Liver Cancer: Assessment and Management Options

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April 29, 2017
Objectives

• Review HCC epidemiology and surveillance guidelines

• Describe a diagnostic algorithm for the assessment of HCC

• Review the BCLC System for staging of liver cancer

• Discuss primary treatments for HCC based on the stage of disease
HCC: Epidemiology

### Table 3. Groups for whom HCC surveillance is recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

<table>
<thead>
<tr>
<th>Surveillance recommended</th>
<th>Threshold incidence for efficacy of surveillance (&gt; .25 LYD)(%/year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian male hepatitis B carriers over age 40</td>
<td>0.2</td>
<td>0.4-0.6%/year</td>
</tr>
<tr>
<td>Asian female hepatitis B carriers over age 50</td>
<td>0.2</td>
<td>0.3-0.6%/year</td>
</tr>
<tr>
<td>Hepatitis B carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
</tr>
<tr>
<td>African/North American Blacks with hepatitis B</td>
<td>0.2</td>
<td>HCC occurs at a younger age</td>
</tr>
<tr>
<td>Cirrhotic hepatitis B carriers</td>
<td>0.2-1.5</td>
<td>3-8%/yr</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5</td>
<td>3-5%/yr</td>
</tr>
<tr>
<td>Stage 4 primary biliary cirrhosis</td>
<td>1.5</td>
<td>3-5%/yr</td>
</tr>
<tr>
<td>Genetic hemochromatosis and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt; 1.5%/year</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin deficiency and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt; 1.5%/year</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5</td>
<td>Unknown</td>
</tr>
<tr>
<td>Surveillance benefit uncertain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B carriers younger than 40 (males) or 50 (females)</td>
<td>0.2</td>
<td>&lt; 0.2%/yr</td>
</tr>
<tr>
<td>Hepatitis C and stage 3 fibrosis</td>
<td>1.5</td>
<td>&lt; 1.5%/yr</td>
</tr>
<tr>
<td>Non-cirrhotic NAFLD</td>
<td>1.5</td>
<td>&lt; 1.5%/yr</td>
</tr>
</tbody>
</table>
AASLD and EASL guidelines recommend abdominal US every 6 months

AFP lacks sensitivity and specificity
HCC Diagnosis: AASLD Algorithm

Fig. 1. Diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.

HCC Diagnosis: Radiological Features

4-Phase CT

Non-contrast

Arterial phase

Portal venous phase

Delayed phase

Radiological Hallmark of HCC: Arterial hypervascularity and venous/late phase washout

Case courtesy of Dr Hani Al Salam, Radiopaedia.org, rID: 9982
HCC Diagnosis: LIRADS Classification

Algorithm for CT, MRI with ECA, MRI with HBA

Imaging-detected abnormality in high-risk patient

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

LR-Treated

LR-1

LR-2

Definite or probable malignancy, not HCC specific

LR-M

Tumor in vein

LR-5V

LI-RADS Table

Count number of features below:

- "Washout" (excluding peripheral "washout")
- "Capsule"
- Threshold Growth

Measure diameter

Arterial phase hypo-or iso-enhancement

<table>
<thead>
<tr>
<th>Measure diameter</th>
<th>Arterial phase hypo-enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 mm</td>
<td>None</td>
</tr>
<tr>
<td>≥ 20 mm</td>
<td>LR-3</td>
</tr>
</tbody>
</table>

Arterial phase hyperenhancement (excluding rim enhancement)

<table>
<thead>
<tr>
<th>Measure diameter</th>
<th>Arterial phase hyper-enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mm</td>
<td>LR-3</td>
</tr>
<tr>
<td>10-19 mm</td>
<td>LR-4 (LR-5)</td>
</tr>
<tr>
<td>≥ 20 mm</td>
<td>LR-5</td>
</tr>
</tbody>
</table>

Apply ancillary features and then tie-breaking rules to adjust category

LR-4, if there is ≥50% diameter increase in ≤6 months (equivalent to OPTN 5A-g), LR-5 if there is both "washout" and visibility as nodules at antecedent surveillance ultrasound (AASLD HCC criteria), LR-4 otherwise.

