UAB Liver Tumor Clinic

Referrals: 205 996 5970 (phone)
          205 996 9037 (fax)
          800 UAB MIST

HCC Treatment Decision Tree

Treatment Algorithm
- Transplant
- Surgical Resection
- Ablation
- Other Locoregional Approaches
- Chemotherapy
HCC Clinical Staging Schemes

Pons F et al. HPB 2005; 7:35

BCLC Staging and treatment schedule

Llovet JM et al. Lancet 2003; 362:1907
Hepatocellular Carcinoma

N=706pts with HCC <3.5cm
Hepatology 2011;53:136-147

BCLC Staging and treatment schedule

Llovet JM et al. Lancet 2003; 362:1907
HCC Treatment Decision Tree

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BCLC Staging and treatment schedule

Llovet JM et al.  Lancet 2003; 362:1907
Hepatocellular Carcinoma
Liver Transplantation

Non-Resectable Patients

Milan Criteria:
• 1 tumor 2-5cm
• Up to 3 tumors less than 3cm
• No vascular invasion
• No extrahepatic disease

Hepatocellular Carcinoma

Liver Transplantation

- 18% of all Liver Tx in US (~6700)¹
- ~72% 5 year survival
- Considerations
  - Waiting time (UAB 1.1 months)
  - Bad biology?
  - Bridging therapies?
  - “Cures” underlying liver disease
  - What about resectable patients?


HBP Surgeon Role for HCC

Treatment Algorithm

- Transplant
- **Surgical Resection**
- Ablation
- Other Locoregional Approaches
- Chemotherapy
BCLC Staging and treatment schedule

HCC

Stage 0
PST 0, Child-Pugh A

Stage A-C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Stage D
Okuda 3, PST ≥2, Child-Pugh C

Early stage (A)
Single or 3 nodules < 3cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

Advanced stage (C)
Portal invasion, N1,M1, PS 1-2

Terminal stage (D)
Portal invasion, N1,M1

Resection

Liver Transplantation (CLT/RLDLT)
PE/PF
Chemoembolization
New Agents

Randomized controlled trials (50%)
3yr survival: 26-40%
Symptomatic tic (20%)
1yr survival: 10-20%

Llovet JM et al. Lancet 2003; 362:1907

Hepatocellular Carcinoma
Hepatic Resection

52 yo Female with 21.5cm HCC
Hepatocellular Carcinoma

Hepatic Resection

- Traditionally considered “Gold Standard”
- Morbidity/ Mortality higher than for non-HCC
- Only 10-15% eligible for resection\(^1-3\)
- Recurrence as high as 68% within 2 years\(^4\)


<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>N</th>
<th>Mortality</th>
<th>1 Year</th>
<th>3 Year</th>
<th>5 Year</th>
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<tbody>
<tr>
<td>Kawasaki, 95’</td>
<td>90-93’</td>
<td>112</td>
<td>2%</td>
<td>92%</td>
<td>79%</td>
<td>NR</td>
</tr>
<tr>
<td>Makuuchi, 98’</td>
<td>90-97’</td>
<td>352</td>
<td>&lt;1%</td>
<td>92%</td>
<td>73%</td>
<td>47%</td>
</tr>
<tr>
<td>Fong, 99’</td>
<td>91-98’</td>
<td>154</td>
<td>4.5%</td>
<td>81%</td>
<td>54%</td>
<td>37%</td>
</tr>
<tr>
<td>Poon, 01’</td>
<td>94-99’</td>
<td>241</td>
<td>2.5%</td>
<td>82%</td>
<td>62%</td>
<td>49%</td>
</tr>
<tr>
<td>Belgheti, 02’</td>
<td>90-99’</td>
<td>300</td>
<td>6%</td>
<td>81%</td>
<td>57%</td>
<td>37%</td>
</tr>
<tr>
<td>Cha, 03’</td>
<td>90-01’</td>
<td>164</td>
<td>4%</td>
<td>79%</td>
<td>51%</td>
<td>40%</td>
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<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>1323</td>
<td>3%</td>
<td>85%</td>
<td>63%</td>
<td>39%</td>
</tr>
</tbody>
</table>
HCC Treatment Decision Tree

