Surgical Options for Treatment of HCC – Resection vs. Liver Transplantation (LT)

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Upon completion of this activity, the participants should be better able to:

- Explain data on the prevalence and consequences of HCC
- Demonstrate strategies to incorporate classification, diagnostic and treatment updates into clinical practice to individualize treatment strategies
- Analyze recently approved and emerging treatment options and understand how new agents are improving the standard of care for all HCC patients
Overview

• Resection versus LT for HCC
  – Criteria for surgical management of HCC
  – Comparison of surgical outcomes
    • Likelihood of cure
    • Organ availability/allocation and waitlist dropout
    • LT survival benefit
  – Safety
  – Salvage transplant
BCLC Staging Classification

Stage 0  
PST 0, Child-Pugh A
Very early stage (0)  
Single <2 cm, CA in situ

Stage A-C  
Okuda 1-2, PST 0-2, Child-Pugh A-B
Early stage (A)  
Single or 3 nodules <3 cm, PS 0
Intermediate stage (B)  
Multinodular, PS 0

Stage D  
Okuda 3, PST >2, Child-Pugh C
Advanced stage (C)  
Poral vein invasion, N1, M1, PS 1-2

Terminal stage (D)

HCC

No  
Yes

Single  
3 nodules ≤3 cm

Associated diseases

Portal pressure/bilirubin

Increased  
Normal

Resection  
Liver Transplantation  
PEI/RFA  
TACE  
New agents

Resection  
Liver Transplantation  
PEI/RFA  
TACE  
New agents

Symptomatic Tx  
1-yr survival 10-20%

5-yr survival 50-70%

3-yr survival 20-40%

Adapted from Llovet JM et al. Lancet. 2003; 362: 1907-17.
BCLC Definition of Optimal Resection Candidate

Portal hypertension

No

Extension of hepatectomy

Minor
(<3 segment)

MELD score

≤9

Low risk
5% risk of liver decompensation
Liver-related mortality: 0.5%

Intermediate risk
<30% risk of liver decompensation
Liver-related mortality: 9%

High risk
>30% of liver decompensation
Liver-related mortality: 25%

Yes

Extension of hepatectomy

Major
(≥3 segment)

Minor
(<3 segment)

Major
(≥3 segment)

Extension of hepatectomy

Major

Minor

Hepatocellular Carcinoma
Surgical Treatment for HCC
Cirrhosis and Liver Function

NON-CIRRHOTIC → RESECTION
5% in Western countries
40% in Asia

CIRRHOTIC
Child’s A
• Good liver function

Child’s B/C
• Impaired liver function

TRANSPLANT
Survival Following Resection: Impact of Portal Hypertension

“Ideal” candidate

- Good liver function
- No portal hypertension (suggested by varices, enlarged spleen, platelets <100)
- Normal bilirubin
- Single lesion ≤5 cm
- Location of tumor in left lobe
- Excellent performance status (ECOG 0)

No RCTs evaluating resection vs LT!
Approx 40-50% at 3 yrs and 60-70% at 5 yrs
Approx 40-50% at 3 yrs and 60-70% at 5 yrs

**Predictors of tumor recurrence**

- Vascular invasion
- Multi-focal HCC/satellite tumor nodules
- Tumor size >5 cm
- Positive resection margins
- Lymph node involvement
- High alpha-fetoprotein
Resection for Cirrhosis vs Normal Liver

**A** Cumulative recurrence

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Normal liver</th>
<th>Liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
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<td>60</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>72</td>
<td></td>
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</tbody>
</table>

**B** Disease-specific survival

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Normal liver</th>
<th>Liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>24</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>48</td>
<td>25</td>
<td>28</td>
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<tr>
<td>72</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>96</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>120</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>
Advantages of Liver Transplantation

- Best oncologic resection
- Replaces diseased liver
- Restores normal hepatic function
Intention-to-Treat Analyses Meta-Analyses – Recurrence

Resection Transplantation

Disadvantages of Liver Transplantation

- Limited organ supply and risk of waitlist dropout
- Cost
- Immunosuppression/safety
- ? Limited survival benefit in setting of early HCC and control of underlying liver disease (e.g. viral hepatitis tx with antivirals; EtOH tx with abstinence)
Liver Transplantation for HCC
Milan Criteria

