Optimizing Patient Selection, Organ Allocation, and Outcomes in Liver Transplant (LT) Candidates with Hepatocellular Carcinoma (HCC)

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University of California, San Francisco
Division of GI/Hepatology
OVERVIEW

• Current state of LT for HCC worldwide

• Pushing beyond Milan criteria
  • Down-staging and “All-comers” results
  • Identifying important recurrence risk factors
  • Does the donor matter?

• Assessing individualized post-LT HCC recurrence risk
  • Novel risk scores using explant pathology
  • Standardize surveillance regimens
  • Tailor post-LT immunosuppression
Liver Transplant for HCC

Milan Criteria

- 1 lesion ≤ 5 cm
- 2 to 3, none > 3 cm
- Absence of Macroscopic Vascular Invasion
- Absence of Extra-hepatic Spread

# LT FOR HCC: EXPANDED CRITERIA

<table>
<thead>
<tr>
<th>Liver transplantation criteria for patients with hepatocellular carcinoma</th>
<th>Intention-to-treat survival</th>
<th>Disease-free survival</th>
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| Milan criteria[^31]  
  - Single tumour ≤5 cm or 3 tumours all ≤3 cm | N/A                         | 92% 4 years           | 85% 4 years                   | Based only on size and number |
| UCSF criteria[^39]  
  - Single tumour ≤6.5 cm or 3 tumours all ≤4.5 cm with TTD ≤8 cm | N/A                         | 90.9% 5 years        | 80.9% 5 years                  | Based only on size and number |
| Up-to-7 criteria[^49]  
  - The sum of the maximum tumour diameter and number ≤7 | N/A                         | Beyond Milan but within Up-to-7  
  - 64.1% 5 years | Beyond Milan but within Up-to-7  
  - 71.2% 5 years | Based only on size and number |
| Total Tumour Volume (TTV)[^7]  
  - Total tumour volume ≤115 cm³  
  - AFP ≤400 ng/mL | Beyond Milan but within TTV/ AFP  
  - 53.8% 4 years | Beyond Milan but within TTV/ AFP  
  - 68% 4 years | Beyond Milan but within TTV/ AFP  
  - 74.6% 4 years | Size and number and biological marker (AFP) |
| Extended Toronto Criteria (ETC)[^43]  
  - No limit in size and number  
  - No vascular invasion  
  - No extrahepatic disease  
  - No cancer-related symptoms  
  - Biopsy of largest tumour not poorly differentiated | Beyond Milan but within ETC  
  - 55% 5 years | Beyond Milan but within ETC  
  - 30% 5 years  
  - (Cumulative risk of recurrence) | Beyond Milan but within ETC  
  - 68% 5 years | No size and number limit but biological behaviour (cancer-related symptoms and tumour differentiation) |
| Kyoto Criteria[^55]  
  - Number ≤10 tumours  
  - Size ≤5 cm  
  - DCP ≤400 mAU/mL | N/A                         | Beyond Milan but within Kyoto  
  - 30% 5 years  
  - (Cumulative risk of recurrence) | Beyond Milan but within Kyoto  
  - 65% 5 years | Size and number and biological marker |

AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; TTD, total tumour diameter; UCSF, University of California San Francisco.
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AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; TTD, total tumour diameter; UCSF, University of California San Francisco.
Extended Toronto Criteria

5-yr post-transplant survival
68% ETC; 78% Milan

5-yr recurrence probability
30% ETC; 13% Milan

Sapisochin G et al. Hepatology 2016;64:2077-2088
# LT FOR HCC: EXPANDED CRITERIA

## Table 1 | Liver transplantation criteria for patients with hepatocellular carcinoma

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AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; TTD, total tumour diameter; UCSF, University of California San Francisco.
Extended Criteria & FDG PET/CT

