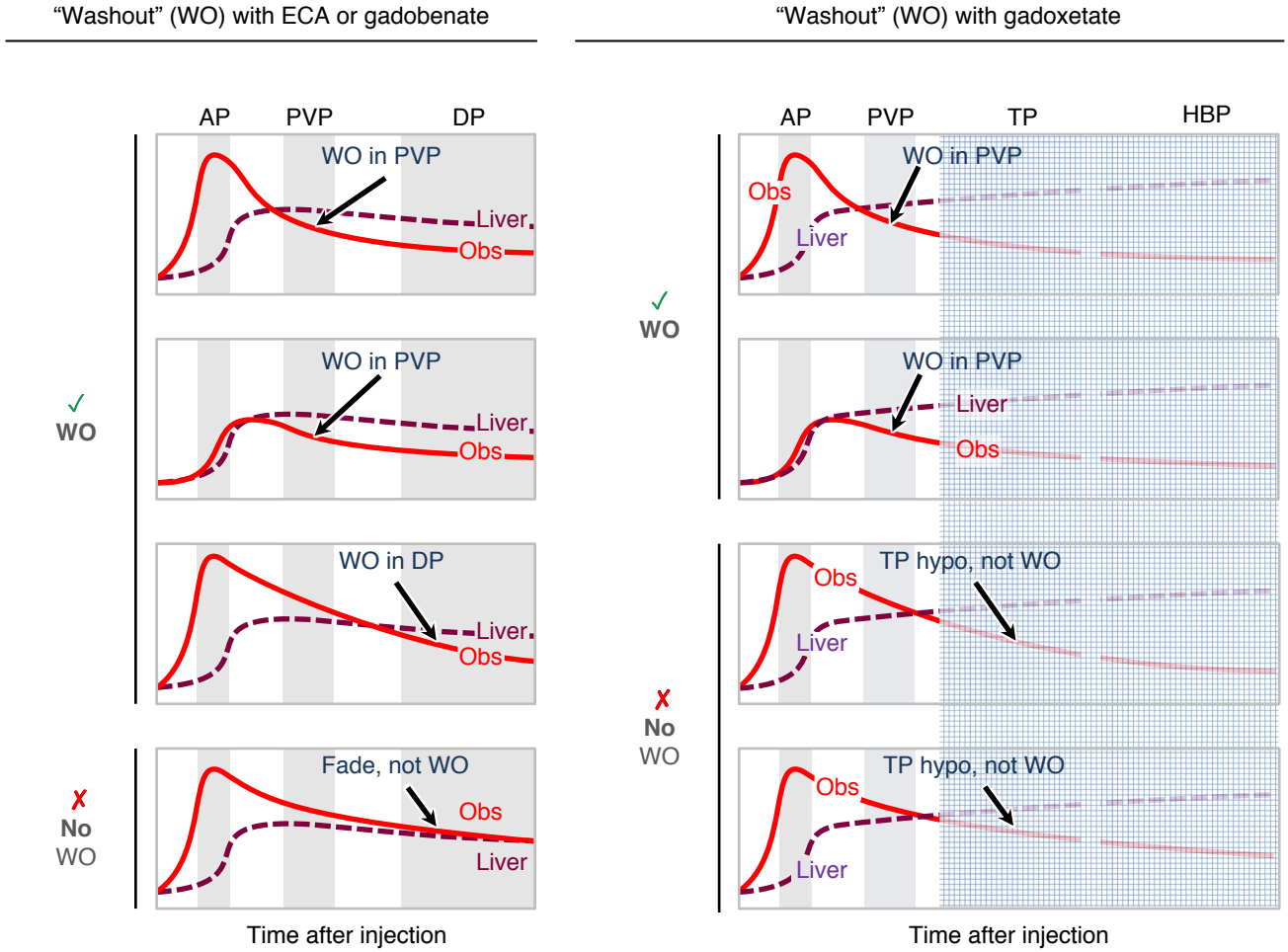
- APHE + “washout” in PVP : 93-100% specificity for HCC
- APHE + 3 min TP hypointensity: 79-95% specificity for HCC

Effect of Gadoxetate on "Washout"

Rationale (Cont'd)

TP hypointensity may be due to multiple factors: low uptake within an observation, progressive background liver enhancement, and/or true "washout". The idealized time-intensity curves below illustrate this concept.

Time-intensity curves



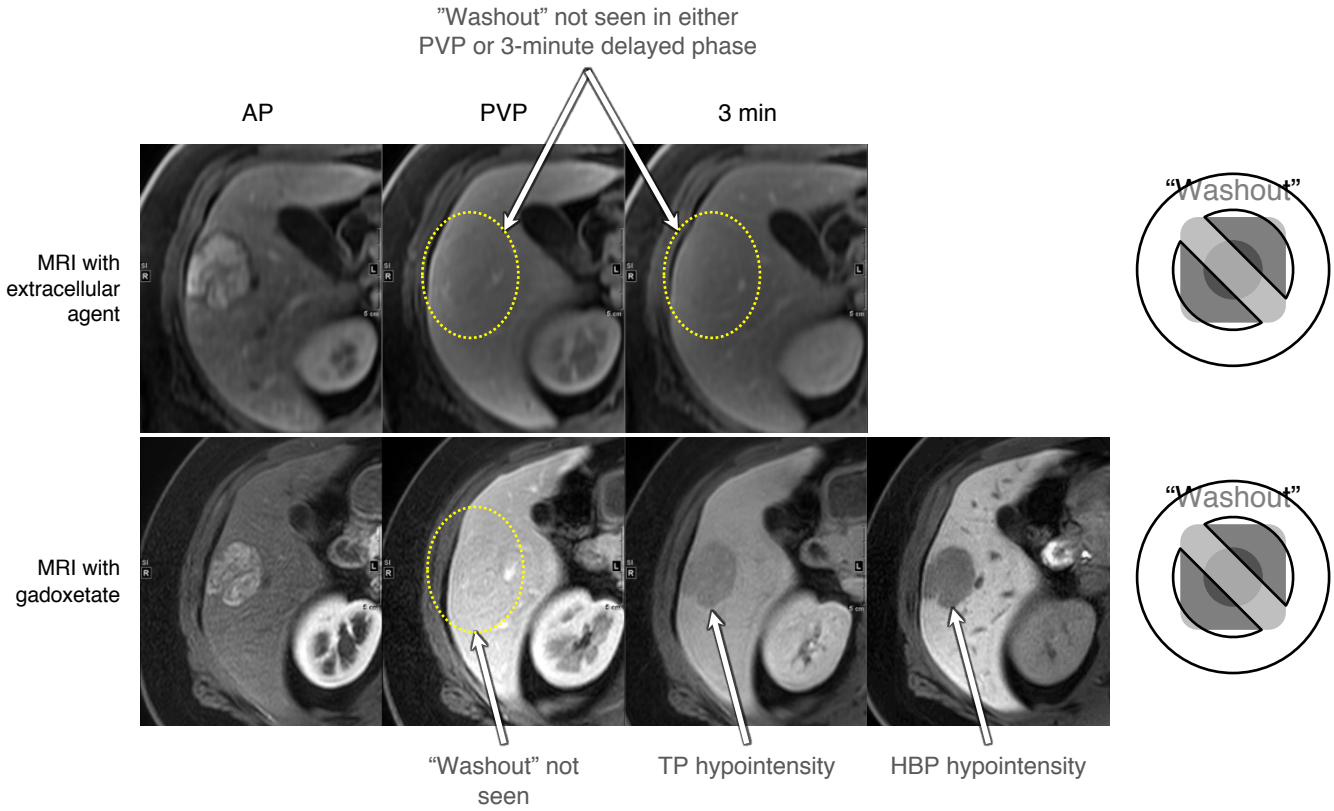
- "Washout" must be assessed in PVP
- Neither TP nor HBP are used to assess "washout"

Effect of Gadoxetate on "Washout"

Rationale (Cont'd)

Rationale is illustrated below in a woman with a hepatocellular adenoma. Since this patient is not at risk for HCC and therefore not in the LI-RADS population, this case is used for illustrative purposes.

