Management of Liver Tumors in 2013

What has changed?
- Earlier detection
- Multidisciplinary team evaluation and treatment
- Guideline driven patient care pathways
- Improved surgical techniques
  - Open / MIS / Ablative
  - Endoluminal techniques
    - Drug eluting beads / Yttrium90
  - New chemotherapeutic options
    - Chemotherapy
    - Biologic agents

Historically
- Liver Tumors
  - Poor prognosis
  - Advanced stage HCC
  - Metastatic disease – Stage IV
  - Few good treatment options
    - High morbidity surgical procedures
    - Ineffective chemotherapy
Facts re: HCC in the US

- Causes of HCC
  - Cirrhosis 80-85%
  - de novo 15-20%
  - Cirrhosis related causes of HCC:
    - HCV 50-70% in the US
    - HBV 10-20%
    - Alcohol 10-20%
  - NASH 5-10%
  - Idiopathic

Guidelines: Surveillance in high risk patients

AASLD Practice Guidelines: Management of HCC
Hepatology: 2011

Should we use surveillance?
- Yes*

Who should get surveillance?
- Cirrhosis*

What tests?
- US* >> CT/MRI (selectively)
- AFP (selectively)

How often?
- Every 6 to 12 months
  (depending on risk)
AASLD Practice Guideline: Management of Hepatocellular Carcinoma Update 2011

Treatment Based on BCLC Staging

**Barcelona Clinic Liver Cancer (BCLC) Staging System, 2008**

1. Liver Function
2. Stage of Cancer

**Management Options in HCC 2013**

- No Treatment
- Resection
- Cryoablation
- Radiofrequency
- Endoluminal Treatments
- Transplant
- Chemoembolization
- Drug Eluting Beads
- Yttrium\(^{90}\) Infusion

Llovet and Bruix, *Hepatology* 2008
Treatment options in HCC

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

- Natural History
  - Largely unknown
  - Typically slow growing
  - HCC is uniformly fatal if no Rx
    - Advanced HCC
      - 80% 1-yr survival
      - 5% 5-yr survival
      - Llovet: Hepatology 1999 (33);423-9

- Chemotherapy
  - May provide long-term survival
  - More available and less costly than transplant
  - 10% -25% of patients with HCC are candidates
    - Poor general health
    - Poor hepatic reserve
    - Multifocal
    - Bilobar disease / Vascular involvement
  - Advances in surgical techniques
  - Advances in perioperative care

Patient Selection for Resection

- Liver Function
  - Child-Pugh Classification
    - PT > 1.6
    - Albumen < 2.0
    - Bilirubin > 2.0
    - Ascites present on medications
    - Encephalopathy any history of
  - Portal Hypertension
    - Platelet count < 100,000/ mm
    - Hepatic vein gradient > 10mmHg

Bruix, J. Gastroenterology 111:1018, 1996

15-25% of cirrhotic patients with HCC are candidates for resection

- Treat both diseases
  - Cancer
  - Cirrhosis >> Future cancer risk

- Livers are a limited resource
  - ~70,000 needed in US
  - ~7000 available
  - Cost

- Who gets a Transplant: Milan Criteria
  - 1 tumor < 5cm
  - 3 tumors < 3cm
  - 65% - 80% 5-year survival
Liver Resection

Resection - Survival

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Cirrhosis (%)</th>
<th>Mortality (%)</th>
<th>5 yr. Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fong – 1999</td>
<td>154</td>
<td>100</td>
<td>4.5</td>
<td>39</td>
</tr>
<tr>
<td>Makushchi – 1998</td>
<td>352</td>
<td>-</td>
<td>-</td>
<td>47</td>
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<td>Fan – 1999</td>
<td>330</td>
<td>49</td>
<td>6.3</td>
<td>45</td>
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<tr>
<td>Mazziotti 1998</td>
<td>229</td>
<td>100</td>
<td>4.6</td>
<td>41</td>
</tr>
<tr>
<td>Franco 1990</td>
<td>72</td>
<td>100</td>
<td>6.9</td>
<td>-</td>
</tr>
<tr>
<td>Cha – 2003</td>
<td>36</td>
<td>100</td>
<td>2.8</td>
<td>69</td>
</tr>
</tbody>
</table>

