Evolving Concepts and Strategies in Liver Transplantation for Hepatocellular Carcinoma

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HEPATOCELLULAR CARCINOMA

Liver Transplantation: Milan Criteria

- Solitary tumor 5 cm or less
- 2 to 3 tumors each of 3 cm or less

Tumor number/size as surrogate marker of biology

- Recurrence rate ~ 10%
- 5-year survival > 70%

Outcome comparable to non-HCC patients

Mazzaferro et al, NEJM 1996
LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Expanded criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation
LIVER TRANSPLANTATION FOR HCC
Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation
HEPATOCELLULAR CARCINOMA

Resection or Transplantation?

compensated cirrhosis with preserved liver function
tumor within Milan criteria
no contraindication for liver transplant
### LIVER TRANSPLANTATION FOR HCC

**Patient Survival using Milan Criteria**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>1-yr SV %</th>
<th>5-yr SV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferro</td>
<td>1996</td>
<td>48</td>
<td>84</td>
<td>75</td>
</tr>
<tr>
<td>Llovet</td>
<td>1998</td>
<td>58</td>
<td>84</td>
<td>74</td>
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<tr>
<td>Bismuth</td>
<td>1999</td>
<td>45</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>Jonas</td>
<td>2001</td>
<td>120</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>Yao</td>
<td>2001</td>
<td>64</td>
<td>87</td>
<td>75</td>
</tr>
</tbody>
</table>
HEPATOCELLULAR CARCINOMA

Hepatic Resection for Transplantable Tumor

135 patients with resection for transplantable HCC
- solitary tumor < 5cm
- 2 or 3 tumors <3 cm

Poon et al, Ann Surg 2002
### SALVAGE TRANSPLANTATION

**Are recurrences transplantable?**

135 patients with resection for transplantable HCC
- solitary tumor < 5 cm
- 2 or 3 tumors < 3 cm

Median time to recurrence 16 months (1 to 84 months)

<table>
<thead>
<tr>
<th>Recurrence Type</th>
<th>No. of Patients</th>
<th>Transplantable %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic recurrence alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>solitary &lt; 5 cm</td>
<td>39</td>
<td>79%</td>
</tr>
<tr>
<td>2-3 nodules &lt; 3 cm</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 nodules</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Extrahepatic recurrence alone</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

_Poon et al, Ann Surg 2002_
SALVAGE TRANSPLANTATION

long term outcome

* \( p < 0.05 \)

Ann Surgery 2003

Belghiti et al

Adam et al

* \( p < 0.05 \)
## SALVAGE TRANSPLANTATION

### long term outcome

<table>
<thead>
<tr>
<th></th>
<th>Proportion with recurrence</th>
<th>Survival rate (%)</th>
<th>Recurrence rate (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>3 years</td>
<td>5 years</td>
</tr>
<tr>
<td><strong>Incidental tumour in explant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 of 8</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>No</td>
<td>10 of 52</td>
<td>96</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td><strong>Salvage transplantation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 of 11</td>
<td>100</td>
<td>63</td>
<td>n.a.</td>
</tr>
<tr>
<td>No</td>
<td>5 of 49</td>
<td>96</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td><strong>Transarterial chemoembolization while on list</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 of 5</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>No</td>
<td>9 of 55</td>
<td>96</td>
<td>84</td>
<td>67</td>
</tr>
<tr>
<td><strong>Graft type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living donor</td>
<td>10 of 43</td>
<td>97</td>
<td>80</td>
<td>58</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>0 of 17</td>
<td>94</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td><strong>Graft weight : standard liver weight ratio ≤ 0.6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 of 37</td>
<td>97</td>
<td>78</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>0 of 23</td>
<td>96</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td><strong>Size of largest tumour nodule (cm) ≤ 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 of 56</td>
<td>96</td>
<td>87</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>1 of 4</td>
<td>100</td>
<td>50</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>No. of tumour nodules</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤ 3</td>
<td>7 of 52</td>
<td>98</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>3 of 8</td>
<td>88</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td><strong>Vascular invasion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 of 18</td>
<td>94</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>No</td>
<td>5 of 42</td>
<td>98</td>
<td>91</td>
<td>74</td>
</tr>
<tr>
<td><strong>Beyond Milan criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 of 16</td>
<td>94</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>No</td>
<td>5 of 44</td>
<td>98</td>
<td>89</td>
<td>71</td>
</tr>
<tr>
<td><strong>Beyond UCSF criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 of 9</td>
<td>89</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>No</td>
<td>7 of 51</td>
<td>98</td>
<td>88</td>
<td>72</td>
</tr>
</tbody>
</table>
Salvage Liver Transplantation Is a Reasonable Option for Selected Patients Who Have Recurrent Hepatocellular Carcinoma after Liver Resection