The National Cancer Korea Criteria

- Total tumor diameter < 10 cm
- Negative $^{18}$F-FDG PET/CT

## HCC MELD EXCEPTION WORLDWIDE

### Table 2: Models using hepatocellular carcinoma exception points to allocate liver grafts

<table>
<thead>
<tr>
<th>Organ procurement organization (region)</th>
<th>Tumour burden to qualify for exception points</th>
<th>Exception points granted</th>
<th>Exception points progression</th>
<th>Exception point cap</th>
<th>Waiting period before receiving exception points</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTN/UNOS (USA)</td>
<td>T2</td>
<td>28</td>
<td>First 3 months assignment of MELD score equivalent to 35% mortality risk. Following months additional MELD score equivalent to 10% increase in mortality</td>
<td>Yes: 34</td>
<td>6 months from listing (calculated MELD score)</td>
</tr>
<tr>
<td>Eurotransplant (Austria, Belgium, Germany, Holland, Slovakia, Croatia)</td>
<td>T2</td>
<td>22</td>
<td>Add point equivalent to a 10% increase in candidate mortality every 3 months</td>
<td>No</td>
<td>No</td>
</tr>
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<td>Human organ procurement and exchange program (Alberta, Canada)</td>
<td>TTV ≤ 115 cm$^3$ &amp; AFP ≤ 400 ng/ml (T1 excluded)</td>
<td>22</td>
<td>Add 2 points every 2 months</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Human organ procurement and exchange program (Ontario, Canada)</td>
<td>UCSF criteria or TTV ≤ 115 cm$^3$ &amp; AFP ≤ 400 ng/ml (T1 excluded)</td>
<td>22</td>
<td>Add 3 points every 3 months</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Brazil</td>
<td>T2</td>
<td>20</td>
<td>Increase to 24 at 3 months and to 29 at 6 months</td>
<td>Yes: 29</td>
<td>No</td>
</tr>
<tr>
<td>Organització catalana de trasplantaments (Cataluna, Spain)</td>
<td>Single HCC &lt; 3 cm and AFP &gt; 200 ng/mL, or single HCC ≥ 3 cm and ≤ 5 cm or 2–3 HCCs ≤ 3 cm</td>
<td>19</td>
<td>Add one point every 3 months</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nord Italian transplant (Italy)</td>
<td>None</td>
<td>No exception points</td>
<td>Prioritization according to risk of progression and response to bridging therapies$^87$ (system under assessment)</td>
<td>No</td>
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AFP, α-fetoprotein; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; OPTN, Organ Procurement Transplantation Network; TTV, total tumour volume; UCSD, University of California San Francisco; UNOS, United Network for Organ Sharing. Modified with permission from Wiley © Tosso, C. et al. Am. J. Transplant. 14, 2221–2227 (2014).

RISING INCIDENCE OF LIVER TRANSPLANT FOR HCC AT UCSF
RISING INCIDENCE OF LIVER TRANSPLANT FOR HCC AT UCSF

% of adult LT done for HCC

Year

05 06 07 08 09 10 11 12 13 14 15

22 LT for HCC in 2006

15%
RISING INCIDENCE OF LIVER TRANSPLANT FOR HCC AT UCSF

Year

22 LT for HCC in 2006
15%

84 LT for HCC in 2015
47%

% of adult LT done for HCC

0% 10% 20% 30% 40% 50% 60%

05 06 07 08 09 10 11 12 13 14 15
Year
Scenario: Your patient with a 3.5 cm HCC is at the top of the wait list and is expecting a liver offer at any time. Today in clinic he asks you what his expected outcomes are after transplant.
**Scenario**: Your patient with a 3.5 cm HCC is at the top of the wait list and is expecting a liver offer at any time. Today in clinic he asks you what his expected outcomes are after transplant.

- **5 yr post-LT survival**: 75-80%
- **5 yr HCC recurrence**: ~15%
Scenario: Your patient with a 3.5 cm HCC is at the top of the wait list and is expecting a liver offer at any time. Today in clinic he asks you what his expected outcomes are after transplant.

