Patients with HCC treated at the Transplantation and HBP Unit Mainz 1/1998 to 5/2007

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>720</td>
</tr>
<tr>
<td>LR</td>
<td>115</td>
</tr>
<tr>
<td>LT</td>
<td>128</td>
</tr>
</tbody>
</table>

34 % were treated by LR or LT
Treatment and Survival of HCC in the USA*

Figures make up 10 to 14 % of the US-population

<table>
<thead>
<tr>
<th>Years</th>
<th>n</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987 to 1991</td>
<td>2063</td>
<td>8.2 %</td>
</tr>
<tr>
<td>1992 to 1996</td>
<td>2573</td>
<td>9.1 %</td>
</tr>
</tbody>
</table>

El Serag HB et al. Hepatology 2001

Fig. 1. The observed survival rates within the first 5 years after the diagnosis of HCC. Each curve represents survival among patients diagnosed in a 5-year period between 1977 and 1996. Early “apparent” improvement in survival all but vanishes by the end of 5-year follow-up.
Liver resection in HCC with versus without cirrhosis

Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>yes</th>
<th>no</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>censored</td>
<td>n = 50</td>
<td>n = 65</td>
<td>0.2124</td>
</tr>
</tbody>
</table>

Survival

- w/o cirrh. 83% 49%
- cirrhosis 80% 40%

P = 0.2124
Survival after Liver Transplantation in Hepatocellular Carcinoma with and without underlying Cirrhosis
01/1988 – 12/2005
Treatment of HCC
Resection in cirrhotic liver
Results influenced by:

- functional decompensation due to cirrhosis
- cirrhosis – risk of liver cancer

Intrahepatic recurrence
70 – 100% after 5 years*

## Treatment of HCC

### Resection in cirrhotic liver

#### Results

<table>
<thead>
<tr>
<th>Study</th>
<th>1-yr. survival</th>
<th>3-yr. survival</th>
<th>5-yr. survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child A</strong></td>
<td></td>
<td>53 %</td>
<td></td>
</tr>
<tr>
<td><strong>Child B</strong></td>
<td></td>
<td>33 %</td>
<td></td>
</tr>
<tr>
<td><strong>Child C</strong></td>
<td></td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Llovet et al 1999</strong></td>
<td>85 %</td>
<td>51 %</td>
<td></td>
</tr>
<tr>
<td>w/o PH, bili normal</td>
<td>91 %</td>
<td>74 %</td>
<td></td>
</tr>
<tr>
<td>PH, bili normal</td>
<td>93 %</td>
<td>50 %</td>
<td></td>
</tr>
<tr>
<td>PH, bili increased</td>
<td>74 %</td>
<td>25 %</td>
<td></td>
</tr>
<tr>
<td><strong>Grazi GL, 2003</strong></td>
<td></td>
<td>64%</td>
<td>42%</td>
</tr>
<tr>
<td><strong>Ezaki T, 2005</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okuda I</td>
<td>92%</td>
<td>48%</td>
<td>14%</td>
</tr>
<tr>
<td>II</td>
<td>83%</td>
<td>37%</td>
<td>12%</td>
</tr>
<tr>
<td>III</td>
<td>66%</td>
<td>30%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Treatment of HCC
Liver transplantation
Results

UNOS data from Yoo HY et al., 2003
### Disease-free 3-year survival in HCC: Resection versus transplantation


<table>
<thead>
<tr>
<th></th>
<th>Resection n = 60</th>
<th>Transplantation n = 60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>27 %</td>
<td>46 %</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&lt; 3cm + 1 or 2 nodules</td>
<td>18 %</td>
<td>83 %</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Indication for liver transplantation

Milan Criteria (n = 48 !)

