Surgical Resection for Small HCC

Resection vs LAT
Resection vs Transplanatation

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Why do we define Small HCC?

• Pathological difference
• Diagnostic Imaging
• Efficacy of Treatment
What is Small

- < 2 cm: International Working Party (‘95 Hepatology)
- < 2 cm: Liver cancer study group of Japan
- TNM staging
- < 3 cm: cut-off for Local Ablation Therapy
- < 4 cm
- < 5 cm: Suitable cut-off when surgery is contemplated and when to compare the Local Tx modality.
- just “small”, “Not advanced”, Treatable
# Natural History of Small HCC

<table>
<thead>
<tr>
<th></th>
<th>Child A/B/C</th>
<th>Survival 1yr</th>
<th>Survival 2yr</th>
<th>Survival 3yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Llovet (Spain) ’99</strong></td>
<td>65/34/3</td>
<td>54</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>Status 0 (n=48)</td>
<td>80</td>
<td>65</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Status 1 (n=54)</td>
<td>29</td>
<td>16</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Barbara (Italy) ’92</strong></td>
<td>&lt;5cm</td>
<td>81</td>
<td>55.7</td>
<td>21</td>
</tr>
<tr>
<td>Child A</td>
<td>13/6/11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child B,C</td>
<td>35.6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ebara (Japan) ’86</strong></td>
<td>&lt;3cm</td>
<td>90.7</td>
<td>55</td>
<td>12.8</td>
</tr>
<tr>
<td>Size</td>
<td>8/6/8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Short-term prognosis in untreated patients with small HCC and Child A is excellent.

• Effectiveness of any current Tx modalities, has to be carefully reconsidered and has to be established only in good studies on long-term f/u.
Evidence-Based Benefit

Locoregional Tx
- Surgical resection
- Percutaneous Tx
  - PEI
  - RFA
  - TACE
- Liver TPL

Systemic Tx
- Tamoxifen, systemic chemo, Interferon
  - 1 (no benefit)
Resection vs LAT
Surgical Resection

• One of local therapies for liver tumor

• More powerful and anatomical ablation than RFA and PEIT
5 year survival rate of surgical resection
≤ 5cm HCC

• 59% – 65%
  – Zhou et al; Cancer 2001
  – Fong et al; Ann Surg 1999
RFA

Koike et al, Cancer 2005 Feb

1999 – 2003, 664 patients

Inclusion criteria:

- Bilirubin <3 mg/dL,
- Platelet >5x10^5/mm3,
- PT>50%

Out of 319 naïve patients (no prior tx), 13 patients excluded due to several nodules left untreated.

306 patients

Follow up: 1 month to 5.1 years

Cumulative 1, 3, 5 year survival: 94.7%, 77.7%, 54.3%
Choice of Local Therapy

• Large tumor:
  Surgery >> TACE

• Small tumor:
  Surgery = RFA=TACE??
A Prospective Randomized Trial Comparing Percutaneous Local Ablative Therapy and Partial Hepatectomy for Small Hepatocellular Carcinoma

Min-Shan Chen, MD,*† Jin-Qing Li, MD,*† Yun Zheng, MD,*† Rong-Ping Guo, MD,*† Hui-Hong Liang, MD,*† Ya-Qi Zhang, MD,*† Xia-Jun Lin, MD,*† and Wan Y. Lau, MD‡

Ann Surg 243(3);321-328, 2006

Conclusion: PLAT was as effective as surgical resection in the treatment of solitary and small HCC. PLAT had the advantage over surgical resection in being less invasive.
Inclusion criteria

- 18 ≤ age ≤ 75 years
- A solitary HCC < 5 cm in diameter
- No extrahepatic metastasis
- No radiologic evidence of major vessel invasion
- Good liver function with Pugh-Child Class A
- ICG-R15 < 30%
- A platelet count of > 40,000/mm3
- No previous treatment of HCC
- Suitable to be treated by either surgical resection or percutaneous local ablative therapy (PLAT)

Mean F/U : less than 2 years

- Noncurrent cohort study conducted as a retrospective analysis of a prospective database in 5 Hospitals
- From Oct 1995 to Jun 2006
- Single $\leq 2\text{cm}$, Child A
- Dx: AASLD criteria
- Exclusion criteria:
  - 1) poor visualization
  - 2) intestinal loops or main bile duct adjacent to the tumor
  - 3) coagulation defect
  - 4) previous HCC tx
  - 5) no foreseeable possibility of liver transplantation
Fig. 1. Estimated 3-year and 5-year survival rates for entire population (218 patients).
Fig. 3. Estimated 3-year and 5-year free-disease survival rates (82 patients).
Surgical Resection For HCC at SNUH

