Liver Transplantation for Hepatocellular Carcinoma

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Hepatocellular Carcinoma

- HCC is the 5th most common cancer and the most common primary liver tumor.
- Incidence of HCC increasing rapidly, second only to thyroid cancer in the change
- Appears most commonly in diseased liver
- Change in prevalence of Hepatitis C and non-alcoholic fatty liver disease driving increase in incidence.
• “Epidemic” of HCV
• Predicted to have long term effects on need for liver transplantation
• HCV major risk factor for HCC.
Age-specific incidence of acute, symptomatic HCV infection reported in four sentinel U.S. counties from 1983 to 1989.

HCV+ by listing year and age – HCC

# HCV+ by listing year and age

- 71+
- 66-70
- 61-65
- 56-60
- 51-55
- 46-50
- 41-45
- 36-40
- 31-35
- 26-30
- 18-25
- 0-17

listing year

Obesity, NASH and HCC
Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
Prevalence of NAFLD and NASH

NAFLD and NASH prevalence

<table>
<thead>
<tr>
<th>Category</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD overall</td>
<td>46</td>
</tr>
<tr>
<td>NAFLD-Hispanic</td>
<td>58.3</td>
</tr>
<tr>
<td>NAFLD-Caucasian</td>
<td>44.6</td>
</tr>
<tr>
<td>NAFLD-African American</td>
<td>35.1</td>
</tr>
<tr>
<td>NASH overall</td>
<td>12.2</td>
</tr>
<tr>
<td>NASH among diagnosed NAFLD</td>
<td>29.9</td>
</tr>
</tbody>
</table>
NASH and HCC

- Recent study of healthcare claims database
  - 59% of the HCC cases were associated with NASH as compared to 22% with HCV.
  - In 38% of the patients, NASH was the only identified risk factor.

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NASH and Liver Transplantation

• By 2020 NASH is expected to exceed HCV as an indication for liver transplantation
Registration for OLT

NASH

NASH & HCC
NASH Demographics

• New Epidemic
• Older patients
  – Diabetes
  – CAD
  – Hypertension
• Management of recurrence after transplantation
Pathogenesis of HCC

• Development of cirrhosis/fibrosis is key step in pathogenesis of HCC
• 88% of patients undergoing resection for HCC had fibrosis, 2% had normal livers.
• Chronic hepatitis C before stage III (bridging fibrosis) or stage IV (cirrhosis) **NOT** found to be at increased risk for HCC
Because of field effect of viral infection and cirrhosis, multiple neoplastic processes can be present at one time.

Development of HCC appears to be a progressive disease in the liver.

HCC, HCC in-situ and dysplastic nodules at the same time.

High frequency of bilobar disease.

Similar to the development of colon CA in familial polyposis and ulcerative colitis
Risk of HCC

- Greatest risk factor for development of HCC is a pre-existing HCC in the liver, similar to breast or colon cancer.
- Development of 2\textsuperscript{nd} HCC is 20%/year vs 3-5%/year in cirrhotics without HCC.
Recurrence of HCC after Ablation

Koike Hepatology 2000

Number of recurrence

<table>
<thead>
<tr>
<th>Overall recurrence</th>
<th>0</th>
<th>49</th>
<th>100</th>
<th>114</th>
<th>127</th>
<th>129</th>
<th>130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence at different site</td>
<td>0</td>
<td>41</td>
<td>86</td>
<td>98</td>
<td>105</td>
<td>107</td>
<td>108</td>
</tr>
<tr>
<td>Recurrence at adjacent site</td>
<td>0</td>
<td>15</td>
<td>27</td>
<td>32</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Patients at risk</td>
<td>236</td>
<td>173</td>
<td>99</td>
<td>56</td>
<td>25</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Overall recurrence
Recurrence at site different from primary lesion
Recurrence adjacent to primary lesion
Early versus Late Recurrence after Liver Resection for HCC

• Intrahepatic recurrence was observed in 143/213 patients
  – 109 early (<2 years) and 34 late recurrences (>2 years)
  – Independent prognostic factors for risk of recurrence were
    • Cirrhosis
    • Chronic active hepatitis (CAH)
    • HCV positivity
  – Cumulative effect for multiple risk factors (92.5% of recurrences in patients with all 3 factors)
  – Only cirrhosis was related to late recurrence