5 yr post-LT survival: ???
5 yr HCC recurrence: ???
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Response to LRT

3.5 cm
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

3.5 cm

Response to LRT

AFP

3.5 cm
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Response to LRT

AFP

3.5 cm

7.5 cm
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

- Response to LRT
- AFP
- Wait Time to LT

- 7.5 cm
- 3.5 cm
LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

- Response to LRT
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LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

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5 yr post-LT survival: ___%
5 yr HCC recurrence: ___%
LIVER TRANSPLANTATION FOR HCC: DOWNSTAGING

5 yr post-LT survival: ___%
5 yr HCC recurrence: ___%
**Down-staging of HCC for Transplant**

- **Definition**: Reduction in the size of tumor using local regional therapy to meet acceptable criteria for liver transplant

- **Tumor response**: Based on radiographic measurement of the size of all viable tumors, not including the area of necrosis from local regional therapy

- **A selection tool** for tumors with more favorable biology that respond to down-staging treatment and also do well after liver transplant

---

Tumor Down-staging Before Liver Transplant

Beyond Milan  Within Milan  Complete necrosis

EASL and mRECIST

Yao & Fidelman. Hepatology 2016;63:1014-1025
Eligibility criteria

Dropout

LRT for tumor down-staging

End-point of Down-staging
(Milan or other criteria)

Minimum observation period

LRT for maintaining tumors within LT listing criteria

Deceased donor Liver Transplant

5-yr survival the same as those meeting criteria without down-staging

Exclusion criteria

HCC Transplant Criteria @ UCSF

**MILAN CRITERIA**
- 1 lesion ≤ 5 cm
- 2-3 lesions ≤ 3 cm
- No extra-hepatic dz

**DOWNSTAGING CRITERIA**
- 1 lesion 5.1-8 cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- TTD ≤ 8 cm
- No extra-hepatic dz

**ALL-COMERS CRITERIA**
- Any number of tumors
- Total tumor burden beyond DS criteria
- No extra-hepatic dz
Down-staging of HCC
Updated UCSF Data

UCSF Criteria for Down-staging
1 tumor ≤ 8 cm
2-3 tumor ≤ 5 cm + total diameter ≤ 8 cm
4-5 tumor ≤ 3 cm + total diameter ≤ 8 cm

Meeting Milan criteria
Dropout (n=41)
Transplant (n=64)

Median f/u 3.8 years
78% 5-yr survival post-transplant
91% 5-yr recurrence-free probability

Post-Transplant Survival

Region 5 Multi-center Experience

- 187 consecutive adult patients with HCC treated under Region 5 down-staging protocol from 3 centers (UCSF, CPMC, Scripps) between 2002 and 2012
- Uniform eligibility criteria, criteria for successful down-staging (within Milan criteria) and minimal observation period of 3 months
- Median time from down-staging to liver transplant of 12.6 months (IQR 6-19)
- Median post-transplant follow-up of 4.3 years

Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)
Post-Transplant Survival

Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)
Post-Transplant Survival

Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)
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*Mehta N et al. Clinical Gastroenterology and Hepatology 2017 (in press)*
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Mehta N et al. *Clinical Gastroenterology and Hepatology* 2017 (in press)
UCSF/Region 5 Down-staging protocol recently accepted as national policy

**UCSF/ Region 5 Down-staging criteria**

- Dropout

**End-point of Down-staging = Milan Criteria**

- LRT for tumor down-staging

**Exclusion criteria**

- Observation period > 3 months

- LRT for maintaining tumors within LT listing criteria

- Liver Transplant

**UCSF/Region 5 Down-staging protocol**

- 1 tumor ≤ 8 cm
- 2-3 tumor ≤ 5 cm +
  total diameter ≤ 8 cm
- 4-5 tumor ≤ 3 cm +
  total diameter ≤ 8 cm

5-yr survival same as Milan criteria without down-staging
• What about patients whose tumor burden exceeds even the Region 5 down-staging protocol?

• Is there an upper limit of tumor burden beyond which LT is a bad idea?
HCC Transplant Criteria @ UCSF

MILAN CRITERIA
• 1 lesion ≤ 5 cm
• 2-3 lesions ≤ 3 cm
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DOWNSTAGING CRITERIA
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“All-comers” Down-staging Protocol

“All-comers”

LRT for tumor down-staging

End-point of Down-staging = Milan Criteria

Observation period ≥ 6 months

LRT for maintaining tumors within LT criteria

Liver Transplant
Meeting All-Comer Criteria (N = 74)

Down-staged to Milan (N = 48) (65%)

Never Downstaged (N = 26) (35%)

