Liver Transplantation for Patients with Hepatocellular Cancer

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Incidence

- Overall, sixth most diagnosed malignancy worldwide & fourth cause of cancer mortality worldwide.

- Highly variable rates (East Asia / Sub-Saharan Africa).

- In US, incidence of 6/100,000 (circa 2010).

- 250 thousand to 1 million deaths annually – second leading cause of CA related death in men, 6th in women.
• Risk factors

• Age

• Male gender

• Chronic liver disease (viral, alcohol, and metabolic)

• DM

• Tobacco

• Obesity

• Environmental (Aflatoxin B exposure).
Surveillance

- Identify at risk population + screening

- American Association of Liver Diseases algorithm (AASLD) “at risk”.
  
  Cohort with an annual incidence of > 1.5-2%.

- Other criteria include
  
  - Chronic hepatitis with or without cirrhosis
  
  - Cirrhosis of any etiology
  
  - Anyone actively listed for a liver transplant.
<table>
<thead>
<tr>
<th>Population group</th>
<th>Threshold incidence for efficacy of surveillance (&gt; .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>
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<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>
Screening

- No single ideal technique
- Multimodal
  - Imaging
    - US
    - CT / MRI
  - AFP 20ng / mL
- Chronic liver disease = Sensitivity 58-68%, Specificity 80-94%
- General population = 25% PPV

<table>
<thead>
<tr>
<th>LI-RADS Category and Interpretation</th>
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<tbody>
<tr>
<td>LR-1</td>
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<tr>
<td>LR-2</td>
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<tr>
<td>LR-3</td>
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<td>LR-4</td>
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<tr>
<td>LR-5</td>
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<tr>
<td>LR-TIV</td>
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<tr>
<td>LR-M</td>
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</tbody>
</table>
Liver Nodule

<1cm
- Repeat US at 3 Months
  - Growing / Changing Character
    - Investigate According to Size
  - Stable

>1cm
- 4-Phase MDCT / Dynamic Contrast Enhanced MRI
  - Arterial Hypervascularity AND Venous or Delayed Phase Washout
    - Other Contrast Enhanced Study (CT or MRI)
      - YES
        - HCC
      - NO
        - Biopsy
Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Cirrhosis: A Meta Analysis

Only 4 in 10 hepatocellular carcinoma are detected at an early stage.

Sensitivity ultrasound alone: 45%

Sensitivity ultrasound + alpha fetoprotein: 63%

What is the best strategy for early detection?

Authors: Tzartzeva, Obi, Rich, Parikh, Marrero, Yopp, Waljee, Singal

Gastroenterology
Presentation

- No pathognomonic symptoms.

- Vague = weight loss, upper abdominal pain, satiety, or abdominal mass.

- Bone pain, intraperitoneal bleed / rupture = rare
  - Rupture = severe abdominal pain, free fluid, hypotension.

- Primary sx related to liver disease = must have high suspicion.

- Majority = diagnosed late.

- Labs = nonspecific (usually related to cirrhosis).
Liver Transplantation for HCC

• Gold standard for unresectable HCC
  • Tumor location, number, and size
  • Underlying cirrhosis

• Eligible recipients are prioritized based on wait time

• Pretransplant locoregional therapy (LRT) mitigates risk of tumor progression
  • Timing in relation to listing and transplant

• Patients with well-compensated disease & single < 3cm HCC with LRT response have reduced urgency
Incidence

Adapted from: PLoS One. 2020 Sep 18;15(9) and OPTN Data Reports: https://optn.transplant.hrsa.gov/data/view-data-reports/
The Gold Standard

Survival from Diagnosis (%)

- LT
- MMT with Resection
- MMT without Resection
- TACE alone
- Sorafenib
- None

Adapted from Rajesh 2014 Transplantation
Since 2019, after 6m median meld of DST [donor service area] -3 points
## DDLT HCC “within” criteria

