Images of liver tumors: imaging diagnosis of HCC

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Contents

• Typical Imaging Features of HCC
• LI-RADS: structured reporting system
• Comparison with other imaging criteria for diagnosis of HCC
HCC

- Most common primary hepatic malignancy
- Hepatocarcinogenesis
  - Multistep pathway
  - De novo pathway

Characteristics of HCC

- Blood supply of hepatic nodule

Typical Features

- Arterial enhancement
  - Portal and/or delay hypo-enhancement (washout)
  - Nearly 100% specificity of HCC in CLD
  - Sensitivity: relatively low
    - CT: 44-53%
    - MRI: 44-62%
Dynamic enhancement

- Arterial/portal venous/equilibrium(delay) phases
- Scan timing
  - Fixed
  - Bolus tracking
  - Test bolus
- Late arterial phase
  - Optimal for arterial hyperenhancement
Liver biopsy

- Risk of needle tract seeding
- Bleeding (0.5%)
  - Especially, underlying LC
- False negative result in small lesions
  - Technical difficulty
- High grade DN containing small HCC foci (about 35% of HGDN)
- Multiple HCCs
Improving sensitivity

- Incorporation of additional features of HCC
  - Tumor capsule
  - Threshold growth
  - Diffusion weighted imaging
  - Hepatobiliary phase MRI using gadoxetic acid or Gd-BOPTA
Capsule

- True tumor capsule: fibrous tissue only
- Pseudocapsule: only imaging appearance

<table>
<thead>
<tr>
<th>MRI findings</th>
<th>No. of nodules</th>
<th>Diagnostic performance, % (95% CI)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TP</td>
<td>FN</td>
<td>FP</td>
<td>TN</td>
</tr>
<tr>
<td>T2 hyperintensity</td>
<td>40</td>
<td>63</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>Intralesional fat</td>
<td>19</td>
<td>84</td>
<td>5</td>
<td>51</td>
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<tr>
<td>Capsule</td>
<td>43</td>
<td>60</td>
<td>2</td>
<td>54</td>
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<tr>
<td>Arterial phase hyperintensity</td>
<td>88</td>
<td>15</td>
<td>20</td>
<td>36</td>
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<tr>
<td>Portal phase hypointensity</td>
<td>51</td>
<td>52</td>
<td>6</td>
<td>50</td>
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<tr>
<td>Delayed phase hypointensity</td>
<td>70</td>
<td>33</td>
<td>7</td>
<td>49</td>
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<tr>
<td>Specific vascular pattern*</td>
<td>60</td>
<td>43</td>
<td>2</td>
<td>54</td>
</tr>
</tbody>
</table>

Threshold growth

- Interval growth of hypervascular nodule
  - Highly predictive feature of HCC
- Median volume doubling time
  - 83.2 days (32.5 to 496.4 days)

Kubota K et al. Dig Dis Sci. 2003;48:581
Jeong YY et al. AJR. 2002;178:1327
Diffusion weighted imaging

• Basically T2 weighted imaging
• B-value (factor): strength of diffusion gradient
Diagnostic value of DWI (1)

• Compared with T2W (mostly clinical Dx.)
  – Improved per-lesion sensitivity
    • 53.9% (T2W) vs. 80.5% (DWI)

• Added DWI to CE-T1W (in explanted liver)
  – >2cm : Sn=96% → 100%
  – 1-2cm : Sn=74% → 76%
  – <1cm : Sn=32% → 38%

Parikh T et al. Radiology 2008;246:812
Park MS et al. Hepatology 2012;56:140
### Sensitivity and Positive Predictive Values for the Detection of 179 HCCs

<table>
<thead>
<tr>
<th>Lesion Group and Imaging Modality</th>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Observer 3</th>
<th>Pooled Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity*</td>
<td>PPV†</td>
<td>Sensitivity*</td>
<td>PPV†</td>
</tr>
<tr>
<td>All lesions (n = 179)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadoxetic acid set</td>
<td>81.0 (145)</td>
<td>98.6 (2)</td>
<td>82.1 (147)</td>
<td>98.7 (2)</td>
</tr>
<tr>
<td>DW imaging set</td>
<td>79.9 (143)</td>
<td>96.6 (5)</td>
<td>77.7 (139)</td>
<td>97.2 (4)</td>
</tr>
<tr>
<td>Combined set</td>
<td>92.7 (166)§</td>
<td>98.2 (3)</td>
<td>91.1 (163)§</td>
<td>98.2 (3)</td>
</tr>
<tr>
<td>Lesions ≤1.0 cm (n = 55)</td>
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<td></td>
<td></td>
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<tr>
<td>Gadoxetic acid set</td>
<td>58.2 (32)</td>
<td>94.1 (2)</td>
<td>61.8 (34)</td>
<td>94.4 (2)</td>
</tr>
<tr>
<td>DW imaging set</td>
<td>63.6 (35)</td>
<td>87.5 (5)</td>
<td>56.4 (31)</td>
<td>88.6 [4]</td>
</tr>
<tr>
<td>Combined set</td>
<td>85.5 (47)§</td>
<td>94.0 (3)</td>
<td>81.8 (45)§</td>
<td>93.8 [3]</td>
</tr>
<tr>
<td>Lesions &gt;1.0 cm (n = 124)</td>
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<tr>
<td>Gadoxetic acid set</td>
<td>91.13 (113)</td>
<td>100 (0)</td>
<td>91.13 (113)</td>
<td>100 [0]</td>
</tr>
<tr>
<td>DW imaging set</td>
<td>87.1 (108)§</td>
<td>100 (0)</td>
<td>87.1 (108)§</td>
<td>100 [0]</td>
</tr>
<tr>
<td>Combined set</td>
<td>96.0 (119)§</td>
<td>100 (0)</td>
<td>95.2 (118)§</td>
<td>100 [0]</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are the number of true-positive lesions.
† Numbers in parentheses are false-positive lesions. PPV = positive predictive value.
‡ Statistically significant difference (P < .001).
§ Values for combined set are significantly higher than those for each set alone (P = .001 or P = .003).
‖ Statistically significant differences among values (P = .003 for observers 1 and 3; P = .006 for observer 2).

