Estimation of Prognosis and Candidacy for Liver Transplantation

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3rd APASL HCC Conference, Cebu, Philippines
Adult Liver Transplantation

Jan 1999 – May 2009

LDLT 286

DDLT 106

- HBV+/-
- HCC
- HCV+/-
- HCC
- Alcoholic
- Re-LTX
- Others
- Budd-Chiari
- HCV+/
- HCC
- HBV+/
- HCC
- PBC
- Wilson's
- HBV+HCV
- HEHE
- Re-transplant

LDLT 286

DDLT 106
Liver Transplantation for HBV

- Lamivudine 100 mg qd
  - HBeAg(+) / HBV DNA(+): pretransplant
  - HBeAg(-) / HBV DNA(-): from POD 1

- Adefovir or Entecavir for mutant

- HBIG 10,000 IU anhepatic phase
  - 2,000 IU qD x 7D

- HBsAb ≥ 100 m IU/mL

Taiwan National Health Insurance Policy
LDLT for HBV

- Actuarial survival rates
  - 1-year 94%
  - 5-year 91%

- 2 HBV recurrence (2.4%)

- Hospital mortalities 3

- Late mortalities 3
  - HCC lung metastasis
  - Gastric carcinomatosis
  - Veno-occlusive disease

Preoperative vaccination

- Anti-HBs titer >1000
  - No prophylaxis
    - Booster vaccination after steroid withdrawal
- Anti-HBs titer <1000
  - Donor Anti-HBc (-)
    - No prophylaxis
  - Donor Anti-HBc (+)
    - Lamivudine for 2 years

Liver Transplantation for HCV

Treatment Guidelines

- ALT ≥ 2X; 2 determinations, 3 months apart within 6 months
- Liver biopsy ≥ F1 fibrosis score
- Pegylated interferon alpha-2a or alpha-2b + Ribavirin

Taiwan National Health Insurance Policy
LDLT for HBV vs. HCV

Survival (HBV and HCV)

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>60.00</td>
</tr>
<tr>
<td>0.2</td>
<td>48.00</td>
</tr>
<tr>
<td>0.4</td>
<td>36.00</td>
</tr>
<tr>
<td>0.6</td>
<td>24.00</td>
</tr>
<tr>
<td>0.8</td>
<td>12.00</td>
</tr>
<tr>
<td>1.0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HBV (N=55)

HCV (N=20)

HCC(+)

HBV 72 months

HCV 57 months

HCC(-)

HBV 66 months

HCV 38 months

p=0.071
# ALF vs. Acute-on-Chronic vs. DELF

## Univariate analysis between subtypes of liver failure versus postoperative outcome after transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALF (n=4)</th>
<th>ACLF (n=22)</th>
<th>CDLF (n=3)</th>
<th>Total (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative mortality</strong></td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
<td>6.9%</td>
<td>0.001*</td>
</tr>
<tr>
<td><strong>Short term morbidity</strong></td>
<td>100%</td>
<td>77.27%</td>
<td>66.67%</td>
<td>77.8%</td>
<td>0.674</td>
</tr>
<tr>
<td><strong>GWSLV recipient % (SD)</strong></td>
<td>75.650 (13.543)</td>
<td>67.750 (21.534)</td>
<td>60.733 (21.786)</td>
<td>68.114 (20.381)</td>
<td>0.639</td>
</tr>
<tr>
<td><strong>Median postoperative ICU days (25-75% CI)</strong></td>
<td>26 (23-69.5)</td>
<td>21.5 (19-31)</td>
<td>32 (31.250-34.250)</td>
<td>24 (20-32)</td>
<td>0.154</td>
</tr>
<tr>
<td><strong>Median extubation day (25-75% CI)</strong></td>
<td>7 (3-18.5)</td>
<td>2 (1-8)</td>
<td>2 (2-9.5)</td>
<td>2 (2-10.25)</td>
<td>0.285</td>
</tr>
<tr>
<td><strong>Mean hospital stay in days (25-75% CI)</strong></td>
<td>65.75 (+/-35.208)</td>
<td>56.636 (+/-18.854)</td>
<td>56 (+/-11.79)</td>
<td>57.828 (+/-20.489)</td>
<td>0.721</td>
</tr>
</tbody>
</table>