<table>
<thead>
<tr>
<th>Group</th>
<th>Criteria</th>
<th>Definition</th>
<th>Survival</th>
<th>Recurrence</th>
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</thead>
<tbody>
<tr>
<td>Mazzaferro</td>
<td>Milan</td>
<td>Solitary tumor ≤ 5 cm or total ≤ 3 tumors and each tumor ≤ 3 cm</td>
<td>4-yr 75%</td>
<td>4-yr RFS 83%</td>
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<tr>
<td>Yao</td>
<td>UCSF</td>
<td>Solitary tumor ≤ 6.5 cm or total ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm</td>
<td>5-yr 75.2%</td>
<td>5-yr RR: 17%</td>
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<tr>
<td>Takada</td>
<td>Kyoto</td>
<td>Tumor number ≤ 10 and maximal diameter of each tumor ≤ 5 cm and serum des-gamma-carboxy prothrombin levels ≤ 400 mAU/mL</td>
<td>5-yr 87%</td>
<td>5-yr RR: 5%</td>
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<tr>
<td>Mazzaferro</td>
<td>Up-to-Seven</td>
<td>Sum of number of tumors ≤ 7 and max size of the largest tumor ≤ 7 cm</td>
<td>5-yr 71.2%</td>
<td>5-yr RR: 9.1%</td>
</tr>
</tbody>
</table>

Adapted from: World J Gastrointest Surg. 2021 May 27;13(5):392-405
DDLT HCC Criteria

AFP can be prognostic of more advanced disease and potential recurrence

>400 ng/mL associated with worse transplant outcomes

increase >50 ng/mL or over 15 ng/mL per month: increased risk of recurrence

Change in AFP can indicate response to locoregional therapy or chemotherapy

High AFP (>1000 ng/mL) in general associated with worse outcomes

Adapted from: World J Gastrointest Surg. 2021 May 27;13(5):392-405

Keck School of Medicine of USC
DDLT HCC Criteria

6 months after listing, the following pts are eligible for MELD Exception (MMAT-3 at listing center)

- Within Milan and AFP < 500 prior to LRT
  - 1 lesion 2-5 cm (T1)
  - 2-3 lesions 1-3 cm (T2)
- Downstaging with LRT
  - 1 lesion 5-8cm
  - 2-3 lesions ≤5cm (sum less than 8cm)
  - 4-5 lesions ≤3cm (sum less than 8cm)
  - AFP≥1000 with decrease to ≤500
- Contraindications to transplant
  - Macrovascular invasion of main PV or HV
  - Extrahepatic disease
  - Ruptured HCC
  - Lesion <2cm
- Caveat: Ruptured HCC and portal vein branch invasion may be considered if stable >12 months
LDLT for HCC

Current schema leaves many without a viable DDLT (19.6% in 2008, 16.9% in 2018)

Up to 30% of patients drop out

LDLT affords these patients an alternate option

Offers a “no competition” perspective, thus shifted ethical paradigm

Often incorporates expanded criteria

- Donors outside Milan

Prior to the requisite wait time
LDLT for HCC

Often utilized for patients with less access to DDLT

Highest utilization was prior to 2002 (pre MELD exception)

Increased rates post 2015, after capping of points @ 34

Older data suggested worse outcomes for LDLT in HCC

Newer analysis shows no difference between DDLT & LDLT for HCC

When segregated for in-criteria patients

Especially beneficial for HCC patients with MELD > 15
LDLT & double equipoise

Donor risk must be justified by an acceptable outcome for the recipient

Extremes should be avoided;

Small well treated tumor in a well-compensated patient

Wait for DDLT or avoid transplant completely

Patient with large tumor & aggressive biology

Outcome cannot justify risk to the donor

Recommended benchmark

5-year post LDLT survival > 60%

<5% severe post-operative complications (Clavien 3/4)
Locoregional Therapies & tumor downstaging in LDLT

Transarterial

Ablative

TACE

Y-90

MWA

PEI
Locoregional Therapies & tumor downstaging in LDLT

Typically performed for DDLT

~60% of patients with HCC considered “all-comers” can be successfully downstaged to within Milan.

ILTS guidelines recommend LRT to within UCSF with AFP < 500 ng/mL + observation period of at least 3 months before LDLT
Recurrence Free Survival following Liver Transplantation for HCC

Complete PR
No/Partial PR

HCC & LDLT Prognostic factors

Similar to DDLT

Should generally stray from expanded criteria

Validated criteria include

- AFP and DCP cutoffs (<400 ng/mL, <7.5ng/mL)
- F-FDG PET
- Response to LRT to ensure acceptable tumor biology
- No extra-hepatic disease
- No macro-vascular invasion
Conclusion

- Excellent long-term outcomes for certain patients
- Recipient selection criteria should include
  - Tumor biology: signs of increased risk
  - Probability of waitlist and post-LT survival
  - Center factors: organ availability/waitlist composition
Session Survey

Kambiz Etgesami, MD | April 20th 10:00 AM-10:30 AM