Diagnosis, Understanding & Treatment of Colorectal Cancer

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Outline

Introduction to the Disease: Colon & Rectum
Risk Factors and Inherited Syndromes
Standard Surgical Treatment of Colorectal Cancer
Treatment Options for Advanced Disease
Recent Advances: Surgical and Medical
Colorectal Cancer (US)

Colorectal Cancer 2012
143,000 new cases & 51,000 deaths
Reduction if death 1990-2006
33% male
28% female

Screening?
Staging?
Therapy?
Segmental Anatomic Resection

- Right hemicolecctomy
- Left hemicolecctomy
- Low anterior resection (LAR)
- Abdominoperineal resection (APR)
Preoperative Planning

Document Symptoms:
- Obstruction, Bleeding and Pain
- Endoscopic evaluation (location & tattoo)
- Staging CT (not PET) and CEA
Screening & Staging

Advanced disease at diagnosis:

- Node positive 37%
- Metastatic 19%
High Risk Genetics

74 y/o F with b/l Breast cancer and newly Diagnosed colon cancer
NL sigmoid endoscopy and CT

Interval development of new cancer in one year
HNPPCC
Mismatch repair defect

Recurrent right side dominant
Cancers at young age
**Most Common Syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP (familial adenomatous polyposis)</td>
<td>APC</td>
<td>90% by age 45</td>
</tr>
<tr>
<td>Attenuated FAP</td>
<td>APC</td>
<td>69% by age 80</td>
</tr>
<tr>
<td>Lynch (HNPCC)</td>
<td>MLH1, MSH2, MSH6 PMS2, EPCAM</td>
<td>40% to 80% by age 75</td>
</tr>
<tr>
<td>MUTYH-associated polyposis</td>
<td>MUTYH</td>
<td>35% to 53%</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>39% by age 70</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>BMPR1A, SMAD4</td>
<td>17% to 68% by age 60</td>
</tr>
</tbody>
</table>
Surgical Textbook
Resection

Clinical staging (intra-operative)
metastasis identified now what?

Generous colonic margins
how far how wide?

Regional lymphadenectomy
what nodes what number?
NCCN Guidelines
“PET/CT only if potentially surgically curable M1 disease”

1. Suspect stage IV by CT
2. Search for extra-hepatic disease that alters Tx

PET altered management in 10% to 20% liver resection
Cost effective if documented liver only disease b/c avoid surgery in up to 30%
PET/CT

CT Chest/abdomen/pelvis cost $4,500 (est.)
PET/CT cost $5,700 (est.)

If >140,000 new colon cancer detected this year it would cost $800 million more to stage with PET/CT
Ultimately alter care of 2% to 4% of patients
Preoperative Planning

Metastatic disease: how much testing?
Sensitivity of CT poor for < 1.0 cm lesions
What is Inadequate?

American College of Surgeons & Commission on Cancer (ACS & CoC): “Resected colon specimens should have at least 12 regional lymph nodes pathologically examined”

American Joint Committee on Cancer (AJCC) 7th ed Cancer Staging Handbook: “It is important that 10-14 nodes be examined”
What is the natural history/survival of stage III (node positive) colon cancer? incurable? 50/50? high cure rate?
Lymphadenectomy

- Therapeutic?
- Increase pathologist detection?
- Stage Migration
- Adjuvant chemotherapy?
N1 Survival by node count
SEER data

N2 Survival by node count
SEER data
What is adequate?
Often the less there is to justify a traditional custom the harder it is to get rid of it.

Mark Twain
### NSABP C-1 through C-5

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Survival</th>
<th>Recurrence-free Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Surgery + 5-FU/LV</td>
<td>0.62</td>
<td>0.55 - 0.70</td>
</tr>
<tr>
<td>Positive Nodes (Nodes Examined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (12 +)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0 (&lt; 12)</td>
<td>1.36</td>
<td>1.13 - 1.65</td>
</tr>
<tr>
<td>1-3 (any)</td>
<td>1.80</td>
<td>1.53 - 2.14</td>
</tr>
<tr>
<td>4 + (any)</td>
<td>3.21</td>
<td>2.69 - 3.85</td>
</tr>
</tbody>
</table>
Adjusted KM Estimate of Recurrence Free Interval Stage III patients

Patients

Surgery 340
5FU/LV 1,371

Events

174
535

HR=0.63 (0.53-0.75), P<0.0001*

Number at Risk

Surgery 152 105 57
5FU/LV 814 662 89

Time in Years

0 2 4 6 8 10 12 14 16
Nodal Ultra-staging?

<1% of any node is examined by H&E
Often < 12 nodes are sampled
Goal Ultra-stage LN with IHC

20% (36 of 177) N0 cases were upstaged N1mi or N1i+
N1mi = 2mm to 0.2mm
N0i+ = <0.2mm

Recurrence 4 yr:

<table>
<thead>
<tr>
<th></th>
<th>N0</th>
<th>N0i+</th>
<th>N1mi</th>
<th>N1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>6.4%</td>
<td>7.4%</td>
<td>22.2%</td>
<td>32.9%</td>
</tr>
</tbody>
</table>

Bilchik Ann Surg 2010
Long Term Results of Laparoscopic Resection
Randomized Clinical Trials

1. COST Trial NCCTG 1994-2001
2. Color Trial 1997-2003
4. CLASICC Trial UK MRC 1996-2002
If you don’t know where you are going, any road will take you there.

