UPDATE TO THE MANAGEMENT OF PATIENTS WITH HCC

HUSSEIN K. MOHAMED MD, FACS.
Transplant and Hepato-biliary Surgery
Largo Medical Center
HCA
DISCLOSURE

• I have no financial relationship(s) relevant to the content of this CME activity.

• I will not discuss off-label use of medications.
OBJECTIVES

- EPIDEMIOLOGY OF HCC
- ETIOLOGY AND PATHOGENESIS OF HCC
- DIAGNOSIS OF HCC
- ROLE OF SCREENING FOR HCC
- DIFFERENT MODALITIES OF TREATMENT
- ROLE OF MULTIDISCIPLINARY APPROACH IN MANAGING PATIENTS WITH HCC
- CONCLUSION AND ANSWERING QUESTIONS
HCC IS A MAJOR HEALTH PROBLEM

- It is the most common type of liver cancer.
- It is the sixth most common cancer worldwide and it is the 5\textsuperscript{th} most common malignancy in men and the 8\textsuperscript{th} in women.
- Hepatocellular carcinoma is now the third leading cause of cancer-related deaths worldwide, with over 600,000 death annually.
- It is 2-4 times higher in men than women.
- 80\% of patients with HCC have underlying cirrhosis
INCIDENCE AND TRENDS
EPIDEMIOLOGY

![Bar chart showing estimated attributable fractions for HBV, HCV, and alcohol in different regions.](chart.png)
INCIDENCE IN THE U.S.

![Graph showing incidence rate over time for men, overall, and women.](attachment://image)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Segments</th>
<th>Years</th>
<th>Start</th>
<th>End</th>
<th>Change (APC)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1</td>
<td>1975-2005</td>
<td>2.6</td>
<td>7.9</td>
<td>−4.1^</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2</td>
<td>1975-1990, 1995-2005</td>
<td>1.6, 1.5</td>
<td>-0.04</td>
<td>-0.04</td>
<td>Jointpoint at arrow</td>
</tr>
<tr>
<td>Women</td>
<td>1</td>
<td>1990-2005</td>
<td>0.8</td>
<td>2.3</td>
<td>−3.8^</td>
<td></td>
</tr>
</tbody>
</table>
ETIOLOGY & PATHOBIOLOGY

Hepatocellular carcinoma: Pathobiology

Chronic liver disease → Cirrhosis

- Viral hepatitis B, C
- Hemochromatosis
- Alcohol
- ?NASH
- Tyrosinemia etc..

Regenerative stimuli

Environment / co-carcinogens

- Aflatoxins
- Hormones

Genetics

HCC

Non-cirrhotic pathway

Stem cell biology: hepatocyte, cholangiocyte
Staging of HCC

*American Joint Committee on Cancer-TNM System*

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0</td>
<td>Single tumor &lt;2cm</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
<td>&gt;2cm or single tumor &lt;2cm + vascular invasion</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N0M0</td>
<td>Single tumor &gt;5cm or &gt;2cm + vascular invasion</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1-3N1M0</td>
<td>Positive Regional Lymph Node</td>
</tr>
<tr>
<td>IVA</td>
<td>T4N0-1M0</td>
<td>Multiple tumors involving major vessels/multiple lobes</td>
</tr>
<tr>
<td>IVB</td>
<td>T1-4N0-1M1</td>
<td>Remote Metastasis</td>
</tr>
</tbody>
</table>

DIAGNOSIS

1- Clinical presentation
2- Radiological testing:
   A) US
   B) CT
   C) MRI
   D) ANGIO
   D) PET Scan
3- Laboratory
4- Pathology
SYMPTOMS

- Abdominal pain and/or swelling
- Fatigue/weakness
- Yellowing of the skin and eyes (jaundice)
- Darkened urine
- Nausea/vomiting
- Unexplained weight loss
- Loss of appetite
- Fever
- Feeling very full after a small meal
- Itchy skin
- Enlarged veins under the skin
DIAGNOSIS

1- Clinical presentation
2- Radiological testing:
   A) US
   B) CT
   C) MRI
   D) ANGIO
   D) PET Scan
3- Tumor markers
4- Pathology
ULTRASOUND

• Advantages:
  • High availability
  • Low cost
  • Non-invasive
  • High Specificity
  • Vascular invasion can be adequately evaluated

• Limitations:
  • Operator experience
  • Obese patients
  • Low sensitivity
  • Limited differentiation of soft tissue
Our Patient: Screening Liver Ultrasound

Transverse View

A hypoechoic rim is visible around the mass.