1 lesion ≤5 cm

2 to 3, none >3 cm

+ Absence of Macroscopic Vascular Invasion
+ Absence of Extra-hepatic Spread

Liver Transplantation for HCC
Stage T2 Criteria

Post-LT
5 year survival: 75-80%
5 year HCC recurrence: ~15%

1 lesion 2-5 cm
2 to 3, none >3 cm
Rising Incidence of Liver Transplant for HCC at UCSF

% of adult LT done for HCC

Year
Rising Incidence of Liver Transplant for HCC at UCSF

- 22 LT for HCC in 2006
- 15%
Rising Incidence of Liver Transplant for HCC at UCSF

- 22 LT for HCC in 2006
- 84 LT for HCC in 2016
- 15% of adult LT done for HCC in 2006
- 47%
Liver Transplant for HCC: Recent Changes

- 6-month mandatory waiting period before awarding MELD exception
<table>
<thead>
<tr>
<th>Delays in HCC-MELD exception</th>
<th>HCC Transplant rates (per 100 person-years)</th>
<th>Non-HCC Transplant rates (per 100 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>108.7</td>
<td>30.1</td>
</tr>
<tr>
<td>3 months</td>
<td>65.0</td>
<td>32.5</td>
</tr>
<tr>
<td>6 months</td>
<td>44.2</td>
<td>33.9</td>
</tr>
<tr>
<td>9 months</td>
<td>33.6</td>
<td>34.8</td>
</tr>
</tbody>
</table>

Liver Transplant for HCC: Recent Changes

- 6-month mandatory waiting period before awarding MELD exception
- Regional variation in access to LT for HCC
Long wait time (LWTR) is regions 1, 5, and 9
Mid wait time (MWTR) is regions 2, 4, 6, 7, and 8 and
Short wait time (SWTR) is regions 3, 10, and 11

Probability of Waitlist Dropout by Wait Time Region and Listing Period

As of May 2019, HCC MELD ladder system has been replaced by awarding median MELD at transplant minus 3 points (MMAT-3) for the area where the candidate is listed.
Down-Staging of HCC for Transplant

- **Definition**: Reduction in the size of tumor using local regional therapy to meet acceptable criteria for liver transplant\(^1\)
- **Tumor response**: Based on radiographic measurement of the size of all viable tumors, not including the area of necrosis from local regional therapy\(^2\)
- **A selection tool** for tumors with more favorable biology that respond to down-staging treatment and also do well after liver transplant\(^1\)

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Down-Staging of HCC for Transplant

Local Regional Therapies for HCC

• Chemoembolization (TACE)
  – Conventional versus Drug-eluting beads

• Ablations
  – Chemical
    • Percutaneous ethanol injection (PEI)
  – Thermal
    • Radiofrequency ablation (RFA)
      – (Laparoscopic, percutaneous or open)
    • Microwave/Cryo – ablation

• Radioembolization (YITTRIUM – 90)

• Stereotactastic Body Radiation (SBRT)
UCSF/Region 5 Down-Staging Protocol

- **Inclusion criteria**
  - 1 lesion >5 cm and ≤8 cm
  - 2 or 3 lesions ≤5 cm w/ total tumor diameter ≤8 cm
  - 4 or 5 lesions ≤3 cm w/ total tumor diameter ≤8 cm
  - No vascular invasion on imaging

- **Minimum 3 month observation period after successful down-staging into Milan before LT can be undertaken**

Post-Transplant Survival


Median post-transplant follow-up 4.0 yrs
No difference in post-LT HCC recurrence

\[ p = 0.69 \]
Region 5 D/S Multi-Center Study: Post-LT Survival

Median post-LT follow-up 4 years
Overall post-LT HCC recurrence 10%

UNOS HCC Cohorts (N=3819)

- **MILAN**
  - N=3,276 (86%)
  - Total tumor diameter: 2.8 cm (2.3-3.7)

- **“UNOS-DS”**
  - N=422 (11%)
  - Total tumor diameter: 5.8 cm (5.3-6.5)

- **“All-comers”**
  - N=121 (3.2%)
  - Total tumor diameter: 9.3 cm (8.5-10.6)

