Liver transplantation and HCC 2019

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Goals for discussion:

• How does liver transplantation fit into the treatment algorithm for early HCCs
• How good is liver transplantation for down-staged HCC and how this has influenced allocation policy
• Changes in organ allocation: how this impacts prioritization of OLT for patients with HCC
Considerations for patients with HCC

• What is the severity of the underlying liver disease?
  Liver transplant provides potential eradication of HCC in the liver but also restores liver function and prolongs life

• Is the patient a candidate for LT independent of the indication for LT?

• What are the alternatives for treating HCC, and how good are they?

• What are the outcomes for transplantation for HCC?

• Future – can systemic therapy make some currently ineligible for LT now eligible (expanded criteria recipient)?
NOTE: MELD score = 9.57 × \( \log_e \text{creatinine mg per dL} \) + 3.78 × \( \log_e \text{bilirubin mg per dL} \) + 11.20 × \( \log_e \text{INR} \) + 6.43 (constant for liver disease etiology: 0 = cholestatic or alcoholic; 1 = all other).
From SRTR Data, Merion et al 2005

<table>
<thead>
<tr>
<th>MELD</th>
<th>Hazard ratio</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td>3.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-14</td>
<td>2.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15-17</td>
<td>1.21</td>
<td>0.41</td>
</tr>
<tr>
<td>18-20</td>
<td>0.62</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>21-23</td>
<td>0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-26</td>
<td>0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>27-29</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-39</td>
<td>0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥40</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Hepatocellular Carcinoma Is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States


Clinical Gastroenterology and Hepatology
Volume 15, Issue 5, Pages 767-775.e3 (May 2017)
DOI: 10.1016/j.cgh.2016.11.034
Policy development. The Board of Directors established under § 121.3 shall develop, in accordance with the policy development process described in § 121.4, policies for the equitable allocation of cadaveric organs among potential recipients. Such allocation policies:

- (1) Shall be based on sound medical judgment;
- (2) Shall seek to achieve the best use of donated organs;
- (3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with § 121.7(b)(4)(d) and (e);
- (4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate;
- (5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;
- (8) Shall not be based on the candidate’s place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section.
Correlation of Post-Transplantation Pathological Confirmation of Early-Stage Hepatocellular Carcinoma with Overall Survival (Panel A) and Recurrence-free Survival (Panel B) among 48 Patients with Cirrhosis

Recurrence free survival at 4 years: 83%

Established that LT was effective therapy for patients with small unresectable HCC in the setting of cirrhosis

Milan Criteria
• 1 lesion between 2-5 cm
• 2-3 lesions with none being larger than 3 cm

What about the small tumor < 2 cm?

Options:

1. do nothing
2. wait and ablate and/or transplant
3. ablate
Retrospective Cohort
Patients diagnosed with UNOS T1 HCC
Hospital of the University of Pennsylvania
March 2004-December 2011

81 patients identified

5 patients excluded
Lack of clinical records

Definitive LRT group
19 patients

TACE
10 patients

RFA
9 patients

Wait-and-not-treat group
57 patients

TACE
28 patients

RFA
2 patients

None
27 patients

23 OLT
2 deceased
1 delisted
1 on waitlist

19 OLT
5 deceased
4 delisted
Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis - Outcomes of transplant with down-staged therapy for adults with cirrhosis awaiting LT and HCC beyond Milan criteria (T3).

**Study Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>1 year survival (post LT)</th>
<th>5 year survival (post LT)</th>
<th>1 year recurrence free survival (post LT)</th>
<th>5 year recurrence free survival (post LT)</th>
<th>3 year survival (post LT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu, 2012</td>
<td></td>
<td>1.13 (1.01, 1.25)</td>
<td>1.17 (1.03, 1.32)</td>
<td>0.99 (0.91, 1.07)</td>
<td>1.02 (0.77, 1.34)</td>
</tr>
<tr>
<td>Heckman, 2008</td>
<td></td>
<td>1.05 (0.80, 1.38)</td>
<td>1.17 (1.03, 1.32)</td>
<td>0.99 (0.91, 1.07)</td>
<td>1.02 (0.77, 1.34)</td>
</tr>
</tbody>
</table>

Subtotal (I-squared = 0.0%, p = 0.627) 1.11 (1.01, 1.23) 100.00

Subtotal (I-squared = 0.0%, p = 0.882) 1.04 (0.93, 1.17) 87.81

Subtotal (I-squared = 5.1%, p = 0.005) 1.04 (0.93, 1.16) 100.00

NOTE: Weights are from random effects analysis

**Hepatology, 67: P 381-400, 2017**
Downstaging of Hepatocellular Cancer Before Liver Transplant: Long-Term Outcome Compared to Tumors Within Milan Criteria