PACS, BIDMC
ADVANTAGES:

1- It is a highly diagnostic test for HCC.
2- Arterial enhancement and venous washout is highly diagnostic for HCC.
3- A 4-phase study is required for diagnosis.

DISADVANTAGES:

1- Limitation includes false negative imaging
2- Contrast toxicity.
CT SCAN
CT SCAN
MRI

• Contrast-enhanced MRI is a highly diagnostic test for HCC

• Advantages:
  
  High sensitivity (82-96)%
  
  High resolution
  
  It has a better diagnostic capability in fatty liver.

• Limitations:
  
  Expensive
  
  Contrast allergy
  
  Patient Dependent
Our Patient: 3 Phase Contrast Enhanced T1 MRI

Arterial Phase
Portal Venous Phase
Delayed Phase

Lesion demonstrates enhancement during the arterial phase and washout during the venous phase
ANGIOGRAM

• ANGIOGRAPHY:
  1- It is both a diagnostic and therapeutic test.
  2- It has been replaced largely by cross-sectional imaging for diagnostic purposes.
IMAGING
PET SCAN

“No evidence of MDP avid osseous metastases.”
ALPHAFETOPROTEIN

• **Alphafetoprotein (AFP):**
  1- It is insufficiently sensitive or specific by itself for diagnosis or surveillance.
  2- It is useful in conjunction with imaging for follow up and for screening.
# HCC Surveillance Guidelines for High-Risk Patients

<table>
<thead>
<tr>
<th>Organization</th>
<th>AFP/US</th>
<th>Imaging Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network (NCCN)</td>
<td>every 6-12 months</td>
<td>every 6 months</td>
</tr>
<tr>
<td>American Association for the Study of Liver Disease (AASLD)</td>
<td></td>
<td>every 6 months</td>
</tr>
<tr>
<td>European Association for the Study of the Liver (EASL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian-Pacific Association for the Study of the Liver (APASL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HIGH RISK GROUP FOR HCC

- 1- Hepatitis C cirrhosis.
- 2- Hepatitis B cirrhosis.
- 3- African Americans with hepatitis B.
- 4- Hepatitis B carrier with family history of HCC.
- 5- Asian male hepatitis B carriers over age 40.
- 6- Asian female hepatitis B carriers over age 50.
- 7- Stage 4 primary biliary cirrhosis.
- 8- Genetic hemochromatosis and cirrhosis.
- 9- Alpha 1-antitrypsin deficiency and cirrhosis.
- 10- Other cirrhosis.
TREATMENT

• 1- Surgical Resection
• 2- Liver Transplantation
• 3- Loco-regional treatment:
  - Trans-arterial Chemo-Embolization
  - Trans-arterial Radio- Embolization
  - Ablation by RFA or Microwave
  - Cyberknife
  - Cryoablation
  - Percutaneous Alcohol Injection
• 6- Chemotherapy
• 7- Combination
SURGICAL RESECTION

• It is the treatment of choice for HCC in non-cirrhotic patients.
• It can be offered for cirrhotic patients with preserved liver function.
• The 5-year survival after resection can exceed 50%.
• Pre or post-resection adjuvant therapy is not recommended.
SURGICAL ANATOMY
SURGICAL ANATOMY
The Patient is a surgical candidate
- General condition
- Liver condition.

The tumor is resectable
## Child-Pugh score

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 point</th>
<th>2 point</th>
<th>3 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>mild</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>none</td>
<td>Grade I-II</td>
<td>Grade III-IV</td>
</tr>
</tbody>
</table>
## Interpretation of Child-Pugh Score

<table>
<thead>
<tr>
<th>Point</th>
<th>Class</th>
<th>One year survival</th>
<th>Two year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>45%</td>
<td>35%</td>
</tr>
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# Child-Pugh score

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MELD SCORE

- Serum Bilirubin, Creatinine and INR
- $0.957 \times \log \text{ (serum creatinine)}$
- $+ 0.378 \times \log \text{ (serum bilirubin)}$
- $+1.120 \times \log \text{ (INR)}$
- $\times 10$
- Round to the nearest whole number