- With ECA: the adenoma fades in the PVP and 3 minutes. It does not "wash out"
- With gadoxetate: the same adenoma is hypointense in the TP and HBP. The hypointensity is due to reduced OATP expression compared to liver, not to "washout"



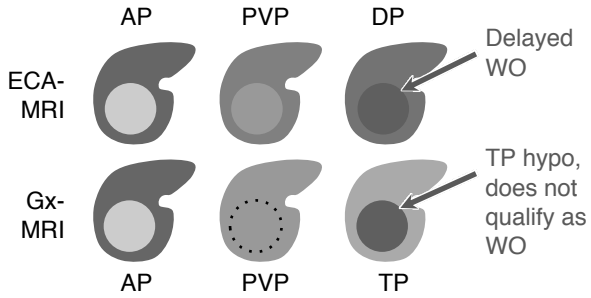
- "Washout" must be assessed in PVP
- Neither TP nor HBP are used to assess "washout"

Effect of Gadoxetate on "Washout"

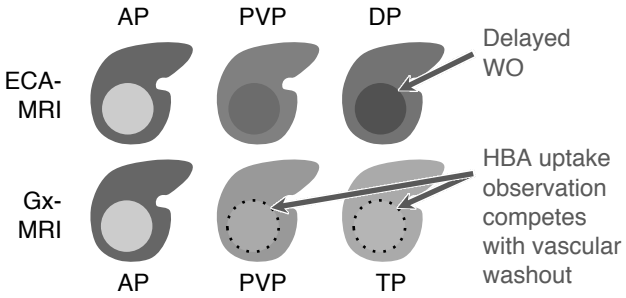
Washout appearance may be difficult to detect on gadoxetate-enhanced MRI

Washout appearance may be more difficult to detect on gadoxetate disodium enhanced MRI than ECA-MRI due to:

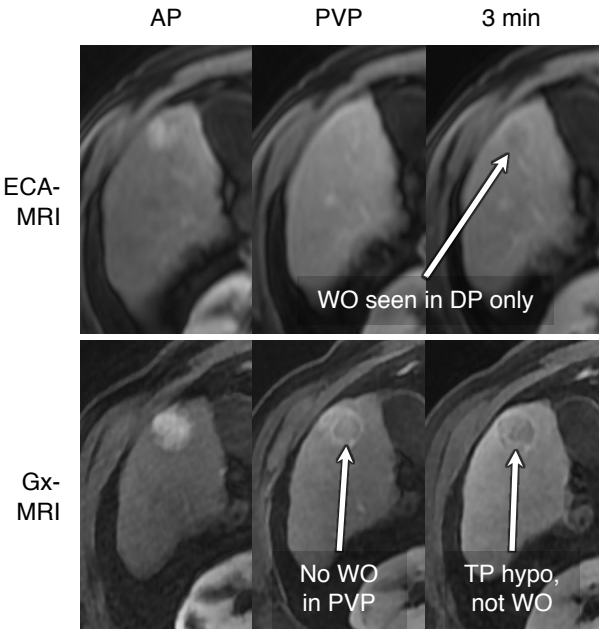
- Narrow temporal window for detection (PVP only)



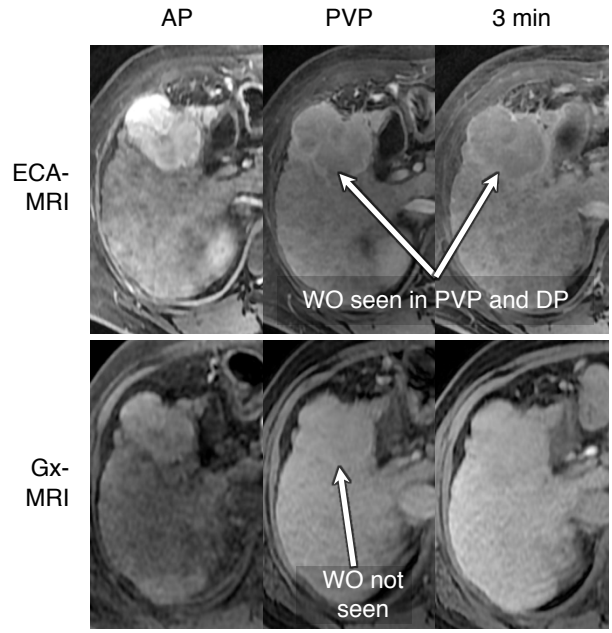
- Uptake of HBA by observation may match liver, sometimes seen in PVP



WO with ECA; but no WO with HBA



WO in PVP & DP with ECA; no WO with HBA



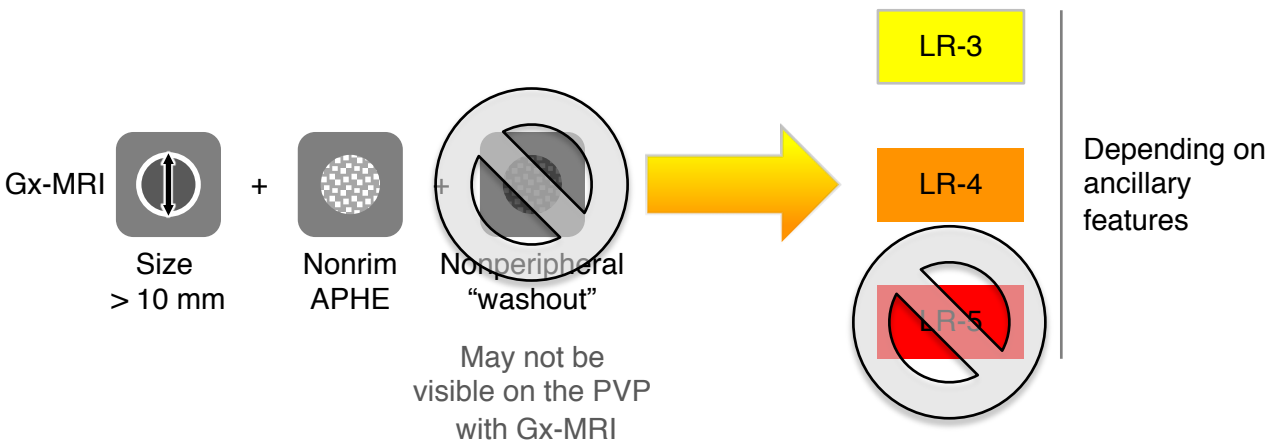
Effect of Gadoxetate on "Washout"

Washout appearance may be difficult to detect on gadoxetate-enhanced MRI

Lack of detection of "washout" can affect the categorization of observations.

For example: a > 10 mm observation with nonrim APHE, nonperipheral "washout", and no other additional major features (i.e., no threshold growth, no enhancing "capsule") is categorized LR-5:

If "washout" is not seen, the same observation would be categorized LR-3 or LR-4:



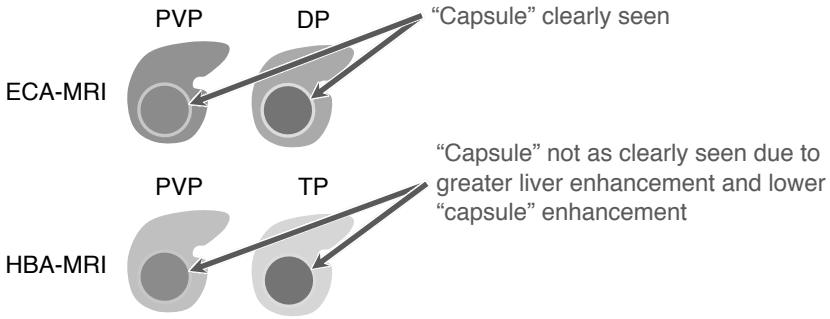
Effect of Gadoxetate on "Capsule"

Enhancing capsule appearance may be difficult to detect on gadoxetate-enhanced MRI

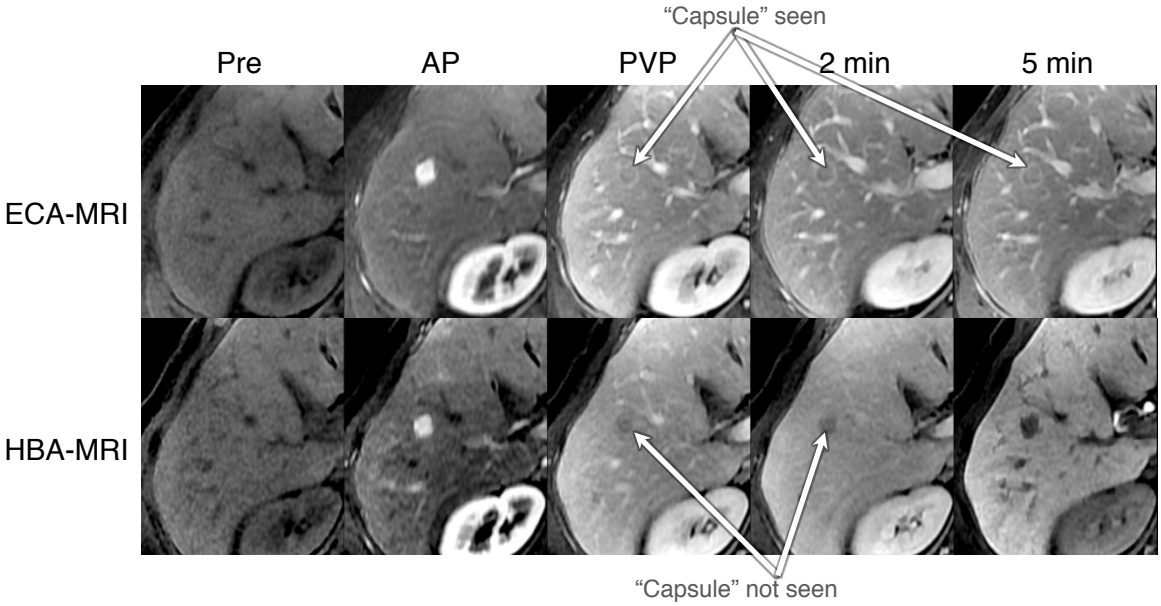
Unlike "washout", which must be characterized in the portal venous phase, enhancing "capsule" may be characterized in both the PVP and TP.

