Cirrhosis: The Double-Edged Sword for CT and MRI Diagnosis of HCC

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What is Cirrhosis?

- Cirrhosis is the end-stage of chronic liver disease resulting from repetitive liver injury and cumulative liver damage.
- Cirrhosis is characterized by the complete replacement of normal parenchyma by innumerable regenerative nodules surrounded by fibrotic scars.

Cirrhosis: Innumerable parenchymal regenerative nodules surrounded by fibrotic scars. In this case, iron-rich (siderotic) nodules appear dark on the photograph of the explanted liver and hypointense on the ex-vivo T2w MR image. Most of the nodules do not contain excess iron and are barely perceptible on the explant specimen photograph or ex-vivo MR image.
Why is Cirrhosis Clinically Important?

DEATH

Depending on stage and treatment, up to 90% per year for advanced HCC

1% per year

HCC

1-10% per year

Compensated Cirrhosis

Stage 1
- No ascites
- No esophageal varices

10% per year

Stage 2
- No ascites
- Esophageal varices, no bleeding

1% per year

Stage 3
- Ascites
- ± Esophageal varices, no bleeding

3% per year

Stage 4
- GI bleeding
- ± Ascites

20% per year

60% per year

DEATH

Why is Cirrhosis Relevant to HCC Imaging?

- Cirrhosis increases the risk of HCC above 1.5% per year to justify surveillance of HCC.
- The pre-test probability of HCC is sufficiently high to justify imaging-based diagnosis of HCC:
  - Pre-test probability of HCC is high & pre-test probability of other lesions mimicking HCC is low → stringent imaging criteria approach 100% positive predictive value for HCC.
  - This enables diagnosis of HCC based on imaging alone, without biopsy.

<table>
<thead>
<tr>
<th>TEST OUTCOME</th>
<th>TRUE CONDITION</th>
<th>In cirrhosis, this number is high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (e.g., imaging indicates HCC)</td>
<td>Positive (e.g., the observation is an HCC)</td>
<td>True Positive</td>
</tr>
<tr>
<td>Negative (e.g., imaging indicates absence of HCC)</td>
<td>Negative (e.g., the observation is NOT an HCC)</td>
<td>False Positive (Type I error)</td>
</tr>
<tr>
<td>↓</td>
<td>False Negative (type II error)</td>
<td>True Negative</td>
</tr>
<tr>
<td>↓</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
</tr>
</tbody>
</table>

For LR-5 criteria, this number is ~100%
As the result of high prevalence and high specificity, this number is ~100%

→ Positive predictive value
→ Negative predictive value
Why is Cirrhosis Relevant to HCC Imaging?

- Cirrhosis-associated abnormalities may reduce diagnostic accuracy:
  - Observations leading to reduced sensitivity: parenchymal heterogeneity, background nodules. These obscure small HCCs.
  - Observations leading to reduced specificity: vascular pseudolesions, non-tumoral lesions. These mimic HCC.

\[
\begin{array}{c|c|c|c|c}
\text{Disease +} & \text{Disease -} \\
\hline
\text{Test +} & TP & FP \\
\text{Test -} & FN & TN \\
\end{array}
\]

\[
\text{Sensitivity} = \frac{TP}{(TP+FN)}
\]

\[
\begin{array}{c|c|c|c|c}
\text{Disease +} & \text{Disease -} \\
\hline
\text{Test +} & TP & FP \\
\text{Test -} & FN & TN \\
\end{array}
\]

\[
\text{Specificity} = \frac{TN}{(TN+FP)}
\]

TP: true positive  
FP: false positive  
TN: true negative  
FN: false negative
Cirrhosis-Associated Abnormalities: Decreased Sensitivity

Pre Arterial phase (AP) Portal venous phase (PVP)

Gadoxetate disodium hepatobiliary agent (HBA)-MRI: Cirrhosis with siderotic nodules (arrows) may distract readers from detecting an observation.