Rassiwala J et al. AASLD 2016
Meeting All-Comer Criteria (N = 74)

Down-staged to Milan (N = 48)

Never Downstaged (N = 26)

Dropout after Down-staging (N = 32)

Awaiting LT (N = 6)

Underwent LT (N = 10) (14%)

Rassiwala J et al. AASLD 2016
Probability of Downstaging by Initial Tumor Burden

Number of Lesions + Largest Tumor Diameter

Rassiwala J et al. AASLD 2016
HCC Recurrence (All-comers group)

Meeting All-Comer Criteria
(N = 74)

Down-staged to Milan
(N = 48)

Underwent LT
(N = 10)

Post LT Recurrence
(N = 3)

Median 21.4 months
from LT to recurrence
Intention-to-Treat Survival

Survival probability

Time since LRT (years)

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<th>DS</th>
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<td>133</td>
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<tr>
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<td>76</td>
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<tr>
<td>6</td>
<td>62</td>
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UCSF-DS
All-Comers

56%
21%
P < 0.001
All-comers Summary

• An upper limit in tumor burden probably exists beyond which successful LT after down-staging becomes an unrealistic goal

• Patients with tumor burden exceeding the Region 5 down-staging criteria must be very carefully selected for consideration of LT
LIVER TRANSPLANTATION FOR HCC: AFP

AFP

3.5 cm

5 yr post-LT survival: ___%
5 yr HCC recurrence: ___%
AFP and Post-transplant Outcome - France

Survival rate (%)

Months after Liver Transplantation

AFP <100
AFP 100-1000
AFP >1000

P < 0.001

Duvoux et al. Gastroenterology 2012;143:986-94
## Prognostic Model: Tumor size, number and AFP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Largest tumor diameter, cm</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td>0</td>
</tr>
<tr>
<td>3-6</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>4</td>
</tr>
<tr>
<td><strong>Number of tumor nodules</strong></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>0</td>
</tr>
<tr>
<td>≥ 4</td>
<td>2</td>
</tr>
<tr>
<td><strong>AFP level, ng/mL</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 100</td>
<td>0</td>
</tr>
<tr>
<td>100-1000</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>3</td>
</tr>
</tbody>
</table>

*Source: Duvoux et al. Gastroenterology 2012;143:986-94*
### Prognostic Model: Tumor size, number and AFP

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<td>100-1000</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>3</td>
</tr>
</tbody>
</table>

**Low risk ≤ 2 points**

Some HCC > Milan but AFP ≤ 100 = Low risk

*Duvoux et al. Gastroenterology 2012;143:986-94*
AFP and Post-transplant Outcome - UCSF

\[ p = 0.03 \]

AFP ≤1000: 80%

AFP >1000: 52%

Hameed B. et al. Liver Transplantation 2014; 945-951
Applying AFP cutoff of >1000 ng/mL to pts within Milan criteria results in exclusion of 5% and 20% reduction in post-LT HCC recurrence.
REDUCING HIGH AFP PRIOR TO LT

Yao F. et al. AASLD 2017
REDUCING HIGH AFP PRIOR TO LT

Yao F. et al. AASLD 2017
High AFP Threshold
• Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception
• If AFP falls <500 after LRT, the candidate is eligible for a standardized MELD exception
High AFP Threshold

- Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception
- If AFP falls <500 after LRT, the candidate is eligible for a standardized MELD exception

However, AFP reduction to <100 after LRT is ideal
LT FOR HCC: METROTICKET 2.0

HCC Specific Survival

LT FOR HCC: METROTICKET 2.0

HCC Specific Survival

HCC Specific Survival

LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

Response to LRT

3.5 cm

5 yr post-LT survival: ___%
5 yr HCC recurrence: ___%
RESPONSE TO LOCAL-REGIONAL THERAPY AS PROGNOSTIC FACTOR

Recurrence Free Survival (%)

- Within Milan, no risk factors
- Beyond Milan, no risk factors
- Within Milan, (+) risk factors
- Beyond Milan, (+) risk factors

Risk factors:
- Radiologic tumor progression
- AFP slope > 15 ng/mL/month

Months after liver transplantation

Recurrence Free Survival (%)