Lewis Carroll (1832-98)
In cancer surgery, disease related factors may require open procedure
**COST Trail NCCTG**
Equivalent cancer related survival at 5 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Open (n = 428)</th>
<th>LAC (n = 435)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>74.6%</td>
<td>76.4%</td>
<td>0.93</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>68.4%</td>
<td>69.2%</td>
<td>0.94</td>
</tr>
<tr>
<td>Local recurrence rates</td>
<td>2.6%</td>
<td>2.3%</td>
<td>0.79</td>
</tr>
<tr>
<td>Overall rates of recurrence</td>
<td>21.8%</td>
<td>19.4%</td>
<td>0.25</td>
</tr>
<tr>
<td>Sites of first recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>0.5%</td>
<td>0.9%</td>
<td>0.43</td>
</tr>
<tr>
<td>Liver</td>
<td>5.8%</td>
<td>5.5%</td>
<td>0.85</td>
</tr>
<tr>
<td>Lung</td>
<td>4.6%</td>
<td>4.6%</td>
<td>0.95</td>
</tr>
<tr>
<td>Other</td>
<td>8.4%</td>
<td>6.1%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*TABLE 1. Five-year Cancer Outcomes for Laparoscopic and Open Colectomy Patients*

COST Trail NCCTG
Kaplan Meier Curves Overall Survival

All Stages

Stage I

Stage II

Stage III

5-yr Overall Survival for:
A: all Stages; B: Stage I; C: Stage II; D: Stage III

FIGURE 3. Five-year overall survival.
Laparoscopic Right Hemicolecctomy
Early Stage T2 N0 (0/37 Nodes)
Do not change the Operation!
Laparoscopic “Cecectomy” for cancer

Required repeat resection for “recurrent” (persistent) disease
Currently NED at 1 yr
Low Anterior Resection
Intact Mesorectum
Total Mesorectal Resection:
Nerve Preserving Technique

Hypogastric Nerves
### Probability of Recurrence

*assuming the patient is alive and recurrence-free at the beginning of the interval*

<table>
<thead>
<tr>
<th></th>
<th>Surgery Alone (%)</th>
<th>Surgery + 5-FU/LV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td>1yr</td>
<td>5.2</td>
<td>19.6</td>
</tr>
<tr>
<td>2yr</td>
<td>6.5</td>
<td>21.4</td>
</tr>
<tr>
<td>3yr</td>
<td>6.5</td>
<td>10.3</td>
</tr>
<tr>
<td>4yr</td>
<td>4.5</td>
<td>5.2</td>
</tr>
<tr>
<td>5yr</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td>6yr</td>
<td>1.3</td>
<td>4.0</td>
</tr>
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</table>
# Effective Chemotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response Rate</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0%</td>
<td>7</td>
</tr>
<tr>
<td>Single Agent 5-FU</td>
<td>20%</td>
<td>10</td>
</tr>
<tr>
<td>5-FU with Leucovorin</td>
<td>20%-30%</td>
<td>12-18</td>
</tr>
<tr>
<td>FOLFOX or FOLFIRI</td>
<td>50%</td>
<td>20</td>
</tr>
<tr>
<td>Above plus molecular agent (VEGF or EGFR)</td>
<td>70%</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Future agents??</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
## The down side

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>Platinum analogue</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Topoisomerase-I inhibitor</td>
<td>Diarrhea, neutropenia</td>
</tr>
<tr>
<td>CPT-11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VGFR antagoninst</td>
<td>Hypertension, Vascular events (DVT, CVA, bleeding)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR antagonist</td>
<td>Cutaneous rash</td>
</tr>
</tbody>
</table>
Complications of Chemotherapy

- Normal Liver
- Steatosis: Fat droplets in hepatocytes
- Perioperative complications following chemotherapy
  - Steatosis independent risk factor for major complications
- Severe steatohepatitis associated with preoperative chemotherapy
Cost and Toxicity

Cost of adjuvant therapy rises exponentially with each additional drug

- 6 month treatment: 5-FU/LV = $650 to $800
- plus oxaliplatin = $47,000 to $68,000
- plus bevacizumab = $50,000 to $67,000
- grand total of $100,000 to $136,000
# Modern Experience: Hepatic Resection for Metastatic Colorectal Cancer:

<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>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdalla (2004)</td>
<td>190</td>
<td>-</td>
<td>-</td>
<td>73</td>
<td>58</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>
</tr>
<tr>
<td>Pawlik (2005)</td>
<td>557</td>
<td>1.0</td>
<td>97</td>
<td>74</td>
<td>58</td>
<td>74</td>
</tr>
</tbody>
</table>

How safe is surgery?
Single institution series?
Multi-institutional experience?

National Surgical Quality Improvement Program (NSQIP)
2313 major hepatectomies (2005-2007)
• Morbidity 19.6%
• Mortality 2.5%
• Cancer patients: 20% received preoperative chemotherapy

Aloia HPB 2009
**Treatment:** Right Hepatectomy & Systemic Chemotherapy

**Choices:** Surgery followed by adjuvant chemotherapy?

or

Chemotherapy before and after Surgery?
Surgery First

1. Tumor may grow and become “unresectable”
2. Chemotherapy may induced irreversible liver damage
3. Adjuvant chemotherapy will be given anyway
4. Safe “standard of care”

Chemotherapy First

1. Smaller tumors are easier to remove
2. Surgical complication may not allow adjuvant chemotherapy
3. Trial evaluation chemotherapy “see what drugs will work”
4. Allows for earlier therapy of occult micrometastatic disease
Options:
1. Left Lateral Hepatectomy plus V and VI (close IV margin but no RFA)

2. Left Hepatectomy plus RFA V and VI (wider IV margin & leaves entire right lobe)
Conclusions:

Surgical resection of the primary & regional nodes can cure the majority of Stage II and III colon cancer

- Early diagnosis and treatment is essential
- Appreciate genetic predisposition to cancer can improve detection & prophylactic surgery
- Incremental benefit of adjuvant therapy