Summary of Pathogenesis

- HCC occurs primarily in the cirrhotic or fibrotic liver
- Multiple neoplastic and pre-neoplastic lesions commonly present
- High risk of recurrence of disease.
Resection vs. Transplantation
Criteria for Resection

- Adequate functional reserve
  - No portal hypertension
  - ? No cirrhosis
- Single Lesion
Radiological Staging

- The sensitivity of current radiological techniques for small hepatocellular carcinoma is low.
- Helical CT scan only detects about 70% (sensitivity range 44-93) of tumor nodules.
- MRI about 80% (sensitivity range 54-93).
- Detection of dysplastic nodules lower because of lack of arterialization.
- Background of cirrhosis makes discrimination difficult.
Current Radiological Techniques

- Frequently miss a second small lesion
- Sensitivity limited by lesion size and degree of progression to HCC
- Many patients with HCC will have a missed metachronous lesion that leads to early recurrence after resection
Early Recurrence After Resection

- Intrahepatic recurrence was observed in 143/213 patients
  - 77% of recurrences within 2 years

- Independent prognostic factors for risk of recurrence were
  - Cirrhosis
  - Chronic active hepatitis (CAH)
  - HCV positivity

- 92.5% of recurrences in patients with all 3 factors
- Only cirrhosis was related to late recurrence

Survival Following Resection

• What are the reported outcomes of resection in HCC?
Average Survival at 3 and 5 years

Jaeck, D  Liver Transplantation 2004
“Best Results Of Resection”

1996 – 2005  Child A → HR HCC < 3 cm
  1.9% mortality
  5 year survival 75%
  5 year disease free survival 53%

“These are the best results that can be achieved by liver resection for HCC in Child A cirrhosis.”

Poon RTP Dig Dis 2007; 25:334
Improving Resection Outcome

• Retinoid Therapy
  – Muto reported a randomized trial of polypranoic acid in prevention of recurrent disease.
  – This retinoid may prevent progression of dysplasia.

• Sorafenib
  – Effective in prevention of progression in late stage HCC
  – No results from trials for adjuvant therapy
“The key still rests in trying to identify these people (who can benefit from a resection) in a prospective manner.”
How To Get Better Resection Outcomes

- Selection of high risk for recurrence - Genetic Markers

![Graph showing survival rates with legend for Good and Poor prognosis, with P=0.003.](image)

**Legend:**
- Good prognosis
- Poor prognosis

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good prognosis</td>
<td>0</td>
<td>131</td>
</tr>
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<td></td>
<td>2</td>
<td>52</td>
</tr>
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<td></td>
<td>4</td>
<td>17</td>
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<td></td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Liver Transplantation
Liver Transplant for HCC
Milan Criteria (Stage I+II)

Single, not > 5cm

Up to 3, none > 3cm

+ Absence of Macroscopic Vascular Invasion
+ Absence of Extrahepatic Spread

Entry Criteria

Milan Criteria


Criteria =

1. tumor ≤ 5cm, or
2. ≤ 3 tumors ≤ 3cm

**Criteria met**

**Criteria not met**

P = 0.002 by the log-rank test

Recurrence-free Survival (%)

Months after Transplantation
# Liver Transplantation for HCC

## Best Reported Outcome

<table>
<thead>
<tr>
<th>Author, Journal, Yr</th>
<th>Center</th>
<th>N</th>
<th>Actuarial Survival 1-Yr</th>
<th>Actuarial Survival 5-Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferro, NEJM 1996</td>
<td>Milan, Italy</td>
<td>48</td>
<td>84%</td>
<td>74%</td>
</tr>
<tr>
<td>Llovet, Hepatology 1998</td>
<td>Barcelona, Spain</td>
<td>58</td>
<td>84%</td>
<td>74%</td>
</tr>
<tr>
<td>Bismuth, Sem Liver Dis 1999</td>
<td>Villejuif, France</td>
<td>45</td>
<td>82%</td>
<td>74%</td>
</tr>
<tr>
<td>Jonas, Hepatology 2001</td>
<td>Berlin, Germany</td>
<td>120</td>
<td>90%</td>
<td>71%</td>
</tr>
<tr>
<td>Yao, Hepatology 2001</td>
<td>San Francisco</td>
<td>64</td>
<td>87%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Adopted from Bruix and Llovet, *Hepatology* 2002;35:519-524
Beyond Milan
Entry Criteria