Hepatocyte specific CA

Biliary excretion

- Gd-EOB-DTPA (Primovist®)
  - 50% biliary; 50% renal excretion

Renal excretion
OATP and MRP

- Gd-EOB-DTPA
  - Taken up through OATPs
  - Excreted via MRP to bile canaliculi and sinusoidal space
Diagnostic value of HSCA (1)

- Differentiating from pseudo-hypervascular lesions
- Hypointense lesion in explanted liver (No control)
  - 97.5% of HCC
  - 70% of HGDN
  - Hyperintense: 96.9% of LGDN
  - 27.5% of HCC: lack of arterial hyperenhancement

## Diagnostic value of HSCA (2)

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>MR exaimation</th>
<th>Vascular patterns</th>
<th>Hepatobiliary pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All iso or hyper-</td>
<td>Hypo- on delay</td>
</tr>
<tr>
<td>HCC</td>
<td>40</td>
<td>0</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>HGDN</td>
<td>30</td>
<td>10</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>LGDN</td>
<td>32</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*From 34 explanted livers

Diagnostic value of HSCA (3)

- HCC: Hyper-intense on HB phase
  - Correlation with expression of OATP8(1A3) and MRP3
  - Pseudoglandular type

Kitao et al. Radiology 2010;256:817
Kim SH, Jeong WK et al. CMH. 2013;19:92
Consensus statement

• International forum for liver MRI (5th)
  – Lesions without arterial enhancement
    • HB phase (+): high likelihood of HGDN or WD-HCC
    • Considered high-risk lesion
    • In this case, Dx of HCC should be determined by pathology
  – Optimal strategy for HGDN: Not established
    • It is reasonable to monitor patients every 3-6 months
Various features of HCC

- Corona enhancement
- T2 hypersensitivity
- Mosaic architecture
- Intra-lesional fat
- Lesional iron sparing
- Lesional fat sparing

“improving sensitivity”
LI-RADS: STRUCTURED REPORTING SYSTEM
LI-RADS $\leftrightarrow$ BI-RADS

- By American College of Radiology (ACR)
- BI-RADS (breast imaging reporting and data system) from 1992
- Mammography, US, MRI
- BI-RADS category IV: suspicious abnormality
  - Risk of malignancy: 30%
- Internationally used for reporting of breast imaging
- Many reports about validation and interobserver agreement
Structure of LI-RADS

• Hierarchical grading (5 grades)
  – Definitely benign (LR-1)
  – Probably benign (LR-2)
  – “?HCC?” (LR-3 to LR-5)
    • Arterial hypervascularity & nodule diameter
    • Major features: wash-out, capsule, threshold growth
  – Tumor in vein (LR-5V)
  – Other malignancy (LR-M)
Observation in high-risk patient

- Treated observation
- Untreated observation
  - Definitely benign
  - Probably benign
  - Neither definitely nor probably benign

- LR-Treated
- LR-1
- LR-2
- Possible non-HCC malignancy
- LR-M
- Tumor in vein
- LR-5V

Diameter (mm):
- "Washout"
- "Capsule"
- Threshold growth

<table>
<thead>
<tr>
<th>Arterial phase hypo- or iso-enhancement</th>
<th>Arterial phase hyper-enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm):</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td>LR-3</td>
<td>LR-3</td>
</tr>
<tr>
<td>LR-3</td>
<td>LR-3</td>
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<tr>
<td>LR-3</td>
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<td>LR-3</td>
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<td>LR-4</td>
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<td>LR-5</td>
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<td>LR-5</td>
<td>LR-5</td>
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<tr>
<td>LR-5</td>
<td>LR-5</td>
</tr>
</tbody>
</table>