Zhenhua Hu\textsuperscript{1,2,3}, Jie Zhou\textsuperscript{1,2,3}, Xiaofeng Xu\textsuperscript{1,2,3}, Zhiwei Li\textsuperscript{1,2,3}, Lin Zhou\textsuperscript{1,2,3}, Jian Wu\textsuperscript{1,2,3}, Min Zhang\textsuperscript{1,2,3}, Shusen Zheng\textsuperscript{1,2,3*}

China Liver Transplant Registry

Huat et al., PLOS one 2012
HEPATOCELLULAR CARCINOMA

Resection vs Transplantation: Intention-to-treat

**Benefit of Initial Resection of Hepatocellular Carcinoma Followed by Transplantation in Case of Recurrence: An Intention-to-Treat Analysis**

David Fuks,1 Safi Dokmak,1 Valérie Paradis,3 Momar Diouf,1 François Durand,2 and Jacques Belghiti1

*(Hepatology 2012;55:132-140)*

<table>
<thead>
<tr>
<th>Number of Pejorative Histological Factors*</th>
<th>Number of Patients</th>
<th>No Recurrence (n = 22) n (%)</th>
<th>Recurrence Within MC (n = 60) n (%)</th>
<th>Recurrence Beyond MC (n = 30) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>41</td>
<td>10 (24)</td>
<td>31 (76)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>10 (23)</td>
<td>24 (56)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>2 (14)</td>
<td>5 (36)</td>
<td>7 (50)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>4-5</td>
<td>6</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (100)</td>
</tr>
</tbody>
</table>

Abbreviations: LT, liver transplantation; MC, Milan criteria.

*Factors included: microscopic vascular invasion; presence of satellite nodules; tumor size > 3 cm; poorly differentiated tumor; and cirrhosis.
HEPATOCELLULAR CARCINOMA

Resection vs Transplantation: Intention-to-treat

Fuks et al, Hepatology 2012
HEPATOCELLULAR CARCINOMA

Incidence of HCC and Organ donation rate

Incidence of HCC

Organ donation rate

Parkin et al, CA Cancer J Clin 2005
HEPATOCELLULAR CARCINOMA

Primary Transplant for Resectable Tumor: Con

• Deceased donor graft:
  – waiting time and drop outs
  – burden on the waiting list

• Living donor graft: risks of donor

• Need for immunosuppressant with adverse effects

• Higher costs

• Possibility of salvage transplant for recurrence after liver resection
LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Expanded criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation
MELD/PELD score

Deaths on Waiting List in US

Kamath et al, Hepatology 2007
### MELD IMPACT IN HCC LTX

#### HCC - Evolution of MELD Prioritization

<table>
<thead>
<tr>
<th>Stage</th>
<th>Original Feb 2002</th>
<th>April 2003</th>
<th>Jan 2004</th>
<th>Jan 2005</th>
</tr>
</thead>
</table>
| Stage I  
1 tumor < 2cm | 15% Risk =MELD 24 | 8% Risk =MELD 20 | 0 Risk =MELD calculated | 0 Risk =MELD calculated |
| Stage II  
1 tumor ≥ 2CM but < 5 cm or 2-3 tumors largest < 3 CM | 30% Risk =MELD 29 | 15% Risk =MELD 24 | 15% Risk =MELD 24 | 15% Risk =MELD 22 |

Centers recertify every 3 months. Patients continuing to meet stage II definition by either CT or MRI receive additional 10% mortality risk points (~3 MELD points)
HEPATOCELLULAR CARCINOMA

Organ Allocation/Priority System

Hepatocellular Carcinoma Patients Are Advantaged in the Current Liver Transplant Allocation System

T2HCC MELD=22

Washburn et al AJT 2010
LIVER GRAFT ALLOCATION
Implementation of MELD in Hong Kong

July 8, 2003:
MELD for liver graft allocation
  Automatic points for FAP/familial hyperoxaluria
    (2 points every 3 months)
  No automatic points for HCC

