Hepatocellular Carcinoma: Bridging to Liver Transplantation

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Disclosures

• Research support from:
  – Bayer
  – Bristol-Myers-Squibb
  – Genentech
  – Salix
  – Glaxo-Smith-Kline
  – Boehringer Ingelheim

• Consulting / Advisory Boards / Honorarium from
  – Astellas
  – Gilead
  – Roche
  – Janssen
Objectives

• To recognize **advantages of liver transplant** over other curative options for HCC

• To review the selection of HCC patients for liver transplant
  – Milan, UCSF, Up to Seven, **TTV & AFP**

• To define and review the **role of bridging therapy** for patients awaiting LT
  – TACE, RFA / PEI, TARE, SBRT, sorafenib
Definitions

• Salvage LT
  – LT after other curative therapy (surgery or RFA) to manage recurrent disease

• Bridging therapy
  – Treatment of HCC while listed for LT to prevent progression beyond LT criteria

• Down-staging
  – Treatment of HCC beyond LT criteria to bring them within appropriate selection criteria
Hepatocellular Carcinoma (HCC)

• Over 750,000 new cases each year
  – 5th most common / 2nd most lethal in men
  – 7th most common / 6th most lethal in women
• Occur usually in a cirrhotic liver
  – HBV most common world-wide
  – HCV most common in North America
  – Obesity & DM are risks [NAFLD]
• Incidence is increasing in Western countries

Global Incidence of HCC

HCC 3x↑ in M and 2x↑ in F in Canada

FIGURE 7.1 Age-standardized incidence rates (1970–2007) and mortality rates (1970–2009) for primary liver cancer, Canada

Analysis by: Chronic Disease Surveillance and Monitoring Division, CCDP, Public Health Agency of Canada
Data sources: Canadian Cancer Registry and Canadian Vital Statistics Death databases at Statistics Canada

Canadian Cancer Society 2013
Liver Transplant for HCC in Alberta

Adapted from Burak KW, Kneteman NM. Can J Gastroenterol 2010;24:643-50.
LT for HCC in Canada [2008]

- 105 of 409 Adult LT (26%) done for HCC

Burak KW. CLTG Data Committee Report 2009.
Treatment for HCC

- Surgery
- Ablation
- **Liver Transplant**
- TACE
- TARE
- Chemotherapy
- Radiation
- Palliative Care

[Diagram showing Venn diagram with categories of Patient, Tumour, and Liver, and the intersection highlighting HCC.]
Canadian Algorithm

BCLC

Stage 0 Very Early
1 (≤2cm)

Stage A Early
1 (≤5cm) or 3 (≤3cm)

Stage B Intermediate
> Milan criteria

Stage C Advanced
PVI, N1, M1

Stage D End Stage

Child Pugh Class

Clinical Questions

Portal HT and / or ↑ bilirubin?

Tumour

LT candidate?

No

Yes

No

Yes

B / C

ECOG Performance Status?

0-1

0-2

>2

Main PVT?

No

Yes

No

Yes

B / C

Treatment

Resection

RFA

LT

Curative Options

5 year survival ~ 50-70%

Prognosis

TACE

Sorafenib

Palliative Options

~ 20 mo

~ 11 mo

Best Supportive Care

~ 3 mo

LT for HCC in Alberta

Adapted from Burak KW, Kneteman NM. Can J Gastroenterol 2010;24:643-50.
# Resection versus Liver Transplant

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Surgery [n=77]</th>
<th>Liver Transplant [n=87]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>Liver failure &amp; recurrence</td>
<td>Organ donor shortage</td>
</tr>
<tr>
<td>Mean age</td>
<td>61 years</td>
<td>55 years</td>
</tr>
<tr>
<td>CP A / B / C</td>
<td>74 / 3 / 0</td>
<td>37 / 38 / 12</td>
</tr>
<tr>
<td>Mean size</td>
<td>3.34 cm</td>
<td>2.41 cm</td>
</tr>
<tr>
<td>Recurrence</td>
<td>70% @ 5yr</td>
<td>4% @ 5yr</td>
</tr>
<tr>
<td>ITT Survival</td>
<td>51% @ 5yr</td>
<td>69% @ 5yr</td>
</tr>
<tr>
<td>Survival by subgroups</td>
<td>74% → 50% → 25% @ 5yr</td>
<td>84% → 54% @ 2yr</td>
</tr>
</tbody>
</table>