• Jan 2000 ~ Dec 2006,
• 387 curative hepatic resections for HCC
• Single surgeon
• Male 329 (82.5%) : Female 70 (17.5%)
• Mean age 53.8 (17 ~ 81)
• Median f/u 28 months (0.2~96.1)
Overall Survival according to tumor size

- \( \leq 5 \text{cm} (n=215) \) 74.5%
- > 5cm (n=172) 42.4%

\( P < 0.01 \)
Overall DFS according to tumor size

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>DFS Rate</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 cm</td>
<td>44.5%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>20.1%</td>
<td></td>
</tr>
</tbody>
</table>
Survival according to size

5YSR

- < 2cm (n=20) 82.5%
- 2~3cm (n=63) 73.8%
- 3~4cm (n=61) 81.9%
- 4~5cm (n=53) 71.8%
- ≥5cm (n=190) 43.7%

≥ 5cm vs others P < 0.05
DFS according to size

- <2 cm (n=20) 67.7%
- 2~3 cm (n=63) 52.2%
- 3~4 cm (n=61) 53.5%
- 4~5 cm (n=53) 32.2%
- ≥5 cm (n=190) 19.6%

5YDFSR

- <2 cm (n=20) 67.7%
- 2~3 cm (n=63) 52.2%
- 3~4 cm (n=61) 53.5%
- 4~5 cm (n=53) 32.2%
- ≥5 cm (n=190) 19.6%

- ≥5 cm vs others  $P < 0.05$
- 3~4 vs 4~5  $P < 0.05$
Why Surgical Resection?

Theoretical Advantages

• Surgery guarantees complete resection with margin
  – Systematic resection of portal blood shed area (Intrahepatic spread via portal vein)

• Local recurrence in local ablation Tx
  – Remaining tumor may have chance of lymphatic meta, drop meta, distant metastasis
  – Significant prognostic factor

• Characteristics of HCC become fierce during local therapy.

• Provide surgical specimen for later research
Even in HCC ≤ 2cm, PV invasion: 27%
Intrahepatic meta: 10%
Nakashima; Hepatology 1995
Surgical Resection  Local Ablation Therapy
CT α

CT ν

MRI
Overall Survival of 168 patients from 1998 to 2001 at SNUH

Cho et al: Anatomic vs Non-anatomic Resection for small Single HCC.
Hepato-Gastroenterology 2007

p = 0.032
Disease free Survival of 168 patients from 1998 to 2001 at SNUH

Anatomic (n=99) vs Non-anatomic (n=69)

Recurrence is significant prognostic factor and definite cause of death


If Removing Power↑, Recurrence ↓ & Survival↑

Liver Transplantation

Surgical resection

RFA

PEI

TACE

RCT by Shina et al : GE 2005
Effectiveness of RFA based on histologic examination of the explanted liver

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean interval RFA to OLT</td>
<td>9.5 months</td>
<td>7.4 months</td>
</tr>
<tr>
<td>Overall complete response</td>
<td>55%</td>
<td>74%</td>
</tr>
<tr>
<td>≤3cm</td>
<td>63%</td>
<td>83%</td>
</tr>
<tr>
<td>&gt;3cm</td>
<td>29%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Why not Surgical Resection?

Op. Mortality
It should be less than < 5%
(0% - 2% in Child A, no portal hypertension)

Recurrence
inevitable but can be reduced by anterior approach, minimal blood transfusion
(no blood transfusion in small HCC, Child A patients.)

Pain, delayed normal activity, cosmetic effect
Laparoscopic hepatectomy
High seeding rate caused by RFA
:surface lesion, poorly diff.
High Bowel injury
Resection vs LT

- Survival and DFS
- Donor problems
- Cost
- Salvage TPL
### Hepatectomy vs Liver transplantation
Subgroup Analysis for Meta-analysis of Cohort Studies
Hosida et al Hepatology 2000

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup</th>
<th>n</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Yr survival</td>
<td>All studies</td>
<td>1974</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>TNM Stage I,II</td>
<td>325</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td>TNM Stage III, IVA</td>
<td>337</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>Year ‘91-’95</td>
<td>642</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Year ‘96-’99</td>
<td>1,332</td>
<td>1.32</td>
</tr>
<tr>
<td>3-Yr DFS</td>
<td>All studies</td>
<td>941</td>
<td>2.46</td>
</tr>
<tr>
<td></td>
<td>Year ‘91-’95</td>
<td>147</td>
<td>2.64</td>
</tr>
<tr>
<td></td>
<td>Year ‘96-’99</td>
<td>794</td>
<td>2.24</td>
</tr>
</tbody>
</table>