UNOS Down-Staging Protocol

3-yr post-LT survival by initial tumor burden criteria

“Milan” (n=3276): 83%
“UNOS-DS” (n=422): 79% (p=0.17 vs Milan)
“AC-DS” (n=121): 71% (p=0.04 vs Milan)
Probability of Down-Staging by Initial Tumor Burden

Recent UNOS Policy Change

Down-staging

- Candidates meeting UNOS-DS criteria who are successfully down-staged into Milan are now eligible for automatic MELD exception similar to patients always within Milan criteria

- Patients initially beyond UNOS-DS ("all-comers") can be considered for MELD exception on a case-by-case basis
AFP and Post-Transplant Outcome – France

High AFP Threshold

- Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception

- If AFP falls <500 after LRT, the candidate is eligible for a standardized MELD exception
Liver Transplantation for HCC
METROTICKET 2.0

Liver Transplantation and Hepatic Resection can Achieve Cure for Hepatocellular Carcinoma

Antonio Daniele Pinna, MD,*, Tian Yang, MD,† Vincenzo Mazzaferro, MD, PhD,‡
Luciano De Carlis, MD, FEBS,§ Jian Zhou, MD, PhD,¶ Sasan Roayaie, MD,‖ Feng Shen, MD, PhD,†
Carlo Sposito, MD, PhD,† Matteo Cescon, MD, PhD,*, Stefano Di Sandro, MD, PhD,§ He Yi-feng, MD,¶‖
Philip Johnson, MD, FRCP,** and Alessandro Cucchetti, MD*

- Multinational study, N=3286 HCC pts treated with LT (n=1218) or resection (n=2068) to estimate statistical cure
## Outcomes: Liver Resection vs. LT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LT (n: 1218)</th>
<th>HR (n: 2068)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53.7 (8.6)</td>
<td>59.1 (12.4)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>54 (48–60)</td>
<td>60 (51–67)</td>
</tr>
<tr>
<td>Radiological number of vital HCCs before surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>329 (27.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Single nodule</td>
<td>504 (41.4%)</td>
<td>1597 (77.2%)</td>
</tr>
<tr>
<td>2–3 nodules</td>
<td>300 (24.6%)</td>
<td>399 (19.3%)</td>
</tr>
<tr>
<td>More than 3 nodules</td>
<td>85 (7.0%)</td>
<td>72 (3.5%)</td>
</tr>
<tr>
<td>Radiological largest vital HCC before surgery, cm †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.0 (2.0)</td>
<td>4.8 (3.3)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.0 (2.0–4.0)</td>
<td>4.0 (2.5–6.0)</td>
</tr>
<tr>
<td>Last AFP before surgery, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10.1 (4.2–42.6)</td>
<td>12.0 (6.3–316)</td>
</tr>
<tr>
<td>Transplant criteria fulfilled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan</td>
<td>993 (81.5%)</td>
<td>1271 (61.4%)</td>
</tr>
<tr>
<td>Radiological up-to-7</td>
<td>1109 (91.1%)</td>
<td>1509 (73.0%)</td>
</tr>
<tr>
<td>UCSF</td>
<td>1072 (88.0%)</td>
<td>1537 (74.3%)</td>
</tr>
<tr>
<td>AFP French model</td>
<td>1057 (86.8%)</td>
<td>1236 (59.8%)</td>
</tr>
<tr>
<td>Shangai–Fudan</td>
<td>1101 (90.4%)</td>
<td>1725 (83.4%)</td>
</tr>
<tr>
<td>Metroticket 2.0</td>
<td>1045 (85.8%)</td>
<td>1226 (59.2%)</td>
</tr>
<tr>
<td>MELD score at surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.2 (5.4)</td>
<td>8.6 (2.0)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>11 (8–14)</td>
<td>8 (7–9)</td>
</tr>
</tbody>
</table>
Liver Transplantation and Hepatic Resection can Achieve Cure for Hepatocellular Carcinoma
Liver Transplantation and Hepatic Resection can Achieve Cure for Hepatocellular Carcinoma

- Liver Resection vs. LT
- Recurrence-Free Survival and Cure

- 74% at 5 yrs can be considered cured with 95% confidence
- 35% at 11 yrs cured with 95% confidence
Resection vs. LT for Single <3 cm HCC

LT Survival Benefit

- Appears that long-term outcomes are better for LT than resection.
  - But are resectable HCC pts really the ones who should be offered LT?
Growing HCC Incidence