Although enhancing "capsule" may be characterized on either phase, this major feature may more difficult to see with HBA-MRI than with ECA-MRI for two reasons:

- Prominent enhancement in the PVP and TP by the liver may obscure any enhancement of the "capsule".
- Reduced distribution of gadoxetate in the extracellular space of the "capsule" may lower the absolute enhancement of the "capsule".



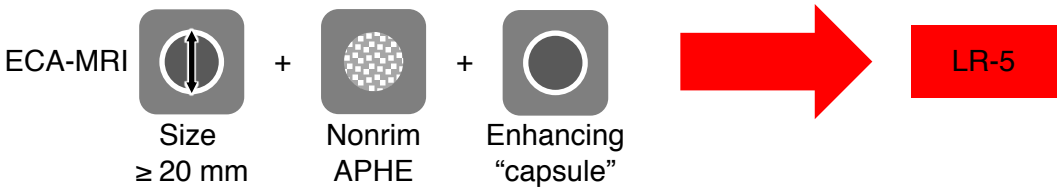
Example: Enhancing capsule appearance detected at ECA-MRI, not HBA-MRI



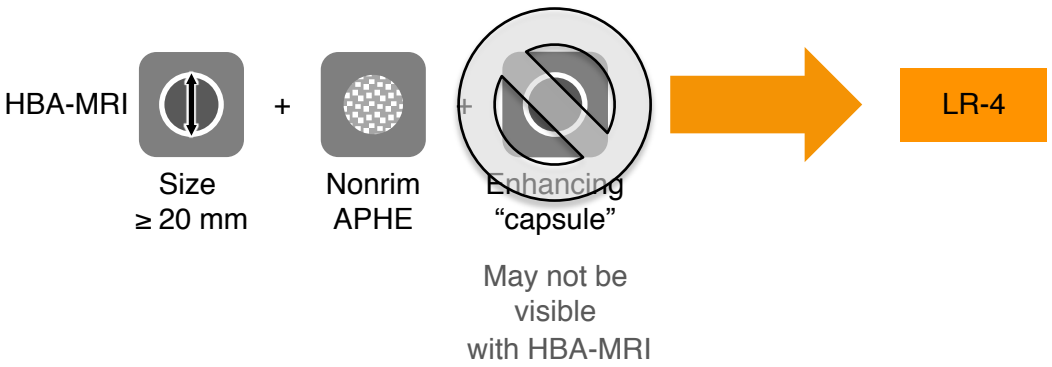
Effect of Gadoxetate on "Capsule"

The suboptimal depiction of enhancing "capsule" can affect the categorization of observations.

For example: a ≥ 20 mm observations with nonrim APHE, enhancing "capsule", and no additional major feature (i.e., no "washout", no threshold growth) is categorized LR-5:



If "capsule" is not seen, the same observation would be categorized LR-4:



Possible Advantages

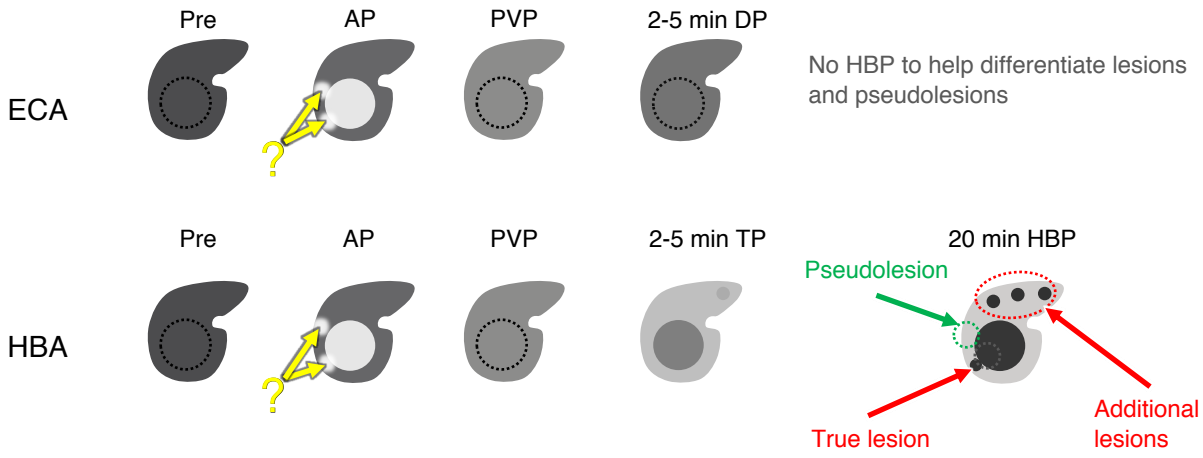
Gadoxetate disodium: possible advantages

Improved sensitivity for HCC

- Additional lesions may be detected on HBP images, including small HCCs and early HCCs, not visible on any other sequence.
- HBP images provide higher contrast-to-noise ratio than other sequences, potentially increasing lesion conspicuity. For instance, lesions detected first on HBP, may be identified in hindsight on other sequences.
- HBP lasts several minutes, enables use of different sequence parameters than dynamic images (rapid techniques are less important). As a result, images with high signal-to-noise ratio, contrast-to-noise ratio, and spatial resolution are possible.

Improved specificity

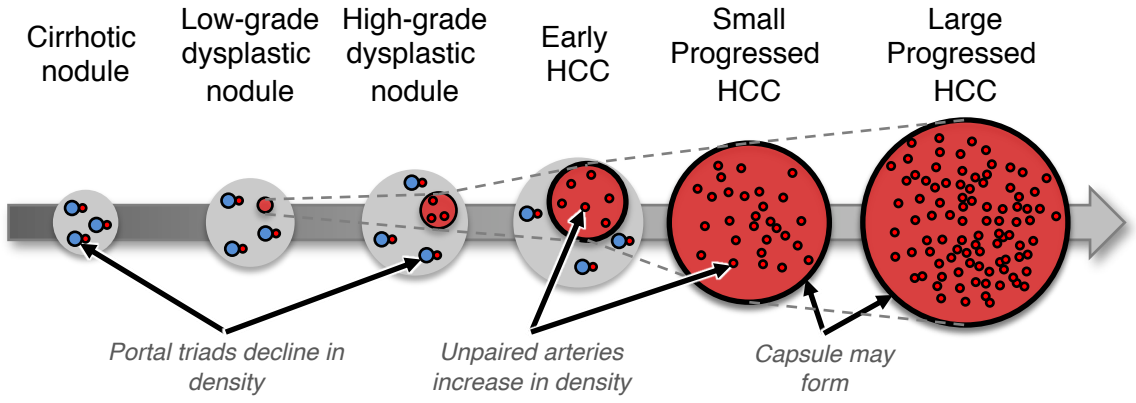
- HBP imaging can differentiate between:
  - *true lesions* with APHE (hypointense on HBP)
  - vascular *pseudolesions* such as arterioportal shunts (isointense on HBP)

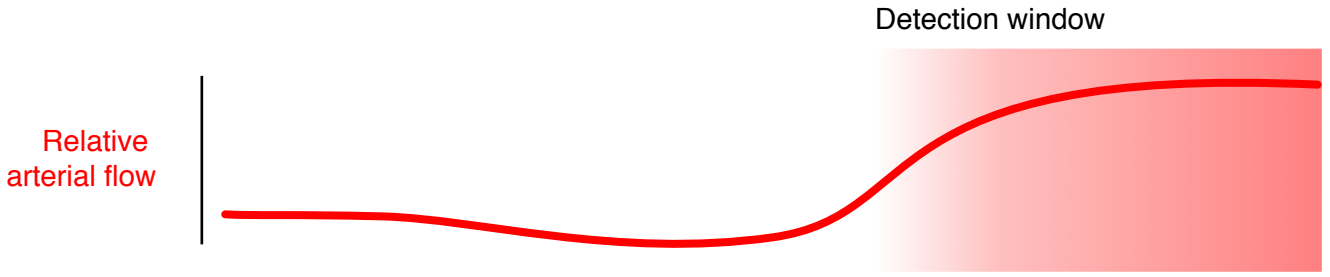


Possible Advantages

Improved detection of early HCCs

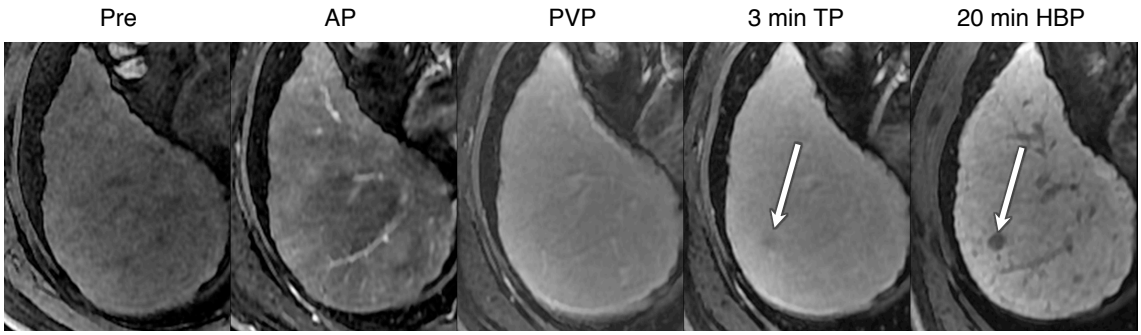
- Early HCCs (eHCCs) have incomplete neoarterialization, frequently are isointense to background liver in vascular phases, therefore cannot be reliably detected with ECA imaging.
- Since OATP expression level decreases during hepatocarcinogenesis prior to complete neoarterialization, such HCCs may be visible first and potentially only on HBP images as hypointense nodules.
- Importantly, differential diagnosis for HBP hypointense nodules without APHE includes high-grade dysplastic nodules, occasional low-grade dysplastic nodules, occasional large cirrhotic nodules, and nodular areas of fibrosis, so this finding is not specific for HCC.