Solitary tumor ≤ 5 cm
or ≤ 3 nodules, ≤ 3 cm


2002: San Francisco Criteria 6.5 cm, 3 nodules
### Survival following LT
Patients meeting the Milan Criteria (MC)

<table>
<thead>
<tr>
<th>Study</th>
<th>1-yr. surv.</th>
<th>5-yr. surv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth, H et al 1999</td>
<td>82 %</td>
<td>74 %</td>
</tr>
<tr>
<td>Mazzaferro V et al. 1996</td>
<td>84 %</td>
<td>74 %</td>
</tr>
<tr>
<td>Llovet JM et al. 1999</td>
<td>84 %</td>
<td>74 %</td>
</tr>
<tr>
<td>Jonas S et al. 2001</td>
<td>90 %</td>
<td>71 %</td>
</tr>
<tr>
<td>Yao FY et al. 2001</td>
<td>87 %</td>
<td>73 %</td>
</tr>
</tbody>
</table>
Prognosis after LT for HCC

Causes of postoperative mortality

Prognosis after LT hampered by:

- Immunosuppression-related complications
- Initial graft damage
- Recurrence of the underlying disease
- Recurrence of the tumor

Accelerated tumor growth by immunosuppression after LT?
Resection versus transplantation
Survival following LR in cirrhosis versus LT;
all patients included

P = 0.0393

LT n = 128
LR n = 50
censored
Survival following LR versus LT in HCC > 1 nodule

Survival curve showing:
- LT: n = 56
- LR: n = 19

p = 0.0064

Years: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10

Survival: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0

Censored data indicated.
Survival following LR versus LT in HCC
1 nodule

Survival

Survival ben

p=0.3369

LT n = 21

LR n = 29

censored
Survival in patients with singular HCC (< 5 cm) and Child-A cirrhosis after LR versus LT

Margarit C et al. Liver Transpl 2005

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>37</td>
<td>85 mo.</td>
</tr>
<tr>
<td>LT</td>
<td>36</td>
<td>86 mo.</td>
</tr>
</tbody>
</table>
Influence of dropout during waiting time on survival in patients with singular HCC after LR versus LT

Dropout rate 41%, if the waiting time exceeds 1 year

**FIGURE 4.** Cumulative survival curves of all patients listed for resection (n = 228) or transplantation (n = 85) for HCC within the Milan criteria from the time they were put on list by intention-to-treat analysis.

Important in surgery for HCC

Is primary resection the first choice for small singular tumors in Child A cirrhosis and is transplantation the second line treatment for those patients who experience tumor recurrence?

Salvage/rescue transplantation: transplantation only for patients with tumor recurrence. Intention to treat = resection
Transplantation as first choice

If primary transplantation: how to treat the patient during the waiting time in order to prevent dropout?

- Resection as a bridge – transplantation de principe after resection.
- RFA
- TACE
Living donation
Which patients are amenable to liver transplantation? Which patients are amenable to LDLT?

<table>
<thead>
<tr>
<th>No vascular invasion</th>
<th>Only macroinvasion visible in imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grading</td>
<td>Sampling error</td>
</tr>
<tr>
<td>Milan criteria</td>
<td>Assessment not reliable</td>
</tr>
</tbody>
</table>
Events (including transplantation) in LDLT versus DDLT

Figure 1: Cumulative probability over time of LDLT, DDLT, death without transplant, and remaining alive on the waitlist, from the point of first potential living donor evaluation (based on the cumulative incidence function).

Figure 2: Probability of freedom from HCC recurrence by time since LDLT or DDLT. Freedom from HCC recurrence was significantly lower in LDLT recipients compared to DDLT recipients ($p = 0.002$, log-rank test).
Influence of dropout during waiting time on survival in patients with singular HCC after LR versus LT

Dropout rate 41 %, if the waiting time exceeds 1 year

But: biologically aggressive tumors are eliminated – microvascular invasion, poorly differentiated, multifocal disease

FIGURE 4. Cumulative survival curves of all patients listed for resection (n = 228) or transplantation (n = 85) for HCC within the Milan criteria from the time they were put on list by intention-to-treat analysis.

