Hepatocellular Carcinoma and Y-90 Radioembolization

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Case: Initial Presentation

- 53-year-old man with new onset hematuria
  Abdominal ultrasound: demonstrated a 7.3 x 8.6 cm mass in the liver

- 3-phase liver protocol CT: Tumor replacing the entire right lobe of the liver with areas of enhancement and areas of necrosis; no lesions in the left lobe

Arterial Phase: Enhancement  Venous Phase: subtle washout
Case

- Labs (normal range)
  - AFP: 137 μg/L (< 10)
  - AST: 68 IU/L (14-20)
  - ALT: 54 IU/L (10-40)
  - Tbili: 0.7 mg/dL (< 0.3)
  - Alk Phos: 95 IU/L (53-128)

- Unresectable due to tumor location and bulk

- Referred for consideration of radiation therapy
HCC - Epidemiology

- **Worldwide:**
  - 5th most common cancer in men, 2nd leading cause of cancer-related mortality
  - 7th most common cancer in women and 6th leading cause of cancer-related mortality

- **Rising incidence in the US:**
  - Increase in hepatitis B (HCV B) and C (HCV C) from 1960s – 1990s
  - Metabolic syndrome associated non-alcoholic steatohepatitis (NASH)

- **Risk Factors:**
  - Infectious: hepatitis B, chronic hepatitis C
  - Genetic: hemochromatosis, alpha-1 antitrypsin deficiency
  - Demographic: older age, black race, aflatoxin
  - Medical History: diabetes mellitus type 2, metabolic syndrome, cirrhosis of any cause
  - Social History: heavy alcohol use, smoking

August 18, 2014
Screening with AFP and Liver US

• Recommended every 6-12 months for the following patients:
  – With cirrhosis:
    • Hep B, C
    • Alcohol
    • Genetic hemochromatosis
    • Non-alcoholic fatty liver disease (NAFLD)
    • Stage 4 primary biliary cirrhosis
    • Alpha 1-antitrypsin deficiency
    • Other causes of cirrhosis
  – Without cirrhosis
    • Hep B carriers
Workup

• A rising AFP or nodule on US should prompt liver imaging studies
  – At least a 3-phase liver protocol CT or MRI
• Labs: hepatitis panel, CMP, CBC, PT or INR, albumin, AFP
• Chest CT
• Bone scan if clinically indicated
Work-up: Imaging

- 3-phase liver protocol CT
- Imaging Characteristics: arterial hyper-enhancement and venous phase washout
Work-Up: Imaging

- 3-phase liver protocol MRI

- Biopsy: not required in select patients with cirrhosis; recommended in patients without cirrhosis (see NCCN guidelines)

T2 hyperintensity

Eovist delayed phase: non-enhancement of lesion compared to background liver
Prognostic factors

• Milan Criteria: to determine eligibility for transplant
  – solitary lesion < 5 cm
  – up to 3 lesions smaller than 3 cm
  – no extrahepatic manifestations
  – no vascular invasion
• Alpha fetoprotein level
• Portal vein thrombosis
• MELD Score: used to quantify end-stage liver disease for purposes of transplant
  – Factors: Tbili, Creatinine, INR
• Child Pugh Score: to quantify degree of liver disease (next slides)
Prognostic Factors

- Child-Pugh Score

<table>
<thead>
<tr>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>&lt; 2 mg/dL</td>
<td>2-3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT (secs)</td>
<td>1-4</td>
<td>4-6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild (detectable)</td>
<td>Severe (tense)</td>
</tr>
</tbody>
</table>

August 18, 2014
Prognostic Factors

- Child-Pugh Designation

<table>
<thead>
<tr>
<th>Class</th>
<th>Points</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5-6</td>
<td>100%</td>
</tr>
<tr>
<td>B</td>
<td>7-9</td>
<td>81%</td>
</tr>
<tr>
<td>C</td>
<td>10-15</td>
<td>45%</td>
</tr>
</tbody>
</table>
Anatomy

