PROMETHEUS UNHEALED!
HEPATOCCELLULAR CARCINOMA

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Disclosures

- None
<table>
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<th>5-14</th>
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<td>Accidents 36</td>
<td>Accidents 234</td>
<td>Accidents 252</td>
<td>Accidents 218</td>
<td>Cancer 511</td>
<td>Cancer 1,460</td>
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<td>Heart disease 3,744</td>
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<td>Congenital abnormalities 94</td>
<td>Homicide 12</td>
<td>Suicide 22</td>
<td>Suicide 172</td>
<td>Suicide 143</td>
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<td>Heart disease 369</td>
<td>Heart disease 948</td>
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<td>Cancer 1,724</td>
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<td>Congenital abnormalities 8</td>
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<td>Liver disease 42</td>
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<td>Accidents 267</td>
<td>Chronic lower respiratory diseases 499</td>
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<td>Unknown causes 21</td>
<td>Influenza &amp; pneumonia 3</td>
<td>Congenital abnormalities 6</td>
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<td>Diabetes 46</td>
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<td>Diabetes 14</td>
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<td>Bronchitis 2</td>
<td>Cerebral Palsy 3</td>
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<td>Episodic &amp; paroxysmal disorders 10</td>
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<td>Stroke 3</td>
<td>Ill-defined and unknown causes 2</td>
<td>Cerebral Palsy 4</td>
<td>Stroke 7</td>
<td>Mental &amp; behavioral disorders due to alcohol 16</td>
<td>Mental &amp; behavioral disorders due to alcohol 39</td>
<td>Kidney disease 73</td>
<td>Septicemia 121</td>
<td>Hypertension 297</td>
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<td>All other 2,810</td>
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<td>11</td>
<td>Undetermined intent 3</td>
<td>Pregnancy &amp; childbirth 7</td>
<td>All other 24</td>
<td>All other 30</td>
<td>All other 89</td>
<td>All other 409</td>
<td>All other 732</td>
<td>All other 1,140</td>
<td>All other 1,613</td>
<td>All other 2,810</td>
<td>All other 8,695</td>
<td>All other 1,870</td>
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Top 5 causes of death are highlighted.
Case Description

55 year old Caucasian male office worker was evaluated by his new PCP for elevated LFT’s >15 years.
Case Description

- Past Medical History:
  - Hypertension, Type 2 DM, Obesity, High TG’s and Elevated LFT’s for >15 years.
- Medications:
  - Antihypertensive, Fibrates, hypoglycemic agent
- Social History:
  - A glass of wine every 6 months, no tattoos, denies IVDU & high risk sexual activity.
- Family History:
  - No liver disease, CAD, DM.
Physical Exam:
Obese 200lbs, 5 ft. 2 inches, BMI 36.9, Waist circumference 107
- Oriented x3, Pedal edema, Vascular spider on his chest. Rest of the exam normal.

Pertinent Labs:
- Anemic, platelets 130, AST/ALT: 88/56, normal bilirubin, low albumin, high total protein, INR 1.1
- Viral Serologies: Negative
- Serum antibodies: Negative
- Transferrin saturation: 36%
Early arterial phase. A heterogeneously enhancing mass, approximately 4-5 cm in size, is visible in the liver.
Late-arterial phase image demonstrates additional enhancement of the mass.
Portal venous phase shows decreased image enhancement
HCC Outline

- Epidemiology
- Etiology/Risk Factors
- Clinical Features
- Surveillance
- Diagnosis
- Treatment
HCC Background Statistics

- HCC is the most rapidly increasing cause of cancer death in the US and the fifth most common cancer worldwide.

- Second leading cause of cancer related death.

- Leading cause of mortality among patients with cirrhosis.

- Characterized by aggressive tumor behavior and poor prognosis.
Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.
HCC: Demographics

- Gender M>F
- Race
- Age

SEER DATABASE
HCC: Incidence

Worldwide estimated new PLC cases and deaths

Demographic risk factors:
- male gender
- geographic area

I:M ratio = 1.05

Globocan, IARC 2012
HCC: Incidence

Age-adjusted HCC incidence rates in the United States between 2000 and 2012

*Gastroenterology* 2017 152, 812-820. e5DOI: (10.1053/j.gastro.2016.11.020)
Cirrhosis: HBV, HCV, NASH, Alcohol etc.
Infections: Hepatitis B virus
Behavioral factors: (Alcohol)
Obesity
Others: Aflatoxins. Mycotoxin. Pesticides

Liver cancer burden varies markedly by sex and geographic region due to risk factor exposure.
HCC: Risk Factors

HCV is the Dominant Risk Factors for HCC in the United States

- HBV most frequent in Asians
- HCV most frequent in whites and blacks

(N=691)
HCC: Risk Factors

NAFLD as a risk factor for HCC

Scientific Registry of Transplant Recipients database.