If OR >1, Favor LT

Overall Survival and DFS Outcome of All Patients Underwent LT at SNUH

Mean survival time: 6.3 ± 0.5 years
1YSR: 81.0%
5YSR: 62.6%

Mean DFS time: 7.2 ± 0.4 years
1YDFSR: 80.3%
5YDFSR: 73.4%

LT

Actual Survival Outcome
281 curative hepatic resection for HCC between 1992 and 1996; all patients were F/U >10 years

1YSR = 82.9%
3YSR = 61.6%
5YSR = 48.0%
10YSR = 28.8%

Median DFS time: 2.1 years
1YDFSR = 69.3%
3YDFSR = 40.6%
5YDFSR = 27.1%
10YDFSR = 18.4%
Resection vs LT

- Survival and DFS
- Donor problems
- Cost
- Salvage TPL
Organ Shortage

- Dropout rate of 15-33% even in western countries.

- Intention-to-treat analysis

"Selection bias"
Intention-to-treat analysis of surgical tx for early HCC: resection vs transplantation
Llovet et al; Hepatology 1999

- Survival rate

<table>
<thead>
<tr>
<th></th>
<th>1yr</th>
<th>3yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tpl</td>
<td>84%</td>
<td>69%</td>
<td>69%</td>
</tr>
<tr>
<td>Resection</td>
<td>85%</td>
<td>62%</td>
<td>51%</td>
</tr>
</tbody>
</table>

- If mean waiting time is 62 days, 2 yr survival is 84%
  162 days, 2 yr survival is 54%

- In Child A, no portal HT, resection was better.
Deceased Donor in Korea

Number of cadaveric donors (pmp)
Number of Patients on the Waiting List and DDLT in Korea

![Graph showing the number of patients on the waiting list and DDLT in Korea from 2000 to 2007. The number of patients on the waiting list shows a steady increase, while the number of DDLT cases remains relatively low.]
Liver Transplantation in Korea

Total: 4357

- LDLT (n=3561)
- DDLT (n=796)

Morbidity of living liver donors

- 67% (after right hepatectomy)  
- 15.8% (survey of 5 Asian centers)  
Lo CM Transplantation 2003
- 37%  
- 40.5%  
Choi SJ et al. Transpl Int 2005
- 9.6%  
Itamoto T et al. Transpl Int 2006
- 47.5%  
Yi et al. Liver Transplantation 2007
## Living Donor Liver Transplantation

### Donor Risk - Mortality and Liver Failure

<table>
<thead>
<tr>
<th>Region</th>
<th>Risk Events</th>
<th>Mortality or Liver Failure Details</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamburg (LLL)</td>
<td>pulmonary embolism (2 d)</td>
<td>Malagó 1994</td>
<td></td>
</tr>
<tr>
<td>Lyon</td>
<td>septic shock (11 d)</td>
<td>Boillot 2002</td>
<td></td>
</tr>
<tr>
<td>Essen</td>
<td>liver failure, sepsis (21 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jena</td>
<td>heart failure: LTx (32 d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapel Hill</td>
<td>venous outflow obstruction?</td>
<td>Beavers 2001</td>
<td></td>
</tr>
<tr>
<td>San Antonio (LLL)</td>
<td>anaphylaxis, anesthesia?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Los Angeles</td>
<td>drug overdose (23 mo)</td>
<td>Ghobrial 2002</td>
<td></td>
</tr>
<tr>
<td>New York</td>
<td>aspiration, C. Perf, gastritis (3 d)</td>
<td>Miller 2004</td>
<td></td>
</tr>
<tr>
<td>Washington</td>
<td>BCS: LTx (8 d), rescued</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>South America</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curitiba</td>
<td>cerebral bleeding (7 d)</td>
<td>Wiederkehr 2004</td>
<td></td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyoto (1/1,000)</td>
<td>liver failure (NASH), LTx (9 mo)</td>
<td>Akabayashi 2004</td>
<td></td>
</tr>
</tbody>
</table>

11 / ~ 8,500 LDLTs = 0.13%

*From Dr. Shin Hwang*
Role of Live Donor Liver Transplantation for small HCC, Child A

- Is it ethical to risk a healthy donor when there is an alternative option of resection with comparable long-term survival?

