Surgical Treatment of HCC: What is the Limit?

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Founder and Chairman, Hong Kong Liver Cancer and Gastrointestinal Cancer Foundation
Medical Director, Hong Kong Integrated Oncology Centre
HCC in Asian Countries

- Predominantly HBV-related HCC, 80% associated with cirrhosis

- Majority of patients present with relatively advanced stage (large tumor, multifocal tumors, portal vein invasion, extra-hepatic metastasis)

- More aggressive surgical approach in high-volume centers
Current Treatments for HCC

- Liver resection
- Liver transplantation
- Local ablative therapies
- Transarterial chemoembolization/radioembolization
- External radiotherapy
- Systemic therapy (Sorafenib)

- Role of liver transplantation and ablation limited to early HCC < 5-7 cm without vascular invasion
- Surgical resection the only curative treatment for more advanced HCC
Challenges for Liver Surgeons

• ‘One patient, two diseases’
  – Liver tumor
  – Liver cirrhosis

• Insufficient liver remnant volume is a main limiting factor for liver resection, especially in cirrhotic liver
BCLC Staging and Treatment Algorithm –
Western Approach to HCC

Lovet et al. JNCI 2008
Asia-Pacific Association for Study of Liver Consensus on Treatment of HCC

Confined to the liver
Main portal vein patent

Solitary or **multifocal** tumor in noncirrhotic liver or Child A cirrhosis

Yes

**Resection / RFA (for < 3 cm HCC)**

Solitary tumor ≤ 5 cm
≤ 3 tumors ≤ 3 cm
No venous invasion

Child A

Local ablation

Child B

Transplantation

Child C

Extrahepatic metastasis
Main portal vein tumor thrombus

Child A / B

Sorafenib or systemic therapy trial

Child C

Tumor > 5 cm
> 3 tumors
Invasion of hepatic / portal vein branches

Child A / B

TACE

Child’s C

Supportive care

Omata, Poon et al. Hepatol Int 2010
Improving Safety of Hepatectomy

1222 patients with hepatectomy at QMH from July 1989 – June 2003

- Comparison of two 7-year periods:
  - Significantly more elderly patients, more co-morbid illnesses and worse liver function (ICG-15) in second period, but in the second period
    - Lower median blood loss (decreased from 1450 ml to 750 ml)
    - Lower morbidity (decreased from 37.3% to 30%)
    - Lower hospital mortality (decreased from 7.5% to 3.7%)

Conclusion: Role of surgical resection of liver cancer can be extended to elderly patients and cirrhotic patients with borderline liver function

Hospital mortality rate in 2010s : 1-2%

Trend of perioperative blood transfusion requirement

Surgical Resection of HCC
- What are the Limits?

• Liver function reserve
  - adequate liver remnant function: higher risk of liver failure with extended hepatectomy (> 4 segments) in cirrhotic liver

• Tumor factors
  - anatomically all tumors can be removed with clear margin:
    difficult with bilobar multifocal tumors or large tumor extending from one lobe to involve vital intrahepatic vessels in the other lobe
  - vascular invasion into main portal vein or IVC
  - extra-hepatic metastasis

relative contraindications
Extended Liver Resection for HCC

Resection > 4 segments

Indications:
- Large HCC extending from one lobe to the other
- Central HCC closely related to hepatic vein-caval junction
## Safety of Extended Liver Resection for HCC in Cirrhosis

<table>
<thead>
<tr>
<th>Resection of HCC in cirrhosis at QMH from 1993-2000</th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs.</td>
<td>55.6</td>
<td>53.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>14.6 +/-7.9</td>
<td>16.4 +/-8.5</td>
<td>0.34</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>8.3</td>
<td>4.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Multiple tumors</td>
<td>13 (31%)</td>
<td>34 (21%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Microscopic vascular invasion</td>
<td>28 (62%)</td>
<td>60 (37%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Group A: extended liver resection (n = 45)

Group B: resection of a lesser extent (n = 160)