October 1, 2009:
Automatic points for T2 HCC-
  upgrade to at least 18 points after on list for 6 months
  additional 2 points every 3 months
LIVER TRANSPLANTATION FOR HCC
Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation
## HEPATOCELLULAR CARCINOMA

### Liver Transplantation: Extended Criteria

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Proposed criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yao, UCSF, 2001</td>
<td>1 nodule &lt; 6.5 cm or ≤3 nodules, ≤4.5 cm, total &lt; 8 cm</td>
</tr>
<tr>
<td>Sugawara, Tokyo 2007</td>
<td>≤5 nodules, ≤5 cm</td>
</tr>
<tr>
<td>Takada, Kyoto 2007</td>
<td>≤10 nodules, ≤5 cm</td>
</tr>
<tr>
<td>Soejima, Fukuoka 2007</td>
<td>Any number, ≤5 cm</td>
</tr>
<tr>
<td>Herrero, Navarra 2007</td>
<td>1 nodule &lt; 6 cm or ≤3 nodules, ≤ 5 cm</td>
</tr>
<tr>
<td>Kwon, Seoul 2007</td>
<td>Any number, ≤5 cm, AFP ≤ 400 ng/ml</td>
</tr>
<tr>
<td>Zheng, Hangzhou 2008</td>
<td>total &lt; 8 cm or total &gt; 8 cm, Grade I/II and AFP &lt; 400 ng/ml</td>
</tr>
<tr>
<td>Mazzaferro, Milan 2009</td>
<td>Up to 7, no microvascular invasion</td>
</tr>
</tbody>
</table>
HEPATOCELLULAR CARCINOMA

Liver Transplantation “Metro Ticket”

The further the distance, the higher the price
LIVER TRANSPLANTATION

Organ Shortage

Demand > Supply: A zero-sum game

Extending criteria = Increasing demand

Organ shortage:

• Mortality on waiting list: when one extended criteria patient receives a graft, another patient on list will die
• Waiting time: increased for all other patients on list

Extending criteria aggravates organ shortage
HEPATOCELLULAR CARCINOMA

Liver Transplantation “Metro Ticket”

The further the distance, the higher the price
HEPATOCELLULAR CARCINOMA

UCSF criteria: How many more?

10 %?

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Milan+</th>
<th>Milan-UCSF+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yao, UCSF 2007</td>
<td>130</td>
<td>38 (29%)</td>
</tr>
<tr>
<td>Duffy, UCLA 2007</td>
<td>173</td>
<td>185 (107%)</td>
</tr>
</tbody>
</table>
HEPATOCELLULAR CARCINOMA

Minimum 5-yr survival justifying OLT in USA

A Novel Model Measuring the Harm of Transplanting Hepatocellular Carcinoma Exceeding Milan Criteria

• Decision analysis using Markov model
• UCSF criteria
• Survival benefit for Milan-UCSF+ HCC patients
• Harms to other patients on list:
  – 44% increase in risk of death
  – Utility loss of 3 quality-adjusted years of life pre/post OLT
– Harm < benefit if 5-yr survival > 61%

Maintaining a zero-sum game

Volk et al AJT 2008
HEPATOCELLULAR CARCINOMA

Minimum 5-yr survival justifying OLT in USA

Wide variation in zero-sum survival threshold

Average 61%
LIVER TRANSPLANTATION FOR HCC
Evolving Concepts and Strategies

• Primary vs salvage transplant
• Prioritization of organ allocation
• Extended criteria
• Biomarkers
• Downstaging
• Living donor liver transplantation
1. Errors in preoperative imaging
   - understaging 20-30%
   - overstaging 10-20%
2. Inter-observer variation in interpretation
3. Difficult to repeat immediately before transplantation
4. Surrogate marker for tumor biology only
   - low volume but high-risk tumor
   - high volume but low-risk
HEPATOCELLULAR CARCINOMA