CI, Confidence interval; *p<0.05 is considered significant
Kaplan-Meier survival curves showing patient survival in the 3 subtypes of liver failure

ALF vs. Acute-on-Chronic vs. DELF
HCC in Asia

Asia accounts for 78% of 600,000 reported globally/year

- Aflatoxin, algal hepatotoxins in contaminated water
- Betel nut chewing, alcohol
- Chronic hepatitis infection

**Chronic HBV:** 1-5% Japan, Singapore, Thailand
6-10% Northern China, Indonesia
>10% Taiwan, Korea, Philippines

**Chronic HCV:** Japan and Taiwan

- HCC disease-control measures involving surgical, locoregional, systemic strategies remain highly relevant

# Child-Turcotte-Pugh Classification

## Definition of the Child-Turcotte-Pugh Stage Classification

<table>
<thead>
<tr>
<th></th>
<th>Class A</th>
<th>Class B</th>
<th>Class C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>none</td>
<td>mild</td>
<td>coma</td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
<td>responsive</td>
<td>unresponsive</td>
</tr>
<tr>
<td>Serum bilirubin, mg/dl</td>
<td>&lt;2.0</td>
<td>2.0–3.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>&gt;3.5</td>
<td>2.8–3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Prothrombin activity, %</td>
<td>&gt;70</td>
<td>40–70</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

Class A: score 5-6  
Class B: score 7-9  
Class C: score 10-15
Japan Society of Hepatology Consensus

BCLC Staging and Treatment Schedule

Stage 0
- PST 0, Child-Pugh A
- Very early stage (0)
  - Single < 2 cm
  - Carcinoma in situ
  - Single
  - Portal pressure/ bilirubin
    - Normal
    - Increased

Stage A-C
- Early stage (A)
  - Single or 3 nodules < 3 cm, PS 0
  - 3 nodules ≤ 3 cm
  - Increased
  - Associated diseases
    - No
    - Yes

Stage D
- Advanced stage (C)
  - Portal invasion, N1, M1, PS 1-2
  - Portal invasion, N1, M1
  - Terminal stage (D)

Treatment Options:
- Resection
- Liver Transplantation (CLT/LDLT)
- PEI/RF
- Chemoembolization
- New Agents

- Curative Treatments (30%)
  - 5-yr survival: 50-70%
- Randomized controlled trials (50%)
  - 3-yr survival: 20-40%
- Symptomatic (20%)
  - 1-yr survival: 10-20%
## Prognostic Variables in the Staging Systems

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tumor stage</th>
<th>Liver function</th>
<th>Health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okuda stage [7]</td>
<td>50% liver involvement</td>
<td>Bilirubin</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ascites</td>
<td></td>
</tr>
<tr>
<td>French [26]</td>
<td>Portal invasion</td>
<td>Bilirubin</td>
<td>Karnofsky</td>
</tr>
<tr>
<td></td>
<td>AFP</td>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>CLIP [27]</td>
<td>Portal invasion</td>
<td>Child-Pugh</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(&lt;/&gt;/) 50% liver involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AFP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCLC [4,11]</td>
<td>Portal invasion</td>
<td>Child-Pugh</td>
<td>PST</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
<td>Portal hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morphology</td>
<td>Bilirubin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Okuda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CUPI [28]</td>
<td>TNM</td>
<td>Ascites</td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td>AFP</td>
<td>Bilirubin</td>
<td></td>
</tr>
<tr>
<td>TNM [29]</td>
<td>Morphology</td>
<td>Alkaline phosphatase</td>
<td>Fibrosis</td>
</tr>
<tr>
<td></td>
<td>Vascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JIS score [30]</td>
<td>TNM</td>
<td>Child-Pugh</td>
<td>–</td>
</tr>
<tr>
<td>ER [31]</td>
<td>Estrogen receptor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HCC in Patients with Cirrhosis

For patients with resectable HCC

- Conventional treatment is partial hepatectomy
- Major hepatic resection can be performed safely
- Key is preservation of liver function after resection
- Treatment modalities to increase remnant liver volume
- Multi-modality treatments to make the tumor operable
For patients with non-resectable HCC

- Best treatment seems to be in combination strategies (TAE, RFA, PEI) with or without systemic chemotherapy
- Drug eluting bead and Y-90 alone with or without chemotherapy has the potential to downstage unresectable HCC to become resectable
- Liver transplantation for select patients
HCC in Patients with Cirrhosis