Treatment options in HCC

- No Treatment
- Transplantation
- Surgical Resection
- **Surgical Ablation**
  - Percutaneous Ablation
  - External Beam XRT
  - Endoluminal
    - TACE
    - Drug Eluting Beads
    - Yttrium90
- Chemotherapy
  - Analogous to resection
  - Parenchymal sparing
  - Broadens the patient pool
  - Minimally invasive techniques
    - Image guided
    - Laparoscopic
  - May be repeated
  - Relatively inexpensive
Radiofrequency Ablation

- Alternating electric field
  - 454,000 Hz
- Ionic oscillation
- Frictional heating
- Temperatures > 100°C
- Cell death immediate at 60°C
  - Protein denaturation
  - Cell wall degradation
  - Vascular thrombosis

Liver Tumor Ablation

~350 procedures
~60 for HCC

- Laparoscopic 85%
- Open 10%
- CT Guided 5%
- Thoracoscopic 1%

2 ½ year follow up
### Staging Laparoscopy

![Image of laparoscopic surgery]

### MIS HBP: Biopsy

![Image of biopsy procedure]

### RFA vs. Resection - Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Morbidity (%)</th>
<th>Disease-Free Survival (%)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al, 2006</td>
<td>RFA: 71</td>
<td>4.2</td>
<td>46.4</td>
<td>67.9</td>
</tr>
<tr>
<td></td>
<td>Resection: 90</td>
<td>55.6</td>
<td>51.6</td>
<td>64.6</td>
</tr>
<tr>
<td>Lu et al, 2006</td>
<td>RFA: 51</td>
<td>8</td>
<td>51.3</td>
<td>87.1</td>
</tr>
<tr>
<td></td>
<td>Resection: 54</td>
<td>11</td>
<td>82.3</td>
<td>86.4</td>
</tr>
<tr>
<td>Hong et al, 2009</td>
<td>RFA: 55</td>
<td>NR</td>
<td>40.2</td>
<td>72.7</td>
</tr>
<tr>
<td></td>
<td>Resection: 93</td>
<td>NR</td>
<td>54.7</td>
<td>83.9</td>
</tr>
<tr>
<td>Lupo et al, 2007</td>
<td>RFA: 60</td>
<td>10</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Resection: 42</td>
<td>16.7</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>Guglielmi et al, 2008</td>
<td>RFA: 109</td>
<td>10</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Resection: 91</td>
<td>36</td>
<td>27</td>
<td>48</td>
</tr>
</tbody>
</table>

*Blumgart’s Surgery of the Liver, Biliary Tract and Pancreas, 5th edition.*

### HAE/RFA vs Resection

- Mean f/u 23 months

<table>
<thead>
<tr>
<th></th>
<th>Resection</th>
<th>HAE/RFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>81%</td>
<td>97%</td>
</tr>
<tr>
<td>3 yr</td>
<td>70%</td>
<td>77%</td>
</tr>
<tr>
<td>5 yr</td>
<td>58%</td>
<td>56%</td>
</tr>
</tbody>
</table>

*Ideal*
- < 3 cm in diameter
- > 2 cm from central biliary structures
Treatment Options in HCC

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

- HCC is radiosensitive
  - Requires higher dose
- Whole Liver Doses > 35 Gy
  - Liver necrosis
- Conformal XRT / SBRT
- Minimal data

Endoluminal Options in HCC

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

- Dual blood supply to the liver
  - Liver parenchyma blood supply - 70% portal venous
  - Tumors blood supply – 70-90% hepatic artery

