Liver Resection for Gastrointestinal Tumors

Yuman Fong MD
Disclosures

- Consultant for Covidien, Amgen, Perfint, Sangamo
- Stock Shareholder for Genelux
Hepatocellular Carcinoma

- >1,000,000 cases/year
- Related to liver injury
  - Hepatitis, Alcohol, Obesity
- 1970’s:
  - incidence = mortality rate

cause of Cirrhosis and Cancer

<table>
<thead>
<tr>
<th></th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
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<tbody>
<tr>
<td>Alcohol</td>
<td>19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>57%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Hepatocellular Carcinoma

Now
- Hepatitis C curable
- Hepatitis B preventable
- Liver surgery: 1% mortality
- Liver cancer curable
  - 60-80% 5-yr Survival

1970’s
- 1 in 10 people in China or Africa infected with hepatitis B virus
- Operative mortality for liver resection 10-20%
- Almost no one cured

Cause of Cirrhosis and Cancer
- Alcohol
- Hepatitis C
- Both
- 90%
- 10%

- Related to liver injury
## Transplantation versus Resection/ Ablation

<table>
<thead>
<tr>
<th>Good Liver Function</th>
<th>Good Liver Function (low likelihood of systemic disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Tumor Burden</td>
<td>RESECTION/ EMBOLIZATION</td>
</tr>
<tr>
<td>SUPPORTIVE CARE</td>
<td>TRANSPLANT</td>
</tr>
<tr>
<td>Poor Liver Function</td>
<td>Poor Liver Function</td>
</tr>
<tr>
<td>Large Tumor Burden</td>
<td>Small Tumor Burden</td>
</tr>
</tbody>
</table>
Large HCC in Patient with HBV and Early Cirrhosis
15 Years after Liver Resection
Partial Hepatectomy for HCC
Outcome for Tumors >10 cm

<table>
<thead>
<tr>
<th></th>
<th>OAS</th>
<th>DFS</th>
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<tr>
<td>1 yr</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>2 yr</td>
<td>62</td>
<td>42</td>
</tr>
<tr>
<td>3 yr</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>5 yr</td>
<td>33</td>
<td>23</td>
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Fong et al., Ann Surg 229:790, 1999
# Liver Transplantation for HCC

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>5-yr Surv Milan</th>
<th>5-yr Surv Extended</th>
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<tbody>
<tr>
<td>Yao</td>
<td>2001</td>
<td>60</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Herrero</td>
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<td>61</td>
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<td>Hemming</td>
<td>2001</td>
<td>112</td>
<td>57</td>
<td>--</td>
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<tr>
<td>Adam</td>
<td>2003</td>
<td>195</td>
<td>61</td>
<td>--</td>
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<tr>
<td>Roayaie</td>
<td>2002</td>
<td>31</td>
<td>--</td>
<td>55</td>
</tr>
<tr>
<td>Kneteman</td>
<td>2004</td>
<td>40</td>
<td>87</td>
<td>83</td>
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<tr>
<td>Yao</td>
<td>2007</td>
<td>168</td>
<td>80</td>
<td>82</td>
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<tr>
<td>Onaca</td>
<td>2007</td>
<td>1152</td>
<td>62</td>
<td>54</td>
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<tr>
<td>Ito</td>
<td>2007</td>
<td>78</td>
<td>--</td>
<td>87</td>
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<tr>
<td>Mazzaferrro</td>
<td>2009</td>
<td>1556</td>
<td>73</td>
<td>54</td>
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<td>Guiteau</td>
<td>2010</td>
<td>445</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Kaido</td>
<td>2013</td>
<td>62</td>
<td>--</td>
<td>82</td>
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</table>
# Resection of Small HCC in Transplant Eligible Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>3-yr Surv</th>
<th>5-yr Surv</th>
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<tbody>
<tr>
<td>Arii</td>
<td>2002</td>
<td>2722</td>
<td>--</td>
<td>58</td>
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<tr>
<td>Kanematsu</td>
<td>2002</td>
<td>303</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>Poon</td>
<td>2002</td>
<td>161</td>
<td>--</td>
<td>44</td>
</tr>
<tr>
<td>Minagawa</td>
<td>2003</td>
<td>334</td>
<td>--</td>
<td>56</td>
</tr>
<tr>
<td>Broelsch</td>
<td>2004</td>
<td>139</td>
<td>65</td>
<td>--</td>
</tr>
<tr>
<td>Ikai</td>
<td>2004</td>
<td>2320</td>
<td>--</td>
<td>66</td>
</tr>
<tr>
<td>Wang</td>
<td>2008</td>
<td>243</td>
<td>64</td>
<td>51</td>
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<tr>
<td>Hsu</td>
<td>2012</td>
<td>268</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Zhong</td>
<td>2014</td>
<td>660</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Yin</td>
<td>2014</td>
<td>88</td>
<td>64</td>
<td>52</td>
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</table>
# Long Term Survival for Malignancy After Cadaveric Liver Transplant