HCC Diagnosis: LIRADS Classification

<table>
<thead>
<tr>
<th>Category code and name</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-0</td>
<td>Inadequately assessed. Abnormality is inadequately assessed due to technical or other factors</td>
</tr>
<tr>
<td>LR-1</td>
<td>Definitely benign. 100% certainty abnormality is benign. Examples: definite cyst or hemangioma</td>
</tr>
<tr>
<td>LR-2</td>
<td>Probably benign. High probability but not 100% certainty observation is benign. Examples: probable cyst, hemangioma, or arterioportal shunt</td>
</tr>
<tr>
<td>LR-3</td>
<td>Intermediate probability for HCC. Benign and malignant entities each have moderate probability. Examples: &lt; 10 mm, arterial phase hypervascularity, resection, echogenic nodule, &lt; 10 mm, hypoechoic phase hypervascularity, echogenic nodule</td>
</tr>
<tr>
<td>LR-4</td>
<td>Probably HCC. High probability but not 100% certainty observation is HCC</td>
</tr>
<tr>
<td>LR-5</td>
<td>Definitely HCC. 100% certainty abnormality is HCC</td>
</tr>
<tr>
<td>LR-5V</td>
<td>Definitely HCC with tumour in vein. 100% certainty there is HCC in vein</td>
</tr>
<tr>
<td>LR-M</td>
<td>Definitely or probably malignant, not HCC specific. 100% certainty or high probability observation is malignant but features are not HCC specific</td>
</tr>
</tbody>
</table>

→ q3-6 months surveillance
→ q3-6 months surveillance or liver biopsy
→ Consider treatment
HCC Staging: BCLC System

HCC Treatment: BCLC Stage 0

- Treatment options include surgical resection, liver transplantation, and ablation
- 5-year survival of 60-80% for patients with single lesions <2cm (T1 stage) and preserved liver function

HCC Treatment: BCLC Stage A

- Resection and liver transplantation are first-line therapy for suitable candidates
- Both associated with 60-80% 5-year survival
- Ablation should be considered for patients who are not candidates for surgery

HCC Treatment: Ablation

• Gaining favor as a first-line treatment for early-stage HCC
• Techniques include radiofrequency, microwave, and ethanol ablation
• All techniques have similar efficacy in solitary HCC <2cm
• Rate of failure increases with HCC >3cm and multifocal HCC
• High recurrence rate (50-80%), but longterm disease control can be achieved
HCC Treatment: Surgical Resection

• Treatment of choice for HCC in non-cirrhotic patients
• Patients with cirrhosis should be carefully selected:
  – No cirrhosis or CP A cirrhosis
  – Absence of clinically significant portal hypertension (HVPG <10)
  – Normal bilirubin
  – Single nodule, with no size limit
• 5-year survival can exceed 70%
• Recurrence rates >70% at 5 years

HCC Treatment: Liver Transplantation

- Best treatment option for HCC patients with decompensated cirrhosis or multifocal HCC
- Milan criteria associated with 75% 5-year survival:
  - 1 lesion ≤ 5 cm
  - 3 lesions, each ≤ 3 cm
  - No macrovascular invasion
  - No extrahepatic metastases
- Patients with at least one 2 cm tumor or two 1 cm tumors are eligible for MELD exception points

Mazzaferro V et al. NEJM. Mar 1996.
• Transarterial chemoembolization is the cornerstone of therapy for intermediate-stage HCC
HCC Treatment: TACE

- Conventional TACE $\rightarrow$ intra-arterial infusion of doxorubicin or cisplatin mixed with Lipiodol (ethiodized oil), followed by embolization
HCC Treatment: TACE

- TACE increases survival time by 1.5-2 fold; survival times of 30-40 months have been described
- Baseline liver function is the most accurate predictor of survival in patients with unresectable HCC treated with TACE
- Liver transplantation can be considered in some patients with acceptable tumor burden after treatment → “downstaging”
- TACE is also an important “bridge therapy” for patients awaiting liver transplantation

HCC Treatment: TACE

- Post-embolization syndrome occurs in 60-80%, self-limited
- Serious adverse events such as liver failure or abscess affect <5% of patients
- Treatment-related mortality of 2-3%
- Absolute contraindications
  - Portal vein thrombosis
  - Biliary obstruction
  - Severe hepatic decompensation (Child C cirrhosis)
HCC Treatment: Y-90