Liver Transplantation: Rationale

- Most HCC multifocal
- Best oncologic resection
- Treat underlying cirrhosis and restore normal liver function
Liver Transplantation for HCC

Potential Advantages

• Eliminates the tumor
• Cures the underlying disease
• Lower recurrence rate
• Good survival in selected cases
Liver Transplantation for HCC

Potential Disadvantages

• High economic cost
• Recurrence of viral diseases
• Limited donor resources
Liver Transplantation for HCC

Indications

- Worsening cirrhosis with poor functional reserve
- Complications: EVB, SBP, encephalopathy
- Limited tumor without vascular invasion
- Age < 65 years
- No contraindication to major surgery
LT for HCC with Cirrhosis

Milan Criteria (Stage I+II)

- Single, not > 5cm
- Up to 3, none > 3cm

+ Absence of Macroscopic Vascular Invasion
  Absence of Extrahepatic Spread

Criteria for Transplantation

Hepatocellular Carcinoma

**Milan criteria**
- Solitary ≤ 5 cm
- ≤3 tumors
  - none > 3 cm

**UCSF criteria**
- Solitary ≤ 6.5 cm
- ≤3 tumors
  - none > 4.5 cm
- Total diameter ≤ 8 cm

- Important factor for tumor recurrence: vascular invasion
- Anticipated by tumor size and number
- Tumor biology & differentiation characteristics
Pre-Transplant Down-Staging

Tumor Beyond Milan

Tumor Fits Milan

Transplantation

Re-stage

Tumor Beyond Milan

Tumor Fits Milan

Re-stage

Tumor Beyond Milan

Tumor Fits Milan

Concejero A, Chen CL et al. Transplantation 2008, 85: 398
Pre-Transplant Down-Staging

Pre-TAE

Post-TAE
Pre-Transplant Down-Staging

Tumor size (cm)

N=8, Beyond Milan criteria

TAE & / or PEI

N=8, Within Milan criteria

Concejero A, Chen CL et al. Transplantation 2008, 85: 398
Initially Beyond Milan Criteria

- biggest 5.5 cm
- diaphragmatic invasion
- 80% necrosis
- 2 satellite nodules (1.5 cm)
- microscopic PVT (+)
Liver Transplantation for HCC

- Sequential Liver Transplantation “salvage transplantation”

- High pathological risk of recurrence after surgical resection: an indication for salvage transplantation

Sala M. Liver Transpl. 2004; 10:1294
Sequential LDLT

Resection
July 12, 2001

Concejero AM, Chen CL et al. Transplantation 2008, 85: 398
Sequential LDLT

LDLT Oct. 23, 2001

6 mm HCC

Concejero AM, Chen CL et al. Transplantation 2008, 85: 398
Salvage Transplantation

Resection June 11, 2002

Concejero A, Chen CL et al. Transplantation 2008, 85: 398
Salvage Transplantation
HCC vs. non-HCC

<table>
<thead>
<tr>
<th></th>
<th>HCC</th>
<th>Non-HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>93.3%</td>
<td>97.4%</td>
</tr>
<tr>
<td>5-year</td>
<td>81.5%</td>
<td>91.2%</td>
</tr>
</tbody>
</table>

p=NS

LDLT for HCC

Non-HCC, n=134
HCC, n=126
LDLT for HCC

Overall vs. Hepatitis

HBV, n=85
Overall, n=126
HCV, n=26

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>93.3%</td>
<td>97.2%</td>
<td>90.0%</td>
</tr>
<tr>
<td>5-year</td>
<td>81.5%</td>
<td>94.4%</td>
<td>57.2%</td>
</tr>
</tbody>
</table>
Non-estimated Survival Rates:

• 1 year: 98%
• 3 year: 96%
• 5 year: 90%

Concejero A, Chen CL et al. Transplantation 2008, 85: 398
Liver Transplantation for HCC

Summary

• More patients are selected for transplantation based on expanded clinical criteria
• Refinement of selection and extension of criteria in number of tumor and use of tumor markers produces acceptable results and benefits
• Eradication of circulating cancer cells may be the focus of future research
• LDLT for early HCC due to graft shortage seems logical
Pediatric Liver Transplantation