Endoluminal Options in HCC - TACE

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

- Locally increased chemotherapy (10-100 times)
  - Cisplatin
  - Doxorubicin
  - Lipiodol
  - Gelfoam
- Complications
  - Post embolization syndrome - 80-90%
  - Pain, fever, nausea and vomiting
  - Non-target embolization
  - Liver failure
  - Death
- Meta-analysis
  - Survival advantage over palliative care

Endoluminal Options in HCC - DEB

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

- DEB-TACE
  - absorbent bead which slowly releases a chemotherapeutic agent
  - doxorubicin and irinotecan
  - 100-300 micron
- Tumor drug levels 100 times systemic
- Slow wash out
- Procedure is similar to standard TACE
  - Well tolerated
  - RUQ pain 3-7 days
  - 23 hour stay
DEB – CR by RECIST Criteria

DEB - PR by RECIST Criteria

Endoluminal Options in HCC – Y90

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

• TheraSpheres
• SIR-spheres
  - Yttrium90 is a beta particle emitter
  - range 2-3mm
  - t1/2 – 64 hours
  - Adhered to polymer beads
  - 20-30 micron
  - Embed in microvasculature
  - Less embolic effect
  - Radionecrosis of the tumor and vasculature

Drug Eluting Beads and Y-90

Non-randomized, single institution retrospective review of drug-eluting beads and yttrium-90 beads in the treatment of hepatocellular carcinoma


Methods
Retrospective review of 143 HCC cases from 2005-2011
- 59 pts initially treated with Y-90
- 18/59 went on to treatment with additional modalities (DEB being the most common)
- 80 pts initially treated with DEB
- 12/80 went on to treatment with additional modalities (Y-90 being the most common)

Results
Response Rates based on modified RECIST criteria:

<table>
<thead>
<tr>
<th></th>
<th>Initial Response</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>34 (42%)</td>
<td>54 (38%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>72 (38%)</td>
<td>87 (40%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>7 (8%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>38 (27%)</td>
<td>27 (15%)</td>
</tr>
</tbody>
</table>
Mean age 64.0
Female : Male 29 : 114
Mean body mass index 28.0
Mean size of largest tumor (cm) 5.37
Ascites 30/135 (22%)
Partial vein thrombosis 34/143 (24%)
Bilobar disease 38/138 (28%)
Extrahepatic disease 13/136 (9.6%)
BCLC Stage
B : C : D
61 : 74 : 2
45% : 54% : 1%

Patient demographics and tumor characteristics

Single Tumor
2 Tumors 30 (21%)
3 Tumors 9 (6%)
4 Tumors 4 (3%)
> 4 Tumors 23 (16%)

Overall Survival by Best Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Median Survival (months)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>70.2</td>
<td>14.9 - 125.5</td>
</tr>
<tr>
<td>Partial Response</td>
<td>16.1</td>
<td>12.8 - 19.4</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>7.2</td>
<td>0 - 18.6</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>3.7</td>
<td>2.9 - 4.5</td>
</tr>
<tr>
<td>Overall</td>
<td>18.1</td>
<td>12.3 - 22.8</td>
</tr>
</tbody>
</table>

Treatment options in HCC

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy
  - Doxorubicin
  - Cisplatin
  - Gemcycotbine
    - The efficacy of cytotoxic chemotherapy is modest in patients with HCC, and in general, the duration of benefit is limited
    - No single regimen has emerged as superior to any other, although few randomized trials have been conducted.
- Sorafenib
Treatment options in HCC

- No Treatment
- Transplantation
- Surgical Resection
- Surgical Ablation
- Percutaneous Ablation
- External Beam XRT
- Endoluminal
  - TACE
  - Drug Eluting Beads
  - Yttrium90
- Chemotherapy

Sorafenib in Advanced Hepatocellular Carcinoma

- Sorafenib
  - Orally active, small molecule tyrosine kinase inhibitor
  - Multicenter, phase III trial randomly assigned 602 patients with inoperable HCC and Child-Pugh A cirrhosis to sorafenib or placebo