*Poon et al, Ann Surg 2002*
## Perioperative Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay, days</td>
<td>17.3 ± 12.4</td>
<td>14.1 ± 9.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Complications</td>
<td>14 (31%)</td>
<td>58 (36%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Liver failure</td>
<td>3 (6.7%)</td>
<td>6 (3.7%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hospital deaths</td>
<td>3 (6.7%)</td>
<td>8 (5.0%)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Poon et al, Ann Surg 2002
Extended Liver Resection for HCC
- Safety Limit of Liver Function Reserve

- Indocyanine green clearance test
  - ICGR at 15 minutes < 14% for major hepatic resection
  - ICGR at 15 minutes < 20% for major hepatic resection

- Liver remnant volumetry 30% of estimated standard liver volume in cirrhotic liver
Future Remnant Liver Volume Predicts Postoperative Mortality and Liver Dysfunction

- In normal liver, a FRL $< 26.5\%$ predicted postoperative liver dysfunction with 66.7% sensitivity, 97.1% specificity;
- In diseased liver (cholestasis/cirrhosis or cholestasis), a FRL value of $< 31\%$ predicted postoperative liver dysfunction with 75% sensitivity, 79.1% specificity.

*Ferrero et al. World J Surg 2007*

- After trisectionectomy, 90% of patients with $\leq 25\%$ of liver remaining developed hepatic dysfunction, compared with none of the patients with more than 25% of liver remaining (P $< 0.0001$).

*Shoup et al. J Gastro Surg 2013*
Limit for Safe Hepatic Resection

Literature review

Gulielmi et al. Dig Surg 2012
Portal Vein Embolization

Liver remnant hypertrophy: 4-6 weeks
Extended Right Hepatectomy after PVE

Pre-PVE:
L lobe volume 23% ESLV

4 weeks post-PVE:
L lobe volume 41%

** 20-30% patients will not have adequate hypertrophy of liver remnant
Right Portal Vein Ligation Combined With In Situ Splitting Induces Rapid Left Lateral Liver Lobe Hypertrophy Enabling 2-Staged Extended Right Hepatic Resection in Small-for-Size Settings

Andreas A. Schnitzbauer, MD,* Sven A. Lang, MD,* Holger Goessmann, MD,† Silvio Nadalin, MD,§ Janine Baumgart, MD,¶ Stefan A. Farkas, MD,* Stefan Fichtner-Feigl, MD,* Thomas Lorf, MD,¶ Armin Goralczyk, MD,¶ Rüdiger Hörbelt, MD,# Alexander Kroemer, MD,* Martin Loss, MD,* Petra Rümmele, MD,¶ Marcus N. Scherer, MD,* Winfried Pauberg, MD,# Alfred Königsrainer, MD,§ Hauke Lang, MD,¶ Aimán Obed, MD,¶ and Hans J. Schütt, MD*
<table>
<thead>
<tr>
<th></th>
<th>De Santibanes 2012</th>
<th>Li 2013</th>
<th>Schnitzbauer 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Pathology</td>
<td>CRM (10)</td>
<td>CRM (3)</td>
<td>CRM (14)</td>
</tr>
<tr>
<td></td>
<td>HCC (1)</td>
<td>Klatskin(3)</td>
<td>HCC (3)</td>
</tr>
<tr>
<td></td>
<td>Klatskin (1)</td>
<td>Intrahepatic</td>
<td>ICC (2)</td>
</tr>
<tr>
<td></td>
<td>Neuroendocrine (3)</td>
<td>cholangio (3)</td>
<td>Klaskin (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Others (4)</td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal liver</td>
<td>&lt; 30%</td>
<td>&lt;25%/0.5%BW</td>
<td></td>
</tr>
<tr>
<td>Diseased liver</td>
<td>&lt; 40%</td>
<td>&lt;30%/0.8%BW</td>
<td></td>
</tr>
<tr>
<td>Preop mean FLR(ml) i.e. LLS</td>
<td>403 (237-572)</td>
<td></td>
<td>Median 310 (197-444)</td>
</tr>
<tr>
<td>FLR/TLV or FLR/BW</td>
<td>27% (15-44%)</td>
<td>22.9%/0.48 BW</td>
<td>0.38 (0.25-0.49)/BW</td>
</tr>
<tr>
<td>Postop mean FLR (ml)</td>
<td>706 (468-1030)</td>
<td>Median volume gain 87.2%</td>
<td>536 (273-881) or 74%</td>
</tr>
<tr>
<td>FLR/TLV</td>
<td>46.9% (31.7-67)</td>
<td></td>
<td>0.61 (0.35-0.95)</td>
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</table>
## Success Rate of ALPPS