- The number of early HCC detected is increasing
  - Up to 65% in a recent series

LT Survival Benefit

• How do we optimize transplant survival benefit for patients with HCC?
## LT Survival Benefit

<table>
<thead>
<tr>
<th>A. Benefit risk factors</th>
<th>B. Median benefit</th>
<th>C. Median benefit gain</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC-OUT at LT or DO</td>
<td>34-5</td>
<td></td>
<td>11-7</td>
</tr>
<tr>
<td>MC-IN at LT or DO</td>
<td>22-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD at LT or DO &gt;13</td>
<td>39-1</td>
<td></td>
<td>19-3</td>
</tr>
<tr>
<td>MELD at LT or DO ≤13</td>
<td>19-8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HCC pts within Milan & MELD <13 derive less LT survival benefit

Predictors of Dropout – UNOS

Cumulative incidence of waitlist dropout

Time since HCC exception (months)

0 12 24 36

- 0
- 0.1
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6

20%
5%
12%
29%

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>“Low risk group”</th>
<th>All others</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Low risk group”</td>
<td>245</td>
<td>1807</td>
</tr>
<tr>
<td>All others</td>
<td>162</td>
<td>756</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

• How do we optimize transplant survival benefit for patients with HCC?

Post-LT life expectancy – waitlist life expectancy

HCC pts who are resectable (i.e. low MELD and CP A) have a very long waitlist life expectancy → likely derive minimal LT benefit
# Safety of Liver Resection & LT – M&M

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>N</th>
<th>Overall</th>
<th>Mb (%)</th>
<th>Mt (%)</th>
<th>Rec (%)</th>
</tr>
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<tbody>
<tr>
<td>NRSX LT</td>
<td></td>
<td></td>
<td>5-YR</td>
<td>5-YR</td>
<td></td>
<td></td>
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<tr>
<td>Iwatsuki 1991</td>
<td>17</td>
<td>71</td>
<td>0%</td>
<td>41%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ringe 1991</td>
<td>131c</td>
<td>61c</td>
<td>36%</td>
<td>15%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bismuth 1993</td>
<td>60</td>
<td>60</td>
<td>50%</td>
<td>47%</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Vargas 1995</td>
<td>35</td>
<td>11</td>
<td>58%</td>
<td>81%</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Tan 1995</td>
<td>12</td>
<td>15</td>
<td>33%</td>
<td>63%</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Michel 1997</td>
<td>102</td>
<td>113</td>
<td>31%</td>
<td>32%</td>
<td>39</td>
<td>38</td>
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<tr>
<td>Mazzioti 1998</td>
<td>238</td>
<td>41</td>
<td>41%</td>
<td>69%</td>
<td>42</td>
<td>80</td>
</tr>
<tr>
<td>Otto 1998</td>
<td>52</td>
<td>50</td>
<td>37%</td>
<td>44%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Weimann 1999</td>
<td>32</td>
<td>31</td>
<td>34%</td>
<td>63%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yamamoto 1999</td>
<td>294</td>
<td>270</td>
<td>47%</td>
<td>54%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Llovet 1999</td>
<td>77</td>
<td>87</td>
<td>51%</td>
<td>69%</td>
<td>4.2</td>
<td>80</td>
</tr>
<tr>
<td>Figuera 2001</td>
<td>35</td>
<td>85</td>
<td>51%</td>
<td>60%</td>
<td>NR</td>
<td>6.7</td>
</tr>
<tr>
<td>De Carlis 2001</td>
<td>131</td>
<td>91</td>
<td>38%</td>
<td>65%</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Shabahang 2002</td>
<td>44</td>
<td>65</td>
<td>57%</td>
<td>66%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total (weighted mean, including Tables 1 and 2)</td>
<td>5,831</td>
<td>3,921</td>
<td>48%</td>
<td>52%</td>
<td>44%</td>
<td>45%</td>
</tr>
</tbody>
</table>

- Morbidity similar
- Mortality 60% less

Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.
## Table 2. Risk of Infection-Related Malignancies in US Transplant Recipients