<table>
<thead>
<tr>
<th>Period</th>
<th>3 MONTH</th>
<th>1 YEAR</th>
<th>5 YEAR</th>
<th>10 YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1593</td>
<td>1593</td>
<td>3391</td>
<td>3905</td>
</tr>
<tr>
<td>%</td>
<td>93%</td>
<td>85%</td>
<td>63%</td>
<td>46%</td>
</tr>
</tbody>
</table>

UNOS Annual Report
Liver Transplant in USA

UNOS Data
Liver Transplant by Donor Type

UNOS Data
Median months to liver transplant for wait-listed adult patients

UNOS Annual Report 2011
Liver Transplantation

Deceased Donor

Living Donor

<table>
<thead>
<tr>
<th>Liver transplant activity per million of the population</th>
<th>LDLT 2010</th>
<th>LDLT 2006</th>
<th>DDLT 2010</th>
<th>DDLT 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>0.70</td>
<td>0.40</td>
<td>24.50</td>
<td>23.50</td>
</tr>
<tr>
<td>Belgium</td>
<td>3.00</td>
<td>1.80</td>
<td>12.50</td>
<td>18.60</td>
</tr>
<tr>
<td>Austria</td>
<td>0.50</td>
<td>0.20</td>
<td>19.00</td>
<td>16.80</td>
</tr>
<tr>
<td>USA</td>
<td>0.95</td>
<td>1.00</td>
<td>17.00</td>
<td>21.30</td>
</tr>
<tr>
<td>Italy</td>
<td>0.40</td>
<td>0.60</td>
<td>11.50</td>
<td>18.50</td>
</tr>
<tr>
<td>UK</td>
<td>0.50</td>
<td>0.20</td>
<td>10.50</td>
<td>10.10</td>
</tr>
<tr>
<td>Germany</td>
<td>1.50</td>
<td>1.00</td>
<td>9.00</td>
<td>11.80</td>
</tr>
<tr>
<td>AUS</td>
<td>0.40</td>
<td>1.10</td>
<td>7.00</td>
<td>7.50</td>
</tr>
<tr>
<td>Taiwan</td>
<td>16.00</td>
<td>5.00</td>
<td>4.00</td>
<td>3.10</td>
</tr>
<tr>
<td>HK</td>
<td>7.00</td>
<td>6.90</td>
<td>5.00</td>
<td>3.30</td>
</tr>
<tr>
<td>Korea</td>
<td>17.00</td>
<td>12.90</td>
<td>6.00</td>
<td>2.40</td>
</tr>
<tr>
<td>Japan</td>
<td>4.00</td>
<td>4.10</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Religious Beliefs and Liver Transplantation

<table>
<thead>
<tr>
<th>Religion</th>
<th>Tenets</th>
<th>Views in transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buddhism</td>
<td>‘Spiritual consciousness’ remains in the body for days after the last breath; its departure is the actual moment of death; during this time, the body must not be disturbed because it might adversely affect the person’s next rebirth. Selfless giving</td>
<td>Opposes deceased organ donation</td>
</tr>
<tr>
<td>Confucianism</td>
<td>One is born with complete body and should end the same way. Modern Confucians: Jen and righteousness are valued more than preserving integrity of the dead body.</td>
<td>Unfilial and disrespectful Approves deceased organ donation</td>
</tr>
<tr>
<td>Shintoism</td>
<td>The body after death is impure, dangerous and powerful; Interfering with a corpse brings bad luck and might injure the relationship between dead and bereft.</td>
<td>Opposes deceased organ donation</td>
</tr>
<tr>
<td>Taoism</td>
<td>Naturalness, vitality, peace and non-action (to flow of nature). Modern Taoist: body is only shelter to more important parts of life.</td>
<td>Seen as attempt to change natural process: opposes deceased organ donation Approves deceased organ donation</td>
</tr>
<tr>
<td>Islam</td>
<td>Violating human body (living or dead) is forbidden; customary to bury dead within 24h. Necessity overrides prohibition.</td>
<td>Opposes deceased organ donation Uncertainties: seek advice of local imam</td>
</tr>
<tr>
<td>Hinduism</td>
<td>Selfless giving, physical integrity of body is not crucial for reincarnation.</td>
<td>Approves deceased organ donation</td>
</tr>
<tr>
<td>Sikhism</td>
<td>Physical body is not crucial for cycle of rebirth.</td>
<td>Approves deceased organ donation</td>
</tr>
<tr>
<td>Christianity</td>
<td>Act of selflessness</td>
<td>Approves deceased organ donation</td>
</tr>
</tbody>
</table>

