Neoadjuvant Therapy for Rectal Cancer is Overrated

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University of Colorado
8/31/2009
Objectives

- Brief overview of staging rectal cancer
- Current guidelines for evaluation and treatment of rectal cancer
- Data without benefit for five-year survival (5YSR)
- “Benefit” of neoadjuvant therapy
- Conclusions
Staging: American Joint Committee on Cancer (AJCC)

Box 1
Tumor-node-metastasis (TNM) staging system for rectal cancer

*Primary tumor (T)*
- Tx: Primary tumor cannot be assessed
- Tis: Tumor invades submucosa
- T1: Tumor invades muscularis propria
- T3: Tumor invades through the muscularis propria into the subserosa
- T4: Tumor invades other organs or structures, or perforates visceral peritoneum

*Regional lymph nodes*
- Nx: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in one to three regional lymph nodes
- N2: Metastasis in four or more regional lymph nodes

*Distant metastasis*
- Mx: Presence or absence of distant disease cannot be determined
- M0: No distant metastasis detected
- M1: Distant metastasis detected


## Stage-based Survival

### Table 1
Stage-specific survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grouping</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>II</td>
<td>T3, N0, M0</td>
<td>60%–85%</td>
</tr>
<tr>
<td>III</td>
<td>T4, N0, M0</td>
<td>60%–85%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2, N1, M0</td>
<td>55%–60%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4, N1, M0</td>
<td>35%–42%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T-1-4, N1, M0</td>
<td>25%–27%</td>
</tr>
<tr>
<td>IV</td>
<td>T1-4, N0-2, M1</td>
<td>5%–7%</td>
</tr>
</tbody>
</table>

Diagnostic Evaluation

- Establishing locoregional involvement with transrectal ultrasound
- Possible role of MRI to evaluate mesorectal node involvement
- Evaluation of distant metastases by CT scan
- Still controversial role of combined PET/CT for evaluation of distant metastases

Meredith et al. Surg Clin of N Amer. 2009
Treatment Standard of Care

- **Neoadjuvant Chemotherapy**: 5-fluorouracil (5-FU), leucovorin, & oxaliplatin (FOLFOX)
- **Neoadjuvant Radiotherapy**: External beam radiation (XBR) – no consensus on dose but 28 fractions, total 50.4 Gy used often
- **Surgical resection**: Low anterior resection (LAR), abdominal perineal resection (APR), local excision

Fry et al. Sabiston Textbook of Surgery. 2007
German Rectal Cancer Study Group

- Randomized controlled trial (RCT) of preop vs. postop chemoradiotherapy
- Multicenter (26) trial with n=823, 421 in preop arm; 1° Endpoint of overall survival
- 50.4 Gy XBR and 5-FU
- Median follow-up 46 months
- Overall 5 YSR of 76% vs 74% (p=0.80)

Sauer et al. NEJM. 2004
Cochrane Database Review

- 2007 Review of preoperative radiotherapy for localized resectable adenocarcinoma of rectum
- 20 randomized controlled studies
- Included studies with other included therapies if uniformly applied to both arms
- 19 studies failed to show significant overall survival benefit

Wong et al. Cochrane Database Sys Rev. 2007
### Analysis 1.1. Comparison 1 PREOP RT vs S alone, Outcome 1 Overall mortality.

**Review:** Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma

**Comparison:** 1 PREOP RT vs S alone

**Outcome:** 1 Overall mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio Exp((O-E)/V) Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (published data only)</td>
<td>0/50</td>
<td>0/60</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Bouls Wassif 1979</td>
<td>295/424</td>
<td>293/425</td>
<td>1.08 [0.92, 1.27]</td>
</tr>
<tr>
<td>Cedermark 1995</td>
<td>72/159</td>
<td>68/150</td>
<td>1.00 [0.56, 1.77]</td>
</tr>
<tr>
<td>Dahl 1990</td>
<td>125/231</td>
<td>132/228</td>
<td>0.98 [0.76, 1.26]</td>
</tr>
<tr>
<td>Gerard 1988a</td>
<td>140/230</td>
<td>149/245</td>
<td>1.04 [0.83, 1.30]</td>
</tr>
<tr>
<td>Goldberg 1994b</td>
<td>89/158</td>
<td>87/162</td>
<td>0.00 [0.00, 0.00]</td>
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<tr>
<td>Higgins 1986</td>
<td>0/1</td>
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<td>Illenyi 1994</td>
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<td>Kapitoijn 2001</td>
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<tr>
<td>MRC 1984 (Multi fc)</td>
<td>164/278</td>
<td>171/285</td>
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<td>Petersen 1998</td>
<td>25/47</td>
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<td>0.65 [0.38, 1.10]</td>
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<td>Rider 1977</td>
<td>41/60</td>
<td>47/65</td>
<td>0.88 [0.57, 1.35]</td>
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<td>Stockholm 1996</td>
<td>107/272</td>
<td>127/285</td>
<td>0.79 [0.60, 1.03]</td>
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<tr>
<td>Swedish RCT 1997</td>
<td>245/583</td>
<td>304/585</td>
<td>0.78 [0.66, 0.92]</td>
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<td>14/28</td>
<td>22/37</td>
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**Total (95% CI):**