Treatment Algorithm

- Transplant
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- Chemotherapy

BCLC Staging and treatment schedule

Llovet JM et al. Lancet 2003; 362:1907
Hepatocellular Carcinoma
Percutaneous Ablation

Rational
• Tumor Treated in situ
• Percutaneous or Operative Approaches
• Tumor Coagulative Necrosis

Chemical Ablation Fallen out of Favor
Radiofrequency vs. Microwave Ablation
AASLD: Front Line Therapy for Small HCC

1Hepatology 2005 42(5): 1208
HCC Treatment Decision Tree

Treatment Algorithm
- Transplant
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BCLC Staging and treatment schedule

Llovet JM et al. Lancet 2003; 362:1907
Hepatocellular Carcinoma

**TACE (TransArterial ChemoEmbolization)**

**Rational**
- Obliteration of Arterial Tumor Blood Flow
- Intra-Tumoral Chemotherapy Administration

**AASLD:** Treatment for Non-Transplantable, Non-Resectable HCC>3cm

\(^1\)Hepatology 2005 42(5): 1208
Hepatocellular Carcinoma

TACE

A

Author, Journal year

Patients

L. In., Gastroenterology 1996

93

GETCH, NEJM 1996

98

Buek, Hepatology 1998

89

Pellegrini, J Hepatol 1998

73

Li, Hepatology 2002

79

Llovet, Lancet 2002

112

OVERALL

503

Heterogeneity, Q=7.73, P=0.14

TACE Predictors of >90% Tumor Necrosis

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariable</th>
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<tbody>
<tr>
<td></td>
<td>Odds Ratio 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Peripheral HCC Location</strong>*</td>
<td>3.60 (1.27,11.87)</td>
<td>0.015</td>
</tr>
<tr>
<td>Clear Feeding Vasculature</td>
<td>0.95 (0.45,1.99)</td>
<td>0.881</td>
</tr>
<tr>
<td>Lobe (Right vs. Other)</td>
<td>0.97 (0.41,2.31)</td>
<td>0.948</td>
</tr>
<tr>
<td>Maximal Tumor Dimension</td>
<td>0.72 (0.58,0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single Lesion</td>
<td>1.57 (0.75,3.30)</td>
<td>0.231</td>
</tr>
<tr>
<td>Arterial Phase Enhancement**</td>
<td>1.05 (1.01,1.10)</td>
<td>0.046</td>
</tr>
<tr>
<td>Portal Venous Washout***</td>
<td>1.56 (0.58,4.35)</td>
<td>0.382</td>
</tr>
</tbody>
</table>

Bryant MK et al.  HPB Journal 2013
Hepatocellular Carcinoma

TACE

Hepatocellular Carcinoma

90Yttrium Radiomicrosphere Therapy

Rational

• Tumor Treated in situ
• 90Yttrium Microspheres Trapped in Tumor
• NO Hepatic Artery Embolization
• Preferential in case of portal vein thrombosis
• Multifocal Disease

AASLD: No recommendations

Low Morbidity/ Well Tolerated

$$$$$$$$$$
**Hepatocellular Carcinoma**

*External Beam Radiotherapy*

**Rational**
- Tumor Treated in situ
- Unfractionated or Hyper-fractionated Dosing

Excellent adjunct to Ablation and TACE
(Control of Tumor Periphery)