Months after liver transplantation

- Within Milan, no risk factors
- Beyond Milan, no risk factors
- Within Milan, (+) risk factors
- Beyond Milan, (+) risk factors

Risk factors
- Radiologic tumor progression
- AFP slope > 15 ng/mL/month

Recurrence Free Survival (%) Months after liver transplantation

- **Within Milan, no risk factors**: 90%
- **Beyond Milan, no risk factors**: 68%
- **Within Milan, (+) risk factors**: 42%
- **Beyond Milan, (+) risk factors**: 90%

**Risk factors**
- Radiologic tumor progression
- AFP slope > 15 ng/mL/month

LIVER TRANSPLANTATION FOR HCC: OPTIMIZING SELECTION CRITERIA

3.5 cm

Wait Time to LT

5 yr HCC recurrence: ___%
POST-LT HCC SURVIVAL IN UNOS DATABASE: IMPACT OF WAITING TIME

Schlansky et al, Liver Transplantation 2014; 1045-56
U.S. MULTI-CENTER STUDY ON WAIT TIMES

- Multi-center cohort study of all adults with HCC within Milan criteria by imaging listed with MELD exception from 2002-2012 (n=911)

- 3 study centers chosen to capture spectrum of wait times:
  - Long (UCSF - Center 1)
  - Medium (Mayo Clinic Rochester - Center 2)
  - Short (Mayo Clinic Jacksonville - Center 3)

- Wait time started at HCC diagnosis

Mehta N, et al. Transplantation 2017
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Multivariable HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wait Time to LT &lt;6 or &gt;18 mo</td>
<td>1.6 (1.01-2.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>AFP at HCC dx &gt;400 vs ≤400</td>
<td>3.0 (1.7-5.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Wait time of <6 or >18 mo associated w/ AFP >100 at LT (HR 1.6, 95% CI 1.04-2.6, p<0.03)

Mehta N, et al. Transplantation 2017
THE WAIT TIME “SWEET SPOT”: 6-18 MONTHS

$p=0.049$

- 6-18 months: 10%
- <6 or >18 months: 16%

Mehta N, et al. Transplantation 2017
The “sweet spot” wait time of 6-18 months from HCC diagnosis should be the target to:
1) Minimize HCC recurrence after LT
2) Avoid unnecessary dropout seen with very prolonged wait times

Mehta N, et al. Transplantation 2017
LIVER TRANSPLANTATION FOR HCC: DONOR INFLUENCE ON OUTCOMES?

Donor Factors

3.5 cm

5 yr post-LT survival: ___%
5 yr HCC recurrence: ___%
MARGINAL LIVERS INFLUENCE ON OUTCOMES (HCC AND NON-HCC)

p=0.08 for Standard Liver vs Marginal Liver (DCD, split, steatosis >30%, CIT >12 hrs, donor age>70)

Halazun K et al. Ann Surgery 2016: 441-449
Marginal Livers more likely to have HCC (21% vs 10%)
DONOR INFLUENCE ON HCC RECURRENCE?

**a** Donor diabetes

<table>
<thead>
<tr>
<th>Donor diabetes</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1085</td>
<td>933  727  503  350  225</td>
</tr>
<tr>
<td>No donor diabetes</td>
<td>8528</td>
</tr>
</tbody>
</table>

**b** Donor BMI

<table>
<thead>
<tr>
<th>Donor BMI ≥35 kg/m²</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>8787  7767  6370  4846  3614  2566</td>
</tr>
<tr>
<td>BMI &lt;35 kg/m²</td>
<td>937  819  632  454  324  217</td>
</tr>
</tbody>
</table>

**c** Donor age

<table>
<thead>
<tr>
<th>Donor age &lt;50 years</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6145</td>
<td>5498  4548  3493  2636  1850</td>
</tr>
<tr>
<td>Donor age 50–60 years</td>
<td>1920</td>
</tr>
<tr>
<td>Donor age &gt;60 years</td>
<td>1659</td>
</tr>
</tbody>
</table>
COLD ISCHEMIA TIME INFLUENCE ON HCC RECURRENCE?

LIVER TRANSPLANTATION FOR HCC: DCD INFLUENCE ON OUTCOMES?