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>No. of Cases</th>
<th>SIR (95% CI)</th>
<th>P Value</th>
<th>Incidence/100,000 Person-Years</th>
<th>EAR/100,000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1504</td>
<td>199.4</td>
<td>7.54 (7.17 to 7.93)</td>
<td>&lt;.001</td>
<td>194.0</td>
</tr>
<tr>
<td>Nodal</td>
<td>831</td>
<td>136.6</td>
<td>6.08 (5.68 to 6.51)</td>
<td>&lt;.001</td>
<td>107.2</td>
</tr>
<tr>
<td>Extranodal</td>
<td>673</td>
<td>62.8</td>
<td>10.72 (9.93 to 11.56)</td>
<td>&lt;.001</td>
<td>86.8</td>
</tr>
<tr>
<td>Liver</td>
<td>930</td>
<td>80.5</td>
<td>11.56 (10.83 to 12.33)</td>
<td>&lt;.001</td>
<td>120.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>152</td>
<td>90.9</td>
<td>1.67 (1.42 to 1.96)</td>
<td>&lt;.001</td>
<td>19.6</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>120</td>
<td>2.0</td>
<td>61.46 (50.95 to 73.49)</td>
<td>&lt;.001</td>
<td>15.5</td>
</tr>
<tr>
<td>Oropharynx including tonsil</td>
<td>106</td>
<td>52.8</td>
<td>2.01 (1.84 to 2.43)</td>
<td>&lt;.001</td>
<td>13.7</td>
</tr>
<tr>
<td>Anus</td>
<td>90</td>
<td>15.4</td>
<td>5.84 (4.70 to 7.18)</td>
<td>&lt;.001</td>
<td>11.6</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>85</td>
<td>23.7</td>
<td>3.58 (2.86 to 4.43)</td>
<td>&lt;.001</td>
<td>11.0</td>
</tr>
<tr>
<td>Vulva</td>
<td>58</td>
<td>7.6</td>
<td>7.60 (5.77 to 9.83)</td>
<td>&lt;.001</td>
<td>7.5</td>
</tr>
<tr>
<td>Cervix</td>
<td>45</td>
<td>43.6</td>
<td>1.03 (0.75 to 1.38)</td>
<td>.88</td>
<td>5.8</td>
</tr>
<tr>
<td>Penis</td>
<td>22</td>
<td>5.3</td>
<td>4.13 (2.59 to 6.26)</td>
<td>&lt;.001</td>
<td>2.8</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>8</td>
<td>8.3</td>
<td>0.96 (0.42 to 1.90)</td>
<td>&gt;.99</td>
<td>1.0</td>
</tr>
<tr>
<td>Vagina</td>
<td>7</td>
<td>3.0</td>
<td>2.35 (0.94 to 4.84)</td>
<td>.07</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10,656</strong></td>
<td><strong>5080.6</strong></td>
<td><strong>2.10 (2.06 to 2.14)</strong></td>
<td>&lt;.001</td>
<td><strong>1374.7</strong></td>
</tr>
</tbody>
</table>

Abbreviations: EAR, excess absolute risk; SIR, standardized incidence ratio.

*Includes invasive cancers arising during 775,147 person-years. Incidence is presented for the entire cohort, but can be calculated separately for males or females for sex-specific malignancies based on follow-up of 465,521 person-years in males and 309,626 person-years in females. Cancer types are listed in order of decreasing frequency.

*Includes non-infection-related malignancies presented in Table 3.

Multiple studies performed assessing the strategy of resection and only if recurrence occurs within conventional transplant criteria to then pursue salvage LT.
Successful SLT: No recurrence LT if recurred