Milan Criteria


Criteria = 1 tumor ≤ 5cm, or ≤ 3 tumors ≤ 3cm

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![Graph showing recurrence-free survival over time after transplantation. The graph compares patients who met the Milan Criteria with those who did not. The x-axis represents months after transplantation, ranging from 0 to 48, and the y-axis represents recurrence-free survival in percent. Over time, the survival rates for patients meeting the criteria are higher and more stable compared to those who do not meet the criteria. A statistical significance of P = 0.002 by the log-rank test is indicated.](image-url)
Transplantation for tumors > 5cm

A. Recurrence-free survival based on tumor size

- tumors 5-7 cm
- tumors > 7 cm

B. Recurrence-free survival based on presence of vascular invasion

- no vascular invasion
- micro- or macro-
How To Select Patients With Biologically Favorable Tumors

• Wait to see which tumors behave poorly.
  • Hope tumor doesn’t change while you wait/Control

• Measure something about the tumor that predicts tumor biology.
  – Microsatellites
  – Bone marrow for tumor
  – Albumin mRNA
DOWN-STAGING OF HCC THEORETICAL CONSTRUCT?

Paradigm- “A 8-cm HCC is always a 8-cm HCC”
UCSF DOWN-STAGING PROTOCOL
INCLUSION CRITERIA

• No vascular invasion on imaging
• 1 lesion $>5$ cm but $\leq 8$ cm
• 2 or 3 lesions, none $>5$ cm and total tumor diameter of all lesions $\leq 8$ cm.
• 4 or 5 lesions, none $>3$ cm and total tumor diameter of all lesions $\leq 8$ cm.

Successful Down-staging Criteria

+ 3 months
## Baseline Characteristics (N=88)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>58.4 (45.3-72.8)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>72/16</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>51 (58%)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>21 (24%)</td>
</tr>
<tr>
<td>Median AFP (range)</td>
<td>24.4 (2.7-10,310)</td>
</tr>
<tr>
<td>Child Class</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>47 (53%)</td>
</tr>
<tr>
<td>B</td>
<td>31 (35%)</td>
</tr>
<tr>
<td>C</td>
<td>10 (11%)</td>
</tr>
</tbody>
</table>
Meet down-staging criteria (n=88)

- Pre-OLT Treatment Failure
  - n=24
  - Tumor progression 19
  - Deaths without OLT 5

- Awaiting OLT
  - n=11

- OLT n=50
  - CLT 47
  - LDLT 3

- Excluded from OLT (censored)
  - n=3

- Complete tumor necrosis 22
- Pathologic stage T2 23
- Pathologic stage >T2 5

- Alive without recurrence 42
- Post-OLT deaths unrelated to HCC 5
- Post-OLT deaths related to HCC 1
- Post-OLT recurrence 2
Post-Transplant Survival

Kaplan-Meier Probabilities

Follow-up in Years

N=50

97.6%

83.8%
Recurrence-Free Probability

Kaplan-Meier Probabilities

Follow-up in Years

N=50

97.8% after 4 years

95.0% after 5 years
Successful down-staging can be achieved in the majority of carefully selected patients with HCC exceeding conventional T2 criteria, and is associated with excellent post-transplant outcome.

Down-staging allows selection of a subgroup of tumors with more favorable biology that are more likely to respond and do well after liver transplantation.

Down-staging may eliminate the need for criteria
Entry Criteria
Milan Criteria

Criteria = 1 tumor ≤ 5cm, or ≤ 3 tumors ≤ 3cm

P = 0.002 by the log-rank test

Ablate and Wait

- Results in down-staged patients appear better than patients with lower stage disease who undergo transplantation.
- Down-staging suggests that waiting after ablation culls out patients at risk for recurrence.
- Should all patients be ablated and wait prior to transplantation to select patients who have occult extra-hepatic disease or bad tumor biology?
Future Course

• Criteria for transplantation
  – Dependent on tumor biology related to size and number
  – Time will tell the biology
  – Tumor biology should have time to be expressed

• Resection/Ablation/TACE
  – Should be used to prevent tumor evolution
  – Allow time for maturity

• Low MELD HCC patients should have low priority for transplantation
  – HCC Patients with low MELD should have time to express biology
  – HCC Patients with high MELD should be transplanted with criteria
Liver Transplantation for HCC

- Prevents recurrent disease
- In current US environment, waiting times favor transplantation.
- Downstaging of tumor outside of Milan appear to be effective if we allow enough time for tumor recurrence to appear.