- Chisq = 18.29, df = 13 (P = 0.15); I² = 29%
- Test for overall effect: Z = 2.06 (P = 0.039)

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Wong et al. *Cochrane Database Sys Rev.* 2007
**Analysis 1.2.** Comparison I PREOP RT vs S alone, Outcome 2 Overall mortality using CCGG + published data.

Review: Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma

Comparison: 1 PREOP RT vs S alone

Outcome: 2 Overall mortality using CCGG + published data

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</table>

**Total (95% CI)**

Heterogeneity: $\chi^2 = 17.50$, df = 13 ($P = 0.18$); $I^2 = 26\%$

Test for overall effect: $Z = 1.52$ ($P = 0.13$)

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Colorectal Cancer Collaborative Group. Lancet. 2001
5 Year Survival Benefit

- Prospective randomized multicenter trial with preoperative XBR (25 Gy over one week) versus surgery alone
- N=1168, 583 radiotherapy vs 585 control
- Local recurrence 11% vs 27% in control
- Overall 5 YSR 58% in experimental arm vs 48% in control

Swedish Rectal Cancer Trial. *NEJM*. 1997
Swedish Rectal Cancer Trial

Swedish Rectal Cancer Trial. *NEJM*. 1997
Discrepancies Exist

• There is no evidence of control of post-operative adjuvant therapies
• A local recurrence rate of 27% in the control arm is exorbitantly high
• Surgeons in neither arms performed total mesenteric excision (TME)
• “Why is this study different from all other studies?”

Swedish Rectal Cancer Trial. NEJM. 1997
Total Mesenteric Excision

- In conjunction with either low anterior resection or abdominal perineal resection
- No blunt dissection of the mesorectum during rectal resection
- Careful sharp dissection, direct visualization, and care in preservation of autonomic nerves
- Avoid violation of “tumor package,” (i.e. mesorectal envelope)
- Reported local recurrence rate of 6% without neoadjuvant therapy with n=301

Heald. Eur J Cancer. 1995
Dutch Colorectal Cancer Group

- Randomized multi-center controlled trial, n=1805; 897 preoperative XBR and TME, 908 TME alone
- Statistically significant increase in blood loss (p<0.001) and “perineal complications” (26% vs 18% p=0.05) in XBR group

E Kapiteijn et al.

• Overall 2 year survival rate was 82% in experimental arm and 81.8% in control; Hazard ratio 1.02
• No significant differences in distant and overall recurrence
• Significant decrease in local recurrence: 2.4% in neoadjuvant arm versus 8.2% (p<0.001)
Local Recurrence & Survival

- GA Higgins. Cancer. 1986
- M Buyse. JAMA. 1988
- B Cedermark. Cancer. 1995
- S Petersen. Chirug. 1998
Management of Local Recurrence

• Locally recurrent rectal cancer has 5 YSR of 22-31% and local control of 50-71%
• Degrades quality of life; 1° symptom: Pain
• Surgery remains mainstay of treatment: APR, total pelvic exenteration, abdominosacral resection
• Multimodality therapy: Surgery, XBR, chemotherapy (again, FOLFOX), intraoperative radiotherapy

Management of Local Recurrence

- Is there a survival benefit with combined modalities?
- A debate for another day.

Conclusions

• No evidence of benefit of neoadjuvant therapies in 5 year survival rate
• Local recurrences are troubling but do not appear to impact overall survival
• Neoadjuvant chemoradiotherapy is overrated…
Conclusions (continued)

Buy a Swedish car, not a Swedish operation
Tack själv
(Thank You in Swedish)
References