Flow Cytometric DNA Analysis of Hepatocellular Carcinoma

Fig. 2. The survival curves subdivided by DNA content (diploid vs. aneuploid) $P < 0.001$.

Survival: Vascular Invasion & DNA Ploidy

Liver Transplantation for Hepatocellular Carcinoma in Cirrhosis

Survival [%]

- euploid (n=26)
- aneuploid (n=36)

Years

p = 0.0003

Virchow-Klinikum Berlin
TACE protocol in HCC before LT

within Milan criteria  
  n = 24  
  n TACE median 4 (2-10)

beyond Milan criteria  
  n = 36  
  n TACE median 5 (2-14)

Diagnosis (Biopsy)
Listing
TACE initiation

6 wks.

Diagnosis (Biopsy)
TACE initiation

Re-evaluation
Listing

Survival of 96 patients after inclusion in the TACE protocol. The difference in the 5-year survival in responders (transplanted) and nonresponders (not transplanted) is highly significant ($P < 0.0001$). (Intention-to-treat analysis)

Otto G et al. Liver Transpl 2006
Survival and recurrence of patients after LT pretreated by repeatedly performed TACE


Survival and recurrence of patients after LT pretreated by repeatedly performed TACE

Bridging the waiting time

Selection of biologically favourable tumors

Survival n = 60
Recurrence-free survival n = 60
censored

Days

Survival

Recurrence-free survival
censored

P = .0001

No progress n = 44
progress n = 16
censored

Freedom from recurrence

Days

Questions regarding LT:

- Is it advisable to perform LT as soon as possible after diagnosis of HCC? (Biologically aggressive tumors are not eliminated by time!)

- Therefore: Is living donation preferable as it may be immediately performed?

- Which method of bridging? (resection, RFA, TACE)

- Is local-ablative approach as a bridge to LT only a process of selection by time?

- Are biological markers (loss of heterocigosity, aneuploidy etc.) capable of solving the problem of patient selection? (Living donation!)
Resection is preferable in non-cirrhotic liver

Cirrhosis is the crucial prognostic factor in liver resection: functional capacity, premalignant lesion

Liver resection in Child A cirrhosis and for singular HCC results in similar survival as transplantation – inferior costs, sparse grafts

Only a small proportion of patients is amenable to LT if recurrence occurs after LR

Liver transplantation treatment of choice for patients with small oligonodular tumors in cirrhosis
Calculated and realized rate of rescue transplantation after LR for solitary HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Liver resection n</th>
<th>Intrahep. recurrence n</th>
<th>LT estimated %</th>
<th>LT realized %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam R et al Ann Surg 2003</td>
<td>98</td>
<td>75</td>
<td>79 %</td>
<td>23 %</td>
</tr>
<tr>
<td>Belghiti J et al. 2005</td>
<td>47</td>
<td>23</td>
<td>39 %</td>
<td>--</td>
</tr>
<tr>
<td>Tanaka S et al. J Am Coll Surg 2007</td>
<td>87</td>
<td>30</td>
<td>77 %</td>
<td>--</td>
</tr>
<tr>
<td>Margarit C et al. Liver Transpl 2005</td>
<td>37</td>
<td>22</td>
<td>59 %</td>
<td>27 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 *</td>
<td>70 % *</td>
<td>23 % *</td>
</tr>
</tbody>
</table>

*plus 4 patients with hepatic decompensation
Comparison: LDLT versus DDLT for HCC

Multivariate analysis of tumor recurrence after LT: Salvage LT and beyond UCSF criteria are significant

**Fig. 1** Comparison of cumulative recurrence rates in patients with early irresectable hepatocellular carcinoma after living donor liver transplantation (LDLT) or deceased donor liver transplantation (DDLT). $P = 0.029$ (log rank test)

Liver transplantation: Assessment of the number of nodules
Reliability of preoperative staging

Sotiropoulos GC et al 2005: DDLT accuracy 63%
            LDLT accuracy 57%

Own results: diagnostic accuracy in CT scan: 60%

Kaihara S et al 2003: correct diagnosis of nodules <3cm
            preoperatively: 21/56 (37.5%)