Survival after Surgical Resection

Survival after Surgical Resection

RFA

• Superior to alcohol ablation (PEI)

• Size >2.5cm predicts recurrence

• Cure possible for BCLC stage 0
  – 218 HCC ≤ 2cm treated with RFA
  – 97% complete response, 2% complications
  – 5 yr survival 69% in operable sub-group (n=100)
# RFA vs Surgery RCTs

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Inclusion criteria</th>
<th>Sample Size (ITT → treated)</th>
<th>Disease Free Survival (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen MS (Ann Surg 2006)</td>
<td>1 HCC ≤ 5 cm</td>
<td>Surgery = 90 → 109</td>
<td>87  77  69  52  -</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RFA = 90 → 71</td>
<td>86  69  64  46  -</td>
<td></td>
</tr>
<tr>
<td>Huang J (Ann Surg 2010)</td>
<td>Milan criteria</td>
<td>Surgery = 115 → 122</td>
<td>85  74  61  55  51</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RFA = 115 → 108</td>
<td>82  59  46  34  27</td>
<td></td>
</tr>
<tr>
<td>Feng K (J Hepatol 2012)</td>
<td>≤ 2 HCC ≤ 4 cm</td>
<td>Surgery = 84</td>
<td>91  77  61  -  -</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RFA = 84</td>
<td>86  67  50  -  -</td>
<td></td>
</tr>
</tbody>
</table>

# Liver Transplant Selection Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tumour Size and Number</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milan</td>
<td>1 \leq 5 cm or up to 3 \leq 3 cm</td>
<td>OS 85% @ 4 yrs RFS 92% @ 4 yrs</td>
</tr>
<tr>
<td>USCF</td>
<td>1 \leq 6.5 cm or up to 3 \leq 4.5 cm and total diameter \leq 8 cm</td>
<td>OS 75% @ 5 yrs</td>
</tr>
<tr>
<td>Alberta</td>
<td>1 &lt; 7.5 cm or multiple &lt; 5 cm on sirolimus post-LT</td>
<td>OS 83% @ 4 yrs</td>
</tr>
<tr>
<td>Up to Seven</td>
<td>Sum of size of largest tumour + tumour number totals \leq 7</td>
<td>OS 71% @ 5 yrs</td>
</tr>
<tr>
<td>Toronto</td>
<td>Any size or number but NOT high grade on biopsy</td>
<td>OS 70% @ 5 yrs RFS 66% @ 5 yrs</td>
</tr>
</tbody>
</table>
UCSF criteria

• 70 consecutive LT for HCC (17 beyond Milan)
  – Recurrence in 11.4%

• 5 yr survival
  – 72.4% within Milan vs 74.1% beyond Milan

• Univariate analysis
  – AFP > 1000, poorly diff, age >55, TTD > 8 cm

• UCSF = 1 ≤ 6.5 cm or 3 ≤ 4.5 cm & TTD ≤ 8 cm
  – Within = 1 yr survival 90%, 5 yr survival 75%
  – Beyond = 1 yr survival 50%

Alberta Experience

Recurrences

Milan → 2 of 34 patients (6%)

>Milan → 6 of 36 patients (17%)

Toronto Experience

• 189 within Milan
• 105 beyond Milan (any size / any number)
  – Confined to the liver
  – Not poorly differentiated on biopsy
• Imaging can understage or overstage
• 5 yr survival = 72% Milan vs 70% > Milan
  – Protocol biopsy and aggressive bridging
• AFP > 400 had poorer DFS (HR 2.3)

LT beyond Milan Criteria

www.hcc-olt-metroticket.org

Mazzzaferro V. Liver Transpl 2007; 13: S44-S47.

