HCC: diagnosis and response to therapy

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Disclosure

- Research grant: Bayer
HCC – worldwide incidence
Background

- Primary liver cancer: 2nd most common cause of cancer death worldwide
- Fastest growing cause of cancer death in USA (incidence tripled in last two decades), numbers likely to further increase due to obesity epidemic
- USA: 40,710 adults diagnosed with primary liver cancer, with estimated 28,920 deaths in 2017(cancer.net)
HCC

- Risk factors:
  - Cirrhosis of any cause: 80-90%
  - Most common cause of cirrhosis now: HCV
  - Most common cause of cirrhosis by 2030: NASH
  - Other: HBV, EtOH, obesity, diabetes, smoking, male sex

- Annual HCC incidence in patients with cirrhosis
  - 2-8% overall
  - Highest in patients with HCV or multiple risk factors
Role of imaging in HCC

Established:
- Screening
- Diagnosis
- Staging

Not established:
- Prediction of aggressiveness and grade
- Prognostication
- Prediction of gene expression
Imaging modalities

- MDCT widely performed (quadruple phase: pre, AP, PVP, LVP)
- MRI: less available, has advantages:
  - Post-treatment (subtraction)
  - Lack of radiation
  - Liver specific agents
- Need late arterial phase imaging for CT and MRI (bolus tracking/care bolus)
Liver MR Protocol with EC GBCA (all BH except DWI)

- Axial/coronal T2 HASTE
- Axial 2D or 3D T1 in- out-of-phase
- Fat/iron quantification
- Axial DWI (50,400, 800, c1600)
- Axial dynamic 3D GRE T1 pre- post-contrast (2 ART phases, PVP 1 min, EQU 3 min)-Bolus tracking-Autosub
Liver MR Protocol with Gd-EOB-DTPA (Eovist/Primovist)

- Coronal T2 HASTE
- Axial 2D or 3D T1 in- out-of-phase
- Fat/iron quantification
- Axial dynamic 3D GRE T1 pre- post-contrast (2 ART, PVP, EQU)
- Axial T2 HASTE (long TE)
- Axial DWI (50, 400, 800, c1600)
- Hepatobiliary phase 10-20 min
HCC detection: CT vs. EC-MRI

- MRI considered generally superior to CT for lesions 1-2 cm
- Sens. CT: 50%-80%, sens. EC-MRI: 52%-93% depending on size
- Rode (JCAT 2001): Sens. for HCC detection US 46.2%, CT 53.8%, MRI 76.9%
- Burrel (Hepatology 2003): lesion sensitivity MRI > CT (76% vs. 61%), MRI superior to CT for nodules 1-2 cm (84% vs. 47%)
- MRI: optimal technique for HCC staging

HCC detection: EC-MRI vs EOB-MRI

- Advantages of EOB-MRI: additional information, improved confidence, possibility of detecting early HCC, ? Use AP + HBP, use for HCC screening (AMRI)
- Limitations: cost, added table time, lower quality of AP (TSM)
- No clear advantage of EOB over ECCM demonstrated
- Min. Hepatology 2018: compared diagnostic performance of LR-5 using ECCM vs EOB. ECCM had higher sensitivity (77.9% vs. 66.3%) and accuracy (82.1% versus 72.6%) then EOB
Gd-EOB-DTPA for HCC detection (Ahn, Radiology 2010)

- 9/84 HCCs seen only on HBP
- Sensitivity increased, but not statistically significant
- Diagnostic accuracy higher with HBP

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>&lt; 1 cm</th>
<th>1-2 cm</th>
<th>&gt; 2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic MRI</td>
<td>50.0</td>
<td>83.4</td>
<td>97.0</td>
</tr>
<tr>
<td>Dynamic MRI + HBP</td>
<td>66.7</td>
<td>88.5</td>
<td>97.7</td>
</tr>
</tbody>
</table>
## Correlation with liver explant (10y experience ISMMS): per-patient detection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT</strong></td>
<td>86.3%</td>
<td>97.7%</td>
<td>98.0%</td>
<td>84.9%</td>
<td>91.3%</td>
</tr>
<tr>
<td><strong>EC GBCA-MRI</strong></td>
<td>89.5%</td>
<td>97.7%</td>
<td>99.0%</td>
<td>90.6%</td>
<td>94.4%</td>
</tr>
<tr>
<td><strong>EOB-MRI</strong></td>
<td>95.2%</td>
<td>94.1%</td>
<td>98.8%</td>
<td>80.0%</td>
<td>95.0%</td>
</tr>
<tr>
<td><strong>P (CT vs. EC GBCA-MRI)</strong></td>
<td>0.43</td>
<td>0.393</td>
<td>0.52</td>
<td>0.15</td>
<td>0.187</td>
</tr>
<tr>
<td><strong>P (CT vs. EOB-MRI)</strong></td>
<td>0.002</td>
<td>0.236</td>
<td>0.551</td>
<td>0.391</td>
<td>0.079</td>
</tr>
<tr>
<td><strong>P (EC GBCA-MRI vs. EOB-MRI)</strong></td>
<td>0.047</td>
<td>0.09</td>
<td>0.826</td>
<td>0.046</td>
<td>0.749</td>
</tr>
</tbody>
</table>
Sensitivity stratified by size