Krinsky GA et al 2003: lesions <1cm detected in MRI: 4%
Prognosis after liver transplantation in HCC is influenced by:

- Vascular infiltration
- Histological grading
- Multinodular disease
- (Size of tumor)
Natural course and prognosis following treatment in HCC (LT, LR, percutaneously)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Natural course</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage</td>
<td>65 % (3 yrs.)</td>
<td>50 to 70 % (5 yrs.)</td>
</tr>
<tr>
<td>Intermediate stage</td>
<td>8 to 50 % (2 yrs.)</td>
<td>24 to 63 % (2 yrs.)</td>
</tr>
<tr>
<td>Final stage</td>
<td>&lt; 6 mo.</td>
<td>--</td>
</tr>
</tbody>
</table>

Llovet JM J Gastroenterol 2005
Issues in decision:
Liver resection versus liver transplantation

- Only early HCC amenable to surgery – both
- Functional limits in liver resection
- Precancerous liver - risk of intrahepatic recurrence
- Only a small proportion of patients is amenable to LT if recurrence occurs after LR
- Sparse grafts – drop out during waiting time in LT (decrease in survival in intention-to-treat analysis)
- Prognosis after LT hampered by
  - initial graft damage
  - rejection
- recurrence of original disease
- immunosuppression-related complications

Accelerated tumor growth by immunosuppression after LT?
Molecular prognostication of liver cancer: End of the beginning

Snorri S. Thorgeirsson, Ju-Seog Lee, Joe W. Grisham


Fig. 1. (A) Hierarchical clustering of 91 HCC tumors with 406 ‘survival genes’. The data are presented in matrix format in which rows represent the individual gene and columns represent each tissue. Each cell in the matrix represents the expression level of a gene feature in an individual tissue. The red and green colors in cells reflect high and low expression levels. (B) Significant association of gene expression patterns with patient survival. Kaplan–Meier plot of overall survival of HCC patients grouped on the basis of gene expression profiling shown in panel A.
Comparison: LDLT versus DDLT for HCC

<table>
<thead>
<tr>
<th></th>
<th>LDLT n = 43</th>
<th>DDLT n = 17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>beyond MC</td>
<td>11</td>
<td>5</td>
<td>0.76</td>
</tr>
<tr>
<td>beyond UCSF</td>
<td>7</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Incidental HCC</td>
<td>3</td>
<td>5</td>
<td>0.035</td>
</tr>
<tr>
<td>Salvage LT</td>
<td>10</td>
<td>1</td>
<td>0.014</td>
</tr>
<tr>
<td>TACE before LT</td>
<td>1</td>
<td>4</td>
<td>0.001</td>
</tr>
<tr>
<td>waiting time</td>
<td>27 Tage</td>
<td>110 Tage</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Comparison: living donation for HCC within versus beyond Milan criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>within MC</th>
<th>beyond MC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>3 yrs.</td>
<td>n</td>
</tr>
<tr>
<td>Todo et al. 2004</td>
<td>137</td>
<td>80 %</td>
<td>172</td>
</tr>
<tr>
<td>Hwang et al. 2005</td>
<td>151</td>
<td>91 %</td>
<td>62</td>
</tr>
<tr>
<td>Takada et al 2006</td>
<td>49</td>
<td>68 %</td>
<td>44</td>
</tr>
</tbody>
</table>
Liver Transplantation for Hepatocellular Carcinoma in Cirrhosis: Is Clinical Tumor Classification before Transplantation Realistic?