<table>
<thead>
<tr>
<th>Sorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>10.7 months</td>
</tr>
<tr>
<td>TTP</td>
<td>5.5 months</td>
</tr>
</tbody>
</table>

- Treatment was well tolerated

- These results have established sorafenib monotherapy as the new reference standard systemic treatment for advanced HCC

Summary

- HCC is on the rise
- Numerous effective treatment options
  - Surgical Evaluation
    - Transplant
    - Resection / Surgical Ablation
  - Interventional Radiology
    - Image Guided Ablation
    - Endoluminal
  - Systemic Chemotherapy - Sorafenib
- The key is early detection
  - Screen all patients with cirrhosis
    - US every 6-12 months
    - CT/MRI, no biopsy if characteristic for HCC
    - AFP selectively
Colorectal Liver Metastases

Colon and Rectal Cancer in the United States

**American Cancer Society**

- 147,000 Cases will be diagnosed in 2012
- 58,000 patients will die of CRCa in 2012

**Oregon State Cancer Registry 2004-2008**

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>158.2</td>
<td>1905</td>
</tr>
<tr>
<td>Rectum</td>
<td>1918</td>
<td>13811</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>13936</td>
<td></td>
</tr>
</tbody>
</table>

- 30-40% will develop CRLM

**Trends in Five-year Relative Survival (%)**, 1975-2006

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>54</td>
<td>68</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>Colon</td>
<td>52</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Leukemia</td>
<td>36</td>
<td>42</td>
<td>55</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>83</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>69</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Rectum</td>
<td>74</td>
<td>78</td>
<td>81</td>
</tr>
</tbody>
</table>

*5-year relative survival rates based on follow up of patients through 2007
Colon and Rectal Cancer

- Why is Survival Improving?
  - Screening
  - Earlier Diagnoses
  - New Chemotherapeutic Options
    - New chemotherapy
    - Biologic agents
    - Endoluminal therapies
  - Newer and Safer Extirpative Treatments
    - New resection technologies
    - Ablative technologies
    - Minimally invasive approaches

Management Options in CRLM 2013

- No Treatment
- Resection
- Cryoablation
- Radiofrequency
- Microwave
- Ablations
- Chemotherapy
- Infusional Treatments
  - Drug Eluting Beads
  - Yttrium® Infusion
  - Chemoembolization
- Potentially Curative
- Potentially Palliative
- Long-Term Palliation
Management Options in CRLM 2013

- No Treatment
- Resection
- Cryoablation
- Radiofrequency
- Microwave
- Ablations
- Infusional Treatments
- Chemotherapy
- Drug Eluting Beads
- Yttrium90 Infusion
- Chemoembolization
- Combination of Therapies

**CRLM: Who can we cure?**

- Extensive CRLM?
- Portal LN?
- Lung Met?
- Peritoneal Met?

**Limitations on Resection/Ablation**

- Two contiguous liver segments
- > 20% of functional liver reserve
- > 30% if heavily pretreated with chemo
- Adequate Portal inflow
- Adequate venous outflow

4-6 weeks for complete regeneration

**Do we really cure anyone with stage IV CRC?**

- Survival Probability
- Years
  - Initially Resectable: 66%, 48% (P = .01)
  - Initially Unresectable: 33%, 30%, 23%


**Portal LN?**

**Lung Met?**

**Peritoneal Met?**
What are the limits on liver resection?

- Right Trisection
  - May require staged extirpation of segments 2/3
  - May require pre-resection portal vein embolization
  - Requires L lateral section to be > 20% of liver

