Integrating Chemotherapy and Liver Surgery for the Management of Colorectal Metastases

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## Estimated New Cancer Deaths By Sex
### United States, 2011

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th>Percentage</th>
<th>Females</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>85,600</td>
<td>28%</td>
<td>71,340</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>33,720</td>
<td>11%</td>
<td>39,520</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,250</td>
<td>8%</td>
<td>24,130</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>19,360</td>
<td>6%</td>
<td>18,300</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>13,260</td>
<td>4%</td>
<td>15,460</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,740</td>
<td>4%</td>
<td>9,570</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,910</td>
<td>4%</td>
<td>9,040</td>
<td>3%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,670</td>
<td>4%</td>
<td>8,120</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,750</td>
<td>3%</td>
<td>6,330</td>
<td>2%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,270</td>
<td>3%</td>
<td>5,670</td>
<td>2%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>300,430</strong></td>
<td><strong>100%</strong></td>
<td><strong>271,520</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Estimated 2005 US incidence, new cases ~145,290
Estimated 2005 US mortality ~56,290

12.3% of patients presented with recurrent CRC.

24.5% Stage II*
32.6% Stage III*
12% Stage I*
18.6% Stage IV*

*2002 data.
5-Year Relative Survival By AJCC Stage

Colorectal Cancer with Hepatic Metastases

• Approximately 30% to 40% of patients will have liver-only metastases at time of recurrence
• Approximately 20% to 30% will have liver-only metastases on initial evaluation

Outcomes Following Hepatic Resection for Metastatic Colorectal Cancer

- Complete resection, OS (n = 473)
- Disease-free survival
- Incomplete resection (n = 72)

# Results of Hepatic Resection for Metastatic Colorectal Cancer: Modern Experience

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>No. of Patients</th>
<th>Op Mort (%)</th>
<th>Survival 1-yr (%)</th>
<th>Survival 3-yr (%)</th>
<th>Survival 5-yr (%)</th>
<th>Survival 10-yr (%)</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choti (2002)</td>
<td>226</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>-</td>
<td>73</td>
<td>58</td>
<td>-</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>

* For recent period (1993-1999)

Liver Metastases in Colorectal Cancer: Outcomes

Liver Metastases

- RESECTABLE (~25%)
  - Survival Benefit
    - ~50% OS at 5 years
    - 15% DFS at 10 years

- NON RESECTABLE (~75%)
How do we define resectable?

- Capability to remove all gross disease (R0 resection) and leave an adequate inflow, outflow, and remnant liver volume

- High quality cross-sectional imaging
- Selective 3D rendering and CT volumetrics
- FDG PET to rule out more extensive disease
Integrating Chemotherapy and Liver Surgery for Metastatic Colorectal Cancer

LIVER METASTASES

RESECTABLE
~25%

NON RESECTABLE
~75%

SURVIVAL BENEFIT
~ 50% OS AT 5 YEARS
15% DFS AT 10 YEARS

"Neoadjuvant"

"Adjuvant"

"Conversion"

Chemotherapy
## Improving Systemic Chemotherapy for Advanced CRC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response %</th>
<th>Median Surv (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>5FU/ LV(^1)</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Irinotecan(^1)</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>IFL(^1)</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>FOLFOX(^2) or FOLFIRI(^2)</td>
<td>54 – 56</td>
<td>20 - 22</td>
</tr>
<tr>
<td>With bevacizumab(^3) or cetuximab(^4)</td>
<td>~70</td>
<td>&gt;24</td>
</tr>
</tbody>
</table>

\(^1\) Saltz LB. *NEJM* 2000  
\(^2\) Tournigand C. *J Clin Oncol* 2004  
\(^3\) Hoff, PM. GI ASCO, 2006  
\(^4\) Diaz Rubio E. ASCO, 2005

IFL = bolus 5FU, folinic acid, and irinotecan  
FOLFOX = infusion 5FU, folinic acid, and oxaliplatin  
FOLFIRI = infusion 5FU, folinic acid, and irinotecan
Liver Metastases in Colorectal Cancer: Outcomes