Possible Advantages

Example: detection of early HCC



eHCC is seen only as a 11 mm observation without APHE or WO, but with TP and HBP hypointensity

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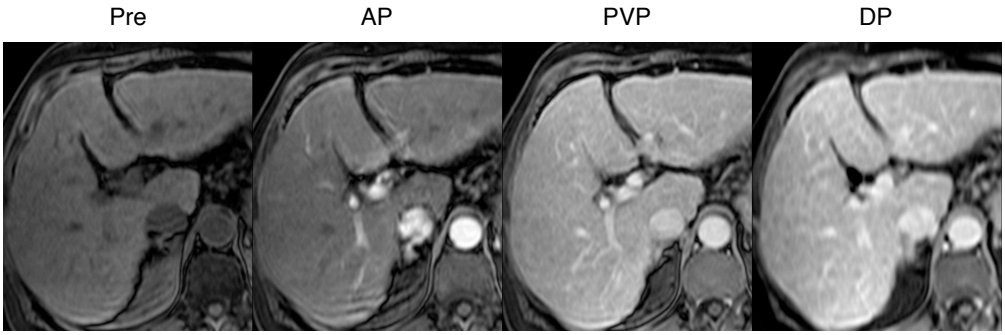
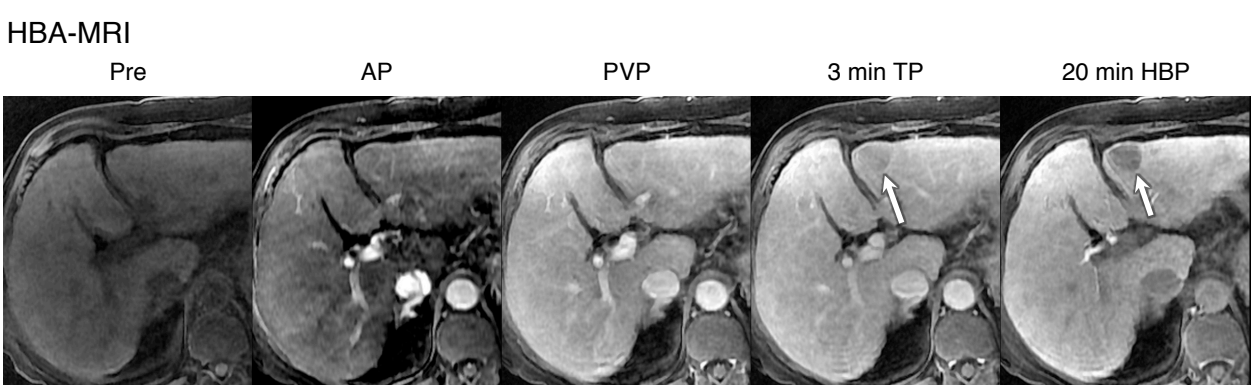
Example: detection of hypovascular HCC

ECA-MRI



No observation is seen on ECA-MRI

HBA-MRI

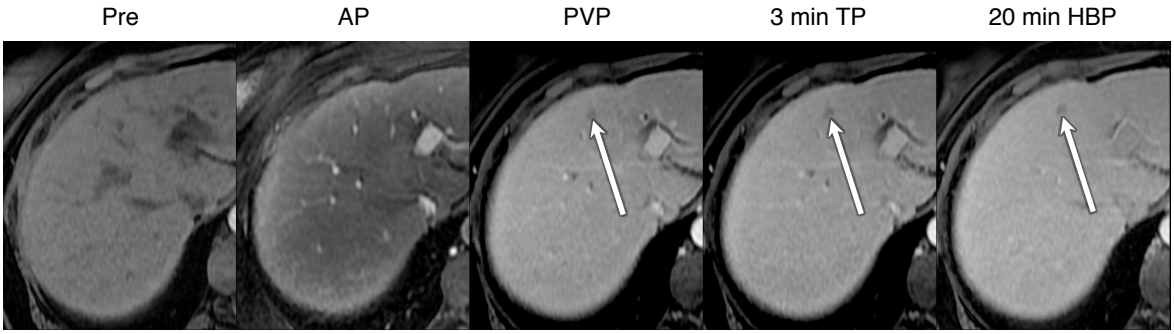


A 23 mm observation without APHE or WO is seen on TP and HBP

Possible Advantages

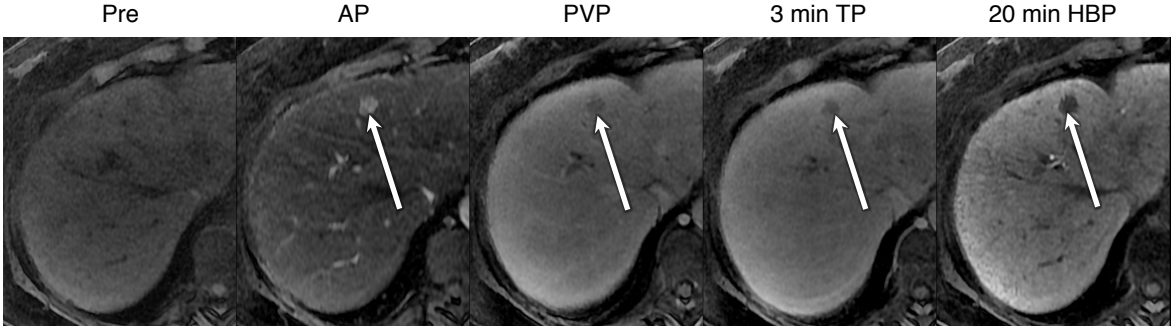
Example: detection of early HCC and HCC precursors

Initial gadoxetate-MRI



A 6 mm observation without APHE, with PVP WO and hypointensity on TP and HBP: categorized as LR-3 based on major features and upgraded to LR-4 based on AFs favoring malignancy

Follow-up gadoxetate-MRI in 2 years

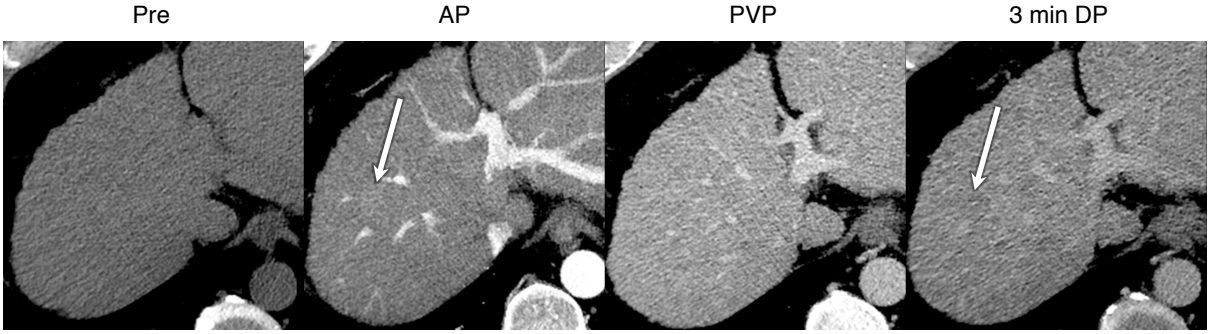


2 years later, the observation has grown to 17 mm, and it has developed APHE. The observation is now categorized LR-5 (10-19 mm, nonrim APHE, PVP washout appearance).