Failed SLT: Liver failure or Recurrence w/o LT

Post-resection predictor of successful SLT strategy included stage T1 or T2

### Salvage LT vs Primary LT

**5-yr Post-LT Survival**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SLT Events</th>
<th>SLT Total</th>
<th>PLT Events</th>
<th>PLT Total</th>
<th>Weight</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam 2003</td>
<td>7</td>
<td>17</td>
<td>119</td>
<td>195</td>
<td>2.2%</td>
<td>0.45 [0.16, 1.22]</td>
</tr>
<tr>
<td>Belghiti 2003</td>
<td>10</td>
<td>18</td>
<td>37</td>
<td>70</td>
<td>1.3%</td>
<td>1.11 [0.39, 3.16]</td>
</tr>
<tr>
<td>Bhangui 2016</td>
<td>10</td>
<td>31</td>
<td>135</td>
<td>340</td>
<td>3.0%</td>
<td>0.72 [0.33, 1.58]</td>
</tr>
<tr>
<td>Del Gaudio 2008</td>
<td>10</td>
<td>16</td>
<td>107</td>
<td>147</td>
<td>1.5%</td>
<td>0.62 [0.21, 1.83]</td>
</tr>
<tr>
<td>Faciutto 2008</td>
<td>5</td>
<td>5</td>
<td>19</td>
<td>32</td>
<td>0.1%</td>
<td>7.62 [0.39, 149.49]</td>
</tr>
<tr>
<td>Hu 2012</td>
<td>465</td>
<td>859</td>
<td>3454</td>
<td>5727</td>
<td>80.5%</td>
<td>0.78 [0.67, 0.90]</td>
</tr>
<tr>
<td>Margarit 2005</td>
<td>2</td>
<td>6</td>
<td>11</td>
<td>36</td>
<td>0.4%</td>
<td>1.14 [0.18, 7.15]</td>
</tr>
<tr>
<td>Sapisochin 2010</td>
<td>9</td>
<td>17</td>
<td>22</td>
<td>34</td>
<td>1.3%</td>
<td>0.61 [0.19, 2.00]</td>
</tr>
<tr>
<td>Scatton 2008</td>
<td>13</td>
<td>20</td>
<td>40</td>
<td>73</td>
<td>1.2%</td>
<td>1.53 [0.55, 4.28]</td>
</tr>
<tr>
<td>Vennarecci 2007</td>
<td>8</td>
<td>9</td>
<td>23</td>
<td>37</td>
<td>0.2%</td>
<td>4.87 [0.55, 43.18]</td>
</tr>
<tr>
<td>Wang 2006</td>
<td>35</td>
<td>76</td>
<td>131</td>
<td>295</td>
<td>5.6%</td>
<td>1.07 [0.64, 1.77]</td>
</tr>
<tr>
<td>Wu 2012</td>
<td>25</td>
<td>36</td>
<td>111</td>
<td>147</td>
<td>2.6%</td>
<td>0.74 [0.33, 1.64]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>SLT Events Total</th>
<th>PLT Events Total</th>
<th>Weight</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1110</td>
<td>7133</td>
<td>100.0%</td>
<td>0.81 [0.71, 0.92]</td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi²=10.12, df=11 (P=0.52); I²=0%

**Test for overall effect:** Z=3.25 (P=0.001)

• Resection status requires assessment of portal hypertension, MELD score, and extent of resection

• Resection associated with higher recurrence than LT but still 1st line tx, especially with single small tumor and in setting of organ shortages
• Similar post-LT survival observed for Milan and UNOS D/S patients → Down-staging now national policy

• Pts with initial tumor burden within “all-comers” should be carefully selected for LT given poor post-LT outcomes

• AFP is an excellent marker of tumor biology with worse post-LT outcome as AFP rises. AFP >1000 is exclusion from LT nationally unless <500 ng/ml with LRT
Case Presentation
55 year-old man with chronic hepatitis C and biopsy proven cirrhosis, found on screening ultrasound to have a 3 cm lesion in the right lobe. Quad-phase CT of the abdomen showed a 2.5 cm arterial enhancing lesion in segment 6 with washout. No symptoms other than mild fatigue. No history of substance abuse. Examination showed no spider nevi. Spleen tip palpable. Dx: LI-RADS 5 per Tumor Board review

Laboratory evaluation showed bilirubin 1.7, ALT 128, AST 98, albumin 3.5, INR 1.3, platelets 85,000, AFP 36.

What treatment would you recommend?

1. Anatomic resection
2. Wedge resection
3. Liver transplantation
4. Percutaneous radiofrequency ablation (RFA)
55 year-old man with chronic hepatitis C and biopsy proven cirrhosis, found on screening ultrasound to have a 3 cm lesion in the right lobe. Quad-phase CT of the abdomen showed a 2.5 cm arterial enhancing lesion in segment 6 with washout. No symptoms other than mild fatigue. No history of substance abuse. Examination showed no spider nevi. Spleen tip palpable. Dx: LI-RADS 5 per Tumor Board review.