Diagnosis distribution among incident HCC in HealthCore

Flemming et al. Hepatology 2017

Goldberg et al. Gastroenterology 2017
HCC: Incidence

NAFLD is now the commonest cause of HCC in the North East UK

Patients with NAFLD associated HCC had a higher incidental presentation (38.2%) and lower prevalence of cirrhosis (77.2%).
Impact Of Universal Vaccination On HBV Infection & HCC In Taiwanese Children

HCC: Incidence

HCC after DAA-induced SVR
Cumulative HCC incidence rates by SVR

Log rank
p-value <0.001

No SVR

SVR

N at risk (N HCC)
SVR 19518 (85) 19372 (68) 14364 (29) 6128 (1) 0 (0) 0
No SVR 2982 (35) 2453 (36) 1617 (14) 636 (3) 5 (0) 0

Months after end of treatment
CLINICAL FEATURES
Symptoms

- RUQ pain.
- Weight Loss.
- Decompensation in a Cirrhotic.
- Obstructive jaundice.
- Intraperitoneal bleeding (tumor rupture).
- Fever.
Signs

- Reflect underlying liver disease.
- Manifestations of paraneoplastic Syndromes.
Paraneoplastic phenomena

- Dermatomyositis
Pemphigus foliaceus
Porphyria cutanea tada
Paraneoplastic Syndromes

- Hypoglycemia
- Erythrocytosis
- Hypercalcemia
- Diarrhea.
Found ~10% of patients at diagnosis.

Patterns of spread:
- Lung
- Intraabdominal LN.
- Bone.
- Brain.
- Adrenal gland.
SURVEILLANCE

Reduce Mortality
Improve survival
Detect early stage curative HCC
Cirrhosis from any cause The prevalence of cirrhosis among patients with HCC has been estimated to be 85%-95%.

Hepatitis B carriers A randomized surveillance study performed in HBV carriers, showed a 37% reduction in mortality for those who underwent surveillance.
SURVEILLANCE

- **Hepatitis B carriers**
  - Asian males 40 years
  - Asian females 50 years
  - Hepatitis B carriers with family history of HCC

**Other Cirrhosis**
- HCV Cirrhosis
- Stage 4 PBC
- Genetic Hemochromatosis and cirrhosis
- A1AT Deficiency and cirrhosis
Modes of Surveillance

- Surveillance for HCC should be performed using ultrasonography with or without Alpha-fetoprotein-AFP.

- Patients should be screened at 6 month intervals.
DIAGNOSIS
SURVEILLANCE

Surveillance ultrasound with or without AFP

Interpretation

Negative
Repeat US with or without AFP in 6 mo

Subthreshold (< 10 mm lesions)
Repeat US with or without AFP in 3-6 mo

Positive (≥ 10 mm lesions or AFP ≥ 20 ng/mL)
Multiphase CT or MRI in select patients

DIAGNOSIS

Diagnostic imaging for HCC with multiphase CT or MRI

Interpretation

No observation detected

Categorize each observation detected

Negative
No observation
Return to surveillance in 6 mo

LI-RADS NC
Noncategorizable
Repeat or alternative diagnostic imaging in ≤ 3 mo

LI-RADS 1
Definitely Benign
Return to surveillance imaging in 6 mo
Consider repeat diagnostic imaging in ≤ 6 mo

LI-RADS 2
Probably Benign
Return to surveillance imaging in 6 mo

LI-RADS 3
Intermediate
Repeat or alternative diagnostic imaging in 3-6 mo

LI-RADS 4
Probably HCC
Recommend multidisciplinary discussion for tailored workup that may include biopsy (select cases), or repeat or alternative diagnostic imaging in ≤ 3 mo

LI-RADS 5
Definitely HCC
HCC confirmed

LI-RADS M
Malignant, not definitely HCC
Recommend multidisciplinary discussion for tailored workup that may include biopsy (most cases), or repeat or alternative diagnostic imaging in ≤ 3 mo

If biopsy
Pathology diagnosis

Pathology diagnosis

Footnotes

a. Multiphase CT or MRI in select patients

Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound being on the transplant waiting list and other factors).
STAGING, PROGNOSIS AND MANAGEMENT
Staging helps in:
- Prognosis
- Choice of therapy with greatest survival potential.

Prognosis is complicated in HCC patients as the underlying liver function also affects outcome.
It is recommended that the staging system takes into account tumor stage, liver function and prognosis (Child Pugh, MELD) and physical status.

- BCLC- Barcelona Clinic Liver Cancer is the only staging system that accomplishes these aims.
**Staging**

**HCC**

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

- **Stage A-C**
  - PST 0-2, Child-Pugh A-B
  - Early stage (A)
    - Single or 3 nodules ≤3 cm
    - 3 nodules ≤3 cm
  - Intermediate stage (B)
    - Multinodular, PS 0
  - Advanced stage (C)
    - Portal invasion, N1, M1, PS 1-2

- **Stage D**
  - PST >2, Child-Pugh C
  - Terminal stage (D)