<table>
<thead>
<tr>
<th></th>
<th>Size 1-2 cm</th>
<th>Size ≥ 2cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>34.4%</td>
<td>93.1%</td>
</tr>
<tr>
<td>EC GBCA-MRI</td>
<td>64.6%</td>
<td>91.5%</td>
</tr>
<tr>
<td>Full EOB-MRI</td>
<td>67.3%</td>
<td>87.7%</td>
</tr>
<tr>
<td>P (CT vs. EC GBCA-MRI)</td>
<td>0.012</td>
<td>0.529</td>
</tr>
<tr>
<td>P (CT vs. Full EOB-MRI)</td>
<td>0.003</td>
<td>0.987</td>
</tr>
<tr>
<td>P (EC GBCA-MRI vs. EOB-MRI)</td>
<td>0.249</td>
<td>0.528</td>
</tr>
</tbody>
</table>
Some LGDN, many HGDNs, many early HCCs, and most progressed HCCs have reduced OATP expression.

Intra-nodular blood supply

Only progressed HCCs have arterial hypervascularity.
HCC – Imaging characteristics

Radiological hallmarks

- Arterial hyperenhancement
- Venous washout
- Capsular enhancement

Arterial phase
Equilibrium phase
Venous phase
HCC – Imaging characteristics

Enhancement pattern depends on tumor size and differentiation (Yoon SH et al, AJR 2009)

<table>
<thead>
<tr>
<th>Size</th>
<th>% with classic enhancement pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10mm</td>
<td>52</td>
</tr>
<tr>
<td>10-19</td>
<td>70</td>
</tr>
<tr>
<td>20-29</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>% with classic enhancement pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>WD</td>
<td>53</td>
</tr>
<tr>
<td>MD</td>
<td>79</td>
</tr>
<tr>
<td>PD</td>
<td>60</td>
</tr>
</tbody>
</table>
HCC – Imaging characteristics

Mosaic pattern

Necrosis
HCC – Imaging characteristics

Infiltrative HCC with tumor thrombus
WD HCC assessed with ECCM and EOB-DTPA

Besa et al, Acta Radiologica Reports 2015
WD fat containing hypovascular HCC with Gd-EOB
HCC with macrovascular invasion
MD HCC with wash-in/wash-out on CE-MRI, hypointensity on HBP and restricted diffusion on b1000
LI-RADS® diagnostic categories = relative probabilities

- **LR-NC**: Not categorizable
- **LR-1**: Definitely benign
- **LR-2**: Probably benign
- **LR-3**: Intermediate prob. of malignancy
- **LR-M**: Probably or definitely malignant, not necessarily HCC
- **LR-4**: Probably HCC
- **LR-5**: Definitely HCC
- **LR-TIV**: Tumor in vein

Courtesy, Claude Sirlin, UCSD
LI-RADS® diagnostic table assigns LR-3, LR-4, and LR-5z

CT/MRI Diagnostic Table

<table>
<thead>
<tr>
<th>Arterial phase hyperenhancement (APHE)</th>
<th>No APHE</th>
<th>APHE (not rim)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation size (mm)</td>
<td>&lt; 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Count additional major features:</td>
<td>None</td>
<td>LR-3</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>LR-3</td>
</tr>
<tr>
<td></td>
<td>≥ Two</td>
<td>LR-4</td>
</tr>
</tbody>
</table>

Observations in this cell are categorized LR-4, except:
- LR-5g, if ≥ 50% size increase in < 6 months (~ OPTN 5A-g)
- LR-5us, if “washout” and visibility at screening US (AASLD HCC criteria)

If unsure about the presence of any major feature: characterize that feature as absent
HCC Response to Therapy
Response of HCC to LRT

Yaghmai & Taouli, et al. AJR 2013
Response criteria in HCC

Lencioni R, Llovet JM. Semin Liver Dis 2010
EASL-EORTC clinical practice guidelines: management of HCC. J Hepatol 2012
Yaghmai & Taouli, et al. AJR 2013
RECIST vs. mRECIST
<table>
<thead>
<tr>
<th></th>
<th>EASL*</th>
<th>mRECIST**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart</td>
<td>Disappearance of any intratumoral arterial enhancement in all target lesions</td>
</tr>
<tr>
<td>PR</td>
<td>At least 50% reduction in total tumor load of all measurable lesions (determined by two observations not less than 4 w apart)</td>
<td>At least 30% decrease in the sum of diameters of viable target lesions</td>
</tr>
<tr>
<td>SD</td>
<td>Any cases that do not qualify for either PR or PD</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>At least 25% increase in size of one or more measurable lesions or the appearance of new lesions</td>
<td>At least 20% increase in the sum of the diameters of viable target lesions</td>
</tr>
</tbody>
</table>