Post-LT HCC Survival

DBD and DCD Matched Cohorts with HCC

Post-LT HCC Recurrence

Croome KP, et al.
Am J Transpl 2015; 2704-11
• Donor age >60, donor steatosis/diabetes/obesity, and increased cold ischemia time may lead to small increase in recurrence
• When using marginal livers for HCC, need to maximize chance of a good outcome whenever possible:
  – E.g. Well-compensated patient with well treated tumor likely will not benefit from DCD donor
  – Limit # of risk factors (e.g. if cold ischemia time >10 hours then hopefully donor age <60)
  – Normothermic perfusion for DCD or steatotic livers
OVERVIEW

- Current state of LT for HCC worldwide
- Down-staging and “All-comers” results
- Pushing beyond Milan criteria
  - Identifying important recurrence risk factors
  - Does the donor matter?
- Assessing individualized post-LT recurrence risk using the explant to:
  - Standardized surveillance regimens
  - Tailor immunosuppression
Tumor recurrence is the most common cause of death after LT for HCC with a median survival of ~1 year.

Explant provides a wealth of objective (?) data to better stratify recurrence risk.

Several post-LT models have been recently proposed to estimate post-transplant recurrence (and survival):
- Post- or Combo-MORAL score
- US Multicenter HCC Transplant Consortium nomogram
- RETREAT score

RETREAT SCORE

- Multi-center study, 1060 LT recipients w/ HCC meeting Milan criteria by imaging, developed + validated prediction index for HCC recurrence

- The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score incorporates 3 variables that independently predict recurrence
  - Last AFP prior to LT
  - Microvascular invasion
  - Largest viable tumor diameter + number of viable tumors on explant

Mehta N, et al. JAMA Oncology 2017
RETREAT: EXPLANT TUMOR BURDEN

- Sum of the largest diameter of viable tumor + number of viable tumors on explant

1 viable lesion 4 cm = 5

2 viable lesions 4 cm & 2 cm = 6
2 completely necrotic lesions are not counted
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFP at LT</strong></td>
<td></td>
</tr>
<tr>
<td>21-99</td>
<td>1</td>
</tr>
<tr>
<td>100-999</td>
<td>2</td>
</tr>
<tr>
<td>≥1000</td>
<td>3</td>
</tr>
<tr>
<td><strong>Micro-vascular Invasion</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td><strong>Largest Viable Tumor Size (cm)</strong> + <strong>Number of Viable Lesions</strong></td>
<td></td>
</tr>
<tr>
<td>1-4.9</td>
<td>1</td>
</tr>
<tr>
<td>5-9.9</td>
<td>2</td>
</tr>
<tr>
<td>≥10</td>
<td>3</td>
</tr>
</tbody>
</table>

No RETREAT points scored for: AFP 0-20, no microvascular invasion, and explant pathology stage score of 0

*Mehta N, et al. JAMA Oncology 2017*
RETREAT SCORE: 1 YR RECURRENCE

C Concordance Statistic 0.77

RETREAT Score

- 0: 1% (N=149)
- 1: 3% (N=220)
- 2: 4% (N=155)
- 3: 5% (N=73)
- 4: 11% (N=45)
- ≥5: 39% (N=47)
RETREAT SCORE: 5 YR RECURRENCE

<table>
<thead>
<tr>
<th>RETREAT Score</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>149</td>
<td>3%</td>
</tr>
<tr>
<td>1</td>
<td>220</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>11%</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>29%</td>
</tr>
<tr>
<td>≥5</td>
<td>47</td>
<td>75%</td>
</tr>
</tbody>
</table>
RETREAT VALIDATION IN UNOS (N=3392)

C Statistic 0.75 for HCC recurrence prediction in UNOS
RETREAT VALIDATION IN UNOS (N=3392)

C Statistic 0.75 for HCC recurrence prediction in UNOS

Log-rank $p < 0.001$

RETREAT FOR HCC SURVEILLANCE

<table>
<thead>
<tr>
<th>RETREAT Score</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
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</tr>
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<td>4</td>
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</tr>
<tr>
<td>≥5</td>
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</tr>
</tbody>
</table>
**RETREAT FOR HCC SURVEILLANCE**