Possible Advantages

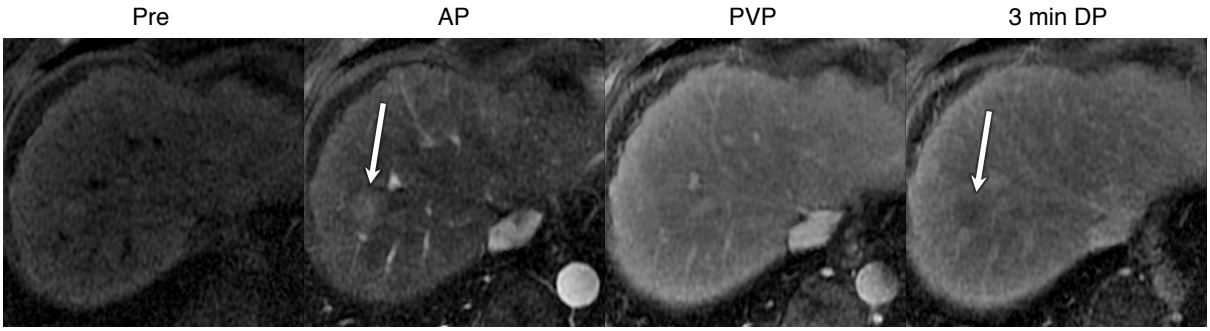
Example: detection of minimally hypervascular HCC

CT



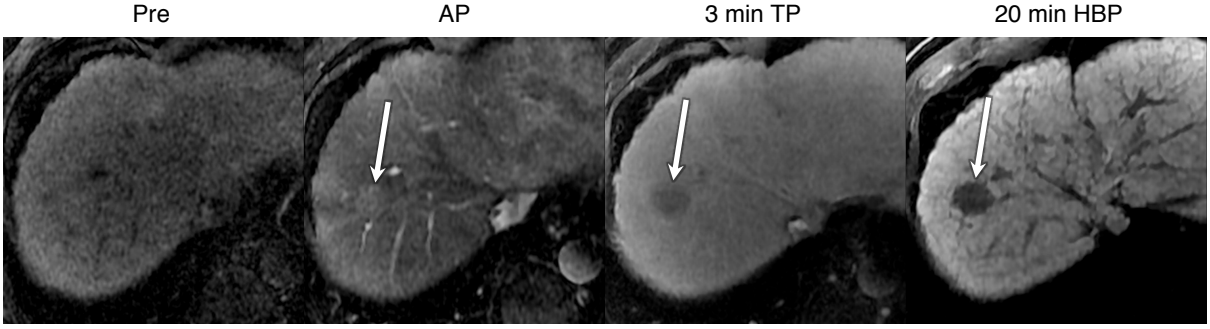
18 mm observation is very subtle on AP and DP

ECA-MRI



18 mm observation has subtle APHE and subtle WO on DP

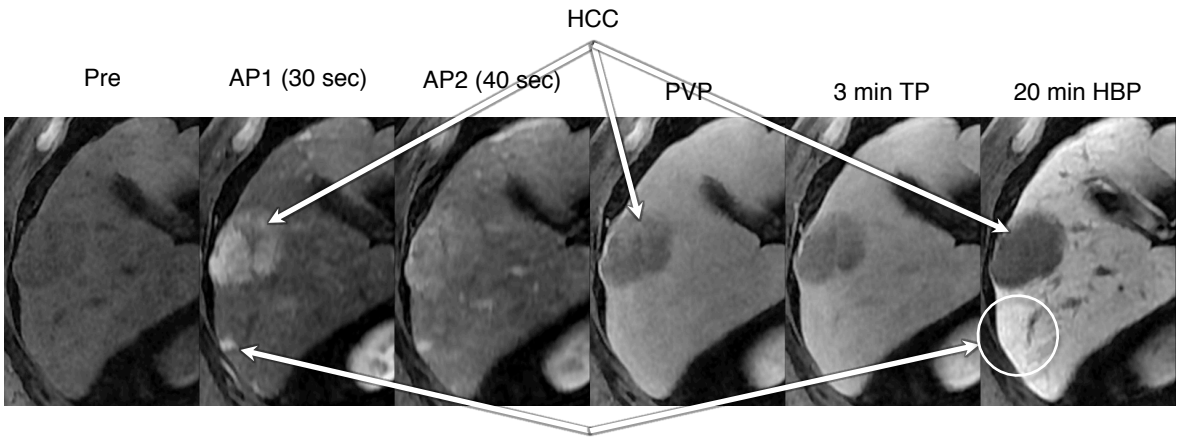
Gadoxetate-MRI



The contrast-to-noise ratio between the observation and the background is highest in the TP and HBP

Possible Advantages

Example: assess vascular pseudolesions



HCC demonstrates APHE, PVP WO and TP/HBP hypointensity.
Perfusion alteration can be appropriately categorized as LR-1 or LR-2 given isointensity on HBP.

Possible Advantages

Prediction of tumor differentiation

- Poorly differentiated HCCs are hypointense in the HBP (98%) more frequently than well- or moderately-differentiated HCCs (86%).
- HCCs with HBP hyperintensity are associated with molecular features of mature hepatocytes and with histologic features associated with more favorable outcomes.

Prediction of microvascular invasion (MVI)

- Peritumoral HBP hypointensity is associated with higher odds of MVI.

Improved selection for liver-directed treatments (TACE, RFA, resection)

- Prospective and retrospective observational studies demonstrate improved overall and recurrence-free survival in patients selected for treatment based on CT and HBA-MRI, compared with CT alone.

Prognostic information in liver transplantation patients

- Satellite nodules and peritumural hypointensity in the HBP of the pre-transplant MRI are independent predictors of tumor recurrence, for patients transplanted both within and outside Milan criteria

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Prognostic information in liver resection patients

- Peritumoral HBP hypointensity is a predictor of post-resection recurrence

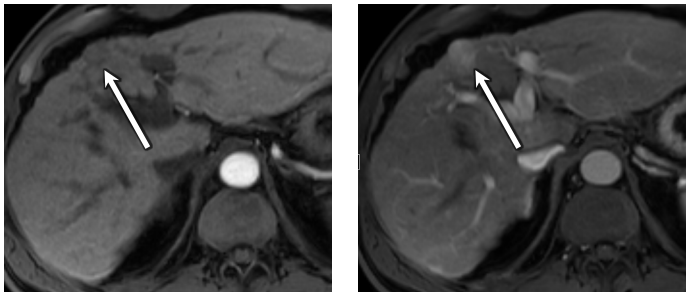
---

Pitfalls and Practical Considerations

Quality of arterial phase may be degraded by several factors

- Bolus timing more challenging
  - Low volume bolus results in a narrow peak of contrast and window for AP acquisition, harder to capture optimal AP.
  - Test bolus technique less desired option for timing due to potential for liver uptake, may limit accurate means of bolus timing on some scanners.

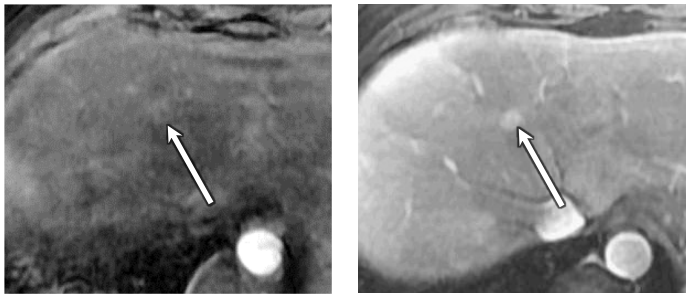
AP: HBA-MRI | AP: ECA-MRI 3 months prior



AP timing is too early on Gx-MRI, and APHE is not demonstrated. Late AP with ECA-MR depicts APHE.

- Less gadolinium per dose (0.025 vs 0.1 mmol/kg)
  - Lower dose of gadolinium may reduce peak arterial enhancement of lesions.

AP: gadoxetate-MRI | AP: ECA-MRI 3 months prior

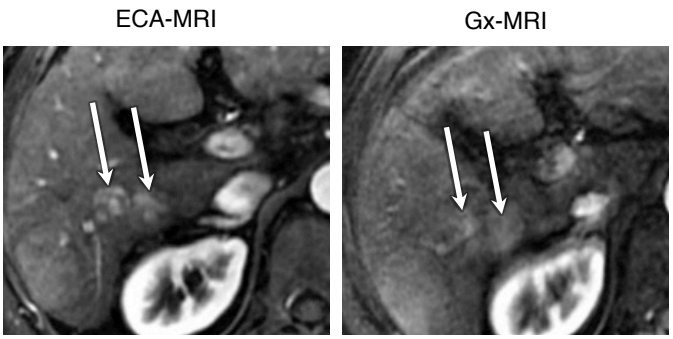


APHE is less pronounced on gadoxetate-MRI compared with ECA-MRI

Pitfalls and Practical Considerations

Quality of arterial phase may be degraded by several factors (Cont'd)

- Respiratory motion may degrade AP image quality
  - Patients may experience transient self-limiting dyspnea (also known as transient severe motion) shortly after contrast injection, around the time of AP.
  - Affects 15-39% of gadoxetate-MRIs, compared with 3-10% of ECA-MRIs.
  - Degradation of AP images limits assessment for APHE, a feature that is required for LR-5 categorization (*Chapter 16, page 19*).
  - Cause of motion on HBA is controversial:
    - Nonallergic-like mechanism?
  - Various studies report increased incidence with
    - Male sex
    - Higher BMI
    - Higher dose of gadoxetate
    - Previous episodes of transient severe motion
    - Chronic obstructive pulmonary disease



Compared with ECA-MRI, AP with HBA-MRI is degraded by motion artifact

Pitfalls and Practical Considerations

Difficulty in visualization of enhancing “capsule” (*page 13-20*)

“Washout” can be assessed ***only on PVP*** (cannot be assessed on the TP) (*page 13-15*)

Possible lower sensitivity for TIV:

- Gadoxetate disodium tends to generate weak contrast between vessels and background liver during the AP, PVP and TP, in part because low dose reduces peak arterial enhancement of neoplastic tissue including tumor in vein.
- Early clearance of contrast from vessels may reduce conspicuity of TIV (i.e., TIV and vessels are equally hypointense)
- All imaging methods have limited sensitivity for segmental TIV. There is not yet any high-level evidence on the comparative performance of different methods for this purpose

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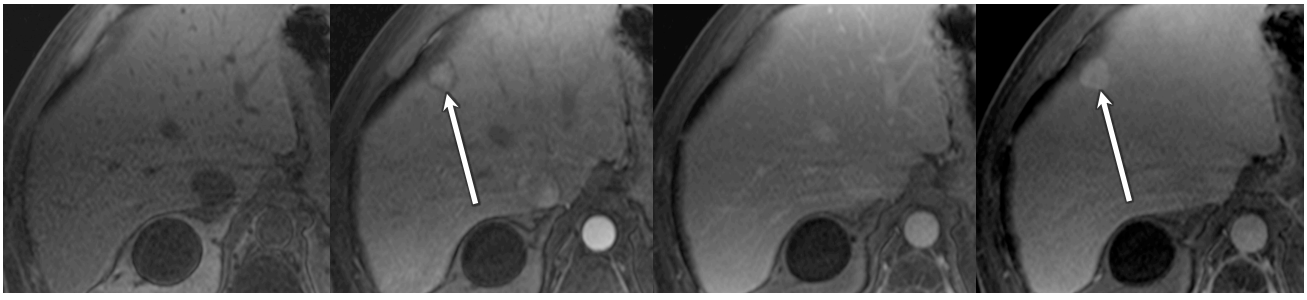
Prolonged exam time:

- Despite protocol optimization, acquisition of HBP makes scan time longer compared to ECA-MRI.

Pitfalls associated with HBP

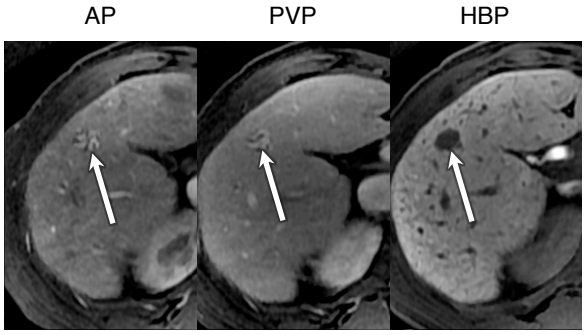
- 5-10% of HCCs are hyperintense on the HBP



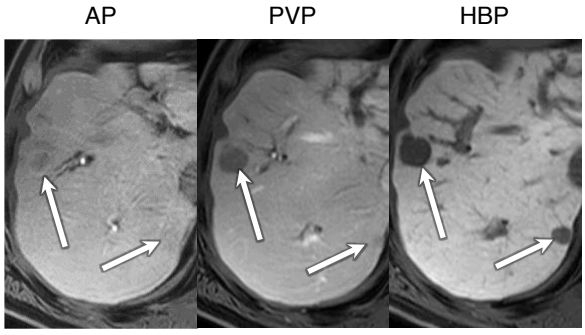
HCC demonstrates APHE, no WO and HBP hyperintensity

Pitfalls Associated with Hepatobiliary Phase

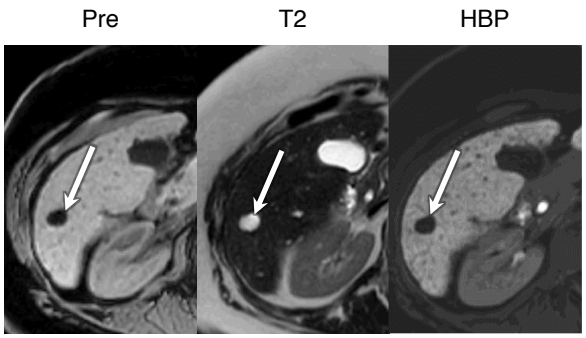
- HBP non-specificity
  - Any lesion not composed of functioning hepatocytes may appear hypointense in HBP, including benign entities (e.g., hemangiomas, nodular or confluent areas of fibrosis, some atypical perfusion alterations) and non-HCC malignancies (e.g., ICCs, metastases).



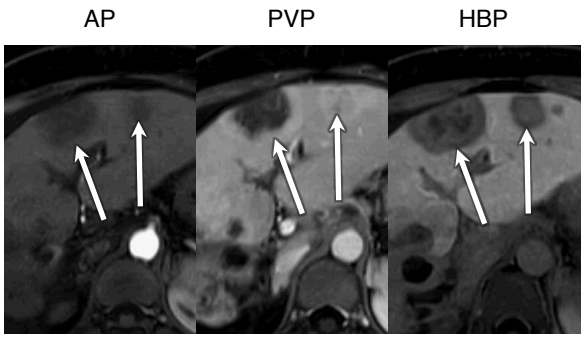
Hemangioma



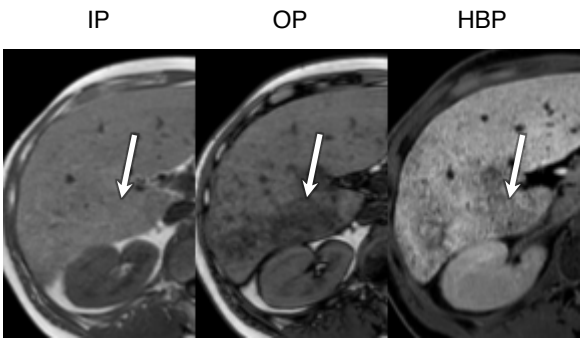
Carcinoid metastases



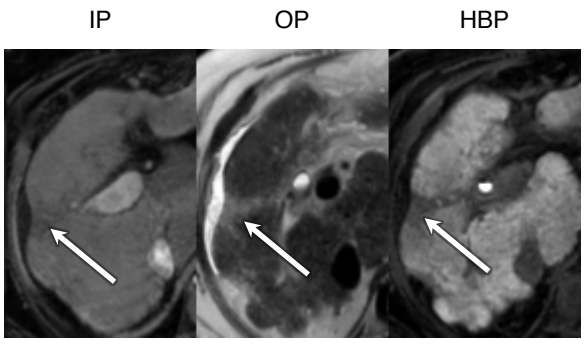
Cyst



Multifocal cholangiocarcinoma



Focal steatosis

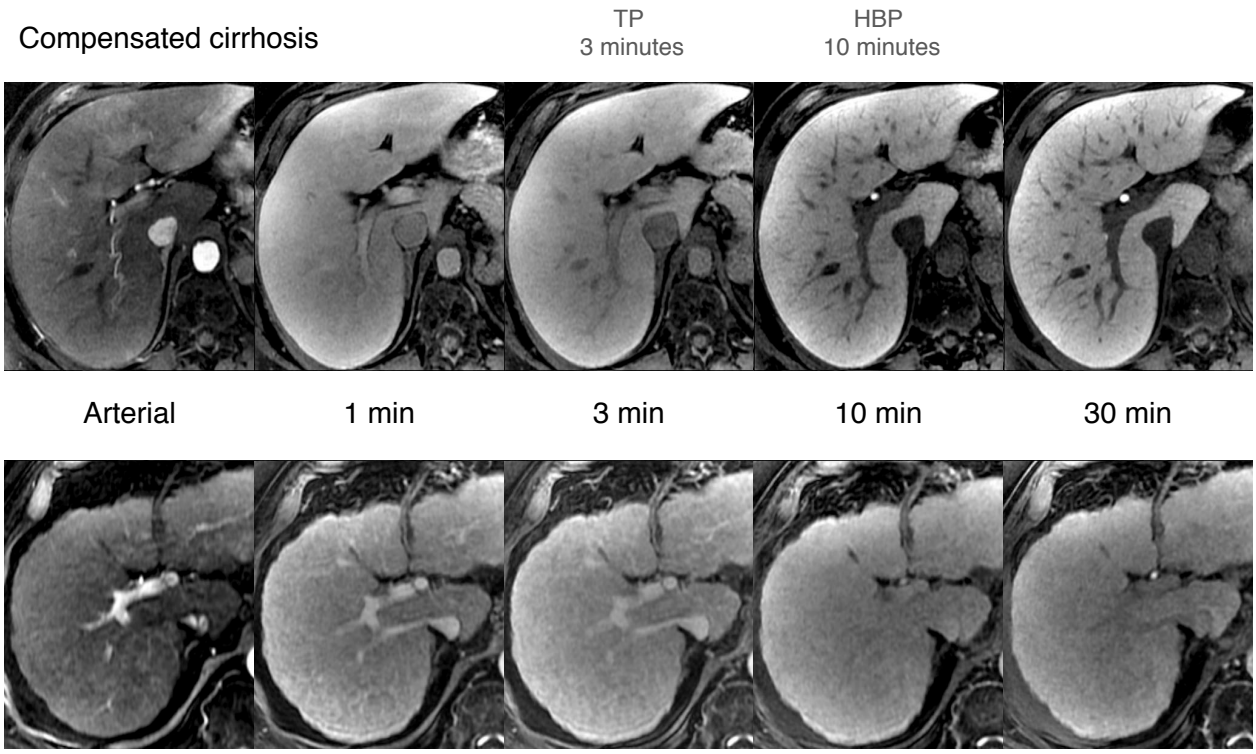


Confluent fibrosis

Pitfalls Associated with Hepatobiliary Phase

Pitfalls associated with hepatic dysfunction

The transitional phase may be prolonged and the hepatobiliary phase inadequate and delayed in patients with severe hepatic dysfunction (e.g., decompensated cirrhosis).