**AASLD:** No recommendations

Low Morbidity/ Well Tolerated

---

**BCLC Staging and treatment schedule**

**HCC**

- **Stage 0**
  - PST 0, Child-Pugh A

- **Stage A-C**
  - Okuda 1-2, PST 0-2, Child-Pugh A-B

- **Stage D**
  - Okuda 3, PST ≥2, Child-Pugh C

**Very early stage (BI)**
- Single or 3 nodules < 3cm, PS 0

**Early stage (A)**
- Multinodular, PS 0

**Intermediate stage (B)**
- Advanced stage (C)
  - Portal invasion, N1, M1, PS 1-2

**Terminal stage (D)**
- Portal invasion, N1, M1

- Resection
- Liver Transplantation
- PEI/PF
- Curative Treatments (30%)
  - 5-yr survival: 50-70%

- New Agents
- Randomized controlled trials (50%)
  - 3yr survival: 20-40%
  - 1yr survival: 10-20%

- Symptomatic ttc (20%)

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Llovet JM et al. Lancet 2003; 362:1907
Hepatocellular Carcinoma
External Beam Radiotherapy

HCC Treatment Decision Tree

Treatment Algorithm
- Transplant
- Surgical Resection
- Ablation
- Other Locoregional Approaches
- Chemotherapy

Hawkin MA et al. Cancer 2006;106:1653-63
Hepatocellular Carcinoma

Chemotherapy

Sorafenib is recommended by the NCCN for the following patients with unresectable HCC and have Child-Pugh A or B disease\(^a,\)\(^b\):

- Not transplant candidates (category 1)
- Inoperable by performance status or comorbidity, local disease only (category 1)
- Metastatic disease (category 1)

\(^a\) The impact of sorafenib on patients eligible for transplant is unknown. Data are inadequate to define dosing for patients with abnormal liver function (Child-Pugh Class B or C).

\(^b\) Caution: There are limited safety data available for Child-Pugh B patients. Use with extreme caution in patients with elevated bilirubin levels.

Widespread Underutilization of Curative or (more Commonly) Life Prolonging HCC Therapies

8730 Medicare patients with HCC over 14 years:

- Resection: 8.7%
- Liver transplantation: 1.4%
- Ablation: 3.6%
- Transarterial chemoembolization: 16%
- NOTHING >60%!!!
Multimodal Therapy

Rational
• Taylor to Disease Pattern
• Taylor to Underlying Liver Function and Overall Patient Functional Status
• Taylor to Patient Response to Therapy
• Optimize Treatment Efficacies

Future Direction for HCC Treatment

Hepatocellular Carcinoma

*TACE/ Ablation*

Pre-TACE, Pre-post TACE, Pre-post TACE, Post-Ablation
Hepatocellular Carcinoma

TACE/ XRT

Pre-TACE, Pre-XRT, Post-TACE, Post-XRT

UAB HCC Downstaging Protocol

1. UCSF Criteria:\(^1\)
   - 1 tumor up to 6.5 cm
   - Up to 3 tumors, each less than 4.5 cm
   - Total tumor diameter less than 8 cm
2. NO vascular invasion
3. AFP less than 400
4. No constitutional symptoms
5. 6 months observation between bridging intervention and transplant listing

---

Liver Regeneration

HCC Downstaging Protocol

Evaluation: 2 HCC (4.1 and 2.1 cm) June 2009
First TACE July 2009
Hyperfractionated Radiotherapy October-November 2009
Second TACE September 2009
Liver Transplant July 2010
Path: No Viable Tumor Detected

Sorafenib Combined with TACE

- Phase II randomized study comparing Sorafenib vs. placebo in combination with TACE: reduced risk of vascular invasion and tumor progression
- Phase III NIH-sponsored STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma): 1100 patients in combination with RFA or TACE
- ECOG 1208

http://clinicaltrials.gov/show/NCT00692770
CALGB Study

Nexavar vs. Nexavar + Doxycrubicin

Special Thanks to the Liver Tumor Clinic

Support Staff:
Beth Comeaux
Meaghan Birch
Sandy Willingham
Lesley Miller

Locoregional Interventional Experts:
Souheil Saddekni
David Bolus
Kevin Smith
UAB Liver Tumor Clinic

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