LIVER METASTASES

RESECTABLE ~25%

SURVIVAL BENEFIT
~ 50% OS AT 5 YEARS
15% DFS AT 10 YEARS

NON RESECTABLE ~75%

Downsizing

RESECTABLE 10-20%
Survival After Liver Resection of Unresectable Colorectal Metastases Following Systemic Chemotherapy

Initially Resectable
- 66%

Initially Unresectable
- 52%
- 33%

P = .01

Years
Survival Probability
0 1 2 3 4 5 6 7 8 9 10
30% 23%
Downsizing the Unresectable Patient

**CELIM Trial**

114 patients, 17 centers in Germany and Austria

Unresectable liver metastases defined as technically unresectable or ≥5 metastases

Randomized to cetuximab plus FOLFOX6 or FOLFIRI

RESULTS: response rate 68% and 57%

R0 resection in 38% and 30%

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**How Objective Are We in Defining Resectability?**

Retrospective central review of imaging:

- Resectability increased from 32% to 60%
- 32% of patients were judged resectable at baseline
- Several patients deemed unresectable by experts got an R0 resection

Folprecht et al. *Lancet Oncol* (Jan 2010)
Questions

1. Do all areas where tumor initially existed need to be resected?
2. How do we manage the complete radiologic response?
3. Do the margins need to be wider in the tumor that responded?
Downsizing the Unresectable Patient: Are They All the Same?
Detection of Tumor-Specific Mutated DNA in the Margin Surrounding a Colorectal Cancer Liver Metastasis

What is the role of adjuvant therapy or neoadjuvant therapy in initially resectable patients undergoing hepatic resection?
Combining Chemotherapy with Liver Resection in the Initially Resectable Patient

Therapy is generally recommended in the chemo-naive patient.
- based on stage IV chemotherapy indications and efficacy.
- Extrapolation of stage III adjuvant data
- No data on the role of biologics in this setting
- Little data to guide us in the patient with previous chemo

Randomized trials
- Regional HAI chemotherapy trials (systemic ± HAI)
- Portier et al (JCO 2006) (post-op vs. surgery alone)
- EORTC 40983 (peri-op vs. surgery alone)
EORTC 40983

Progression-Free Survival: Eligible Patients

HR = 0.77; CI: 0.60-1.00, p = 0.041

Periop CT

36.2%

Surgery only

28.1%

+8.1%

At 3 years

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>N</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>171</td>
<td>125</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
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<tr>
<td>171</td>
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Impact of Chemotherapy Prior to Hepatectomy in the Resectable Patient

ADVANTAGES

1. Allows time for other sites to declare themselves
2. Allows for earlier therapy of occult micrometastatic disease
3. Allows for in vivo gauge of chemoresponse, facilitating postoperative chemotherapy planning
4. Response may allow for smaller resection
5. Response is a prognostic factor
Neoadjuvant Chemotherapy Prior to Hepatectomy in the Resectable Patient

DISADVANTAGES

1. Tumors may progress to unresectable status
2. Split regimen may have detrimental effect
3. Discouraged compliance for subsequent therapy
4. Chemotherapy-associated hepatotoxicity
5. Potential for increased postoperative complications
6. Response may hinder finding all sites of metastatic disease
FOLFOX + bevacizumab
Disappearing colorectal liver metastases after preoperative chemotherapy

- Disappearing metastases occurred in 24% of patients treated with preoperative chemotherapy.
- Disappearance was associated with high tumor number, longer duration of chemotherapy, and small lesion size.
- 53% of DLM were found during surgery.
- When metastases were not found at the time of surgery, only 24% were resected.
- Local recurrence occurred in 70% when DLM were left untreated.
- Survival was not significantly impacted if DLM were left untreated.

Van Vledder et al. J Gastrointest Surg (Nov 2010)
Summary

1. Liver resection for colorectal metastases has been shown to be an increasingly safe and effective therapy.

2. Surgical assessment and intraoperative planning is important to achieve safe and complete (R0) resection.

3. Preoperative “conversion” chemotherapy can be used to downsize unresectable patients to resectable status.

4. The optimal sequencing of chemotherapy in the initially resectable patient has yet to be defined.