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3. Liver transplantation
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BCLC Definition of Optimal Surgical Candidate

Portal hypertension

- Yes
  - Extension of hepatectomy
    - Minor (<3 segment)
    - Major (≥3 segment)
      - MELD score
        - ≤9 Low risk
          - 5% risk of liver decompensation
            - Liver-related mortality: 0.5%
        - >9 Intermediate risk
          - <30% risk of liver decompensation
            - Liver-related mortality: 9%
          - ≥3 segment
            - Major (≥3 segment)
              - MELD score >9 High risk
                - >30% of liver decompensation
                  - Liver-related mortality: 25%
              - MELD score ≤9

56 year-old man with chronic HBV, well suppressed on antiviral therapy. He received inadequate HCC surveillance and was found to have two LI-RADS 5 tumors in the right lobe measuring 5 cm and 3 cm. Asymptomatic (ECOG 0). No substance abuse. No significant medical history.

**Laboratory**: HCT 42.4, platelets 84,000, creatinine 0.6, total bilirubin 0.9, albumin 4.2, hepatitis B DNA (-), AFP 49 ng/mL.
56 year-old man with chronic HBV, well suppressed on anti-viral therapy. He received inadequate HCC surveillance and was found to have two LI-RADS 5 tumors in the right lobe measuring 5 cm and 3 cm. Asymptomatic (ECOG 0). No significant medical history.

Laboratory: HCT 42.4, platelets 84,000, creatinine 0.6, total bilirubin 0.9, albumin 4.2, hepatitis B DNA (-), AFP 49 ng/mL.

**What treatment would you recommend?**

1. Resection
2. Microwave ablation
3. Sorafenib
4. Liver transplant after down-staging to within Milan criteria
56 year-old man with chronic HBV, well suppressed on anti-viral therapy. He received inadequate HCC surveillance and was found to have two LI-RADS 5 tumors in the right lobe measuring 5 cm and 3 cm. Asymptomatic (ECOG 0). No significant medical history.

Laboratory: HCT 42.4, platelets 84,000, creatinine 0.6, total bilirubin 0.9, albumin 4.2, hepatitis B DNA (-), AFP 49 ng/mL.

**What treatment would you recommend?**

1. Resection
2. Microwave ablation
3. Sorafenib
4. Liver transplant after down-staging to within Milan criteria
Inclusion criteria
- 1 lesion >5 cm and ≤8 cm
- 2 or 3 lesions ≤5 cm w/ total tumor diameter ≤8 cm
- 4 or 5 lesions ≤3 cm w/ total tumor diameter ≤8 cm
- No vascular invasion on imaging

This protocol has recently been adopted as national policy for automatic priority listing in patients who have been successfully down-staged to within Milan criteria

Case Presentation

Radioembolization with TheraSphere/Y-90

Tc-MAA
Case Presentation

Pre-Y90  1 mo p Y90#1  1 mo p Y90#2
          4 mo p Y90#1
56 year-old man with chronic HBV, well suppressed on antiviral therapy. He received inadequate HCC surveillance and was found to have two LI-RADS 5 tumors in the right lobe measuring 5 cm and 3 cm. Asymptomatic (ECOG 0). No substance abuse. No significant medical history. He undergoes two Y90 procedures with a CT abdomen 1 month later showing no residual enhancing disease. AFP has decreased from 49 to 7.

Question:
Is there an optimal AFP cutoff prior to LT?
Liver Transplantation for HCC
METROTICKET 2.0

HCC Specific Survival

Number of tumor nodules summed to the size (in cm) of the largest nodule

Case Presentation

56 year-old man with chronic HBV, well suppressed on anti-viral therapy. He received inadequate HCC surveillance and was found to have two LI-RADS 5 tumors in the right lobe measuring 5 cm and 3 cm. Asymptomatic (ECOG 0). No substance abuse. No significant medical history. He undergoes two Y90 procedures with a CT abdomen 1 month later showing no residual enhancing disease. AFP has decreased from 49 to 7.

Question:

Is there an optimal AFP cutoff prior to LT? Recurrence risk begins to increase at AFP ~ 20 with very poor outcome w/ AFP >1000.
Reducing High AFP Prior to LT

High AFP Threshold

- Candidates with lesions meeting T2 criteria but with an AFP >1000 are not eligible for a standardized MELD exception
- If AFP falls <500 after LRT, the candidate is eligible for a standardized MELD exception

However, AFP reduction to <100 ng/ml is ideal
Thank You!

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