CT 4 weeks later: Siderotic nodules are not depicted; 12 mm observation, with AP hyperehancement (long arrow), PVP “washout” (short arrow) and “capsule” (arrowhead) is categorized as LR-5 (Definite HCC).
In retrospect, the LR-5 observation was present on MRI but was obscured by the presence of the multiple siderotic nodules.

CT 4 weeks later: Siderotic nodules are not depicted; 12 mm observation, with AP hyperenhancement (long arrow), PVP “washout” (short arrow) and “capsule” (arrowhead) is categorized as LR-5 (Definite HCC).
Cirrhosis-Associated Abnormalities: Decreased Specificity

Parenchymal heterogeneity on the AP may mimic multifocal HCC, potentially causing harmful diagnostic error. Clue to correct diagnosis: the “masses” fade to isoattenuation in PVP without “washout”.

Mild parenchymal heterogeneity on the AP remains, confirming heterogeneous enhancement due to benign perfusion alterations rather than multifocal cancer.

Comparison – Multifocal HCC: Multiple masses with AP hyperenhancement and PVP “washout”. The presence of “washout” clinches the diagnosis of multifocal HCC.
Why is Cirrhosis Relevant to HCC Imaging?

- Liver parenchymal dysfunction can result in inadequate hepatobiliary contrast agent uptake.
- Third spacing can dilute intravascular contrast material and reduce the magnitude of vascular, parenchymal, and tumor enhancement → compromised quality of enhanced images.
- Hemodynamic vascular alterations can delay the arrival of contrast material to the liver → AP mistiming.
- Ascites can contribute to the presence of severe artifact on MRI, obscuring observations in or outside the liver.
- Encephalopathy and other co-morbidities can decrease patient compliance with breath holding.

Large volume ascites resulting in central dark signal, a common artifact related to dielectric effect and RF attenuation.
What Morphologic Manifestations Arise in Cirrhosis?

- Left lateral segment hypertrophy
- Caudate lobe hypertrophy
- Prominent fissures
- Expanded gallbladder fossa
- Right posterior hepatic notch
- Expanded perihilar space
- Nodular contour
- Anterolateral flattening
- Surface retraction
- Atrophy of segments 5, 6, 4A, 4B

* Of note, early cirrhosis may have a normal appearance on US, CT or MRI
Morphological Alterations of Cirrhosis

- **Morphologic change:** Regenerative nodules immediately under liver capsule

- **Imaging manifestation:** Surface nodularity
  - High specificity for cirrhosis in select clinical setting (supporting risk factors)
    - Specificity is not 100% as some non-cirrhotic conditions may manifest surface nodularity
  - Provides low sensitivity for early cirrhosis, when liver surface may be smooth
Morphological Alterations of Cirrhosis

- **Morphologic change**: Global atrophy
- **Imaging manifestation**:
  - Small liver volume
  - Generalized hepatic contraction with expansion of following spaces
    - Space between liver and anterior abdominal wall
    - Perihilar, gallbladder fossa, and fissures for ligamentum teres and venosum
Morphological Alterations of Cirrhosis

- **Morphologic change**: Segmental volume redistribution
- **Imaging manifestation**:  
  - Relative or absolute hypertrophy of caudate and/or lateral left lobe  
  - Atrophy of anterior right lobe and/or medial left lobe  
  - Surface nodularity  
  - Anterolateral flattening  
  - Increased caudate-right lobe ratio
Morphological Alterations of Cirrhosis

- **Morphologic change**: Regional or focal parenchymal contraction
- **Imaging manifestation**:
  - Liver surface retraction associated with areas of confluent fibrosis
  - Notching of posterior right lobe, medially

Liver surface retraction

Notching of the posterior right lobe
Parenchymal Alterations of Cirrhosis

- **Parenchymal alteration**: Parenchymal nodules
- **Imaging manifestation**:
  - Parenchymal nodules may or may not be visible
  - If visible, these vary widely in size and other imaging features
  - MRI is more sensitive for depiction of discrete parenchymal nodules compared with CT and US