Apply ancillary features and then tie-breaking rules to adjust category.
## Major feature of HCC

<table>
<thead>
<tr>
<th>Dynamic imaging</th>
<th>Arterial: hypo or iso</th>
<th>Arterial: hyper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>&lt;20</td>
<td>≥20</td>
</tr>
<tr>
<td>Wash-out</td>
<td>None</td>
<td>LR-3</td>
</tr>
<tr>
<td>Capsule</td>
<td>One</td>
<td>LR-3</td>
</tr>
<tr>
<td>Threshold growth</td>
<td>≥ Two</td>
<td>LR-4</td>
</tr>
</tbody>
</table>

LI-RADS defines **threshold growth** as 50% or more diameter increase during a ≤ 6-month time interval or as 100% or more diameter increase during a > 6-month time interval.
Ancillary features

Favor HCC
- Mild-moderate T2 High
- DWI (+)
- Corona enhancement
- Mosaic architecture
- Nodule-in-nodule
- Intra-lesional fat
- Lesional iron sparing
- Lesional fat sparing
- Blood product
- Sub-threshold growth

Favor benignity
- Homogeneous marked T2 High
- Homogeneous marked T2 or T2* Low
- Undistorted vessel
- Parallels blood pool enhancement
- Diameter reduction
- Diameter stability (≥2 years)
Characteristics of LI-RADS

- Hypovascular HCC: probable HCC
- Subcentimeter HCC: probable HCC
- MR based: including T2 and DWI
- Hierarchical system
  - Improving sensitivity, but threshold setting is crucial (LR-4 or less)
  - Degrading specificity?
- Treated HCC vs. naïve HCC
Subcentimeter HCC

- Gd-EOB-DTPA MRI
  - Diagnostic performance was still low (Sn: 46%-60%)
  - Specificity and PPV: comparable to over HCC
  - Hypo on HBP improve the performance

Contrast-enhanced US

- Normally Kupffer cell uptake: phagocytosis
- Increasing feasibility of RFA
  - Inconspicuous lesion on fusion imaging (US+CT/MRI)
  - CEUS+fusion imaging: converted to feasible lesion (83.3%)

Min JH, Lim HK, Lee MW et al. CMH 2014;20:61
Other guidelines for HCC

<table>
<thead>
<tr>
<th>Institution</th>
<th>Recent pub</th>
</tr>
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<tbody>
<tr>
<td>KLCSSG (대한간암연구학회)</td>
<td>2009</td>
</tr>
<tr>
<td>APASL (Asia-Pacific)</td>
<td>2010</td>
</tr>
<tr>
<td>JSH (Japanese)</td>
<td>2010</td>
</tr>
<tr>
<td>EASL-EORTC (European)</td>
<td>2012</td>
</tr>
<tr>
<td>AASLD (American)</td>
<td>2010</td>
</tr>
<tr>
<td>OPTN (Organ Procurement and Transplantation Network, USA)</td>
<td>2008</td>
</tr>
</tbody>
</table>

Song DS, Bae SH. CMH 2012;18:258
OPTN/UNOS Liver and Intestinal Organ Transplantation Committee Meeting
APASL & JSH guideline

- Considering hypovascular
- CEUS & SPIO (APASL)/EOB (JSH)
- So complex
## Comparison: HCC Dx guidelines

<table>
<thead>
<tr>
<th>Imaging features</th>
<th>KLCSG</th>
<th>APASL</th>
<th>JSH</th>
<th>EASL-EORTC</th>
<th>AASLD</th>
<th>OPTN</th>
<th>LI-RADS (v. 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10mm + wash-out</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td></td>
<td></td>
<td>HCC</td>
<td>Probable HCC</td>
</tr>
<tr>
<td>10-19mm + wash-out</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>Probable HCC</td>
</tr>
<tr>
<td>10-19mm + wash-out + capsule</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
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<td>≥20mm + wash-out</td>
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<tr>
<td>≥20mm + capsule</td>
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<td>Hypervascular + HB image (+)</td>
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<td>Hypervascular + Kupffer image (+)</td>
<td>HCC</td>
<td>HCC</td>
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</tbody>
</table>
Limitations of guidelines

• Problem of adaptation
  – Different status in various countries
  – Difference of etiology, diagnostic tools (eg. CEUS), frequency of deceased donor LT

• Complexity of diagnostic algorithm
  – Block to application by radiologists
  – Risk of inter-rater variability (experience level)

• Hypovascular HCC: not consensus in international guidelines (eg. EASL-EORTC, AASLD)
  – applied in LI-RADS, JSH, APASL
Summary

- Imaging diagnosis of HCC
  - HIGH SPECIFICITY, BUT LOW SENSITIVITY
- Technical advances of radiology
  - Improving SENSITIVITY OF HCC
- LI-RADS: standard reporting and data system
  - Hierarchical system of HCC diagnosis
  - Improving sensitivity by variable & changeable ancillary features
  - Improving interobserver agreement
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