USE OF MELD SCORE:
- Survival of patients with variceal hemorrhage (TIPS)
- General surgery outcome
- Liver transplantation
MELD SCORE

• MELD score is a reliable index in the preoperative evaluation of liver function in cirrhotic patients undergoing partial hepatectomy for hepatocellular carcinoma (HCC)
According to international guidelines [European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)], portal hypertension (PHTN) is considered a contraindication for liver resection for hepatocellular carcinoma (HCC), and patients should be referred for other treatments.
Indeed, the presence of esophageal varices as determined by endoscopy or significant splenomegaly (major diameter >12 cm) with a platelet count of <100 000/mm³ are considered surrogate markers of clinically significant PHTN.
SURGICAL RESECTION

• The Patient is a surgical candidate
  – General condition
  – Liver condition.
• The tumor is resectable
HEPATIC RESECTION
HEPATIC RESECTION
# Hepatic Resection

## Resection Summary Table

<table>
<thead>
<tr>
<th>Resection</th>
<th>Volume (cc)</th>
<th>% out of liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical</td>
<td>282.9 cc</td>
<td>21.4 %</td>
</tr>
<tr>
<td>Total Resected</td>
<td>282.9 cc</td>
<td>21.4 %</td>
</tr>
<tr>
<td>Total Remained</td>
<td>1040.6 cc</td>
<td>78.6 %</td>
</tr>
</tbody>
</table>

## Findings

<table>
<thead>
<tr>
<th>Finding Name</th>
<th>Volume resected (remained)</th>
<th>% resected</th>
</tr>
</thead>
</table>
HEPATIC RESECTION
HEPATIC RESECTION
HEPATIC RESECTION
HEPATIC RESECTION
HEPATIC RESECTION
HEPATIC RESECTION
Liver Transplantation

• It is an effective treatment for HCC under the following selection criteria:
  1- Within Milan Criteria (solitary HCC <5 cm or with up to 3 nodules smaller than 3 cm each).
  2- No extra-hepatic malignancy.
  3- No vascular invasion.
• The 5-year survival of these early stage patients exceeds 70%.
• Pre-transplant TACE/ablation is recommended while the patient on the waiting list.
DOWN STAGING PROTOCOL

• Inclusion Criteria:
  – One tumor above 5 cm and up to 6.5 cm in size
  – Multiple tumors not exceeding total tumor size of 8 cm
  – No vascular invasion
  – No extra-hepatic spread.

• Down Staging Definition:
  – Tumor shrink to within Milan Criteria or
  – No viable tumor seen on imaging
DOWN STAGING PROTOCOL

• Listing Criteria:
  – Tumor must be within successful down stage definition.
  – Must be maintained within the down stage definition for at least 3 month.
  – The AFP must be either decreasing and maintained at a level < 400 ng/mi at the time of listing.
  – No evidence of extra-hepatic disease.
  – Imaging and AFP to be done at 3 month intervals while on the list.
CHEMOEMBOLIZATION

LC Bead microspheres are compressible, visibly-tinted N-fil Hydrogel microspheres supplied in convenient single 2 ml vials.
CHEMOEMBOLIZATION

- Beads block the capillaries and chemo leaks out causing more regional cell death.
- Doxorubicin cell death increases with hypoxia, embolization cuts off arterial supply and oxygen and they have a SYNERGISTIC effect.
- TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread.
CHEMOEMBOLIZATION

- Pre embolization, HCC
- Post embolization, HCC
RADIOFREQUENCY ABLATION
HOW IT WORKS

Ionic Agitation

Alternating current
RADIOFREQUENCY ABLATION

TEMPERATURE PROFILE WITH 100% TISSUE PERFUSION

CELLULAR DAMAGE WITH 100% TISSUE PERFUSION
To combat the physical limitations of a single probe several designs have been constructed.