Poor Prognostic Factor: Vascular Invasion
LIVER TRANSPLANTATION FOR HCC

Biomarkers: Plasma Albumin mRNA

Cheung et al, Transplantation 2008
## BIOMARKERS FOR HCC

*Liver Transplantation: prognostic role of AFP*

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients</th>
<th>cut-off level of AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figueras, 2001</td>
<td>307</td>
<td>AFP &lt; 300 ng/mL</td>
</tr>
<tr>
<td>Ravaioli, 2004</td>
<td>70</td>
<td>AFP &lt;/= 300 ng/mL</td>
</tr>
<tr>
<td>Shetty, 2004</td>
<td>109</td>
<td>AFP &lt;/= 300 ng/mL</td>
</tr>
<tr>
<td>Leung, 2004</td>
<td>144</td>
<td>AFP &lt;/= 100 ng/mL</td>
</tr>
<tr>
<td>Todo, 2004</td>
<td>316</td>
<td>AFP &lt;/= 20 ng/mL</td>
</tr>
<tr>
<td>Yang, 2007</td>
<td>63</td>
<td>AFP &lt;/= 200 ng/mL</td>
</tr>
<tr>
<td>Zheng, 2008</td>
<td>195</td>
<td>AFP &lt;/= 400 ng/mL</td>
</tr>
<tr>
<td>Ravaioli, 2008</td>
<td>177</td>
<td>AFP &lt;300 ng/mL</td>
</tr>
<tr>
<td>Toso, 2009</td>
<td>6478</td>
<td>AFP &lt;/= 400 ng/mL</td>
</tr>
</tbody>
</table>
LIVER TRANSPLANTATION FOR HCC

Progression of AFP as Prognostic Factor

Retrospective study of 153 patients

AFP progression: > 15 ng/mL per month

Vibert et al, AJT 2010
# Liver Transplantation for HCC

**Revised Scoring System**

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. of points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>≤3</td>
</tr>
<tr>
<td>Tumor no. (nodules)</td>
<td>1</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>≤20</td>
</tr>
</tbody>
</table>

3 – 6 points: transplantable
7 – 12 points: not transplantable

*Yang et al, Surgery 2007*
## LIVER TRANSPLANTATION FOR HCC

### Hangzhou Criteria

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Tumor size less than or equal to 8 cm</th>
<th>Preoperative AFP level (≤400 ng/mL)</th>
<th>Histopathologic grades I or II</th>
<th>Fulfilling Hangzhou criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>84</td>
<td>Yes</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Hangzhou criteria (p<0.001)*

Zheng et al, Transplantation 2008
LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation
DOWNSTAGING

Definition - Liver Transplantation

Neo-adjuvant therapy to reduce tumor burden in order to meet criteria for OLT

Beyond criteria

Downstaging

Within criteria
To achieve a 5-yr survival comparable to Milan criteria
DOWNSTAGING

Transarterial Chemoembolization

Proven efficacy for unresectable HCC:
- 50 to 70% response rate
- Improves survival
- Reduce tumor size and number
- Response as indicator of tumor biology
Downstage in size
Downstage in number
DOWNSTAGING

Tumor Necrosis after TACE and Survival

- TACE tumor necrosis + (n=15)
  - 95% (Survival time 1 year)
  - 87% (Survival time 2 years)
  - 87% (Survival time 5 years)

- No TACE (n=57)
  - 74% (Survival time 1 year)
  - 66% (Survival time 2 years)
  - 60% (Survival time 5 years)

- TACE tumor necrosis – (n=39)
  - 72% (Survival time 1 year)
  - 54% (Survival time 2 years)
  - 47% (Survival time 5 years)

DOWNSTAGING
Local Ablation or Resection

Is this successful downstaging?
Should the patient be eligible for transplantation?
## DOWNSTAGING

**Response to TACE**

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Eligibility criteria</th>
<th>Response rate</th>
<th>No. of OLT after downstaging</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majno/1997</td>
<td>Any number &gt; 3 cm</td>
<td>WHO 54%</td>
<td>19</td>
<td>71% at 5 yr</td>
</tr>
<tr>
<td>Graziadei/2003</td>
<td>&gt; Milan no upper limit</td>
<td>WHO 67%</td>
<td>10</td>
<td>41% at 4 yr</td>
</tr>
<tr>
<td>Otto/2006</td>
<td>Milan no upper limit</td>
<td>RECIST 44%</td>
<td>27</td>
<td>75% at 5 yr</td>
</tr>
<tr>
<td>Millonig/2006</td>
<td>&gt; Milan &lt; UCSF</td>
<td>RECIST 85%</td>
<td>28</td>
<td>65% at 5 yr</td>
</tr>
<tr>
<td>Chapman/2008</td>
<td>Milan no upper limit</td>
<td>RECIST 22%</td>
<td>17</td>
<td>94% at 5 yr</td>
</tr>
</tbody>
</table>
## DOWNSTAGING