<table>
<thead>
<tr>
<th>RETREAT</th>
<th>Proposed surveillance regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No surveillance  (20-25% of the cohort)</td>
</tr>
</tbody>
</table>

*Mehta N, et al.  JAMA Oncology 2017*
RETREAT SCORE: 5 YR RECURRENCE

RETREAT Score

0% 3% 8% 11% 14% 29% 75%

0 1 2 3 4 ≥5

RETREAT Score
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*Mehta N, et al.  JAMA Oncology 2017*
RETREAT SCORE: 5 YR RECURRENCE

RETREAT Score

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<td>HCC surveillance every 6 months for 5 years</td>
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Mehta N, et al.  JAMA Oncology 2017
RETREAT SCORE: 1 YR RECURRENCE

RETREAT Score

0% 1% 3% 4% 5% 11% 39% ≥5

RETREAT Score
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<tr>
<td>4</td>
<td>HCC surveillance every 6 months for 5 years</td>
</tr>
<tr>
<td>5+</td>
<td>HCC surveillance every 3-4 months for 2 years; then every 6 months for years 2-5</td>
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Mehta N, et al. JAMA Oncology 2017
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<tr>
<td>1-3</td>
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<td>4</td>
<td>HCC surveillance every 6 months for 5 years</td>
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<tr>
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<td>HCC surveillance every 3-4 months for 2 years; then every 6 months for years 2-5</td>
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Surveillance should be performed w/ multiphasic abdominal CT or MRI, chest CT, and AFP at the recommended interval
## RETREAT FOR HCC SURVEILLANCE

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<tr>
<td>5+</td>
<td>HCC surveillance every 3-4 months for 2 years; then every 6 months for years 2-5</td>
</tr>
</tbody>
</table>

Consensus statement from participating centers in the multi-center cohort (UCSF, Mayo Clinic Rochester, Mayo Clinic Jacksonville, U. Toronto)

Mehta N, et al. JAMA Oncology 2017
• AFP at Transplant- 42.3
• Explant
  - Evidence of HCC in explant: Necrotic nodule, no viable tumor.
  - Number of tumors: 1, well-circumscribed.
  - Largest Tumor: 3.6 cm, entirely necrosed.
  - Vascular invasion: Necrotic nodule abuts large vessel but does not invade it.
  - Local extension of tumor: Confined to liver.
### Risk Factors for HCC Recurrence

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td><strong>AFP at LT</strong></td>
<td></td>
</tr>
<tr>
<td>0-20</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>100-999</td>
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<tr>
<td><strong>Microvascular Invasion</strong></td>
<td></td>
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<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td><strong>Explant Largest Viable Tumor Size (cm) Plus Number of Viable Lesions</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<tr>
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<td>3</td>
</tr>
</tbody>
</table>
## Predicted HCC Recurrence at 1 and 5 Years after LT

<table>
<thead>
<tr>
<th>Total Points Scored</th>
<th>Predicted HCC Recurrence at 1 yr</th>
<th>Predicted HCC Recurrence at 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0%</td>
<td>2.9%</td>
</tr>
<tr>
<td>1</td>
<td>2.9%</td>
<td>8.0%</td>
</tr>
<tr>
<td>2</td>
<td>4.0%</td>
<td>10.8%</td>
</tr>
<tr>
<td>3</td>
<td>5.1%</td>
<td>13.7%</td>
</tr>
<tr>
<td>4</td>
<td>11.4%</td>
<td>28.7%</td>
</tr>
<tr>
<td>≥5</td>
<td>39.3%</td>
<td>75.2%</td>
</tr>
</tbody>
</table>
Proposed surveillance regimen
1-3 HCC surveillance every 6 months for 2 years

Surveillance should be performed w/ multiphasic abdominal CT or MRI, chest CT, and AFP at the recommended interval.
Proposed surveillance regimen

1-3 months: HCC surveillance every 6 months for 2 years

Surveillance should be performed with multiphasic abdominal CT or MRI, chest CT, and AFP at the recommended interval.