- Leveen RF probe with umbrella shaped array
- RITA probe also has umbrella shaped array and allows infusion of saline through 4 tines
- Triangular shaped configuration
RADIOFREQUENCY ABLATION

- Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation.
- Patients with HCC lesions < 2 cm subject to RFA showed a 5-year survival of 70%, comparable to that of surgical resection in optimal candidates.
- It is not recommended for subscapsular location and poor tumor differentiation.
RADIOFREQUENCY ABLATION

- **Cons**
  - Grounding pads necessary (which can cause skin burns)
  - Destroys tissue planes in heat field
  - Not recommended for subcapsular lesions or close to skin
  - Painful, usually requiring general anesthesia
  - Very susceptible to heat sink
MICROWAVE ABLATION

- Principles of tissue heating and cell death are exactly the same as RF
- Probes are needle shaped and radiate MW away from the probe
- Size of burn is dependent on probe size
- Larger burns (6-7 cm) require very large probes... up to 1 cm in diameter
- Probe technology is not perfected, early probes made teardrop shaped burns due to deflection from needle and wave-wave interactions
MICROWAVE ABLATION

- When a proper probe is used the burn is very consistent and has very little, maybe no, heat sink effect due to high energy deposition in short amount of time
- Shorter burn times
ADVANTAGES OF MICROWAVE ABLATION

- Does not require grounding pads
- No gas tanks required (cryo)
- Has great potential and will likely replace RF if probe size can be decreased eventually… sorry LeVeen
SORAFENIB

- Sorafenib is recommended by the NCCN for the following patients with unresectable HCC and have Child-Pugh A or B disease\textsuperscript{a,b}
  - Not transplant candidates
  - Inoperable by performance status or comorbidity, local disease only
  - Metastatic disease
Sorafenib Targets Tumor Cell Proliferation and Angiogenesis

HGF = hepatocyte growth factor.

CLINICAL TRIAL

Sorafenib in HCC – Overall Conclusions

- Sorafenib prolonged OS vs. placebo in advanced HCC\textsuperscript{1,2,3}
  - 44% increase in OS in the SHARP trial
  - 47% increase in OS in the Asia Pacific Trial

- Sorafenib prolonged TTP vs placebo\textsuperscript{1,2,3}
  - 73% prolongation in TTP in the SHARP trial
  - 74% prolongation in TTP in the Asia Pacific Trial

- In both SHARP & AP phase III trials the AEs reported in patients on Sorafenib were predominantly grade 1 and 2 in severity and gastrointestinal, constitutional, and dermatologic in nature\textsuperscript{2,3}
BCLC Staging System and Treatment Strategy

Stage 0
- PST 0, Child–Pugh A
  - Very early stage (0)
    - 1 HCC <2cm
    - Carcinoma in situ <3cm
    - Portal pressure/bilirubin
      - Increased
      - Normal
    - Associated diseases
      - No
      - Yes
  - Resection

Stage A–C
- PST 0–2, Child–Pugh A–B
  - Early stage (A)
    - 1 HCC or 3 nodules <3cm
  - Intermediate stage (B)
    - Multinodular, Portal invasion
    - PST 0
    - N1, M1, PST 1–2
  - Advanced stage (C)
  - Curative treatments
    - Resection
    - Liver transplantation
    - PEI/RFA

Stage D
- PST >2, Child–Pugh C
  - End stage (D)
  - Symptomatic treatment
    - TACE
    - Sorafenib
    - Randomised controlled trials

KEYS FOR SUCCESSFUL TREATMENT OF HCC

• Screening and early detection
• Early referral
• Early implication of the most appropriate treatment
• Treatment using multidisciplinary approach
MULTIDISCIPLINARY APPROACH CENTER

- Radiology
- Oncology
- Hepatology
- Hepatobiliary surgery
- Coordinator
- Pathology
- Hospitalist
- PCP/GI
- Transplantation surgery
CONCLUSION

- HCC has become a cancer that can be prevented, detected at early stage, and effectively treated.
- Patients who are at high risk for developing HCC should be entered into surveillance programs.
- The BCLC staging system is effective and widely used both for staging and treatment allocation.
- Even though we are getting better results from TACE, RFA, MICROWAVE ablation and PEI, individually or in combinations. Surgical resection and liver transplantation remains as the only curative modalities for treating HCC.
CONCLUSION

• Sorafenib is recommended as first line option in patients who can not benefit from resection, transplantation, ablation or TACE and still have preserved liver function.

• The best results can be achieved for patients with HCC when their management carried by a MULTI-DISCIPLINARY TEAM USING A MULTI-DISCIPLINARY APPROACH.
Figure IV-7: Proportion of Liver Transplant Recipients with a Waiting Time of 90 days or Less by Region

Source: SRTR Analysis, Data as of May 2009.