1984.3 – 2010.3

LDLT 191

Biliary Atresia

- Cryptogenic
- Urea cycle
- Re-transplant
- Fulminant
- Polycystic
- Alagille
- Wilson
- GSD
- NH

DDLT 40

Biliary Atresia

- Re-transplant
- Wilson
- NH
- GSD
- Urea cycle
- Polycystic
- Fulminant
- Alagille
- Wilson
- GSD
- NH
LDLT for Biliary Atresia

June 1994 – September 2005

- 237 LDLT
- 124 pediatric LDLT
- 100 LDLT for BA
- mean follow-up: 85 months (range: 13-148)

LDLT for Biliary Atresia

Real-Time Survival Rates

- 6 – month  99%
- 1 – year    98%
- 5 – year    98%

First Successful Liver Transplant in Asia

March 22, 1984

Liver Transplantation for Wilson’s Disease
Report of the first successful liver transplant in Taiwan
November 3, 1985

Liver Transplant for Wilson’s Disease

- Life-saving procedure for end-stage Wilsonian cirrhosis
- Normalization of biochemical defects of copper metabolism
- Reversion of neurological impairments
- Disappearance of Kayser-Fleischer rings
- Abatement of secondary amenorrhea

Liver Transplant for Wilson’s Disease

Liver Transplant for Wilson’s Disease

Liver Transplant for Wilson’s Disease

Neurological Improvement

Liver Transplant for Wilson’s Disease

Kayser-Fleischer rings

Pre-transplant

Post-transplant

Liver Transplant for Wilson’s Disease

- Mean follow-up: 114.1 months
  range: 36-192

- 6 of 7 Wilson’s disease adolescents are surviving after transplant to date

- The only mortality died of traffic accident 3 years post transplant
• 13 GSD / 400 LTx = 3%
  13 GSD / 174 Ped LTx = 7.5%

• GSD type I  10
  GSD type II  3

• Mean age at presentation : 6.98 years

• All presented with metabolic abnormalities

• All unresponsive to medical treatment

• Mean post transplant follow-up : 47.40 months

## Biochemical Parameters Pre and Post Transplantation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-Tx</th>
<th>Post-Tx 3m</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>34.24</td>
<td>6.34</td>
<td>0.002</td>
</tr>
<tr>
<td>AST</td>
<td>272.73</td>
<td>34</td>
<td>0.036</td>
</tr>
<tr>
<td>ALT</td>
<td>209.18</td>
<td>25.09</td>
<td>0.014</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>473.36</td>
<td>158.09</td>
<td>0.008</td>
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<tr>
<td>Cholesterol</td>
<td>258.62</td>
<td>143.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.463</td>
<td>0.609</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Catch-up weight-for-age and height-for-age in children with pre-transplant growth retardation after LDLT

Pediatric LDLT

Better long-term survival due to

- Careful preoperative planning
- Better anesthesia management
- Meticulous surgical techniques
- Prompt detection and treatment of complications
- Improved use of immunosuppression
Thank You For Your Kind Attention
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Actuarial Survival</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzafero</td>
<td>1996</td>
<td>90% 75%</td>
<td>NEJM</td>
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<tr>
<td>Bechstein</td>
<td>1998</td>
<td>88% 71%</td>
<td>Transplant Int</td>
</tr>
<tr>
<td>Llovet</td>
<td>1999</td>
<td>84% 74%</td>
<td>Hepatology</td>
</tr>
<tr>
<td>Iwatsuki</td>
<td>2000</td>
<td>73% 49%</td>
<td>J Am Coll Surg</td>
</tr>
<tr>
<td>Yao</td>
<td>2001</td>
<td>91% 72%</td>
<td>Hepatology</td>
</tr>
<tr>
<td>Margarit</td>
<td>2002</td>
<td>81% 58%</td>
<td>World J Surg</td>
</tr>
<tr>
<td>Perez- Saborido</td>
<td>2003</td>
<td>79.3% 50.3%</td>
<td>Transplant proc</td>
</tr>
<tr>
<td>Leung</td>
<td>2004</td>
<td>80.3% 46.7%</td>
<td>Liver transplantation</td>
</tr>
<tr>
<td>Zavagilia</td>
<td>2005</td>
<td>84% 72%</td>
<td>Am J Gastroenterol</td>
</tr>
<tr>
<td>Grasso</td>
<td>2006</td>
<td>79% 53%</td>
<td>Transplantation</td>
</tr>
<tr>
<td>Sugawara</td>
<td>2007</td>
<td>91% 75%</td>
<td>Dig Dis</td>
</tr>
<tr>
<td>Chen CL</td>
<td>2008</td>
<td>98% 90%</td>
<td>Transplantation</td>
</tr>
</tbody>
</table>
HBcAb(+) Donor