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*De Santibanes et al. J Gastrointest Surg 2013*
*Schintzbauer et al. Ann Surg 2013*
*Li J et al. J Gastrointest Surg 2013*
First HCC Case at QMH

- A 62-year old man, known hepatitis B carrier, not on antiviral medication
- CT scan showed a 13cm tumor
- ICG @ 15mins: 19.0%

Discharged home 8 days after second operation

Left liver: 280ml, 26% whole liver

Left liver: 360ml, whole liver 33.5%

10 days
Anterior Approach for In-situ Split

- Pros: avoids adhesions from perihepatic and pericaval areas, and tumor rupture/tumor cell dissemination in case of large tumor

- Cons: difficulty to control bleeding from deep transection surface

Complete in-situ split down to IVC
Extending Surgical Indication for Bilobar HCC - Combined Resection and Ablation

- Bilobar multifocal tumors – resection of predominant lesion(s) in one lobe and ablation of lesion(s) in the other lobe

- Multiple tumors in cirrhotic liver with inadequate liver function reserve (resection of peripheral lesions, ablation of central lesions or lesions close to vital vessels)
Combined Resection and RFA for Multifocal HCC at QMH

• 19 patients with multiple HCCs and no major venous invasion received hepatectomy in combination with RFA with curative intent (combined treatment group)

• 54 patients with multifocal HCC undergoing hepatectomy alone in the same period were selected as case control (resection alone group)

Cheung et al. World J Gastroenterol 2010
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Combined treatment group (n = 19)</th>
<th>Resection alone group (n = 54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh class A</td>
<td>19</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count (×10⁹/L)</td>
<td>165 (91 – 64.5)</td>
<td>177 (86 – 458)</td>
<td>0.396</td>
</tr>
<tr>
<td>ICG (% at 15 minutes)</td>
<td>11.8 (3 – 25.7)</td>
<td>9 (3.7 – 18.2)</td>
<td>0.083</td>
</tr>
<tr>
<td>AFP level (ηg/ml)</td>
<td>248 (6 – 38040)</td>
<td>133 (2 – 530600)</td>
<td>0.915</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>6 (1.2 – 14)</td>
<td>6 (1 – 12.5)</td>
<td>0.782</td>
</tr>
<tr>
<td>Tumor number</td>
<td>3 (2 – 9)</td>
<td>3 (2 – 9)</td>
<td>0.574</td>
</tr>
<tr>
<td>Bilobar involvement</td>
<td>14 (73.6%)</td>
<td>3 (5.5%)</td>
<td>0.040*</td>
</tr>
</tbody>
</table>
# Histopathologic Data

<table>
<thead>
<tr>
<th></th>
<th>Combined treatment group (n = 19)</th>
<th>Resection group (n = 54)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin involvement</td>
<td>0 (0%)</td>
<td>4 (7.4%)</td>
<td>0.567</td>
</tr>
<tr>
<td>Vascular permeation</td>
<td>7 (36.8%)</td>
<td>31 (57.4%)</td>
<td>0.123</td>
</tr>
<tr>
<td>Microsatellite lesion</td>
<td>3 (15.8%)</td>
<td>14 (25.9%)</td>
<td>0.530</td>
</tr>
<tr>
<td>Poorly differentiated cell type</td>
<td>2 (10.5%)</td>
<td>8 (14.8%)</td>
<td>0.857</td>
</tr>
<tr>
<td>Histological proof of HCC at ablation sites</td>
<td>19 (100%)</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>
Overall Survival Results