- Y-90 radioembolization involves the intra-arterial injection of microspheres loaded with yttrium-90, delivering local radiation therapy
- An effective approach in patients early (bridge to transplant), intermediate and advanced stage HCC
- Labor intensive and costly
- Cohort studies showed a median survival time of 17.2 months for intermediate-stage HCC and 12 months for advanced stage HCC with portal vein invasion
- In phase 2 studies, Y-90 has increased time to progression of disease compared to TACE

Sorafenib is the first treatment option for patients with HCC of BCLC stage C

BCLC stage A or B patients who are not candidates for surgical or locoregional treatments due to tumor burden are also candidates for systemic therapy with sorafenib.
HCC Treatment: Sorafenib

- Oral multi-kinase inhibitor
- Reduces tumor cell proliferation and angiogenesis, while increasing apoptosis
- SHARP trial demonstrated modest survival benefit: 10.7 months with sorafenib vs 7.9 months without

HCC Treatment: Sorafenib

- Contraindicated in patients with severe hyperbilirubinemia or Child C cirrhosis

Table 3  Incidence of drug-related adverse events of sorafenib treatment

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>SHARP&lt;sup&gt;[5]&lt;/sup&gt; (n = 297)</th>
<th>AP&lt;sup&gt;[6]&lt;/sup&gt; (n = 149)</th>
<th>GIDEON (second interim analysis)&lt;sup&gt;[69]&lt;/sup&gt; (n = 1571)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>80</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>21</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>16</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Anorexia</td>
<td>14</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9</td>
<td>NA&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>World J Gastroenterol  2014 April 21; 20(15): 4131-4159</sup>
# HCC Treatment: Sorafenib

## Table 1. Summary of Phase III trials reported following approval of sorafenib.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>N</th>
<th>Median OS (m)</th>
<th>HR (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brivanib</td>
<td>FGFR, VEGFR</td>
<td>1,155</td>
<td>9.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>c-Ki, VEGFR, PDGFR</td>
<td>1,074</td>
<td>10.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Sorafenib +</td>
<td>EGFR, BRAF, VEGFR, PDGFR</td>
<td>720</td>
<td>8.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td>1,035</td>
<td>9.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Linifanib</td>
<td>EGFR, BRAF, VEGFR, PDGFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brivanib</td>
<td>FGFR, VEGFR</td>
<td>395</td>
<td>8.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>546</td>
<td>7.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>VEGFR2</td>
<td>565</td>
<td>7.6</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Emerging Immunotherapy for HCC

- **Nivolumab:**
  - Human IgG4 monoclonal AB inhibitor of PD-1
  - Immune Checkpoint Inhibitors: cancer cells have checkpoint ligands that inhibit immune system attack of cancer cells
  - CheckMate 040 Trial: Phase I/II trial, 262 patients with advanced HCC
    - 9-mo OS 74%
    - Disease Control Rate 64%
    - Duration of Response 9.9mo
  - CheckMate-459: Phase III Nivolumab vs. Sorafenib, primary endpoint time to progression and OS
Given their poor prognosis, patients with extensive tumor burden or advanced liver disease should receive supportive care.

Conclusions

• At-risk individuals should undergo HCC surveillance with abdominal US every 6 months.

• Liver nodules greater than 1cm in size should be assessed with 4-phase CT or MRI.

• The LIRADS system can be used to accurately characterize liver lesions.

• A liver biopsy is considered if imaging is inconclusive.

• The BCLC staging system provides a useful framework for staging and prognostication of liver cancer patients.
Conclusions

- Treatments for HCC include ablation, TACE, Y-90, resection, liver transplantation, and sorafenib

- Future therapies for advanced HCC may involve immunotherapy; ‘checkpoint inhibition’ is promising

- Tumor burden, liver function and performance status should be used to guide treatment decisions in a multi-disciplinary environment
Thank You

A multi-disciplinary team approach is needed for the care of patients with liver cancer

Swedish Liver Center
Offering state-of-the-art therapies, procedures and facilities to manage and treat the full range of liver conditions.