Georgios C. Sotiropoulos,¹ Massimo Malagó,¹,4 Ernesto Molmenti,¹ Andreas Paul,¹ Silvio Nadalin,¹ Eirini Brokalaki,¹ Hilmar Kühl,² Olaf Dirich,³ Hauke Lang,¹ and Christoph E. Broelsch¹

Transplantation 2005;79: 483–487

<table>
<thead>
<tr>
<th>Results</th>
<th>Milan (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLTx-group, n=35</td>
<td></td>
</tr>
<tr>
<td>Pre-/Posttransplant accuracy</td>
<td>20 (57.1)</td>
</tr>
<tr>
<td>Pathologic up-staging</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Pathologic down-staging</td>
<td>10 (28.6)</td>
</tr>
<tr>
<td>CLTx-group, n=35</td>
<td></td>
</tr>
<tr>
<td>Pre-/Posttransplant accuracy</td>
<td>22 (62.8)</td>
</tr>
<tr>
<td>Pathologic up-staging</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Pathological down-staging</td>
<td>4 (11.5)</td>
</tr>
<tr>
<td>Overall LTx, n=70</td>
<td></td>
</tr>
<tr>
<td>Pre-/Posttransplant accuracy</td>
<td>42 (60)</td>
</tr>
<tr>
<td>Pathologic up-staging</td>
<td>14 (20)</td>
</tr>
<tr>
<td>Pathologic down-staging</td>
<td>14 (20)</td>
</tr>
<tr>
<td>P value in chi-square test: accuracy vs. no accuracy between LDLTx-CLTx groups</td>
<td>0.807</td>
</tr>
</tbody>
</table>
Survival in patients with HCC < 5 cm /1-2 nodules after liver transplantation and liver resection.

Einfluss des Dropout während der Wartezeit auf Gesamtüberleben bei Patienten mit singulärem HCC nach LR versus LT (intention-to-treat-Analyse)

Dropout rate 41 %, wenn die Wartezeit 1 Jahr überschreitet

**FIGURE 4.** Cumulative survival curves of all patients listed for resection \((n = 228)\) or transplantation \((n = 85)\) for HCC within the Milan criteria from the time they were put on list by intention-to-treat analysis.


Roberts MS et al Liver Transplantation 2004 (UNOS-Daten)
Überlebensdauer

Cum Survival

Survival Functions

MaxMailand-Kriterien

Ja  Nein  Ja-censored  Nein-censored

P = 0.653

ja n = 5
nein n =
Überlebensdauer

Cum Survival

Survival Functions

ML_erfüllt
Explantat_kat

ja n = 7:
nein n = P = 0.209
Überlebensdauer

Cum Survival

Survival Functions

Tumorprogress

ja n = 11
nein n = 65

P = 0.0000
Survival following liver resection in HCC according to the number of nodules

Survival

Days

P = 0.0395

Nodules

1 n = 32
2 n = 4
3 n = 3
m n = 11
+ censored
Tumor recurrence after LDLT versus DDLT

Figure 3: Probability of recurrence-free patient survival by time since LDLT or DDLT. Recurrence-free survival was lower in LDLT recipients compared to DDLT recipients, but the difference was not significant (p = 0.38, log-rank test).

Survival in patients with singular HCC (< 5 cm) and Child-A cirrhosis after LR versus LT

**FIGURE 1.** Cumulative survival curves of the resection group (n = 204) and the transplantation group (n = 43).

**FIGURE 3.** Recurrence-free survival curves of the resection group (n = 194) and the transplantation group (n = 43).

**TABLE 3.** Concordance of Tumor Grade on Preoperative Needle Core Biopsy Versus Final Surgical Pathology Using 3-Tier Grading System ($\kappa$ statistic = 0.18)

<table>
<thead>
<tr>
<th>Preop. Needle Biopsy</th>
<th>Final Surgical Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well</td>
</tr>
<tr>
<td>Well</td>
<td>17</td>
</tr>
<tr>
<td>Moderate</td>
<td>15</td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>34</td>
</tr>
</tbody>
</table>
Impact of Milan Criteria on outcome of LT for HCC

Onaca L et al. Liver Transplant 2007
Impact of Milan Criteria on outcome of LT for HCC

Onaca L et al. Liver Transplant 2007