Survival Following Resection for CRLM

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>No. of Patients</th>
<th>Op Mort (%)</th>
<th>1-yr (%)</th>
<th>3-yr (%)</th>
<th>5-yr (%)</th>
<th>10-yr (%)</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi (2002)</td>
<td>229</td>
<td>1.0</td>
<td>93</td>
<td>57</td>
<td>58*</td>
<td>26</td>
<td>46</td>
</tr>
<tr>
<td>Abdalla (2004)</td>
<td>190</td>
<td>-</td>
<td>-</td>
<td>73</td>
<td>58</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>Fernandez (2004)</td>
<td>100</td>
<td>1.0</td>
<td>88</td>
<td>66</td>
<td>59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pawlik (2005)</td>
<td>557</td>
<td>1.0</td>
<td>97</td>
<td>74</td>
<td>58</td>
<td>-</td>
<td>74</td>
</tr>
</tbody>
</table>

Safety of a Major Liver Resection:

Providence Portland Cancer Center

**COLORECTAL RESECTION**

- Mortality: 2.4%
- Morbidity: 15-26%
- Blood Transfusion: 5.2%
- ICU Utilization: ~10%
- Hospital Stay:
  - Open 11 days
  - Lap 6.4 days
- NSQIP 2005-20011

**LIVER RESECTION**

- Mortality: 1.9%
- Morbidity: 15.8%
- Blood Transfusion: 8.9%
- ICU Utilization: 4-10%
- Hospital Stay: 5.4 days

CRLM: Who can we cure?
RESULTS:

- 184 patients: 1988 and 2002
- Mean 5.3 mets
- Bilobar in 76%
- Extrahepatic disease in 27%
- Surgery was possible after one (74%) or more (26%) lines of chemotherapy
- Five- and 10-year overall survival rates were 33% and 27%, respectively

CRLM: Who can we cure?

Lung Met?

Portal Met?

Peritoneal Met?

Concomitant Extrahepatic Disease in Patients With Colorectal Liver Metastases

<table>
<thead>
<tr>
<th>Variable</th>
<th>CLM + EHD</th>
<th>CLM only</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response of all metastases</td>
<td>11 (100%)</td>
<td>126 (100%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Status at last follow-up</td>
<td>CLM + EHD</td>
<td>CLM only</td>
<td></td>
</tr>
<tr>
<td>Alive without disease</td>
<td>21 (11%)</td>
<td>209 (32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alive with disease</td>
<td>52 (28%)</td>
<td>202 (31%)</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>113 (61%)</td>
<td>240 (37%)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistical significance was determined by Fisher's exact test.
CRLM: Case #1

- 62 y/o man
  - Perforated colon cancer
  - Extended LAR
    - T4N1M1 1+/15LN
    - KRAS Wild type
  - Widespread liver metastases
  - Tolerates rectal surgery well
  - Wants aggressive treatment

8 cycles FOLFOX with Avastin

8/2012 re-evaluated

Mixed progression of liver disease
  - Some smaller
  - Some larger, but partially cystic
  - Some unchanged
  - 3 new lesions

Laparoscopic staging procedure
  - Liver parenchyma appeared normal

Needed for cure
  - Extended left
  - Aggressive RFA R

Multiple RFA’s right lobe

Planned Ext L +/- PVE
CRLM: Case #1

- Left Lobe Resection
  - 33% residual liver
  - No complications
- Now 17 months out
  - NED

Presentation Case #2

- Pregnant with twins
- Presented with abdominal pain
- US shows liver mass
- MRI
  - Resected primary colon cancer
  - RFA/wedge L Lat Liver

Post-Chemotherapy

Response Rates to Modern Chemotherapy
- FOLFOX6 with Cetuximab 68%
- FOLFIRI with Cetuximab 57%

Folprecht et al. Lancet Oncol: Jan 2010

Post R Trisection Resection

- 12 months post resection
  - NED
Summary: CRLM

- ~600 patients per year in Oregon
- New treatment options
- Expanded pool of treatable patients
- We do cure stage IV patients
- M&M of Liver Resection = Colon Resection

- Multi-disciplinary Evaluation
- Early referral for surgical evaluation