Neoadjuvant Chemoradiotherapy for Rectal Cancer: Overrated

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Grand Rounds
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Rectal Cancer Staging

- DRE
- Colonoscopy
- Rigid Proctosigmoidoscope
- EUS/MRI
- CT
- CEA

Digital-rectal examination and/or rectovaginal exam and rigid proctoscopy to determine if sphincter-saving surgery is possible. [7,18,19]

Complete colonoscopy to rule out cancers elsewhere in the bowel. [7]

Pan-body computed tomography (CT) scan to rule out metastatic disease. [7]

Magnetic resonance imaging (MRI) of the abdomen and pelvis to determine the depth of penetration and the potential for achieving negative circumferential (radial) margins, as well as to identify locoregional nodal metastases and distant metastatic disease. [18]

Endorectal ultrasound (ERUS) with a rigid probe or a flexible scope for stenotic lesions to determine the depth of penetration and identify locoregional nodal metastases. [19,21]

Positron emission tomography (PET) to image distant metastatic disease. [18]

Measurement of the serum carcinoembryonic antigen (CEA) level for prognostic assessment and the determination of response to therapy. [22,23]
Current Recommendations

• Neoadjuvant chemoradiation for stage II/III
• Tumor regression, downstaging and improvement in resectability, and a higher rate of sphincter preservation and local control
Standard of Care

- Neo-Adjuvant Therapy
- Radiation
- Chemotherapy: 5-FU, Leucovorin, Oxaliplatin
- Surgical Excision
  - Local Excision
  - Low Anterior Resection
  - Abdominal Perineal Resection
### Table 2. TNM Staging System for Colorectal Carcinoma.  

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classification</th>
<th>Five-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1–2, N0, M0</td>
<td>&gt;90</td>
</tr>
<tr>
<td>IA</td>
<td>T1, N0, M0</td>
<td>60–85</td>
</tr>
<tr>
<td>IB</td>
<td>T1, N0, M0</td>
<td>60–85</td>
</tr>
<tr>
<td>IIA</td>
<td>T1–2, N1, M0</td>
<td>25–45</td>
</tr>
<tr>
<td>IIB</td>
<td>T1–4, N1, M0</td>
<td>5–7</td>
</tr>
<tr>
<td>IIC</td>
<td>T4 any, N2, M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T4 any, N any, M3</td>
<td></td>
</tr>
</tbody>
</table>

#### Primary tumor (T)
- **TX:** Primary tumor cannot be assessed
- **Tis:** Carcinoma in situ
- **T1:** Tumor invades submucosa
- **T2:** Tumor invades muscularis propria
- **T3:** Tumor penetrates muscularis propria and侵犯les subserosa
- **T4:** Tumor directly invades other organs or structures or perforates visceral peritoneum

#### Nodal status (N)
- **NX:** Regional lymph nodes cannot be assessed
- **N0:** No metastases in regional lymph nodes
- **N1:** Metastases in one to three regional lymph nodes
- **N2:** Metastases in four or more regional lymph nodes

#### Distant metastases (M)
- **M0:** Presence or absence of distant metastases cannot be determined
- **M1:** Distant metastases detected

*The information is from Gerssen et al.*

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**TNM Staging**
Dukes' classification

- **A**: Limited to the bowel wall
- **B**: Through the bowel wall. **B1**: tumors invade into the muscularis propria. **B2**: tumors completely penetrate the smooth muscle layer into the serosa
- **C**: Regional lymph nodes metastasis. **C1**: tumors invade the muscularis propria with fewer than four positive nodes. **C2**: tumors invade the muscularis propria with more than four positive nodes
- **D**: Distant mets

### Dukes Staging

<table>
<thead>
<tr>
<th>TNM Classification (American Joint Commission on Cancer)</th>
<th>Dukes' Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stages</strong></td>
<td><strong>T</strong></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
</tr>
<tr>
<td></td>
<td>T2</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
</tr>
<tr>
<td></td>
<td>T4</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2</td>
</tr>
<tr>
<td></td>
<td>T3, T4</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>
Major Studies