- Before Dec. 31, 1997
  No Prophylaxis

- After Jan. 1, 1998
  Pre Tx vaccination
  Post Tx lamivudine, if anti-HBs < 1000

<table>
<thead>
<tr>
<th></th>
<th>HBcAb(+) donor</th>
<th>de novo HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prophylaxis</td>
<td>8</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>PreTx vaccination ± Post Tx 3TC</td>
<td>94</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

### HBcAb(+) Donor

<table>
<thead>
<tr>
<th>HBs Ab</th>
<th>de novo hepatitis B</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>&gt; 1000 IU/L</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>&lt; 1000 IU/L</td>
<td>2 (15.4%)</td>
<td>11</td>
</tr>
</tbody>
</table>

Fisher’s exact test < 0.05

Strategies on Patient Follow-up

- Low immunosuppression as long as the liver functions are within acceptable limits
- Avoid intravenous bolus steroids, OKT3, whenever possible, in rejection cases

Concejero A, Chen CL et al. Transplantation 2007 (in press)
Liver Transplantation for HCC

Future Directions

- Better understanding of tumor biology
- Specific molecular targets
- Control / cure Hepatitis C
### TABLE 6. Comparison of Era II Right Liver Living Donor Liver Transplantation and Deceased Donor Liver Transplantation Recipient Survivals

<table>
<thead>
<tr>
<th></th>
<th>1 Yr</th>
<th>3 Yr</th>
<th>5 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLDLT (n = 184)</td>
<td>97.3%</td>
<td>88.7%</td>
<td>85.1%</td>
</tr>
<tr>
<td>DDLT (n = 91)</td>
<td>93.4%</td>
<td>91.1%</td>
<td>88.1%</td>
</tr>
<tr>
<td><strong>P</strong> = 0.784</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All except HCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLDLT (n = 128)</td>
<td>96.1%</td>
<td>93.4%</td>
<td>93.4%</td>
</tr>
<tr>
<td>DDLT (n = 76)</td>
<td>93.4%</td>
<td>91.9%</td>
<td>88.2%</td>
</tr>
<tr>
<td><strong>P</strong> = 0.493</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLDLT (n = 56)</td>
<td>100%</td>
<td>77.5%</td>
<td>65.5%</td>
</tr>
<tr>
<td>DDLT (n = 15)</td>
<td>93.3%</td>
<td>86.7%</td>
<td>86.7%</td>
</tr>
<tr>
<td><strong>P</strong> = 0.507</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC within Milan criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLDLT (n = 34)</td>
<td>100%</td>
<td>84.1%</td>
<td>72.0%</td>
</tr>
<tr>
<td>DDLT (n = 10)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>P</strong> = 0.091</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 3.** Hepatocellular carcinoma right liver living donor liver transplantation recipient survivals: within versus beyond the Milan criteria.
Asian Experience

Korean Experience

Asan Medical Center

- Resection, 2456
- Transplantation, 685

Year


Number

Asian Experience

Asan Medical Center Criteria (Korea)

TABLE 3. Multivariate Analysis of Significant Risk Factors for Hepatocellular Carcinoma Recurrence and Patient Survival in 206 Surviving Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hepatocellular Carcinoma Recurrence</th>
<th>Patient Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Largest tumor diameter &gt; 5 cm</td>
<td>6.08</td>
<td>2.72-13.59</td>
</tr>
<tr>
<td>Tumor number &gt; 6</td>
<td>6.65</td>
<td>3.02-14.63</td>
</tr>
<tr>
<td>Gross vascular invasion present</td>
<td>2.53</td>
<td>1.39-6.28</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
### Table 1. Recurrence-free rates (%) according to the classifications

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1 year</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Milan criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within (n = 68)</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>Exceeding (n = 10)</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Tokyo 5-5 rule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within (n = 72)</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>Exceeding (n = 6)</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>
Asian Experience