Combined treatment vs. resection alone

• No hospital mortality in both groups

• Median survival: 53.0 vs. 44.5 months

• Overall survival rates: 3-year 63% vs. 52%

p=0.496
Large Tumor Encroaching Major Hepatic Veins
Tumors Encroaching All 3 Hepatic Veins

- M/64, 6-cm segment 4 tumor extending to seg. 8
Extended Left Hepatectomy with MHV Reconstruction

- Extended left hepatectomy with segment 8 resection but preservation of segment 5 and reconstruction of MHV using Gortex graft.
Surgical Resection of HCC with Macroscopic Venous Invasion

M/67 HBsAg +ve, Child A cirrhosis
Presented with RUQ pain and obstructive jaundice – ERCP with stenting
Right lobe HCC with right PV invasion and bile duct invasion

Treatment: ? Resection ? TACE ? Systemic therapy
Right hepatectomy + excision of bile duct + left hepaticojejunostomy July 06
Latest CT scan in Feb 2015 – no recurrence
506 patients with HCC with portal vein tumor thrombus underwent hepatic resection, including 98 patients with tumor thrombus extending to main PV or SMV

• Operative mortality 0.2%

• 3-year survival 13%

Shi et al. Ann Surg Oncol 2010
Resection for HCC with Macroscopic Venous Invasion – China Experience

3-yr. survival rate

Type 1  25.1%
(segmental branch involvement)
Type 2  17.7%
(R or L PV involvement)
Type 3  3.6%
(main PV involvement)
Type 4  0%
(SMV involvement)

Shi et al. Ann Surg Oncol 2010
Aggressive Surgery for HCC with Main PV Tumor Thrombus

- 42 yrs. old HBV carrier, R lobe HCC with R, main and L portal vein tumor thrombus
  - R trisectionectomy and main portal vein resection with Gortex graft reconstruction
  - Survived 32 months
Resection after Downstaging by Transarterial Therapy

M/50 HBsAg +ve, Child A cirrhosis

Right lobe HCC with PV tumor thrombus extending to SMV

Transarterial Yttrium-90 radioembolization induced partial response, followed by R hepatectomy

Survived 3 years
Resection of IVC Tumor Thrombus after Systemic Therapy

- 38 yr. HBsAg+ve, R lobe HCC with invasion into IVC, treated with TOCE and then sorafenib for one year with tumor shrinkage
### Hepatectomy for HCC 1995-2011 (1282 Patients)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=1282)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [Median (Range)]</strong></td>
<td>57 (5-89)</td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td>1035:247</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>1092 (85.2%)</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>55 (4.3%)</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>783 (61.1%)</td>
</tr>
<tr>
<td><strong>AFP [Median (Range)]</strong></td>
<td>83.5 (1-1,335,900)</td>
</tr>
<tr>
<td><strong>Tumor size [Median (Range)]</strong></td>
<td>5.2 (0.7-28.0)</td>
</tr>
<tr>
<td><strong>Solitary: Multiple</strong></td>
<td>924:358</td>
</tr>
<tr>
<td><strong>Macroscopic venous invasion</strong>*</td>
<td>105 (8%)</td>
</tr>
</tbody>
</table>

*PV 83; HV 19; IVC 3*
Overall Survival Results of 1282 Patients

Median OS

- 1-year: 84%
- 3-year: 65%
- 5-year: 53%

Median DFS

- 1-year: 60%
- 3-year: 42%
- 5-year: 34%
Survival of Patients with Macroscopic Venous Invasion

<table>
<thead>
<tr>
<th></th>
<th>Without macrovascular invasion (n=1169)</th>
<th>With macrovascular invasion (n=113)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival Median</td>
<td>70</td>
<td>11.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-year</td>
<td>87%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>68%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>5-year</td>
<td>56%</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>