- Swedish Rectal Cancer Trial - 1997
- German Rectal Cancer Study Group - 2004
- Dutch Colorectal Cancer Group - 2007
1168 Patients younter than 80. 25 Gy – 5 fractions in one week followed by surgery in 1 week vs surgery alone.
Rectal Cancer: The Basingstoke Experience of TME

All Recurrence: 32% at 5y and 34% at 10y
Local Recurrence: 6% at 5y and 8% at 10y
Disease Free Survival: 80% at 5y and 78% at 10y
Dutch Colorectal Cancer Group: TME Trial

<table>
<thead>
<tr>
<th></th>
<th>Local Recurrence 5 Year</th>
<th>Overall Survival 5 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TME</td>
<td>10.9%</td>
<td>64.2%</td>
</tr>
<tr>
<td>XRT + TME</td>
<td>5.6%</td>
<td>63.5%</td>
</tr>
</tbody>
</table>

Ann Surg 2007;246:693-701

1861 randomized to TME vs. 25 Gy in 5 fractions over 5-7 days followed by TME NO chemo
Subgroup analysis suggests XRT most beneficial in pts with nodal involvement and tumor distance 5-10 cm from anal verge.
Preoperative vs. Postoperative Chemoradiotherapy for Rectal Cancer: German Rectal Cancer Study Group

- Preoperative Chemoradiotherapy
- Decreased local recurrence
- Increase sphincter preservation
- Less acute and late toxicity
- Same overall survival

Sauer NEJM 2004;351:1731-40

Chemo: 5-FU
Sauer NEJM
2004;351:
1731-40

Figure 1: Overall Survival (Panel A) and Disease-Free Survival (Panel B) among the 770 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiation. Statistical inference is to be conducted at the higher level of analysis. Follow-up data were available for 721 patients.
Figure 2: Cumulative Incidence of Local Recurrences (Panel A) and Distant Metastases (Panel B), among the 40 Mesothelioma Patients Assigned to Neoadjuvant or Postoperative Chemoradiotherapy According to an Intention-to-Treat Analysis. Follow-up data were available for 78 patients.
Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Chemoradiotherapy (N=415)</th>
<th>Postoperative Chemoradiotherapy (N=384)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal resection deemed necessary — no. (%)</td>
<td>116 (28)</td>
<td>78 (20)</td>
<td></td>
</tr>
<tr>
<td>Sphincter-preserving surgery performed — no./total no. (%)</td>
<td>45/116 (39)</td>
<td>15/78 (19)</td>
<td>0.004</td>
</tr>
<tr>
<td>Type of Toxic Effect</td>
<td>Preoperative Chemoradiotherapy (N=359)</td>
<td>Postoperative Chemoradiotherapy (N=237)</td>
<td>P Value</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>Hematologic effects</td>
<td>6</td>
<td>8</td>
<td>0.27</td>
</tr>
<tr>
<td>Dermatologic effects</td>
<td>11</td>
<td>15</td>
<td>0.09</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>27</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Long-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal effects†</td>
<td>9</td>
<td>15</td>
<td>0.07</td>
</tr>
<tr>
<td>Strictures at anastomotic site</td>
<td>4</td>
<td>12</td>
<td>0.003</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>2</td>
<td>4</td>
<td>0.21</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>14</td>
<td>24</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Sauer NEJM 2004;351:1731-40
Timing of Surgery

- Group A: 28-41 days (4-6 weeks) b/w CRT and surgery
- Group B: 42-56 days (6-8 weeks) b/w CRT and surgery
  - Does not improve CRT response
  - Does not improve sphincter preservation
  - Does not decrease morbidity or local recurrence

Summary of Chemoradiotherapy

- Advantages
  - Decrease Local Recurrence
  - Improved Sphincter Preservation
- Disadvantages
  - Diarrhea
  - Wound Healing Complications
  - Sexual/Bladder/Sphincter Dysfunction
  - Radiation Enteritis
  - Intestinal Obstruction
  - Acute/Chronic Toxicity
  - No significant overall survival difference
THIS IS MY RAISING THE PITY SHIRT