Francis Y. Yao,¹,² Neil Mehta,¹ Jennifer Flemming,¹ Jennifer Dodge,² Bilal Hameed,¹ Oren Fix,¹ Ryutaro Hirose,² Nicholas Fidelman,³ Robert K. Kerlan, Jr.,³ and John P. Roberts²

Inclusion criteria
HCC exceeding UNOS T2 criteria, but meeting one of the following criteria:
1. Single lesion \( \leq 8 \) cm
2. 2 or 3 lesions each \( \leq 5 \) cm with the sum of the maximal tumor diameters \( \leq 8 \) cm
3. 4 or 5 lesions each \( \leq 3 \) cm with the sum of the maximal tumor diameters \( \leq 8 \) cm
Absence of vascular invasion based on cross-sectional imaging
• 58% (n=64/118) successfully down-sized using multiple therapies and underwent LT.
• Outcomes of T2 (n=322) versus downsized HCC (n=64)
Led to change in UNOS allocation policy:

**Standard MELD exception for candidates downsized to within Milan if initially with:**

- Total diameter of all lesions less than or equal to 8 cm
- A single lesion >5 cm <8 cm
- Four or five lesions each less than 3 cm, and a total diameter of all lesions less than or equal to 8 cm
- No exception for those with AFP >1,000 ng/ml unless they respond to <500 ng/ml.

- Candidates exceeding these criteria who downsized to within T2 can be reviewed by RRB/NLRB
Climbing the T2 MELD ladder for LT for HCC

• Tries to balance wait list mortality of other patients versus drop-off for progression of disease in patients with HCC
• Problem – with a fixed score, disparity in allocation occurs in regions due to differences in organ availability between regions

Bottom line – led to increased HCC transplant of candidates on the wait list compared to non-HCC candidates, disparity in allocation led to early transplant in some regions with increased futility
Solution – add a wait time after listing
Allocation opportunity
HCC Cap and Delay (2015)

• 6 month delay HCC exception score
• Decreases disparity in access between HCC and non-HCC patients
• Allows for biologic selection
• Capped exceptions at 34

Calculated MELD
Time 0

Calculated MELD
3 months

MELD exception 28
6 months

Heimbach et al Hepatology 2015: 61:1643-1650
Allocation opportunity: Transplant rate for HCC and non-HCC patients is now similar
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• UNOS licensed by US Government to allocate organs
• Eleven Regions in the country
Fixed Distance from Donor Hospital

Advantages:
• Easy to explain
• Extends distribution area, particularly for medically urgent patients

Disadvantages:
• Fixed boundaries
• Differences in population density may affect patients with similar matching characteristics
Livers from deceased donors older than age 70, and/or those who die as a result of cardiorespiratory failure, will be distributed differently.
Upcoming Policy Implementation: NLRB

• Initial phase will be implemented in 2019, prior to liver distribution changes

• NLRB
  • Establishes a NLRB with 3 specialty review boards
  • Scores for standardized exceptions (within Milan/downstaged) will be tied to the median MELD at transplant in the DSA/zone
NLRB: Structure

• NLRB is comprised of 3 specialty review boards
  • Adult HCC
  • Adult Other Diagnosis
  • Pediatrics

• Representation
  • Every liver transplant program may appoint a representative
## Adult Standard Exception Points

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Current Exception Points Assignment</th>
<th>Recommended Proposed Exception Points Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangiocarcinoma</td>
<td>MELD 22 (w/ 10% point escalator)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>MELD 22 (w/ 10% point escalator)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy</td>
<td>MELD 22 (w/ 10% point escalator)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>MELD 40</td>
<td>MELD 40 for DSA</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>MELD 22 (w/ 10% point escalator if PaO₂ remains under 60 mmHg)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
<td>MELD 22 (w/ 10% point escalator if repeat heart cath shows MPAP &lt;35)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Primary Hyperoxaluria</td>
<td>MELD 28 (w/ 10% point escalator)</td>
<td>MMaT for DSA</td>
</tr>
<tr>
<td>HCC</td>
<td>Delay 6 months, then 28, 30, 32, 34</td>
<td>MMaT - 3 for DSA (after delay)</td>
</tr>
</tbody>
</table>

MMaT = Median MELD at Transplant
NLRB: Details

MMaT Calculation

• OPTN will re-calculate MMaT every 180 days using the previous 365-day cohort.
• At 180 day update, candidates with existing standardized score exceptions will be adjusted
Expectations for the new allocation schema:

• Wait times around the country will be more even
• There will be a better balance between HCC allocated organs and non-HCC allocated organs – rebalancing can occur by changing the priority relative to local MMaT

• It will initially be confusing time for patients and referring physicians to understand how their patients will achieve transplantation
It is our job to educate, and offer alternatives – LDLT, better LRT and systemic therapies