Hepatocellular Carcinoma (HCC): Using Imaging and LI-RADS to Choose Optimal Therapy

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Hepatocellular Carcinoma

- HCC comprises 90% of the primary liver malignancies worldwide\textsuperscript{1}, and is the second leading cause of cancer death in the world\textsuperscript{2}.

- The most important risk factor is liver cirrhosis; up to 20% of cases occur in non-cirrhotic patients\textsuperscript{1}.

- The annual incidence is 2-8% in cirrhotic livers and < 0.5% in non-cirrhotic livers\textsuperscript{2}.

- Surveillance for HCC is beneficial in patients with certain risk factors\textsuperscript{3}.

- Its natural history falls within a continuum shown below\textsuperscript{4}.

The authors do not have any conflict of interest to declare.
In how many of the following patient groups is HCC surveillance recommended? (click for answer)

- Hepatitis C (HCV) cirrhosis
- Hepatitis B (HBV) cirrhosis
- Genetic hemochromatosis and cirrhosis
- Stage 4 primary biliary cirrhosis
- α1-antitrypsin deficiency and cirrhosis

All of these groups would benefit from surveillance!

In addition, the following HBV carriers without cirrhosis would also benefit:
- Asian males >40 years
- Asian females > 50 years
- Africans >20 years
- Family history of HCC

Note: the benefits of surveillance are uncertain in
- HBV carriers younger than 40 (males) or 50 years of age (females)
- Hepatitis C and stage 3 fibrosis
- Non-cirrhotic NAFLD
Key Facts in Imaging Assessment of HCC

- Value of imaging in HCC is paramount, as it can make the diagnosis without a biopsy\(^5\).
- Appearance of HCC varies depending on tumor histology.
- Dynamic contrast imaging shows shift to arterial supply in the tumor as well as cellular dysplasia\(^6\).
- Ancillary imaging features support a diagnosis of HCC; more features increase confidence in the diagnosis\(^6\).
- This is the basis of the LI-RADS classification which is designed to assess hepatic lesions in patients at risk of HCC.
LI-RADS

Liver Imaging-Reporting and Data System (LI-RADS) provides a standardized lexicon and algorithm of HCC diagnosis using CT and MR imaging.

Summary of the LI-RADS algorithm adapted from http://nrdr.acr.org/ liirads/
## LI-RADS Examples

<table>
<thead>
<tr>
<th>LI-RADS Category</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>Typical hemangioma</td>
<td>A. T2WI. B,C,D LAVA multiphase MRI.</td>
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<tr>
<td>LR-2</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>Atypical cyst (hydatid cyst)</td>
<td>A. simple, B. arterial, C. portal, D. venous CT.</td>
<td></td>
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<tr>
<td>LR-3</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>Intermediate probability of being HCC</td>
<td>Mass &lt; 20 mm with arterial hyperenhancement, no wash out, no capsule, stable for 2 years. A. simple, B. arterial, C. venous, D. venous 2 years after MRI.</td>
<td></td>
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<tr>
<td>LR-4</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
</tr>
<tr>
<td>Probably HCC</td>
<td>Mass &gt; 20 mm with arterial phase hyperenhancement and no additional major features. A. simple, B. arterial, C. portal, D. venous CT.</td>
<td></td>
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<tr>
<td>LR-5</td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
</tr>
<tr>
<td>Definitely HCC</td>
<td>40 mm mass with arterial phase hyperenhancement (B,C) with capsule and wash out(D). MRI.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Typical LI-RADS examples; adapted from ECR 2014-C1928
Using multi-detector CT (MDCT), what is the specificity of arterial hyperenhancement and venous phase washout in cirrhotic livers for HCC?

- 60-70%
- 70-80%
- 80-90%
- >90%

These two features, when occurring together, are very specific for HCC. They form its typical enhancement pattern.

The third typical feature is capsule appearance, which is seen in more advanced HCC’s.
The typical HCC appearance is seen here in a patient with HCV and alcoholic cirrhosis.

This patient also had a thrombus in the portal vein, which was best seen on the coronal image.
Ancillary Features Suggestive of Malignancy

HCC tumors do not always show the typical appearance. In those circumstances, ancillary features are used to support the diagnosis. Note that LR5 cannot be achieved with ancillary features.