* Bidimensional, ** Unidimensional measurements
CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease
**RECIST vs mRECIST**


- mRECIST and EASL guidelines independently predicted overall survival in patients with HCC treated with TACE (Shim. Radiology 2012; Kim BK. Eur J Cancer 2012)

- Significant association between survival and EASL and mRECIST responses, no association between survival and RECIST 1.1 (Gillmore. J Hepatol. 2011)

- Limitation of mRECIST:
  - Difficult to measure diffusely necrotic lesions with intervening viable components
Image subtraction
HCC post TACE/RFA with CR

T1 pre  T1 post-contrast  Subtraction
61 patients with 97 HCCs who underwent liver Tx after LRT with or $^{90}$Y RE (n=5).

RECIST, EASL, mRECIST, % necrosis on subtraction, and DWI all significant predictors of CPN (AUCs 0.810-0.815), while RECIST and ADC were not. ADC had poor performance (AUC 0.622).

Image subtraction demonstrated the strongest correlation (r=0.71-0.72, p<0.0001) with pathologic degree of tumor necrosis.
Advanced HCCs treated with nivolumab (anti-PD1)
mpMRI in HCC treated with Y90 radioembolization

Hectors. ISMRM 2018

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>6w</th>
<th>Mean % change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_a$ (ml/100g/min)</td>
<td>132±48</td>
<td>57±34</td>
<td>-53.2</td>
<td>0.002</td>
</tr>
<tr>
<td>$F_t$ (ml/100g/min)</td>
<td>166±28</td>
<td>95±45</td>
<td>-42.5</td>
<td>0.010</td>
</tr>
<tr>
<td>ART (%)</td>
<td>79±19</td>
<td>57±17</td>
<td>-24.6</td>
<td>0.006</td>
</tr>
<tr>
<td>$v_e$ (%)</td>
<td>69±19</td>
<td>34±29</td>
<td>-49.2</td>
<td>0.027</td>
</tr>
<tr>
<td>$D^*$ (10^{-3} mm^2/s)</td>
<td>38.5±20.4</td>
<td>20.3±7.6</td>
<td>-41.0</td>
<td>0.004</td>
</tr>
<tr>
<td>ADC (10^{-3} mm^2/s)</td>
<td>1.2±0.2</td>
<td>1.5±0.3</td>
<td>27.5</td>
<td>0.037</td>
</tr>
</tbody>
</table>
Summary

- Imaging: essential tool in patients with HCC
- Choice of CT vs. MRI depends on local expertise and availability
- HCC diagnosis still relies on washin/washout
- EOB-DTPA: added value needs more data
- Response to therapy: relies on mRECIST and subtraction
Gd-EOB-DTPA MRI: recurrent HCC
Cholangiocarcinoma

- 2nd most common primary cancer (10% of primary cancers)
- US incidence 1.67/100,000
- Arises from epithelium lining the small intrahepatic bile ducts
- Risk factors:
  - Chronic biliary diseases: PSC, intrahepatic lithiasis, liver fluke infections (C. sinensis), RPC, choledochal cysts
  - HCV, cirrhosis, alcohol, obesity, NAFLD
  - Most cases are sporadic
- Tumors form masses or spread along biliary system, mass-forming, sclerosing or polypoid, can have mucin production
- Important to differentiate from HCC in cirrhosis: contra-indication for Tx
ICC-MRI appearance

- T1 hypo, T2 hyperintense heterogeneous mass, ± central T2 hypointensity, ± capsular retraction ± peripheral biliary distention
- DWI: restricted diffusion, target sign
- EC GBCA: early rim enhancement followed by progressive centripetal heterogeneous enhancement ± peripheral wash-out
- EOB-DTPA: early peripheral enhancement, becomes hypo in LVP and HBP in most cases
- HBP: increased lesion conspicuity, better delineation of satellite nodules and intrahepatic mets

Maetani. AJR 2001; Chung. Radiographics 2009
Peporte, EJR 2013; Kang, Radiology 2012
ICC with EC GBCA
ICC in HCV cirrhosis (EOB-DTPA)
Case #1: Patient with cirrhosis
MRI in- and out-of-phase
AP and PVP extracellular GBCA: 3 HCCs
Case #2
Hx HCC resection high AFP, CT negative
Major pathologic features of HCC

