Hepatocellular Carcinoma: Diagnosis and Management

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Co-director, SMC Liver Tumor Board
April 30, 2016
Objectives

• Review screening/surveillance guidelines
• Discuss diagnostic algorithm for HCC
• Describe the BCLC Staging System
• Discuss primary treatments for HCC based on stage of disease.
HCC Clinical Case – Ms. Jones

She is a 56 yo woman with cirrhosis due to chronic HCV infection, with a disease course complicated by variceal bleeding s/p endoscopic band ligation, mild ascites well-controlled on diuretics, and mild hepatic encephalopathy. She has recently completed treatment with Harvoni and achieved a sustained virologic response. Overall, she is healthy appearing with no appreciable sequelae of liver disease on physical examination, and she continues to work full-time as an administrative assistant.

She is referred to your office for further evaluation of a 2.3cm right lobe nodule discovered on surveillance ultrasound.
HCC Clinical Case: Ms. Jones

Labs:
WBC 6, hemoglobin 9.5, Platelets 89
Na 138, K 4.2, Creat 0.6
Total bilirubin 1.6, AST 23, ALT 26, Alkaline phosphatase
INR 1.2
AFP 8.6
CTP Class B (CTP score of 7) and MELD score 10

Abdominal ultrasound:
Shrunken liver with nodular contour, 2.3cm right hepatic lobe nodule, patent hepatic vasculature, dilated portal vein, enlarged spleen, minimal ascites.
HCC Clinical Case – Ms. Jones

Questions:

1) Given that she cleared HCV infection, was HCC surveillance warranted?

2) What is the next step in diagnostic evaluation of her liver nodule? Is a biopsy required?

3) What stage of liver cancer does she have according to the BCLC staging system?

4) What is the ideal treatment approach?
HCC: Epidemiology

HCC: At-risk populations

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>Population group</th>
<th>Threshold incidence for efficacy of surveillance (≥0.25 LYG) (%/year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<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 hemachromatosis 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>

HCC: At-risk populations

Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.

1. Cirrhotic patients, Child-Pugh stage A and B*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

HCC: Surveillance

- AASLD and EASL guidelines are aligned
- Both recommend abdominal US every 6 months
- Shorter surveillance intervals are not effective
- AFP lacks sensitivity and specificity
HCC Diagnosis: AASLD Algorithm

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

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 haemangioma.</td>
</tr>
<tr>
<td>LR-2</td>
<td>Probably benign. High probability but not 100% certainty observation is benign. Examples: probable cyst, haemangioma, 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;25 mm, arterial phase hypoenhancement, nodular, otherwise occult.</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>

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
• No data to guide decisions for management of small tumors
• Liver transplantation has been reserved for patients with HCC recurrence after treatment or with high-risk features on histological evaluation

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: Surgical Resection

- Treatment of choice for HCC in non-cirrhotic patients
- 5-year survival can exceed 70%
- 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

HCC Treatment: Surgical Resection

• Anatomic resection preferred
• Right hepatectomy associated with higher risk of hepatic decompensation
• TACE, portal vein embolization, and sorafenib as adjuvant or neoadjuvant therapy are not effective

HCC Treatment: Surgical Resection

• Recurrent rates >70% at 5 years
• Predictors of recurrence:
  – Microvascular invasion
  – Additional tumor sites
• Molecular profiling may help refine risk assessment in the future

HCC Treatment: Surgical Resection

- Adjuvant and neoadjuvant treatments are not effective
HCC Treatment: Surgical Resection

- Patients at high risk of HCC recurrence should be considered for liver transplantation

Survival of high-risk patients after surgical resection

Survival of transplanted patients

HCC Treatment: Liver Transplantation

• Best treatment option for HCC patients with decompensated cirrhosis

• Milan criteria:
  – 1 lesion ≤ 5 cm
  – 3 lesions, each ≤ 3 cm
  – No macrovascular invasion
  – No extrahepatic metastases