US, CT and MRI in a 65-year-old man with hepatitis C cirrhosis

Discrete parenchymal nodules are not discerned on US or CT
Numerous parenchymal nodules of variable size and signal on both T1w and T2w
Parenchymal Alterations of Cirrhosis

- **Parenchymal alteration**: Fibrotic scars
- **Imaging manifestation:**
  - May be visible as a diffuse lace-like thin bands
  - Precontrast imaging:
    - CT: Mildly hypoattenuating
    - MR: Hypointense on T1w images, hyperintense on T2w and low-b-value DW images
  - Postcontrast imaging:
    - Enhance progressively, hyperintense in the portal venous and delayed phases
    - Tend to be hypointense on hepatobiliary phase (see images two slides later)
  - Usually imperceptible on US, may manifest as parenchymal heterogeneity
Parenchymal Alterations of Cirrhosis

• **Parenchymal alteration:** Parenchymal nodules and bands of fibrosis

• **Imaging manifestation:**
  – Nonspecific parenchymal heterogeneity
    • If the above parenchymal alterations are beneath the size threshold of imaging, the parenchyma may appear mottled or coarse without distinct internal nodularity or scarring.

Heterogeneous and mottled parenchyma on various sequences
Parenchymal Alterations of Cirrhosis

- **Parenchymal alteration**: Confluent hepatic fibrosis
  - Broad, mass-like areas of scar tissue
- **Imaging manifestation**:
  - Characteristically wedge-shaped with concave borders, radiate from hilum to liver periphery, retract liver surface
  - Similar intensity and enhancement characteristics as fibrotic scars.
  - May resemble intrahepatic cholangiocarcinoma (iCCA), a typically fibrotic tumor that similarly may be retractile and show progressive dynamic-phase enhancement.
  - Key difference: confluent fibrosis lacks densely cellular and vascularized rim, and so, does not have targetoid appearance typical of iCCA

Wedge-shape area extending from hilum to the periphery; signal and enhancement typical of fibrosis
Parenchymal Alterations of Cirrhosis

- Parenchymal alteration: Fat
- Imaging manifestation:
  - Fatty liver (steatosis) can be diffuse, regional, or focal.
    - Frequently occurs in NASH, alcoholic liver disease, hepatitis due to certain genotypes of HCV
  - Fat regresses as cirrhosis progresses and hepatocellular function worsens.
    - The heavily scarred, end-stage liver is often devoid of fat

Diffuse, marked loss of signal in the liver parenchyma on the opposed-phase compared with in-phase sequence confirms steatosis

Due to the substantial steatosis in this case, the cirrhosis is likely early

Trichrome stain of liver biopsy specimen showing fat deposition (clear vacuoles) and fibrosis (stains blue) in early cirrhosis.

Case courtesy of Dr. M.I. Minervini of UPMC
Parenchymal Alterations of Cirrhosis

- **Parenchymal alteration**: Iron
- **Imaging manifestation**:
  - Iron overload (siderosis) can be diffuse, regional, or focal.
    - Cirrhosis due to hereditary hemochromatosis is almost always associated with iron overload. In this case, the iron comes first, the liver disease follows.
    - Cirrhosis due to other chronic liver disease (e.g., HBV, HCV, alcohol-induced liver disease, NASH) may be associated with iron overload. In these conditions, the liver disease comes first, the iron follows.

Diffuse loss of signal in the liver parenchyma on the longer echo GRE sequence compared with shorter echo sequence confirms iron deposition. Contrast to prior slide where signal loss on OP indicated the presence of fat.