• Meta-analysis of 19 studies
  – Within Milan better OS [HR 1.68, 95%CI 1.39-2.03]

Metro Ticket System

36 centres = 444 LT within Milan & 1112 LT beyond Milan

MVI doubled the chance of death

Impact of Size vs Number

Risk of Death

Up To Seven

Total Tumour Volume

- LT for HCC in Alberta [n=52]
  - Validated in Toronto [n=154] & Colorado [n=82]
- TTV 115 cm$^3$ determined by ROC analysis
- TTV $\leq$115 cm$^3$
  - Outcomes similar to Milan and UCSF
- TTV $>$115 cm$^3$
  - More recurrences and lower survival
    [Alberta and Colorado but not Toronto]

Survival after Liver Transplantation

Survival (%)

USA [SRTR database]
[n=6478, 3.2% >Milan]

≤ Milan
> Milan but ≤ UCSF
> UCSF but ≤ TTV115
> TTV115

Survival after Liver Transplantation

TTV ≤ 115 AND AFP ≤ 400

TTV > 115 OR AFP > 400

Survival after LT

Survival probabilities for different groups:
- No HCC
- Within Milan, AFP < 16
- Within Milan, AFP ≥ 16
- Beyond Milan, AFP < 16
- Beyond Milan, AFP ≥ 16

Sample sizes:
- No HCC: 31,789
- Within Milan, AFP < 16: 9,614
- Within Milan, AFP ≥ 16: 387

Data source: UNOS 02/02 – 06/11

# Selection Criteria for LT in Alberta

<table>
<thead>
<tr>
<th>Category</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>TTV $\leq 115 cm^3$</td>
</tr>
<tr>
<td>Lab</td>
<td>AFP $\leq 400$ ng/mL</td>
</tr>
<tr>
<td>Age</td>
<td>Typically $&lt; 70$</td>
</tr>
<tr>
<td></td>
<td>No comorbidities if age 65-69</td>
</tr>
<tr>
<td>Medical</td>
<td>No major cardiopulmonary issues, non-smoker, HIV negative, appropriate nutritional status, etc.</td>
</tr>
<tr>
<td>Social</td>
<td>Adequate support, compliance, appropriate abstinence and rehabilitation if addiction issues</td>
</tr>
</tbody>
</table>

Adapted from Burak KW, Kneteman NM. Can J Gastroenterol 2010;24:643-50.
Post LT Survival

Overall Survival

Disease Free Survival

P=0.715

n=82

P=0.340

n=21

Toso C. Hepatology 2012; 56(4) Suppl: 277A.
Risk of Drop-out

n=183

P<0.001

Toso C. Hepatology 2012; 56(4) Suppl: 277A.
Bridging for HCC at UofA

- Since Jan 2007 (TTV115 + AFP400)
- 167 of 705 patients (24%) listed for HCC
- 44 delisted (26%)
- 96 LT
  - Wait time = mean 345d, median 237d
  - 84% had bridging
- 27 still waiting
  - All but two recently listed have had bridging
# Bridging to LT

<table>
<thead>
<tr>
<th>Ref (year)</th>
<th>Study design</th>
<th>≤ Milan criteria</th>
<th>Bridging therapy</th>
<th>N</th>
<th>Mean wait time</th>
<th>Dropout</th>
<th>1 yr</th>
<th>2 yrs</th>
<th>3 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi (2004)</td>
<td>Retro</td>
<td>100%</td>
<td>TACE</td>
<td>20</td>
<td>11 mo</td>
<td>35%</td>
<td>~85</td>
<td>~70</td>
<td>~62</td>
<td></td>
</tr>
<tr>
<td>Maddala (2004)</td>
<td>Retro</td>
<td>87%</td>
<td>TACE</td>
<td>54</td>
<td>7 mo</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>Decaens (2005)</td>
<td>Retro CC</td>
<td>71%</td>
<td>TACE</td>
<td>100</td>
<td>4.2 mo</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td>100</td>
<td>4.3 mo</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Lu (2005)</td>
<td>Retro</td>
<td>81%</td>
<td>RFA</td>
<td>52</td>
<td>12.7 mo</td>
<td>6%</td>
<td>98</td>
<td>84</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Perez-Saborido(2005)</td>
<td>Retro</td>
<td>72%</td>
<td>TACE</td>
<td>18</td>
<td>n/a</td>
<td>n/a</td>
<td>84</td>
<td>61</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td>28</td>
<td>n/a</td>
<td>n/a</td>
<td>77</td>
<td>59</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Yao (2005)</td>
<td>Retro</td>
<td>69%</td>
<td>Multi</td>
<td>103</td>
<td>n/a</td>
<td>n/a</td>
<td>96</td>
<td></td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td>65</td>
<td>n/a</td>
<td>n/a</td>
<td>92</td>
<td></td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Frangakis (2010)</td>
<td>Retro</td>
<td>100%</td>
<td>TACE</td>
<td>22</td>
<td>4.2 mo</td>
<td>3%</td>
<td></td>
<td></td>
<td>76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td>43</td>
<td>5 mo</td>
<td>15%</td>
<td></td>
<td></td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