- Ongoing prospective multi-center study evaluating this surveillance protocol
POST-LT IMS: CNIs

- Standard post-LT IMS is CNI (e.g. tacrolimus) w/ mycophenolate and prednisone

- Postulated that CNIs may increase HCC recurrence risk

Rodriguez-Peralvarez et al.  J Hepatology 2013
mTOR regulates cell growth, proliferation, metabolism, and aging

mTOR inhibitors have shown anticancer properties in *in vitro* and animal models
  - Prevents angiogenesis by interfering with VEGF-mediated pathways, thus *potentially limiting tumor growth*
  - Induces extensive microthrombi, thus *potentially inhibiting tumor growth*

mTOR pathway frequently up-regulated in HCC

Many LT centers have shifted to using mTOR based IMS in HCC pts undergoing LT
POST-LT IMS: MTORi

- Yanik et al: SRTR HCC LT recipients, 2002-2012

- 234 sirolimus within 3 mo of LT vs 3702 never treated with sirolimus
  - Linked w/ national pharmacy claims

- Sirolimus pts more likely to be outside Milan (11% vs 5%) but AFPs similar

- No significant differences between the groups in all-cause mortality, cancer-specific mortality, and HCC recurrence

Yanik EL et al, Liver Txp 2016
SILVER TRIAL

Prospective phase 3, multi-center international RCT

Geissler EK et al, Transplantation 2016
SILVER TRIAL: RFS

Prospective phase 3, multi-center international RCT

Geissler EK et al, Transplantation 2016

<table>
<thead>
<tr>
<th>Time point after LTx</th>
<th>Group A (N=256)</th>
<th>Group B (N=252)</th>
<th>P-value (log-rank test)</th>
<th>HR [95% CI*]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>218 (85.2%)</td>
<td>233 (92.5%)</td>
<td>0.0125</td>
<td>0.50 [0.29;0.87]</td>
</tr>
<tr>
<td>2 years</td>
<td>198 (77.3%)</td>
<td>209 (82.9%)</td>
<td>0.1434</td>
<td>0.75 [0.50;1.11]</td>
</tr>
<tr>
<td>3 years</td>
<td>185 (72.3%)</td>
<td>203 (80.6%)</td>
<td>0.0499</td>
<td>0.70 [0.48;1.00]</td>
</tr>
<tr>
<td>4 years</td>
<td>181 (70.7%)</td>
<td>192 (76.2%)</td>
<td>0.2193</td>
<td>0.81 [0.58;1.14]</td>
</tr>
<tr>
<td>5 years</td>
<td>175 (68.4%)</td>
<td>183 (72.6%)</td>
<td>0.3809</td>
<td>0.87 [0.63;1.19]</td>
</tr>
<tr>
<td>6 years</td>
<td>170 (66.4%)</td>
<td>178 (70.6%)</td>
<td>0.4325</td>
<td>0.88 [0.65;1.21]</td>
</tr>
<tr>
<td>7 years</td>
<td>166 (64.8%)</td>
<td>178 (70.6%)</td>
<td>0.2798</td>
<td>0.84 [0.67;1.15]</td>
</tr>
<tr>
<td>8 years</td>
<td>165 (64.5%)</td>
<td>177 (70.2%)</td>
<td>0.2796</td>
<td>0.84 [0.62;1.15]</td>
</tr>
</tbody>
</table>

Sirolimus

No SIR
SILVER TRIAL: OVERALL SURVIVAL

Geissler EK et al, Transplantation 2016
POST-LT IMS

• Consider moving away from studying mTOR inhibitors in all HCC LT recipients, but focus on those most likely to benefit

• Specifically target those with up-regulation of mTOR pathways, which occurs in ~50% of HCC pts
  • Molecular subtyping of explant tumor may prove important, especially w/ 2nd generation mTOR inhibitors that more widely block downstream targets

• At UCSF, pts w/ RETREAT score ≥4 are converted to MTOR based IMS at 4-12 wks post LT

• Recent development of several risk scores to estimate individual HCC recurrence risk

• Tailor post-LT HCC surveillance regimens based on recurrence risk
  • Ongoing prospective studies to determine if this translates into improved outcomes

• Mixed results using mTOR inhibitors → focus on those most likely to benefit
Thank You!

UCSF Transplant Hepatology Team