### Milan criteria as end-point

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Eligibility criteria</th>
<th>Treatment</th>
<th>Success rate</th>
<th>No. of OLT after downstaging</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Yao/2008        | One ≤ 8 cm  
2-3 ≤ 5 cm  
4-5 ≤ 3 cm  
Total ≤ 8 cm | TACE, RFA, PEI, resection         | 71%          | 35                           | 92% at 4 yr      |
| Ravaioli/2008   | One ≤ 6 cm  
2 ≤ 5 cm  
3-5 ≤ 4 cm  
Total ≤ 12 cm | TACE, RFA, PEI, resection         | 69%          | 32                           | 71% at 3 yr      |
| Lewandowski/2009| no upper limit for up to 3 lesions     | Radioembolization                 | 58%          | 9                            | 89% at 1 yr      |
| De Luna/2009    | no upper limit                         | TACE                             | 63%          | 15                           | 79% at 3 yr      |
| Barakat/2010    | no upper limit                         | TACE, RFA, radioembolization      | 56%          | 14                           | 75% at 2 yr      |
Total tumor diameter up to 8 cm
Min observation period of 3 months
Downstaging treatment:
  - TACE
  - RFA
  - Resection

No. of patients: 61

Procedure related deaths: 2 ((3.3%))
Successful down-staging: 43 (70.5%)
Liver transplant: 35
4-yr post-transplant survival: 92.1%

Yao et al, Hepatology 2008

Predictive factor for treatment failure: AFP > 1000 ng/mL

Milan Criteria

DOWNSTAGING

UCSF Protocol

Number of tumors

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8

Yao et al, Hepatology 2008
Total tumor diameter up to 12 cm
Min observation period of 3 months
AFP < 400 ng/mL
Downstaging treatment:
  - TACE
  - RFA
  - PEI
  - Resection

No. of patients
Successful down-staging
Liver transplant
3-yr post-transplant DFS

48
43 (90%)
32 (67%)
71% (18% HCC recurrence)

Ravaioli et al, AJT 2008
LIVER TRANSPLANTATION FOR HCC

Extended Criteria

Is downstaging necessary?

UCSF downstaging protocol

Bologna downstaging protocol
DOWNSTAGING

Modulation or Selection

• Modulation: change tumor biology
  ➢ A 8 cm tumor will have better tumor biology after being down-staged to 4 cm

• Selection: select tumor biology
  ➢ A 8 cm tumor that can be down-staged to 4 cm has better tumor biology
LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

• Primary vs salvage transplant
• Prioritization of organ allocation
• Extended criteria
• Biomarkers
• Downstaging
• Living donor liver transplantation
HEPATOCELLULAR CARCINOMA

Liver Transplantation: Deceased Vs Living Donor

<table>
<thead>
<tr>
<th>Availability</th>
<th>Deceased donor</th>
<th>Living donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Limited</td>
<td>Unlimited</td>
</tr>
<tr>
<td>Candidacy</td>
<td>Maximal benefit</td>
<td>Risk/benefit analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Objective criteria</th>
<th>Dedicated gift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting time</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Timing</td>
<td>Unpredictable</td>
<td>Planned</td>
</tr>
</tbody>
</table>

LDLT: a non-zero-sum game
LIVER TRANSPLANTATION FOR HCC

Number of Operations

Multi-center survey: Hong Kong, Korea, Japan, Singapore, Taiwan

>95% of transplants for HCC from living donors

De Villa and Lo, The Oncologist 2007
Patients with HCC on list

- No voluntary donor: 26
  - On list for CDLT: 30
    - Died before CDLT: 19
    - Alive, off list: 2
    - Alive, waiting: 1
    - CDLT in mainland: 2
    - CDLT performed: 6 (12%)

- Voluntary donor available: 25
  - Donor not suitable: 4
    - HBsAg positive: 2
    - ABO incompatible: 1
    - Liver dysfunction: 1
  - LDLT performed: 21 (41%)

Lo et al, Liver Transplantation 2004
HEPATOCELLULAR CARCINOMA

Intention-to-treat Patient Survival

Lo et al, Liver Transplantation 2004
LIVING DONOR LIVER TRANSPLANTATION

Donor Deaths

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1 + (2)</td>
<td>5 + (2)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>1 + 1 vegetative state</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2 + (1)</td>
<td>4 + (1)</td>
</tr>
<tr>
<td>France</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>N. America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>3 + (3)</td>
<td>3 + (3)</td>
</tr>
<tr>
<td>S. America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Total: 14 (6)