Mazzaferro V et al. NEJM. Mar 1996.
HCC Treatment: Liver Transplantation

Mazzaferro V et al. NEJM. Mar 1996.
HCC Treatment: Liver Transplantation

• Within Milan criteria: 75% 5-year survival
• Prognosis associated with:
  – tumor number and size
  – grade of differentiation
  – presence of micro/macrovascular invasion
  – AFP
  – extrahepatic spread
• Patients with stage T2 HCC (one lesion >2cm or two lesions >1cm) are eligible for MELD exception points

HCC Treatment: Liver Transplantation

HCC Treatment: Downstaging

• Downstaging is the reduction of HCC burden to meet acceptable criteria for LT (Milan criteria)

• Transarterial chemoembolization is successful in 25% of cases

• Higher success rates (60%) with combination approach (e.g., TACE + RFA)
HCC Treatment: Ablation

- Gaining favor as a first-line treatment for early-stage HCC and also employed as “bridge therapy” for patients awaiting liver transplantation
- 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
- No clear evidence to support combination therapy with TACE and ablation
- Rates of recurrence are similar to those observed after resection
HCC Treatment: RFA
HCC Treatment: RFA

• Superior to percutaneous ethanol ablation in terms of survival and local recurrence
• Can produce a necrotic area of ~4cm, so ideally suited for HCC up to 3cm in size
• Complete response rates of 80-90% for tumors <3cm, 50-70% for tumors 3-5cm in size
• Efficacy also affected by proximity to large blood vessels → “heat sink” phenomenon

Raza and Sood, WJG 2014
HCC Treatment: RFA

• Contraindications:
  – Macrovascular invasion or metastatic disease
  – Ascites
  – Decompensated cirrhosis and not being considered for liver transplantation
  – Suboptimal location (subcapsular, adjacent to another organ or large blood vessel)

Raza and Sood, WJG 2014
HCC Treatment: RFA

- No evidence that RFA is better than surgery for small HCCs, BUT also no strong evidence to suggest that surgery is a superior option
HCC Treatment: BCLC Stage B

- Transarterial chemoembolization is the cornerstone of therapy for intermediate-stage HCC

HCC Treatment: TACE

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

- Best candidates for TACE are asymptomatic patients with unresectable HCC (solitary or limited multifocal HCC) without vascular invasion or extrahepatic spread and well-preserved liver function (CP A or B)
- 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

HCC Treatment: TACE

• Post-embolization syndrome occurs in 60-80%
• 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)
• Relative contraindications:
  – Elevated bilirubin
  – Tumor size >10cm or involving >50% of liver
  – Cardiac or renal insufficiency
HCC Treatment: TACE

- Multiple treatments are often needed; fewer than 2% of patients achieve a complete response after first treatment
- Not clear if on-demand TACE based on response vs regularly scheduled TACE is more effective
- The combination of TACE and RFA might provide a therapeutic benefit
- Adjuvant treatment with sorafenib has not improved outcomes
HCC Treatment: TACE

Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial

HCC Treatment: TACE

• TACE should be stopped when:
  – Two initial rounds of TACE have failed to induce substantial necrosis
  – Followup treatments fails to induce necrosis at sites of recurrence/progression
  – There is significant progression after an initial response
  – There is deterioration of liver function
  – There is poor tolerance.
HCC Treatment: TACE

The ART of Decision Making: Retreatment With Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma

Wolfgang Sieghart,1* Florian Hucke,1* Matthias Pinter,1 Ivo Grazialeti,2 Wolfgang Vogel,2 Christian Müller,1 Harald Heinzl,3 Michael Trauner,1 and Markus Peck-Radosavljevic1

Table 3. Results of Multivariate Stepwise Backward Cox Regression Analysis of Prognostic Factors in Patients With HCC Treated With TACE in the Training Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</th>
<th>ART Score</th>
<th>P-value (Cox Regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>B</td>
</tr>
<tr>
<td>Child-Pugh score increase</td>
<td>Absent</td>
<td>1</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>+ 1 point</td>
<td>2.0</td>
<td>1.2-3.5</td>
</tr>
<tr>
<td></td>
<td>+ ≥2 points</td>
<td>4.4</td>
<td>2.0-9.6</td>
</tr>
<tr>
<td>AST increase &gt;25%</td>
<td>Absent</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>8.4</td>
<td>4.5-15.5</td>
</tr>
<tr>
<td>Radiologic tumor response</td>
<td>Present</td>
<td>1</td>
<td>1.1-2.6</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1.7</td>
<td>1.1-2.6</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; AST, aspartate aminotransferase.