Kyoto University Criteria

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk ratio</th>
<th>95% Confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor number ≥11 nodules</td>
<td>3.048</td>
<td>1.129–8.196</td>
<td>0.0277</td>
</tr>
<tr>
<td>Tumor diameter &gt;5 cm</td>
<td>8.333</td>
<td>2.109–32.258</td>
<td>0.0024</td>
</tr>
<tr>
<td>Beyond MC</td>
<td>1.423</td>
<td>0.183–2.695</td>
<td>0.6073</td>
</tr>
<tr>
<td>AFP &gt;400 ng/ml</td>
<td>1.429</td>
<td>0.192–2.545</td>
<td>0.5880</td>
</tr>
<tr>
<td>PIVKA-II &gt;400 mAU/ml</td>
<td>5.618</td>
<td>2.123–14.925</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Multivariate analysis was performed using Cox’s proportional hazard model.

![Graph showing recurrence rate](image-url)
Asian Experience

Kyushu Criteria

- Size: 5 cm
- No.: Any
- PIVKA II: <300 mAU/ml
Hangzhou Criteria

- Total tumor diameter
  - Less than or equal to 8 cm
  - No macrovascular invasion
  OR

- Total tumor diameter
  - More than 8 cm
  - Histopathology grade I or II
  - AFP less than or equal 400 ng/ml
  - No macrovascular invasion

**5-year Survival Rate**

- Milan criteria 78.3%
- Hangzhou criteria 72.3%
Living Donor Liver Transplantation for Hepatocellular Carcinoma: A Single-Center Experience in Taiwan

Allan Concejero,¹,² Chao-Long Chen,¹,²,⁶ Chih-Chi Wang,¹,² Shih-Ho Wang,¹,² Chih-Che Lin,¹,² Yueh-Wei Liu,¹,² Chin-Hsiang Yang,¹,² Chee-Chien Yong,¹,² Tsan-Shiun Lin,¹,² Bruno Jawan,¹,³ Tung-Liang Huang,¹,⁴ Yu-Fan Cheng,¹,⁴ and Hock-Liew Eng¹,⁵

1, 3, & 5-year survivals of 98%, 96%, & 90%, respectively

None recurred after transplantation

N=8, Beyond Milan criteria
N=8, Within Milan criteria

Transplantation • Volume 85, Number 3, February 15, 2008
TABLE 4.  Histopathologic profile of patients with microvascular tumor invasion, patient management, and outcome (n=9)

<table>
<thead>
<tr>
<th>LDLT no.</th>
<th>Satellite nodule</th>
<th>Degree of necrosis</th>
<th>Presence of capsule</th>
<th>No. of tumors</th>
<th>Tumor size</th>
<th>Histologic grade</th>
<th>Doxorubicin</th>
<th>Recurrence</th>
<th>Alive</th>
<th>Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>—</td>
<td>&gt;60%</td>
<td>+</td>
<td>2</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>81</td>
<td>+</td>
<td>&gt;60%</td>
<td>—</td>
<td>1</td>
<td>&gt;3 cm</td>
<td>Mod Diff</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>92</td>
<td>—</td>
<td>&gt;60%</td>
<td>+</td>
<td>1</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>—</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>119</td>
<td>—</td>
<td>10–60%</td>
<td>+</td>
<td>2</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>—</td>
<td>+</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>172</td>
<td>+</td>
<td>10–60%</td>
<td>+</td>
<td>1</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>—</td>
<td>+</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>180</td>
<td>—</td>
<td>&lt;10%</td>
<td>+</td>
<td>2</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>C</td>
</tr>
<tr>
<td>188</td>
<td>—</td>
<td>&gt;60%</td>
<td>+</td>
<td>2</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>191</td>
<td>—</td>
<td>&lt;10%</td>
<td>+</td>
<td>2</td>
<td>&lt;3 cm</td>
<td>Mod Diff</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>193</td>
<td>+</td>
<td>&lt;10%</td>
<td>+</td>
<td>&gt;5</td>
<td>&gt;3 cm</td>
<td>Mod Diff</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>B+C</td>
</tr>
</tbody>
</table>

Mean follow-up was 32.5 months (range, 13–52 months), excluding LDLT 180.

a Early death (2 months).