Transplantation **versus** Resection/ Ablation

Transplantation **and** Resection/ Ablation
Possibility of Salvage Transplantation

- 88 patients with HCC subjected to transplantation
  - 70 subjected to primary transplant
  - 18 subjected to salvage transplant
    - 14 for recurrence
    - 4 for deterioration of liver function

<table>
<thead>
<tr>
<th></th>
<th>Op Time</th>
<th>Bloodloss</th>
<th>LOS</th>
<th>Mortality</th>
<th>3y Surv</th>
<th>5y Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Transplant</td>
<td>551 min</td>
<td>1191 cc</td>
<td>32 d</td>
<td>6%</td>
<td>82%</td>
<td>59%</td>
</tr>
<tr>
<td>Salvage Transplant</td>
<td>530 min</td>
<td>1282 cc</td>
<td>31 d</td>
<td>6%</td>
<td>82%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Controversies in Selection of Therapy

Alternative Treatments for HCC

Partial Hepatectomy
Transplantation
Ablation
Radiofrequency Ablation

- Generator produces AC at 300-500 kHz (RF range)
  - Ionic agitation produces heat
- Coagulative necrosis
  - 60 °C: Immediate
  - 50-52 °C: 4-6 min
Treatment of Focal Liver Tumors with Percutaneous Radio-frequency Ablation

- 41 centers
- 2320 patients
  - 1610 HCC
  - 501 Metastatic colorectal Cancer
- 3554 lesions
- Six deaths (0.3%)
- 50 major complications (2.2%)

Livraghi et al., Radiology, 226:441, 2003
Randomized Trial of RFA and Resection

- N=180: RFA versus resection
- Solitary tumor, HCC size < 5cm

<table>
<thead>
<tr>
<th></th>
<th>Complications</th>
<th>Mortality</th>
<th>3 yr Survival</th>
<th>4 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA</td>
<td>4%</td>
<td>0</td>
<td>71%</td>
<td>68%</td>
</tr>
<tr>
<td>Surgery</td>
<td>55%</td>
<td>1.1%</td>
<td>73%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Long-term Outcomes Following Microwave Ablation for Liver Malignancies

U. Leung¹, D. Kuk², M. I. D'Angelica¹, T. P. Kingham¹, P. J. Allen¹, R. P. DeMatteo¹, W. R. Jarnagin¹, and Y. Fong¹

¹Department of Surgery, Memorial Sloan-Kettering Cancer Center
²Department of Biostatistics, Memorial Sloan-Kettering Cancer Center

- N= 416 ablations
- Recurrence related to tumor size:
  - <1 cm:  1%
  - 1-3 cm:  9%
  - >3 cm:  33%
- Ablations can be curative
<table>
<thead>
<tr>
<th>Good Liver Function</th>
<th>Poor Liver Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Tumor Burden</td>
<td>Large Tumor Burden</td>
</tr>
</tbody>
</table>

**RESECTION**
- Good Liver Function
- Small Tumor Burden

- Resection or Ablation as first Rx
- Transplant as Possible
- Salvage for Recurrence

**SUPPORTIVE CARE**
- Good Liver Function
- Large Tumor Burden

**TRANSPLANT**
- Poor Liver Function
- Small Tumor Burden
Resection / Ablation Should be Initial Treatment for Small HCC

- Resection or ablation provides 50-70% 5-yr survival
- Transplantation can be performed at recurrence
- 15-20% of patients have systemic disease
- Waiting allows identification of systemic disease

- There are <7500 cadaveric livers available yearly
- Only approximately 300 Living donor liver transplants are performed per year
- Resection/ablation first allows most rational use of cadaveric livers and living donor livers
Ablation or Resection for Small HCC