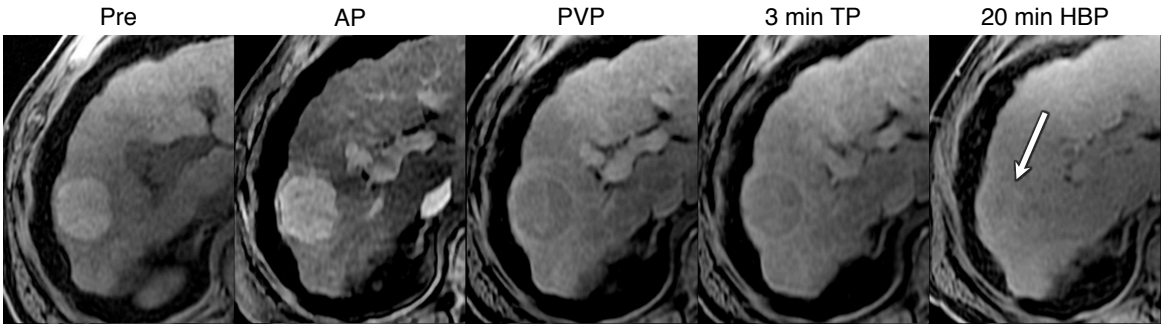
All illustrated above, the HBP is not defined primarily by the timing delay. Rather it is characterized by the enhancement of the hepatic parenchyma and clearance of contrast from the vasculature.

Pitfalls Associated with Hepatobiliary Phase

Pitfalls associated with hepatic dysfunction (Cont'd)

In severe hepatic dysfunction, a malignant neoplasm such as HCC may appear isointense to liver in HBP due to diminished clearance of contrast from extracellular spaces (vascular and interstitial).

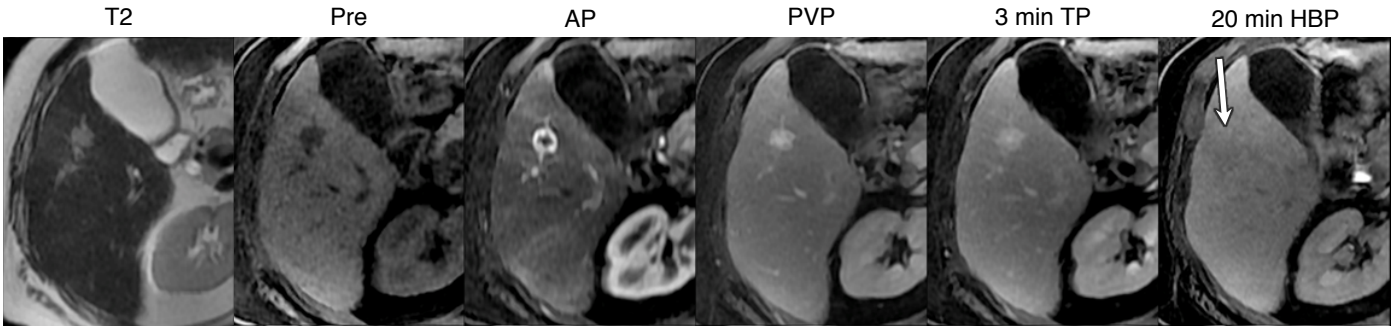
- In cases of suboptimal HBP, HBP isointensity should not be applied as an AF favoring benignity.



HCC in suboptimal HBP: 35 mm observation with APHE, WO and capsule meets criteria for LR-5. On HBP, observation is uniformly isointense to background parenchyma. Recognition that HBP is suboptimal (parenchyma is isointense to intrahepatic vessels) is important so that isointensity to parenchyma is not erroneously interpreted as AF of benignity.

In severe hepatic dysfunction, blood vessels and hemangiomas may appear isointense to liver.

- Due to diminished hepatobiliary excretion, gadoxetate is cleared slowly from the vascular space. Blood vessels and lesions with large blood volumes (e.g., hemangiomas) retain contrast material and may appear isointense to suboptimally enhanced liver.
- In cases of suboptimal HBP, HBP isointensity should not be mistaken as lesional uptake of gadoxetate, which would indicate hepatocellular origin.



Hemangioma in suboptimal HBP: On AP, PVP and TP, observation demonstrates enhancement typical of hemangioma. On HBP, observation is isointense to liver. Recognition that HBP is suboptimal (parenchyma is isointense to intrahepatic vessels) is important so that isointensity to parenchyma is not erroneously interpreted as lesional gadoxetate uptake indicating hepatocellular origin.

HBP Hypointense Nodule without APHE

HBP hypointense nodule without APHE

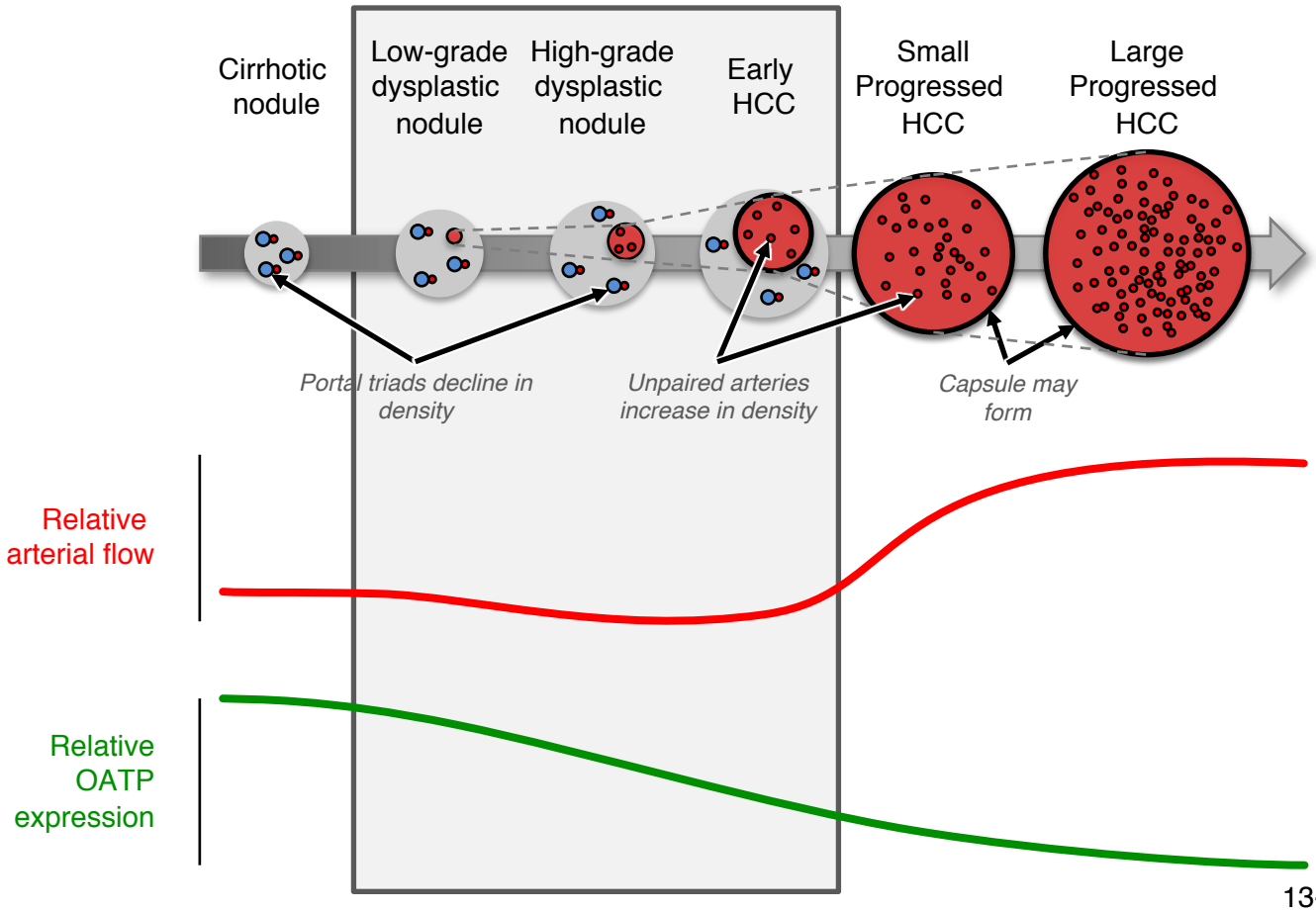
HBP hypointense nodules without APHE (the LI-RADS preferred term) are unique to HBA-MRI, since HBP phase imaging is not available with ECA-MRI.