TABLE 5.  Interval to recurrence, interval to transplantation, and histopathologic profile of patients who underwent liver resection prior to transplantation (N=7)

<table>
<thead>
<tr>
<th>LDLT no.</th>
<th>Interval to recurrence (months)</th>
<th>Interval to transplantation (months)</th>
<th>Months post-LT</th>
<th>Recurrence</th>
<th>No. of tumors</th>
<th>Tumor Size</th>
<th>Histologic grade</th>
<th>Microvascular invasion</th>
<th>Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>—</td>
<td>7</td>
<td>53</td>
<td>—</td>
<td>2</td>
<td>&gt;3 cm</td>
<td>Well-Diff</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>84</td>
<td>3</td>
<td>3</td>
<td>50</td>
<td>—</td>
<td>1</td>
<td>&lt;3 cm</td>
<td>Well-Diff</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>85</td>
<td>—</td>
<td>10</td>
<td>50</td>
<td>—</td>
<td>3</td>
<td>&lt;3 cm</td>
<td>Well-Diff</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>88</td>
<td>18</td>
<td>24</td>
<td>48</td>
<td>—</td>
<td>3</td>
<td>&lt;3 cm</td>
<td>Mod-Diff</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>93</td>
<td>12</td>
<td>14</td>
<td>47</td>
<td>—</td>
<td>1</td>
<td>&lt;3 cm</td>
<td>Mod-Diff</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>139</td>
<td>7</td>
<td>12</td>
<td>29</td>
<td>—</td>
<td>2</td>
<td>&lt;3 cm</td>
<td>Poor-Diff</td>
<td>—</td>
<td>B</td>
</tr>
<tr>
<td>184</td>
<td>79</td>
<td>84</td>
<td>16</td>
<td>—</td>
<td>1</td>
<td>&lt;3 cm</td>
<td>Well-Diff</td>
<td>—</td>
<td>C</td>
</tr>
</tbody>
</table>

LDLT nos. 74 and 85 showed no radiological evidence of recurrence prior to transplant. LDLT no. 84 showed microvascular invasion in tumor specimen at initial resection.
### Degree of Liver Damage by LCSGJ

<table>
<thead>
<tr>
<th>Clinical and laboratory findings</th>
<th>Grade&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Ascites</td>
<td>none</td>
</tr>
<tr>
<td>Serum bilirubin, mg/dl</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>ICGR&lt;sub&gt;15&lt;/sub&gt;, %</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Prothrombin activity, %</td>
<td>&gt;80</td>
</tr>
</tbody>
</table>

<sup>1</sup> Degree of liver damage is designated as class A, B, or C, based on the highest grade containing at least two findings.
Portal micro-invasion and intra-hepatic metastasis occurs in 27% and 10% of tumors with a tumor size of $>2$ cm, respectively, a TNM staging classification setting the cut-off size to 2 cm is necessary.

CTP and LCSGJ-JIS

**Definition of the TNM stages by the LCSGJ**

<table>
<thead>
<tr>
<th>T factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>fulfilling 3 factors</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>fulfilling 2 factors</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>fulfilling 1 factor</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>fulfilling 0 factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;</td>
</tr>
<tr>
<td>Stage II</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;</td>
</tr>
<tr>
<td>Stage III</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;</td>
</tr>
<tr>
<td>Stage IV-A</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;0&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt; or any TN&lt;sub&gt;1&lt;/sub&gt;M&lt;sub&gt;0&lt;/sub&gt;</td>
</tr>
<tr>
<td>Stage IV-B</td>
<td>any TN&lt;sub&gt;0-1&lt;/sub&gt;M&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

**Definition of the JIS score**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Child-Pugh stage</td>
<td>A</td>
</tr>
<tr>
<td>TNM stage by LCSGJ</td>
<td>I</td>
</tr>
</tbody>
</table>

T factor: I = Single; II = <2 cm; III = no vascular involvement.
### Cancer of the Liver Italian Program

<table>
<thead>
<tr>
<th>Component</th>
<th>CLIP score&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Child–Pugh classification</td>
<td>A</td>
</tr>
<tr>
<td>Tumor morphology</td>
<td>Uninodular and extension ≤ 50%</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>&lt; 400</td>
</tr>
<tr>
<td>Tumor thrombus in the portal vein</td>
<td>No</td>
</tr>
</tbody>
</table>