- Aggressiveness: grade (WD/MD/PD or Edmondson-Steiner) and CK19 expression
- Microvascular invasion (thin vs thick walled vessels)

Courtesy, Isabel Fiel, Pathology ISMMS

Roayaie, Gastroenterology 2009
Role of imaging in HCC

Established
- Screening
- Diagnosis
- Staging

Not established
- Prediction of aggressiveness and grade
- Prognostication
- Prediction of gene expression
Example of LR-5 Definite HCC

54 yo man with cirrhosis

MRI Diagnostic Table

<table>
<thead>
<tr>
<th>Arterial phase hyperenhancement (APHE)</th>
<th>No APHE</th>
<th>APHE (not rim)</th>
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</thead>
<tbody>
<tr>
<td>Observation size (mm)</td>
<td>&lt; 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Count additional major features:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• “Washout” (not peripheral)</td>
<td>None</td>
<td>LR-3</td>
</tr>
<tr>
<td>• Enhancing “capsule”</td>
<td>One</td>
<td>LR-3</td>
</tr>
<tr>
<td>• Threshold growth</td>
<td>≥ Two</td>
<td>LR-3</td>
</tr>
</tbody>
</table>
Example of

Man with cirrhosis

- **Pre**
- **Arterial**
- **Portal Venous**
- **Delayed 3 Minutes**

**Nonrim APHE**

**Nonperipheral WO**

27 mm
Example of LR-5: Definite HCC

MRI Diagnostic Table

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<tbody>
<tr>
<td>Observation size (mm)</td>
<td>&lt; 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>10-19</td>
</tr>
<tr>
<td>Count additional major features:</td>
<td>None</td>
<td>LR-3</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>LR-3</td>
</tr>
<tr>
<td></td>
<td>≥ Two</td>
<td>LR-4</td>
</tr>
</tbody>
</table>

- "Washout" (not peripheral)
- Enhancing "capsule"
- Threshold growth

Man with cirrhosis

27 mm
Major pathologic features of HCC

- Aggressiveness: grade (WD/MD/PD or Edmondson-Steiner) and CK19 expression
- Microvascular invasion (thin vs thick walled vessels)

Courtesy, Isabel Fiel, Pathology ISMMS

Roayaie, Gastroenterology 2009

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>MDCT</th>
<th>Dyn MRI</th>
<th>Dyn MRI + HBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All lesions</td>
<td>0.71</td>
<td>0.71</td>
<td>0.71</td>
<td>0.87</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.62</td>
<td>0.87</td>
<td>0.87</td>
<td>0.9</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>0.93</td>
<td>0.93</td>
<td>0.95</td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.46</td>
<td>0.9</td>
<td>0.87</td>
<td>0.93</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>0.7</td>
<td>0.65</td>
<td>0.66</td>
<td>0.85</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>0.6</td>
<td>0.89</td>
<td>0.91</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Significantly higher diagnostic accuracy, sensitivity and NPV was achieved on dynamic + hepatobiliary phase MRI compared with US, MDCT and dynamic phase MRI alone.
Extracellular GBCA for HCC detection

Park. Hepatology 2012: 52 patients/72 HCCs with explant

<table>
<thead>
<tr>
<th></th>
<th>≤ 1 cm</th>
<th>1-2 cm</th>
<th>&gt; 2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWI</td>
<td>0.26</td>
<td>0.42</td>
<td>0.89</td>
</tr>
<tr>
<td>CE T1</td>
<td>0.32</td>
<td>0.74</td>
<td>0.96</td>
</tr>
<tr>
<td>p</td>
<td>0.44</td>
<td>&lt;0.002</td>
<td>0.43</td>
</tr>
</tbody>
</table>
## Correlation with liver explant (ISMMS): per-lesion detection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>59.5%</td>
<td>97.0%</td>
<td>98.0%</td>
<td>70.3%</td>
</tr>
<tr>
<td>EC GBCA-MRI</td>
<td>78.5%</td>
<td>99.1%</td>
<td>99.4%</td>
<td>85.7%</td>
</tr>
<tr>
<td>EOB-MRI</td>
<td>76.8%</td>
<td>91.2%</td>
<td>98.9%</td>
<td>78.2%</td>
</tr>
<tr>
<td>P (CT vs. EC GBCA-MRI)</td>
<td>0.04</td>
<td>0.255</td>
<td>0.384</td>
<td>0.019</td>
</tr>
<tr>
<td>P (CT vs. EOB-MRI)</td>
<td>0.001</td>
<td>0.201</td>
<td>0.446</td>
<td>0.085</td>
</tr>
<tr>
<td>P (EC GBCA-MRI vs. EOB-MRI)</td>
<td>0.28</td>
<td>0.053</td>
<td>0.826</td>
<td>0.483</td>
</tr>
</tbody>
</table>