A large proportion of these nodules are early HCCs and dysplastic nodules: In one retrospective study, 74% of histology-sampled HBP-hypointense nodules without APHE were HCCs and 10% were dysplastic nodules.

Biological basis:

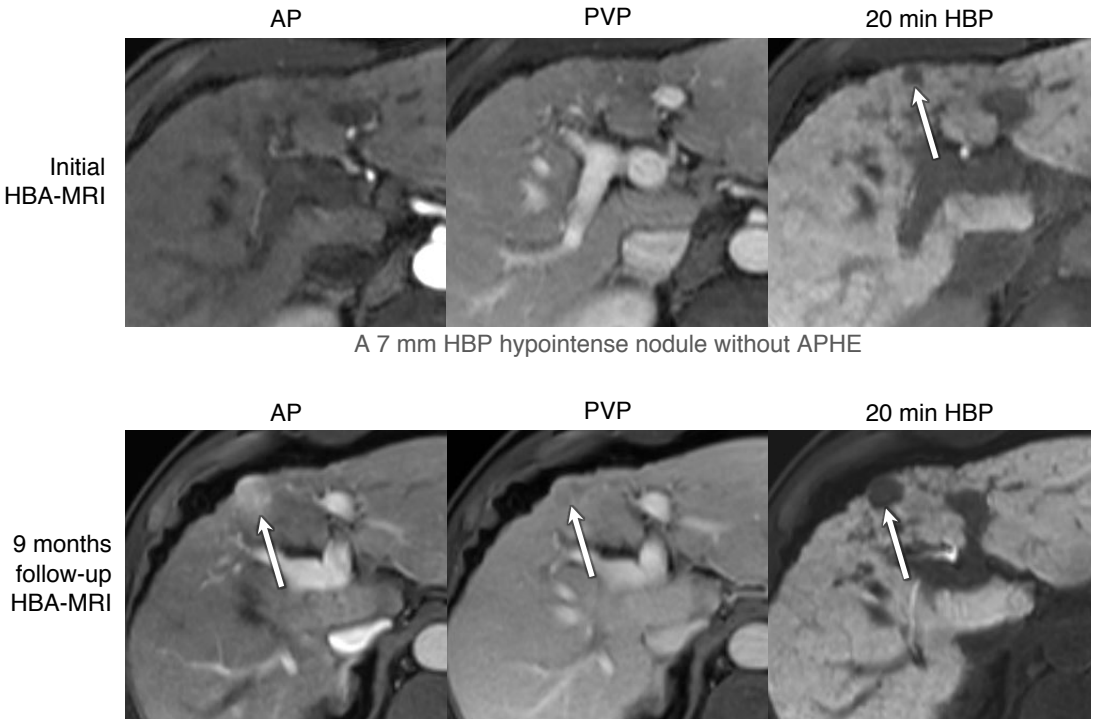
- Neoarterialization becomes complete relatively late in hepatocarcinogenesis, as a nodule transforms from early HCC to progressed HCC.
- OATP expression begins to decline early in hepatocarcinogenesis, sometimes as early as a low-grade dysplastic nodule stage.
- As a result of decreased OATP expression and incomplete neoarterialization, LGDN, HGDN and early HCCs may appear as HBP hypointense nodules without APHE.

HBP hypointense nodule without APHE



HBP Hypointense Nodule without APHE

Example: HBP hypointense nodule without APHE progression to HCC



HBP hypointense nodules without APHE are at high risk of becoming HCC:

- Meta-analysis of HBP-hypointense nodules without APHE reported pooled cumulative incidence hypervascularization rates of 18% at 1 year, 25% at 2 years, and 30% at 3 years.
- Of progressed HCCs, 29-44% were visible as HBP hypointense nodules without APHE on prior imaging.
- 3- and 5-year recurrence-free survival rates improve if HBP-hypointense nodules without APHE are treated at time of HCC resection.

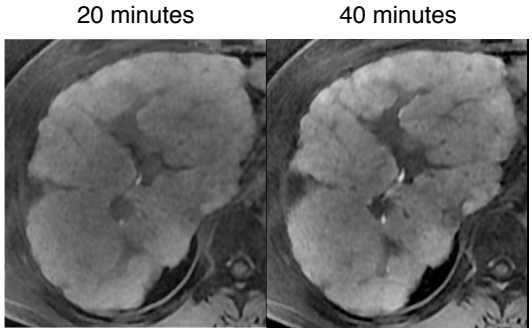
HBP hypointense nodules without APHE are markers of increased risk of HCC development elsewhere in liver:

- Cumulative 3-year rate of HCC development anywhere in liver (not progression of nodule) may be as high as 22%, compared to 6% in patients with no nodules.
- Recurrence rates elsewhere in liver following RFA may be higher in patients with HBP hypointense nodules without APHE compared with patients who lack such nodules.

Technical Tips

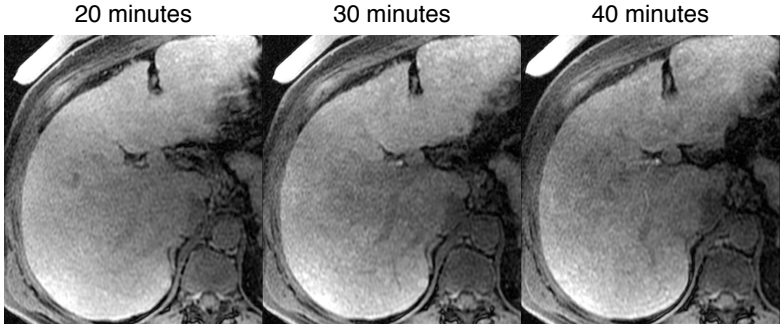
Technical tips

- In cirrhosis with severe hepatic dysfunction, increasing delay for HBP imaging to 30 minutes or more for gadoxetate *may* improve parenchymal enhancement and clearance from vasculature.



HBP quality is better at 40 minutes than 20 minutes

- However, LI-RADS does not recommend routine delay of HBP timing to 30-40 minutes in cirrhosis.
- Delaying the acquisition does not consistently achieve adequate HBP imaging quality.



Increasing the delay from 20 to 30 to 40 minutes results in minimal improvement in image quality. HBP remains inadequate at 40 minutes

- If there is reduced parenchymal signal due to iron overload consider using minimum possible echo time.
- If there is reduced parenchymal signal due to steatosis consider using an in-phase echo time and avoiding fat suppression.
- Consider multiple AP acquisition, dilution of gadoxetate bolus with normal saline, and reduction in injection rate from 2 to 1 ml/second to decrease the incidence of transient motion artifact.
- When AP is nondiagnostic, repeat examination (CT or ECA-MRI) may demonstrate APHE.
- Consider ECA-MRI if gadoxetate-MRI is equivocal for “washout”.

Frequently Asked Questions

When does portal venous phase end and transitional begin?

The progression from the PVP to the TP is gradual, without a defined demarcation point, and depends on various patient-related factors. In general, the transitional phase is a time range in which the blood vessels are approximately isointense to liver. In most patients with preserved liver function, the TP occurs about 2-5 min after injection of gadoxetate although it may be delayed and prolonged in patients with hepatic dysfunction.

Is there a TP with gadobenate dimeglumine (Multihance)?

A prolonged TP does occur with gadobenate dimeglumine, as the contrast agent slowly transitions between being mainly extracellular and mainly hepatocellular. However, uptake of gadobenate by hepatocytes is low and slow, the timing of the TP with gadobenate is variable, and imaging during the TP is not routinely performed with this agent.

How do I gauge if liver enhancement is adequate during the hepatobiliary phase (HBP)?

Liver enhancement during the HBP is adequate if the parenchyma is unequivocally hyperintense relative to hepatic blood vessels. It is suboptimal otherwise. The mechanism for suboptimal HBP enhancement is not well understood but probably reflects reduced number of functional hepatocytes, reduced function of cellular transporters, or competition for transporters. Pitfall: enhancement of the bile ducts does not indicate adequate liver enhancement. See *page 13-11*.

If HBP is suboptimal, should I delay the acquisition or increase the flip angle?

Delaying the HBP acquisition may improve image quality in cirrhotic livers with diminished function, but has unknown impact on diagnostic accuracy. Increasing the flip angle improves lesion-to-liver contrast-to-noise ratio for metastases in normal livers, but has not been studied in the setting of cirrhosis and diminished function.

If liver enhancement during the HBP is suboptimal, how do I characterize observations that are hypointense, isointense, or hyperintense relative to liver?

If an observation is hypointense in the hepatobiliary phase, it may be characterized as such despite suboptimal hepatobiliary phase parenchymal enhancement. However, if an observation is isointense or hyperintense, characterization of hepatobiliary phase intensity may be unreliable.

Frequently Asked Questions

Why is assessment of "washout" restricted to the PVP with gadoxetate disodium?

In retrospective studies, the combination of APHE + PVP "washout" had higher specificity for HCC (98-100%) than the combination of APHE and TP hypointensity (86-95%). Thus, restricting the definition of "washout" to the portal venous phase provides the needed high specificity of LR-5 for HCC, while relaxing the definition of "washout" to include the TP would reduce the specificity.

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