**Features specific for HCC:**
- Distinctive rim (different from late capsule)
- Corona enhancement
- Mosaic architecture
- Nodule-in-nodule architecture
- Intra-lesional fat

**Features suggesting malignancy:**
- Hepatobiliary phase hypo-intensity
- Mild-moderate T2 hyper-intensity
- Restricted diffusion
- Lesional iron or fat sparing
- Blood products
- Diameter increase less than threshold growth

Adapted from http://nrdr.acr.org/lirads/
### Imaging Characteristics

As the number of features suggestive of HCC increases, the diagnosis can be made with certainty. Below are the sensitivity and specificity numbers for typical features on MR².

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hyperenhancement (lesion &gt;20 mm)</td>
<td>82-93%</td>
<td>64-67%</td>
</tr>
<tr>
<td>Arterial hyperenhancement (lesion &lt;20 mm)</td>
<td>31-69%</td>
<td>64-67%</td>
</tr>
<tr>
<td>Venous phase washout (lesion &gt;20 mm)</td>
<td>53%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Venous phase washout (lesion &lt;20 mm)</td>
<td>53%</td>
<td>62-100%</td>
</tr>
<tr>
<td>Arterial hyperenhancement with washout</td>
<td>-</td>
<td>96%</td>
</tr>
<tr>
<td>Diffusion restriction (lesion &lt;20 mm)</td>
<td>57-94%</td>
<td>87%-88%</td>
</tr>
<tr>
<td>Capsule enhancement</td>
<td>43-55%</td>
<td>83-96%</td>
</tr>
<tr>
<td>T1W hypointensity</td>
<td>21-91%</td>
<td>70-100%</td>
</tr>
<tr>
<td>T2W moderate hyperintensity</td>
<td>21-75%</td>
<td>73-100%</td>
</tr>
<tr>
<td>Fat content (micro- or macroscopic)</td>
<td>12-37%</td>
<td>68-100%</td>
</tr>
</tbody>
</table>

[Highlight: most sensitive/ specific]
Typical Appearance on MR Imaging

- T2W hyperintense
- arterial enhancement
- venous washout with capsule
Atypical Enhancement Pattern

- Up to 40% of HCC’s lack obvious arterial phase hyperenhancement $^{6,8,9}$. These cannot be characterized as definite HCC’s (LI-RADS 5) and consist mostly of:
  - Early/ well-differentiated HCC without development of unpaired arteries$^{10}$.
  - Poorly differentiated infiltrative HCC’s$^{11}$.
  - Small HCC’s < 2cm$^{12}$.
  - Large HCC > 5 cm with decreased arterial flow due to build-up of intra-tumor pressure$^4$.

- Portal venous thrombosis (PVT) increases the likelihood of atypical appearance$^{15}$. 
Atypical Large HCC with PVT

Large HCC with virtually no enhancement in the arterial phase. There is extensive PVT.
MR: HCC with PVT

a) T1W fat suppressed: invisible
b) T2W: slightly bright
c) DWI: restricted diffusion and tumor PVT
d) Arterial: infiltrating HCC, segment 7/8, with enhancing and non-enhancing regions
e) Late arterial showing extensive PVT
Large HCC with Hemorrhage Necrosis

- a. T1W: hemorrhage
- b. T2W: mosaic pattern
- c. T2W fat sat: hemosiderin deposit
- d. Post contrast T1: typical capsule and septal enhancement
- e. DWI: susceptibility artifact from hemorrhagic necrosis
What is the sensitivity and specificity of hepatobiliary imaging combined with contrast-enhanced MR (CEMR) in the diagnosis of HCC?

- Sensitivity: ~75%  Specificity: 95%
- Sensitivity: ~80%  Specificity: 95%
- Sensitivity: ~85%  Specificity: 95%
- Sensitivity: ~90%  Specificity: 95%

- HBP + CEMR is the best detection method for HCC.
  - Gadoxetic acid (a hepatobiliary agent) has a combined sensitivity of 91% and specificity of 95% for cirrhotic and non-cirrhotic livers, even for tumors ≤20 mm in size.\(^{16}\)

- MDCT has limited sensitivity (40-78%) but good specificity (93%-99%) for HCC.\(^{2,7}\)
- CEMR imaging is similar accuracy to CT (sensitivity: 14%-82%, specificity: 96-100%).\(^{2}\)
Hepatobiliary Phase (HBP) Imaging