• Middle hepatic vein: divides liver into left and right lobes
• Right hepatic vein: divides R lobe in anterior/posterior segments
• Left hepatic vein: divides L lobe into medial/lateral segments
• Portal vein: divides liver into upper and lower segments
Patterns of Spread

• Regional LN
  – 1/3 have regional disease at diagnosis
  – Hilar, hepatoduodenal ligament, inferior phrenic, caval LNs

• Metastases
  – 1/3 have distant disease at diagnosis
  – Distant metastases: lungs and bones most common
  – Adjacent organs: adrenals, diaphragm, and colon
# HCC Staging – AJCC 7th edition

## Primary Tumor Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary Tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Solitary tumor without vascular invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Solitary tumor with vascular invasion or multiple tumors, none greater than 5 cm</td>
</tr>
<tr>
<td>T3a</td>
<td>Multiple tumors, greater than 5 cm</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor involving a major branch of the portal vein or hepatic vein</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with direct invasion of adjacent organs other than the gall bladder, or perforation of visceral pleura</td>
</tr>
</tbody>
</table>

## Nodal Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No evidence of regional nodal metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Evidence of regional nodal metastases</td>
</tr>
</tbody>
</table>

## Metastatic Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>None</td>
</tr>
<tr>
<td>M1</td>
<td>Yes</td>
</tr>
</tbody>
</table>
HCC Staging - AJCC 7th Edition

<table>
<thead>
<tr>
<th>Stage I</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
BCLC (Barcelona Clinic Liver Cancer) Staging

- More commonly used than AJCC

<table>
<thead>
<tr>
<th>Stage</th>
<th>ECOG PS</th>
<th>Child Pugh Score</th>
<th>Other Criteria</th>
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</thead>
<tbody>
<tr>
<td>0: Very early stage</td>
<td>0</td>
<td>A</td>
<td>Single HCC &lt; 2 cm</td>
</tr>
<tr>
<td>A: Early Stage</td>
<td>0</td>
<td>A-B</td>
<td>Single HCC or up to 3 nodules &lt; 3 cm</td>
</tr>
<tr>
<td>B: Intermediate</td>
<td>0</td>
<td>A-B</td>
<td>Multinodular</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: Advanced Stage</td>
<td>1-2</td>
<td>A-B</td>
<td>Portal invasion, Stage IV disease</td>
</tr>
<tr>
<td>D: Terminal Stage</td>
<td>&gt; 2</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Algorithm - HCC

Transplant Candidate?

Yes

Liver Transplant

No

Resectable?

Yes

Resection

- Chemoembolization
- Systemic Chemo/biologics
- Best Supportive Care

No

Diffuse

Focal

- Radioembolization
- SBRT
- TACE
- RFA
Case

Patient was treated with radioembolization using yttrium-90 microspheres (TheraSphere)

- Radioembolization
  - SBRT
  - TACE
  - RFA

- Chemoembolization
- Systemic Chemo/biologics
- Best Supportive Care
Principals of Radioembolization

• Microspheres are delivered to the liver and intrahepatic tumor through a catheter placed into the hepatic artery, the primary blood supply to liver tumors.

• Since microspheres are unable to pass through the vasculature of the liver and liver tumor due to arteriolar capillary blockade, they are trapped and exert a local radiotherapeutic effect.
TheraSphere

- TheraSphere consists of yttrium-90 (Y-90) as an integral constituent of insoluble glass microspheres.
- Mean sphere diameter 20-30 µm
- Y-90
  - Pure beta emitter
  - Decays to stable zirconium-90
  - Physical half life of 64.2 hours (2.68 days)
  - Average energy of beta emissions is 0.94 MeV
  - Average range of 2.5mm in tissue, with max range < 1cm
SIR-Spheres