The presence of iron may worsen the patient’s prognosis, as it is associated with more rapid progression to end stage liver.
Vascular Alterations of Cirrhosis

• Hepatic artery:
  • Enlargement
  • Tortuosity (corkscrew appearance)

• Portal vein and/or portal vein branch
  • Dilation (≥ 15 mm in diameter for main portal vein)
  • Caliber reduction with long-standing reduction in portal flow
  • Chronic thrombosis; slow, biphasic or reversal of flow (Doppler)
  • Cavernous transformation with occlusion or near occlusion

Axial AP
Coronal MPR PVP
Coronal MPR PVP
Coronal MPR PVP

Tortuous intrahepatic arteries (corkscrew appearance)
Dilated main portal vein (2.1 cm in diameter)
Attenuated main portal vein (0.5 cm in diameter) due to long-standing flow reduction
Multiple tortuous collaterals in the expected location of the main portal vein (chronic PV thrombosis with cavernous transformation)
Vascular Alterations of Cirrhosis

- Portal-systemic collaterals
  - esophageal
  - paraesophageal
  - left gastric
  - retrogastric
  - gastrorenal
  - perisplenic
  - splenorenal
  - paraumbilical
  - caput medusae
  - paravertebral (retroperitoneal)
  - hemorrhoidal

Recanalized paraumbilical vein
Left gastric varices
Splenorenal shunt
Esophageal (long arrow) and paraesophageal (short arrows) varices
Biliary Alterations of Cirrhosis

- **Peribiliary cysts**
  - Cystic dilatation of obstructed periductal glands
  - Tubular structures parallel the large intra- and extrahepatic bile ducts and are located on both sides of the intrahepatic portal vein branches
  - Markedly hyperintense on T2w images with imperceptible, non-enhancing walls
  - These have no clinical relevance except they may cause diagnostic confusion

- **Portal biliopathy**
  - Large collateral vessels from cavernous transformation of the portal vein obstruct the bile ducts, resulting in upstream biliary dilatation.

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**Peribiliary cysts:** Tiny cystic structures along paralleling intrahepatic bile ducts

**Portal biliopathy:** Cavernous transformation of the portal vein (arrowheads) with resultant mild compression of the common bile duct (long arrow) and upstream biliary dilatation (short arrow).
# Cirrhosis-Associated Hepatocellular Nodules

<table>
<thead>
<tr>
<th>Size</th>
<th>Biology</th>
<th>Histology</th>
<th>Gross Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regenerative nodule</strong></td>
<td>Usually &lt; 1 cm</td>
<td>“Benign” *</td>
<td>Identical to background liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No cytologic atypia or architectural changes</td>
<td></td>
</tr>
</tbody>
</table>

*Although they are considered “benign”, regenerative nodules (RN) and low-grade dysplastic nodules (LGDN) may contain molecularly aberrant, neoplastic cells. Despite the molecular aberrations, the cells may be normal phenotypically, undetectable by imaging or routine histology.*
Cirrhosis-Associated Hepatocellular Nodules

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<tr>
<td>Low grade dysplastic nodule</td>
<td>Usually &lt; 1 cm</td>
<td>“Benign”*</td>
<td>Distinctive in color, texture, or degree of bulging</td>
</tr>
<tr>
<td></td>
<td>“Benign”*</td>
<td>No cytologic atypia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild architectural changes ± clonal features</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>± steatosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>± siderosis</td>
<td></td>
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* Although they are considered “benign”, RNs and LGDNs may contain molecularly aberrant, neoplastic cells. Despite the molecular aberrations, the cells may be normal phenotypically, undetectable by imaging or routine histology.