*The regression coefficients (B) were multiplied by 2 and rounded in order to facilitate the bedside calculation of the ART score.
HCC Treatment: BCLC Stage C

- 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
- Recommended for use in patients with extrahepatic lesions, macrovascular invasion, and non-responsive tumor
- 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[^5] (n = 297)</th>
<th>AP[^6] (n = 149)</th>
<th>GIDEON (second interim analysis)[^89] (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[^1]</td>
<td>5</td>
</tr>
</tbody>
</table>

[^5]: SHARP (Sorafenib HCC Assessment Randomized Phase III) [^6]: AP (Aurura Phase II) [^89]: GIDEON (second interim analysis)

World J Gastroenterol 2014 April 21; 20(15): 4151-4159
HCC Treatment: Sorafenib

- There are no available biomarkers to assess response to sorafenib
- Predictors of response have not been established
- Patients with advanced liver disease may not derive benefit
- Cytotoxic chemotherapy is not currently recommended
- Thus far, alternatives to sorafenib are not yet available
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>1.06 (0.31)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>e-Kit, VEGFR, PDGFR</td>
<td>1,074</td>
<td>10.2</td>
<td>1.3 (0.0014)</td>
</tr>
<tr>
<td>Sorafenib + Erlotinib</td>
<td>EGFR, BRAF, VEGFR, PDGFR</td>
<td>720</td>
<td>8.5</td>
<td>0.92 (0.2)</td>
</tr>
<tr>
<td>Linifanib</td>
<td>EGFR, BRAF, VEGFR, PDGFR</td>
<td>1,035</td>
<td>9.8</td>
<td>1.046 (0.52)</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>0.89 (0.33)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>546</td>
<td>7.3</td>
<td>1.05 (0.68)</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>VEGFR2</td>
<td>565</td>
<td>7.6</td>
<td>0.86 (0.13)</td>
</tr>
</tbody>
</table>

HCC Treatment: Emerging Therapies

- Y-90 radioembolization involves the intra-arterial injection of microspheres loaded with yttrium-90, delivering local radiation therapy
- It may be an effective approach in patients with intermediate and advanced stage HCC who are not eligible for TACE or sorafenib
- Can be used in the setting of branch/lobar portal vein thrombosis
- 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
- No RCTs testing efficacy of Y90 vs TACE or sorafenib, so still considered experimental.

HCC Treatment: BCLC Stage D

• Given their poor prognosis, patients with extensive tumor burden or advanced liver disease should receive supportive care.

HCC Clinical Case – Ms. Jones

She is a 56 yo woman with cirrhosis due to chronic HCV infection, with a disease course complicated by variceal bleeding s/p endoscopic band ligation, mild ascites well-controlled on diuretics, and mild hepatic encephalopathy. She has recently completed treatment with Harvoni and achieved a sustained virologic response.

She is referred to your office for further evaluation of a 2.3cm right lobe nodule discovered on surveillance ultrasound.

Review of recent labs shows that she has a CTP score of 7 (Child B cirrhosis) and MELD score of 10. Her AFP was normal.
HCC Clinical Case – Ms. Jones

Questions:
1) Given that she cleared HCV infection, was HCC surveillance warranted?
2) What is the next step in diagnostic evaluation of her liver nodule? Is a biopsy required?
3) What stage of liver cancer does she have according to the BCLC staging system?
4) What is the ideal treatment approach?
HCC Clinical Case – Ms. Jones

Questions:
1) Given that she cleared HCV infection, was HCC surveillance warranted?
   Yes.
2) What is the next step in diagnostic evaluation of her liver nodule? Is a biopsy required?
   4-phase CT or MRI. No biopsy needed if hallmark features of HCC are identified.
3) What stage of liver cancer does she have according to the BCLC staging system?
   BCLC stage A (early stage HCC).
4) What is the ideal treatment plan?
   Evaluation for liver transplantation.
Thank You!

Questions?