TAE / TACE before LT

- 150 HCC waiting for LT (within Milan)
- 67 (45%) had bridging (TAE>TACE)
  - PR 54%
  - CR 33%
  - No response 13%

- Post LT recurrence (multivariate analysis)
  - No bridging [OR = 5.40]
  - Total tumour size [OR = 1.04]

TACE / RFA before LT

- 93 HCC (62% Milan) → 51 TACE / 8 RFA

### Expert Recommendations for TACE

#### Absolute contraindications

- Decompensated cirrhosis (CPB ≥8)
  - jaundice, HE, refractory ascites, HRS
- Extensive tumour
  - massive replacement of both lobes
- Severely reduced PV flow
  - PVT or hepatofugal blood flow
- Technical contraindications to HA therapy (thrombosis, dissection)
- Renal insufficiency (creatinine >180)

#### Relative contraindications

- Comorbidities:
  - Active CV or lung disease
- Untreated varices
- Bile duct occlusion
- Tumour size >10 cm

---

Consider TARE with Y90 as an alternative to TACE

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TARE (Y90) vs TACE for Stage T3

<table>
<thead>
<tr>
<th></th>
<th>TACE</th>
<th>TARE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=35</td>
<td>n=43</td>
<td></td>
</tr>
<tr>
<td>EASL CR</td>
<td>17%</td>
<td>47%</td>
<td>0.13</td>
</tr>
<tr>
<td>Downstaged</td>
<td>31%</td>
<td>58%</td>
<td>0.023</td>
</tr>
<tr>
<td>Solitary</td>
<td>21</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Downstaged</td>
<td>6 (28%)</td>
<td>15 (75%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multifocal</td>
<td>14</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Downstaged</td>
<td>5 (36%)</td>
<td>10 (44%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Transplant</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>2 (18%)</td>
<td>2 (22%)</td>
<td></td>
</tr>
</tbody>
</table>

SBRT before LT

• 10 patients → HCC 2.5 – 10.8cm (80% >Milan)
  – MELD 9 – 17, 50% had failed RFA / TACE
• SBRT well tolerated
• 2 stable, 8 regression (10-50%)
• 2 delisted for HCC growth outside RT field
• 3 waiting LT
• 5 LT → necrosis (0 / 40 / 60 / 90 / 90%)

Sorafenib before LT

• 15 HCC patients (93% >Milan) who had LT
  – TACE 80%, RFA 20%, LR 13%
• Sorafenib 400mg (200 – 800mg) → dose ↓ 11
  – CP A = 4, B = 5, C = 6
  – Median 87 days (12 – 360)
• No complications postLT
• OS and recurrence similar to control group

Conclusions

• HCC is increasing in N. America
  – Increasing burden on LT programs

• LT is the best option for HCC
  – Treats cirrhosis and has lowest recurrence rates

• Extended criteria for HCC are acceptable
  – TTV and AFP

• Bridging is necessary with long wait times and may reduce recurrence post LT
  – TACE, RFA/PEI, TARE, SBRT and sorafenib