Low-grade dysplastic nodule

The same LGDN on CT: 0.9 cm nodule with no AP hyperenhancement and PV “washout” (LI-RADS 3)

Case courtesy of Dr. M.I. Minervini of UPMC
### Cirrhosis-Associated Hepatocellular Nodules

<table>
<thead>
<tr>
<th>High grade dysplastic nodule</th>
<th>Size</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usually &lt; 1.5 cm</td>
<td>Premalignant</td>
<td>Cellular atypia, moderate architectural changes, clonal features ± steatosis ± siderosis</td>
<td>Distinctive in color, texture, or degree of bulging</td>
</tr>
</tbody>
</table>

- High grade dysplastic nodule: dysplastic hepatocytes with ground glass inclusions typical of HBV infection
- US-guided biopsy specimen
- Histology: 20x magnified micrograph
- HBA-MRI with gadoxetate of the same nodule: 2 cm nodule without AP hyperehancement or “washout”, and with HBP hypointensity (LI-RADS 3)

* Although they are considered “benign”, RNs and LGDNs may contain molecularly aberrant, neoplastic cells. Despite the molecular aberrations, the cells may be normal phenotypically, undetectable by imaging or routine histology.
# Cirrhosis-Associated Hepatocellular Nodules

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<th>Size</th>
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<th>Histology</th>
<th>Gross Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early HCC</td>
<td>Usually &lt; 1.5 cm</td>
<td>Well-differentiated malignant cells</td>
<td>Vaguely nodular</td>
</tr>
<tr>
<td></td>
<td>Microinvasive cancer, analogous to “carcinoma-in-situ”</td>
<td>“Stromal invasion”</td>
<td>Indistinct margins</td>
</tr>
<tr>
<td></td>
<td>No vascular invasion</td>
<td>Often steatotic</td>
<td>No capsule</td>
</tr>
<tr>
<td></td>
<td>Rare metastases</td>
<td>Iron resistant</td>
<td></td>
</tr>
</tbody>
</table>

**Gross Pathology**

Early HCC

The same early HCC on MRI: 2 cm lesion with no AP hyperenhancement, with PVP “washout”, no “capsule” and with HBP hypointensity (LI-RADS 4)

*Case courtesy of Jeong Min Lee, MD – Seoul National University Hospital*
## Cirrhosis-Associated Hepatocellular Nodules

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<th>Biology</th>
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<tbody>
<tr>
<td>Small progressed HCC</td>
<td>Malignant ± vascular invasion ± metastases</td>
<td>Moderately differentiated malignant cells Rarely steatotic Iron resistant</td>
<td>Distinctly nodular Well-defined margins Capsule frequent</td>
</tr>
<tr>
<td>≥ 2 cm</td>
<td>More aggressive Often vascular invasion Frequent metastases</td>
<td>Moderately to poorly differentiated Rarely steatotic Iron resistant</td>
<td>Distinctly nodular, Well defined margins Capsule frequent May become permeative (“infiltrative”)</td>
</tr>
</tbody>
</table>

**Gross Pathology**
- **AP**
- **PVP**

**Progressed HCC**
- The same progressed HCC on CT: 3.5 cm lesion with AP hyperenhancement, PVP “washout” and no “capsule” (LI-RADS 5)
Cirrhosis: Summary

- Cirrhosis is the end stage of chronic liver disease.
- Cirrhosis is characterized by innumerable regenerative nodules surrounded by fibrotic scars, alterations in the hepatic microcirculation, and variable loss of hepatocellular function.
- Cirrhosis is the primary risk factor for developing HCC. Because cirrhosis substantially increases the risk of HCC, it allows the use of imaging to noninvasively diagnose HCC if stringent criteria are used.
- The cirrhotic liver may have a normal imaging appearance at US, CT, and MRI.
- Certain morphological, parenchymal, vascular, biliary, and extrahepatic alterations of cirrhosis may be visible at imaging. Their recognition is important so that the radiologist is alerted to the possibility of cirrhosis.
- Cirrhosis-associated abnormalities in and outside the liver may reduce diagnostic accuracy by affecting image quality and altering typical appearance of non-hepatocellular benign lesions.
- Various benign and premalignant hepatocellular lesions associated with cirrhosis may obscure true HCCs (lower sensitivity) or be mistaken for HCCs (lower specificity).
Thank You!

References