( ) Late deaths possibly/unlikely related to surgery

Donor mortality 5/7573 (0.07%)

Donor mortality 7/4598 (0.15%)

Trotter, Adam and Lo Liver Transplantation 2006
LIVING DONOR LIVER TRANSPLANTATION

Benefits and Risks

- Donor's Risk
- Recipient's Benefit

Gain in survival

Donor's Risk
LIVER TRANSPLANTATION FOR HCC

Recurrence Rate: Deceased Donor vs Living Donor

Lo et al, BJS 2007
Fisher et al, AJT 2007

LDLT: Living donor liver transplantation  DDLT: Deceased donor liver transplantation
# LIVER TRANSPLANTATION FOR HCC

*Recurrence Rate: Deceased Donor vs Living Donor*

<table>
<thead>
<tr>
<th></th>
<th>DDLT</th>
<th>LDLT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage transplant</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Waiting time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor behavior</td>
<td>Slow growing</td>
<td>No selection</td>
</tr>
<tr>
<td>Bridging treatment</td>
<td>Responsive</td>
<td>No selection</td>
</tr>
<tr>
<td><strong>Graft size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Regeneration</td>
<td>Less</td>
<td>More</td>
</tr>
</tbody>
</table>
HEPATOCELLULAR CARCINOMA

Living Donor Liver Transplantation
# LIVING DONOR LIVER TRANSPLANTATION

## Right vs Left Lobe

<table>
<thead>
<tr>
<th></th>
<th>Right lobe (n=330)</th>
<th>Left lobe (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor/Recipient sex match</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M to F</td>
<td>34</td>
<td>12</td>
<td>0.000</td>
</tr>
<tr>
<td>F to M</td>
<td>167</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>M to M or F to F</td>
<td>129</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Recipient BW (Kg)</td>
<td>66(42.5-116)</td>
<td>57.5(39.5-79)</td>
<td>0.005</td>
</tr>
<tr>
<td>Donor BW (Kg)</td>
<td>56.5(37-108.5)</td>
<td>73.5(51-109.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>GW (g)</td>
<td>600(320-1140)</td>
<td>410(310-623)</td>
<td>0.000</td>
</tr>
<tr>
<td>GW to Recipient BW (%)</td>
<td>0.91(0.49-1.95)</td>
<td>0.73(0.49-1.28)</td>
<td>0.000</td>
</tr>
<tr>
<td>GW to Recipient SLV (%)</td>
<td>49.3(28.4-89.4)</td>
<td>36.5(27.3-54.9)</td>
<td>0.000</td>
</tr>
<tr>
<td>GW to Recipient SLV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40%</td>
<td>60</td>
<td>15</td>
<td>0.000</td>
</tr>
<tr>
<td>40% to 60%</td>
<td>217</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>&gt;60%</td>
<td>53</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Liver transplantation using small-for-size liver graft in a rat model

Invasive tumor growth and recurrence

Hepatic sinusoidal disruption

Inflammatory cascades
Cell adhesion, migration and invasion

Tumor cell proliferation
Angiogenesis

Mobilization of circulating EPCs

CXCL10

Circulating EPC/10^5PBMC

Day1 Day3 Day5

Man et al, Annals of Surgery 2008
Man et al, Annals of Surgery 2010
HEPATOCELLULAR CARCINOMA

Liver Transplantation “Metro Ticket”

The further the distance, the higher the price

What is the minimum recipient survival that would justify a donor’s risks?

Mazzaferro et al, Lancet Oncology 2009
HEPATOCELLULAR CARCINOMA

Selection criteria for LDLT: QMH Approach

Milan criteria (1996)

UCSF criteria (2001)

For LDLT

Survival estimation

>50% survival at 5 years
HEPATOCELLULAR CARCINOMA

Liver Transplantation

OLT ~15,000

OLT for HCC ~3000

HCC >600,000
LIVER TRANSPLANTATION

Disease Indications

Multi-center survey: Hong Kong, Korea, Japan, Singapore, Taiwan

De Villa and Lo, The Oncologist 2007
LIVER TRANSPLANTATION

*HCC as Disease Indication*

- Europe 10%
- USA 10% (pre-MELD) 20% (post-MELD)
- Asia 30-40%
- Mainland China 50%