- As HCC tumors progress, they gain a characteristic hypointense appearance on HBP\textsuperscript{14,17}.
- This is due to decreased expression of organic anion-transporting polypeptide (OATP) in HCC compared to liver parenchyma.
  - Decreases uptake of HBP intracellular contrast agents.
- Considered an ancillary feature in LI-RADS. Other lesions with similar hypointense appearance in HBP\textsuperscript{17}:
  - Hemangioma: typically show marked hyperintensity on T2W.
  - Cholangiocarcinoma: similar in appearance to HCC, but features suggestive of this include target appearance, ductal dilation and lobulated shape.
  - Dysplastic nodules: do not usually show arterial phase enhancement.
HBP and DWI in Prognostication of HCC

• HBP: OATP expression
  * Sometimes, HCC shows HBP hyperintensity. This has a better prognosis\textsuperscript{14,18}.
  * Mutation in a signaling pathway leads to overexpression of OATPB13.
  * It is associated with higher histological differentiation and more favorable prognosis than other HCC’s.

• DWI: VEGF expression
  * Vascular endothelial growth factor (VEGF) promotes angiogenesis, and it’s expression is linked to increased responsiveness to sorafenib\textsuperscript{19}.
  * Level of VEGF expression is inversely correlated with the ADC value on DWI.
Atypical Appearance on MR

Corona sign in early arterial

Capsule on late arterial/ early venous

Isointense on T2W

DWI negative
Small HCC’s: A Challenging Diagnosis

Small HCC lesions can be challenging to diagnose because of their atypical features. They fall into 2 general categories:

- **Early HCC**
  - Well differentiated
  - Often lack arterial enhancement and washout
  - Typically without distinct margins or capsule

- **Small progressed HCC**
  - Moderate-poorly differentiated
  - Only moderately differentiated show arterial enhancement and washout
  - Typically with distinct margins, capsule and fibrous septa

The addition of hepatobiliary agents greatly improves sensitivity and specificity for both.

Size threshold for LI-RADS 5 (definitely HCC) is ≥10 mm, and smaller lesions can be no more than LI-RADS 4.
Small HCC

Arterial enhancement

No washout
What is the annual incidence of HCC in patients with NASH?

- <0.5 %
- 1.1 %
- 1.8 %
- 2.6 %
- 3.3 %

Non-alcoholic fatty liver disease (NAFLD) is on the rise in Western countries, and its end stage variant, non-alcoholic steatohepatitis (NASH) is a risk factor for HCC in patients without cirrhosis.

The incidence of HCC in patients with NASH is 2.6%. [for comparison, 4% in HCV cirrhosis]^{21}. 
HCC in Non-Cirrhotic Livers

- HCC presents at a later stage in non-cirrhotic patients who are not screened\textsuperscript{23}.
  - 25\% present with extra-hepatic metastases.

- HCC’s in non-cirrhotic livers tend to be larger, well-circumscribed, unifocal and with capsules or small satellite lesions\textsuperscript{24}.

- Similar percentage of atypical appearance of HCC between cirrhotic and non-cirrhotic patients\textsuperscript{24}.

- In non-cirrhotic livers, presence of central scar and radiating septa are associated with HCC\textsuperscript{13,25}. 
Differential for Arterial Enhancing Focal Liver Lesion in the Non-Cirrhotic Liver

- **Focal nodular hyperplasia (FNH):** strongly enhancing in arterial phase fading to isoenhancing in portal-venous phase. It can contain stellate central scar and is hard to differentiate from HCCs.
  - FNH: hyper- or isointense on HBP.
  - HCC: hypointense on HBP.

- **Hepatocellular adenoma (HA):** (very rare) weakly enhancing in arterial phase and isoenhancing in portal-venous and delayed phase. Hypointense in HBP.
  - HA: no washout.
  - HCC: washout more common.

- **Hemangioma:** homogenous enhancement during arterial phase and during portal venous phase.
  - Hemangioma: enhancement as bright as aorta and portal veins.
  - HCC: milder arterial enhancement. Venous washout.
Summary

• HCC can be diagnosed on imaging without biopsy.

• Arterial hyper-enhancement and subsequent washout are specific but not sensitive for HCC.

• HCC could have atypical appearance.

• Ancillary imaging findings improve the diagnostic yield of imaging in HCC.

• HBP imaging with intracellular contrast agents improve sensitivity of CEMR in diagnosing HCCs with atypical enhancement patterns, such as small HCCs.

• Imaging features can correlate with underlying genomic changes that affect prognosis and response to treatment.

References for this presentation are available in printed format on request.