P<0.0001
Survival of Patients with Macroscopic Venous Invasion

<table>
<thead>
<tr>
<th></th>
<th>Portal vein invasion (n=83)</th>
<th>Hepatic vein invasion (n=19)</th>
<th>IVC invasion (n=3)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>10.9</td>
<td>12.1</td>
<td>14.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Median</td>
<td>45%</td>
<td>51%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td></td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td></td>
<td>21%</td>
<td>///</td>
<td></td>
</tr>
<tr>
<td>5-year</td>
<td></td>
<td>14%</td>
<td>///</td>
<td></td>
</tr>
</tbody>
</table>

P=0.75

Cumulative Survival (%)

Overall Survival (Year)

Portal vein invasion (n=83)

Hepatic vein invasion (n=19)

IVC invasion (n=3)
Hong Kong Liver Cancer Staging System

HCC

ECOG 0-1
Child A/B

No EVM*

Early tumor

Stage 1

Resection/ LT/ablation

Intermediate tumor

Stage 2

Resection

Locally advanced tumor

Stage 3

Resection/ TACE

Systemic therapy

Stage 4

ECOG 2-4
Child C

EVM*

Early tumor

Stage 5a

Liver Transplantation

Intermediate/ advanced tumors

Supportive care

Stage 5b

*EVM, extrahepatic vascular invasion/metastasis
Comparison of HKLC and BCLC Staging System

In BCLC-C patients classified as HKLC-II, the survival benefit of radical therapies compared with systemic therapy was pronounced (5-year survival probability, 48.6% vs 0.0%; P < .0001).

Yau et al. Gastroenterology 2014
Concomitant Hepatectomy and Resection of Isolated Extra-hepatic Metastasis

• Previous studies have shown favorable long-term survival in patients with isolated extrahepatic metastasis from HCC
  - median survival 42 months after resection of isolated lung metastasis from HCC in 9 patients  
  \(\text{Lam et al. Br J Surg 1998}\)
  - median survival 36 months after resection of intra-abdominal metastasis (adrenal, LN, abdominal wall, peritoneal) in 10 patients  
  \(\text{Sano et al. Hepatogastroenterology 2011}\)

• Synchronous hepatectomy and resection of isolated extra-hepatic metastasis may be justified in good risk patients
Concomitant Hepatectomy and Resection of Isolated Peritoneal Metastasis

Right hepatectomy + small bowel resection
Surviving after 36 months
Concomitant Hepatectomy and Resection of Isolated Adrenal Metastasis

M/49, Large R lobe HCC with L adrenal metastasis
Survived 17 months
Survival of Patients with Hepatectomy and Resection of Extrahepatic Metastasis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median 1-year Survival (%)</th>
<th>Median 3-year Survival (%)</th>
<th>Median 5-year Survival (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>96.4%</td>
<td>84.9%</td>
<td>69.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage I</td>
<td>86.5%</td>
<td>63.2%</td>
<td>41.8%</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>77.7%</td>
<td>45.9%</td>
<td>29.2%</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>96.4%</td>
<td>84.9%</td>
<td>69.5%</td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>86.5%</td>
<td>63.2%</td>
<td>41.8%</td>
<td></td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>77.7%</td>
<td>45.9%</td>
<td>29.2%</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>69.5%</td>
<td>41.8%</td>
<td>24.1%</td>
<td></td>
</tr>
</tbody>
</table>

Stage IV – extrahepatic metastasis present
Conclusions

- With modern surgical techniques, complex hepatectomy can be performed with a low mortality in well-selected cases in experienced centres.

- PVE and ALPPS extend resection for HCC in patients with inadequate liver remnant.

- Aggressive surgical approaches such as concurrent resection and ablation, vascular resection and reconstruction have extended the role of surgical resection for multifocal or locally advanced HCC with vascular invasion.

- In patients with isolated extrahepatic metastasis, surgical resection may provide long-term survival benefit.

- Development of more effective transarterial and systemic therapies may further enhance the role of resection by downstaging of unresectable HCC to become resectable.