**SIRT**

<table>
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<tr>
<th>Procedure</th>
<th>Liver transplantation (CLT/LDLT)</th>
<th>RF/PEI</th>
<th>TACE</th>
<th>Sorafenib</th>
<th>Best supportive care</th>
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<tbody>
<tr>
<td>Curative treatment (30-40%)</td>
<td>Resection (CLT/LDLT)</td>
<td>RF/PEI</td>
<td>TACE</td>
<td>Sorafenib</td>
<td>Best supportive care</td>
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<tr>
<td>Median OS &gt;60 mo; 5-yr survival: 40-70%</td>
<td>RF/PEI</td>
<td>TACE</td>
<td>Sorafenib</td>
<td>Best supportive care</td>
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<td>Target: 20%</td>
<td>OS: 20 mo (45-14)</td>
<td>TACE</td>
<td>Sorafenib</td>
<td>Best supportive care</td>
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<td>Target: 40%</td>
<td>OS: 11 mo (6-14)</td>
<td>TACE</td>
<td>Sorafenib</td>
<td>Best supportive care</td>
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<td>Target: 10%</td>
<td>OS: &lt;3 mo</td>
<td>TACE</td>
<td>Sorafenib</td>
<td>Best supportive care</td>
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PROGNOSIS
# Child Pugh Class

## Child-Pugh classification of severity of cirrhosis

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<th>Parameter</th>
<th>Points assigned</th>
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<tr>
<td><strong>Ascites</strong></td>
<td>Absent</td>
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<tr>
<td><strong>Bilirubin</strong></td>
<td>&lt;2 mg/dL (&lt;34.2 micromol/L)</td>
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<tr>
<td><strong>Albumin</strong></td>
<td>&gt;3.5 g/dL (35 g/L)</td>
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<tr>
<td><strong>Prothrombin time</strong></td>
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<tr>
<td>Seconds over control</td>
<td>&lt;4</td>
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<tr>
<td>INR</td>
<td>&lt;1.7</td>
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<tr>
<td>Encephalopathy</td>
<td>None</td>
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Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85 percent; class B: 80 and 60 percent; and class C: 45 and 35 percent.

INR: international normalized ratio.
The MELD score is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for bilirubin, creatinine, INR and sodium to predict three-month survival.

HCC within Milan Criteria is assigned a MELD of 22 with a 10% increase every 3 months.
Estimated 3-month survival as a function of the MELD score in patients with cirrhosis

MELD: Model for End-Stage Liver Disease.

MANAGEMENT
Multidisciplinary approach involving Hepatologists, Pathologists, Radiologists, Surgeons and Oncologists.
LIVER TRANSPLANTATION FOR HCC

- Simultaneously cures the tumor and the underlying cirrhosis.

- Confined to single lesion ≤5 cm, up to three lesions, ≤3 cm, no gross vascular invasion, and no metastases—Milan Criteria.

- 75%, 4yr survival.
UNOS - United Network for Organ Sharing allocates livers on the basis of MELD score.

Most HCC patients have minimal liver dysfunction leading to increased waiting time and subsequent tumor progression beyond Milan criteria.

A priority system exists for HCC.
Patients with preserved liver function, no vascular invasion no evidence of p. hypertension.

Best outcome in Child Pugh A.

Perioperative mortality 1-3%

5yr survival ~70- 90%

Recurrence-70% at 5 years
RESECTION FOR HCC

Survival after Surgical Resection for Hepatocellular Carcinoma

Best candidates for resection:
- Solitary HCC ≤ 5 cm
- Child-Pugh A: Low portal hypertension
  - Normal bilirubin

Graph showing survival rates over different time periods:
- Log Rank 0.00001

Survival (%) over months:
- < 10 mmHg HVPG (n=35)
- ≥ 10 mmHg HVPG and normal bilirubin (n=15)
- ≥ 10 mmHg HVPG and Bilirubin >1 mg/dL (n=27)

Loco regional Therapies

- Trans arterial Chemoembolization - TACE
- Radiofrequency Ablation
- Percutaneous Ethanol Injection
- Systemic Chemotherapy
- Yttrium Radio embolization
Injection of anticancer drugs into the hepatic artery followed by embolizing beads.
Transarterial chemoembolization

TACE

HCC_60yr/Male Case Report
ASSESSMENT OF TUMOUR RESPONSE TO TACE

pre treatment
AFP 1824

post treatment
AFP 99

Stable disease by RECIST Complete response by EASL criteria
RADIOFREQUENCY ABLATION

- Tumor necrosis using thermal energy.
- Patients who do not meet resectability criteria.
- Best response <4 cm tumors
- Not used in tumors along the dome and inferior edge of liver and in the neighborhood of a vessel.
- Local recurrence 0-28%.
Percutaneous Ablation: New Methods

- Laser ablation
- Microwave ablation
- Cryoablation
- High-focused ultrasound
- Radiofrequency ablation

High-power generators
Multitined electrodes
Perfusion electrodes
RFA - Early HCC: Long-Term Outcomes

- Recurrence with new lesion: 81%
- Local recurrence: 10%

Lencioni R et al, Radiology 2005
Systemic Chemotherapy

Molecularly targeted therapy
Sorafenib (Nexavar)
multitargeted tyrosine kinase inhibitor
Other nonsurgical modalities

Radiotherapy
Radioembolization
Cryotherapy
THANK YOU

Questions