- Small HCC
  - Good Medical and Liver Condition
    - Peripheral
      - Laparoscopic Resection
    - Deep
      - Ablation
  - Poor Medical Condition
    - Ablation or Systemic Therapy or Support Care
  - Poor Liver Function
    - Transplant
Metastatic Colon Cancer to Liver

- 50% of patients with colorectal cancer will develop liver metastases

- Survival for untreated disease:
  - Median: 5-10 m
  - 5-year survival: 0
Treatment of Metastatic Colorectal Cancer

- Hepatic resection for metastases from colorectal carcinoma is of dubious value

Hepatic Resection is Safe and Effective Treatment for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No. Pts</th>
<th>Mortality (%)</th>
<th>Med Surv</th>
<th>1-year</th>
<th>5-year</th>
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<tbody>
<tr>
<td>Hughes et al (86)</td>
<td>607</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>33</td>
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<tr>
<td>Gayowski et al (94)</td>
<td>204</td>
<td>0</td>
<td>33 mo</td>
<td>91</td>
<td>32</td>
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<tr>
<td>Scheele et al (95)</td>
<td>469</td>
<td>4</td>
<td>40 mo</td>
<td>83</td>
<td>39</td>
</tr>
<tr>
<td>Nordlinger (95)</td>
<td>1568</td>
<td>2</td>
<td>40 mo</td>
<td>80</td>
<td>28</td>
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<tr>
<td>Jenkins et al (97)</td>
<td>131</td>
<td>4</td>
<td>33 mo</td>
<td>81</td>
<td>25</td>
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<td>Jamison et al (97)</td>
<td>280</td>
<td>4</td>
<td>33 mo</td>
<td>84</td>
<td>27</td>
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<td>Fong et al (99)</td>
<td>1001</td>
<td>3</td>
<td>42 mo</td>
<td>---</td>
<td>36</td>
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<tr>
<td>Scheele et al (01)</td>
<td>516</td>
<td>3</td>
<td>---</td>
<td>---</td>
<td>38</td>
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<tr>
<td>Choti et al (02)</td>
<td>226</td>
<td>1</td>
<td>46 mo</td>
<td>96</td>
<td>40</td>
</tr>
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</table>
Hepatic Resection for Colorectal Metastases
Long Term Follow-up for Surgery Alone

- 25 year follow-up
- Memorial Sloan-Kettering Cancer Center

Fortner and Fong, Ann Surg, 2010
Survival Rates:
Liver Resection Plus Adjuvant Therapy

<table>
<thead>
<tr>
<th></th>
<th>FUDR+5-FU</th>
<th>5-FU</th>
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</thead>
<tbody>
<tr>
<td>2-yr survival</td>
<td>85%</td>
<td>69%</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>57%</td>
<td>45%</td>
</tr>
<tr>
<td>10-yr survival</td>
<td>43%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Kemeny and Fong, N Engl J Med. 2005
Colorectal Liver Metastases
Improvements in Survival

No therapy
Liver Resection
Liver Resection
Plus Chemotherapy

Five Year Survival

Improved Drugs for Non-resectable Disease

- Fluorouracil
- Irinotecan
- Oxaliplatin
- Capecitabine
- Cetuximab
- Bevacizumab
- Panitumumab
- Zaltrap
After 5FU/Oxaliplatin

15% Converted to Resectable
Scan 14 Years Later
Avastin Related Perforation of the Colon
Minimally Invasive Liver Resections
Si System

- Dual console
- 3 working arms
- Many more instruments
Case of Hepatocellular Carcinoma

- 50 year old surgeon with history of hepatitis-B sero-positivity presents abdominal pain and is found to have liver mass on scan
- AFP=657
- Margin negative
- AFP returned to normal
- 2.5 hour operative time
- 36 hour hospital stay
- Patient called 1 week later asking whether he can shovel snow
Right Lobectomy for Liver Metastases

- 42 y.o. physician presenting with multifocal liver metastases in 2011
- After systemic treatment, multiple RFA, 1 growing tumor left 5 years later
Robotic Right Lobectomy
Xi

- Easier multi-field surgery
- Easier to move camera - allows multiple angles for better visibility
- New work flow
- New learning curve
Combined Resection of Primary and Liver Metastases

- 427 colorectal cancers with synchronous liver mets
- 326 simultaneous vs 101 staged resections
- 200 rectal cancers with liver mets
  - 145 simultaneous and 55 staged resections