- Is no waiting time really good?
Resection vs LT

- Survival and DFS
- Donor problems
- Cost
- Salvage TPL
입원 진료비 (본인 부담금)

비용 (원)

reseption

transplantation

₩ 4,817,000

₩ 24,079,266
입원 진료비 (전체 의료비)

비용 (원)

- resection
  - W 3,579,131
  - W 4,817,000

- transplantation
  - W 18,910,905
  - W 24,079,266
입원 진료비 (공여자 진료비 포함)

비용 (원)

- resection
  - W 3,579,131
  - W 4,817,000
- transplantation
  - W 9,866,312
  - W 18,910,905
  - W 24,079,266
수술 후 1년간 외래 진료비 (전체 진료비 및 본인 부담 금)

비용 (원)

- resection: ₩706,827
- transplantation: ₩9,573,571
- ₩2,151,248
- ₩335,682
Resection vs LT

- Survival and DFS
- Donor problems
- Cost
- Salvage TPL
Resection first and Salvage Tpl for recurrence or liver failure

“Theoretical Advantage”

• Resection is immediately applicable and simple tx option
• No risk of tumor progression and dropout while in waiting list.
• Reduce use of liver graft
  – In Long-term survivor without recurrence
  – In Extrahepatic metastasis
**Controversial issue**

- Can LT be performed after resection?  
  - Yes, but wide range of 20 ~ 79%

- “Resection + 2° TPL” << “1° TPL” by Intention-to-treat analysis Adam Ann Surg 2003

- Does it increase LT morbidity and mortality?  
  - No : Belghiti Ann Surg 2003

- Similar long term survival in recent reports  
  
Other problems in liver transplantation

- Life long Immunosuppression
- Graft rejection
- Recurrent viral hepatitis
## Summary

<table>
<thead>
<tr>
<th>Resection</th>
<th>LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>=</td>
</tr>
<tr>
<td>DFS</td>
<td>&lt;</td>
</tr>
<tr>
<td>Donor problems</td>
<td>-- +</td>
</tr>
<tr>
<td>Cost</td>
<td>low high</td>
</tr>
</tbody>
</table>
Conclusion 1
Resection vs Transplantation

• For patients with small HCC in well preserved liver function, *Surgical Resection* should be an initial treatment of choice.

• *Liver Transplantation* should be reserved as an option for *salvage* in case of recurrence and liver failure.

• In the high risk of recurrence or advanced liver disease, younger patients favor LT and older patients favor resection.
Conclusion 2
Rsection vs LAT

• Now, we need good randomized controlled trial comparing LAT and surgical resection.
  – HCC less than 2 cm.
    Dx is uncertain, natural history is excellent
  – HCC (2cm - 4cm) : good candidate for RCT
  – HCC > 4cm : Surgical resection should be performed
A Prospective Randomized Study Comparing hepatic resection to Radiofrequency Ablation for Hepatocellular Carcinoma
-Multi-Center Study-

- **Inclusion criteria**
  - 20 ≤ age ≤ 70
  - Child-Pugh class A (score 5-6) (albumin ≥ 3.2g/dL)
  - Number of nodule = 1
  - 2cm ≤ size of nodule ≤ 4cm
  - No previous treatment
  - No portal hypertension (PLT ≥ 80K/mm³)

- **Exclusion criteria**
  - Tumor contacting the first branches of hepatic or portal vein
  - Tumor contacting vessels ≥ 0.5cm in diameter
Schema of Study Flow

Research Meeting

HCC

Selection Criteria (+)

Agree

Refuse

Random Allocation

Hepatic Resection

RFA

Selection Criteria (-)

Medical Research Collaborating Center in SNUH
A Prospective Randomized Study Comparing hepatic resection to Radiofrequency Ablation for Hepatocellular Carcinoma Multi-Center Study
## Progression

<table>
<thead>
<tr>
<th>Institution</th>
<th>Screening</th>
<th>Enroll</th>
<th>Drop out</th>
<th>Progression</th>
<th>Finish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 1</td>
<td>78</td>
<td>45</td>
<td>11</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Hospital 2</td>
<td>17</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Hospital 3</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>99</strong></td>
<td><strong>54</strong></td>
<td><strong>11</strong></td>
<td><strong>42</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>
Survival Curves of Treated and Non-treated cases.

- **Treated**
  - 40-70% (Llovet; 2003)
- **Non-treated**
  - < 20% (Llovet; 1999, Villa; 2000)
Conclusion 2

• It is very hard to make a difference in small HCC less than 2 cm.

• Prospective randomized studies are necessary to compare Surgery with RFA in small HCC (2cm - 4cm)

• Surgical resection should be performed in resectable HCC > 4cm
Resection vs LT

- Survival and DFS
- Donor problems
- Cost
- Salvage TPL