- SIR-Spheres are also microspheres that contain yttrium-90
- They are made of a polymer resin (rather than glass)
- Mean sphere diameter 20 - 60 μm.
Radioembolization Criteria

Inclusion criteria:
- Unresectable hepatocellular carcinoma
- Age > 18 years
- ECOG Performance Status < 2
- Laboratory criteria: WBC > 1.5, Plt > 50, Cr < 2.0, Tbili < 3 mg/dL
- Ability to undergo angiography

Exclusion criteria:
- Uncorrectable flow to the GI tract
- Significant extrahepatic disease
- Lung dose > 30 Gy in a single fraction
- Lung dose > 50 Gy in multiple administrations
Pre-Embolization Evaluation

- Angiography
Hepatic Vascular Anatomy

- Left Hepatic Artery
- Splenic Artery
- Common Hepatic Artery
- Gastroduodenal Artery
- Right Hepatic Artery
- Celiac Trunk
- Hepatic Artery Proper
- Common Hepatic Artery
- Splenic Artery
- Celiac Trunk
Hepatic Vascular Anatomy

- Left portal vein
- Right portal vein
- Portal vein
- Splenic vein
Lung Shunt Fraction

• Assessed during the pre-embolization evaluation to determine extra hepatic flow to the lungs and GI tract

• Technetium-99 macro-aggregated albumin administered through a catheter in the hepatic artery and images obtained via gamma camera

• Lungs can tolerate up to 30 Gy per treatment and 50 Gy cumulatively over multiple treatment
Treatment Planning

Based on pretreatment angiography and 3-dimensional reconstruction of the liver

- \( D = A \times 50 \times (1 - LSF) \times (1 - R) / m \)
- \( A = D \times m / 50 \)

\( D = \text{dose in gray} \)
\( A = \text{activity in GigaBequerels} \)
\( m = \text{mass of the liver in kilograms} \)
\( R = \text{percent of residual activity in the vial after treatment} \)
\( LSF = \text{lung shunt fraction} \)
Toxicities and Management

• Acute side effects: fatigue, nausea/vomiting, flu-like symptoms, abdominal / chest wall pain
  – Managed with NSAIDs, anti-emetics, and pain medication

• Radioembolization-induced liver disease (REILD):
  – Presentation: increased LFTs, edema on CT and pain
  – Monitor if asymptomatic and slow steroid taper if symptomatic

• Radiation pneumonitis
  – Presentation: persistent nonproductive cough, shortness of breath and low grade fever
  – Slow steroid taper

• Gastrointestinal complications: Rare
  – Carafate for GI ulcers, Argon plasma coagulation for symptomatic bleeding
Follow-up

- 6 week follow-up with CBC, CMP, AFP, PT/PTT and CT 3 Phase Liver

- Q 3 - 4 month follow-up for the first 2 years with CBC, CMP, AFP, PT/PTT and 3-phase liver protocol CT
Post-embolization CT

- Arterial Phase: No enhancement
- Venous Phase: No enhancement

- Arterial perfusion on the pre vs. post CT scan measures viable tumor and is associated with 1 year overall survival
- Size of the lesion is not associated with progression or survival
Case: Follow-up

- Improvement in AFP and Interval response in tumor enhancement
- At 2 years, increase in tumor enhancement on 3 Phase Liver CT in the setting of a rising AFP

Arterial Phase: New enhancement
Venous Phase: Washout
Case: Follow-up

• Referred for Angiography
  – Retreatment found not to exceed normal tissue tolerance
• Patient underwent successful repeat radioembolization without acute adverse events
References

- Raza et al. HCC: Treatment and evidence-based medicine. World J Gastroenterol 2014: April 21; 20(15): 4115-4127 ISSN 1007-9327 (print) ISSN 2219-2840
- NCCN guidelines version 2.2014
- Image (slide 12): http://www.cpmc.org/advanced/liver/patients/topics/liver-cancer-profile.html