<table>
<thead>
<tr>
<th></th>
<th>simultaneous</th>
<th>staged</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Mortality</td>
<td>Grade 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood Loss</td>
<td>mean</td>
<td>750±430</td>
<td>1240±810</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>mean</td>
<td>11.9±5.1</td>
<td>19.1±8.3</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

Silberheimer et al., Am J Surg, 2014
Leung and Fong, HBSN, 2014
Robotic Hepatectomy: Staplers
Length of Stay
Robotic Liver Resection

- Length of stay 2 (1-9)
  - Major 5 (3-8)
  - Minor 2 (1-9)
Return to Normal Activities
Robotic Liver Resection

![Graph showing steps over post-operative days]

- Post Operative Day
- STEPS
- Graph showing steps over post-operative days
<table>
<thead>
<tr>
<th>Thermal Ablation Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Radiofrequency ablation</td>
</tr>
<tr>
<td>- Microwave ablation</td>
</tr>
<tr>
<td>- Irreversible electroporation</td>
</tr>
<tr>
<td>- Cryoablation</td>
</tr>
</tbody>
</table>
Combined Ablation Resection (CARe)

N=288

Evard, Poston, Fong et al. PLoSOne, 2014
45 y.o. previously healthy man presents with mild transient abdominal pain.

Workup reveals sigmoid colon cancer, CEA=1450, LDH=1600.
Follow-up 2 Months After Starting Chemotherapy

- Minor Response
- Note caudate lesion
Choices of Therapy
Resection and Regional Chemotherapy

- Surgical Findings: 14 liver tumors on left
- Surgery:
  - 3 resected including caudate
  - 11 ablated by microwave ablation
  - pump placement for chemotherapy
- Sigmoid cancer left in place
Follow-up 3 Months Later

- Tumor response on right after pump FUDR and systemic FOLFIRI
Right Portal Vein Embolization with NO INTERRUPTION of Chemotherapy
Left Liver
Growth after Portal Vein Embolization

Pre PVE

4 Months After PVE
Follow-up: 48 months After Right Lobectomy and Sigmoid Resection

- Liver with no indications of live disease
- CEA = 1450 6.9 LDH = 1600 182
Hepatectomy for Metastases from Neuroendocrine Tumors

- More than 50% of patients will develop liver metastases
- Symptomatic patients
  - Hormonal symptoms
  - Physical symptoms from large
- Cyto-reductive treatments effective because these are slow growing tumors
  - Surgery, Embolization, RFA, Cryoablation
Neuroendocrine Metastases

- 170 patients
- 5 and 10 yr survival = 61 and 35%

Que et al., J Am Coll Surg 197:29, 2003
Neuroendocrine Metastases

5 and 10 year recurrence rate = 84 and 94%
Resection of Neuroendocrine Metastases
Resection of Neuroendocrine Metastases
Combining Resection of Primary with Hepatectomy

Gaujoux et al., Ann Surgical Oncology, 2012
Follow-up After Liver/Pancreatic Resection
Survival After Combined Resection of Primary and Metastatic Disease

Gaujoux and Fong, Ann Surgical Oncology, 2012
Combined Resection of Primary and Metastases

- Resect primary and nodal disease to convert to hepatic only disease
- Resection of extrahepatic disease allows a wide range of liver directed therapies
- Enucleation acceptable for liver tumors
- Resect large hepatic and surface disease to convert to ablatable disease
- Mesenteric/bowel masses cause progressive desmoplastic constriction of mesentery
- Pancreatic masses carry risk of splenic/portal vein obstruction and biliary obstruction
Gastrointestinal Stromal Tumor (GIST)

- GI sarcoma
- Before 2000, surgery was only effective therapy: (60-80% recurrence rate)
- Standard chemotherapy ineffective: <5% response rate
- Survival < 2 yr for patients with metastatic disease
Gleevec / STI-571 for GIST

- Found in screen of molecules to target for kit in CML
- c-kit mutation is the hallmark of GIST
- Responses seen in ~60% of patients with metastases
- Exon 11 mutations have best chance of response

- Median duration of response 9-12 months
Pre-treatment

6 months on STI-571

10 months on STI-571
Complication of Bleeding
Gleevec as Adjuvant Therapy after Resection of Large (>10 cm) GIST

DeMatteo et al., Lancet 373:1097, 2009
Change in Role of Surgeon in Treatment of GIST

- Resection of down-staged patients
- Resection of bleeding patients
- Resection plus adjuvant therapy