Neoadjuvant radiotherapy: Necessary for treatment of rectal cancer

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Rectal Cancer

- 40,870 new cases in the US in 2009
- 49,920 deaths from colorectal cancer
- Second leading cause of cancer death in the US
- Mortality has been decreasing over the past 30 years

Colon vs Rectal Cancer

- Similar genetic, biologic, and morphologic characteristics
- Location in retroperitoneal pelvis, far from small bowel allows treatment with radiation therapy
- Distal 10-12cm of extraperitoneal rectum is oncologic portion of the rectum

Colorectal Cancer Staging

- **T1**: No deeper than submucosa
- **T2**: Not through bowel wall
- **T3**: Through bowel wall
- **T4**: Through the wall involving serosa or adjacent structure
- **N1**: Regional lymph node metastases 1 to 3 nodes
- **M1**: Distant metastases
  - Lung
  - Liver
  - Bone
  - And/or positive peritoneal cytology
  - And/or positive nonregional lymph nodes
Staging work up

1. DRE and rigid proctosigmoidoscopy to determine tumor location and degree of fixation
2. Full colonoscopy to exclude synchronous neoplasms
3. CT abdomen and pelvis to rule out distant metastases and adjacent organ invasion
4. Transrectal ultrasound (TRUS) or MRI
   1. MRI better for T3-T4 lesions
   2. TRUS better for earlier stage lesions
   3. Nodal staging is comparable
5. CXR or Chest CT - rectal cancer is more likely than colon cancer to be associated with lung metastases without liver metastases
6. Preoperative CEA level

Treatment recommendations by stage

- Stage I - local excision (transabdominal versus transanal)
- Stage II - neoadjuvant therapy followed by resection
- Stage III - neoadjuvant therapy followed by resection
- Stage IV - neoadjuvant therapy followed by resection if possible

Why Stage II and III?

- 1990 National Cancer Institute Consensus Conference
  - recommendation for adjuvant postoperative combined modality therapy (CMT) for all T3 and/or N+ rectal cancers
- Retrospective data (2004) showed similar overall survival for T3N0 patients treated with surgery and chemotherapy alone versus CMT
- Accuracy of preoperative TRUS/MRI staging in T3N0 rectal cancer
  - 22% of patients had undetected mesorectal LN involvement
  - These patients would be understaged

Guillem et al. cT3N0 rectal cancer: Potential overtreatment with preoperative chemoradiation therapy is warranted. J Clin Oncol 2008;26:368-373
Benefits of Pre-operative Radiation

- 4 major studies
  - Dutch Trial (The TME Trial)
  - Medical Research Council Trial
  - Swedish Rectal Cancer Trial
  - German Trial
- 1 meta-analysis
Dutch Trial

- Randomized 1861 patients to total mesorectal excision (TME) alone versus preoperative (25Gy) radiation followed by TME
- Decreased 5 year local recurrence (5.6% vs 10.9% P<.001)
- No change in overall survival (64.2% versus 63.5% P=.902)

Peeters et al. The TME trial after a median follow-up of 6 years: Increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Annals of Surgery 2007;246:5.
Medical Research Council Trial

- Prospective randomized trial of 279 patients; surgery alone versus surgery preceded by 40Gy radiotherapy

- Results:
  - Decreased rate of local recurrence at 5 years (65 patients vs 50 patients, hazard ratio 0.68 [0.47-0.98] P=.04)
  - Decreased rate of distant recurrence (67 vs 49 patients, hazard ratio 0.66 [0.46-0.95] P=.02)
  - Improved disease free survival (hazard ratio 0.76 [0.58-1] P=.05)
  - No improvement in overall survival
  - Decreased tumor size and number of involved lymph nodes

Swedish Rectal Cancer Trial

- Randomized 1168 patients to surgery alone versus preoperative radiation (25 Gy) plus surgery
- Results
  - Decreased local recurrence at 5 years (11% vs 27% P<.001)
  - Improved 5 year survival (58% vs 48% P=.004)
  - Improved cancer specific survival (74% vs 65% P=.002)
  - Improved survival at 13 years (38% vs 30% P=.008)
  - Tumor downstaging (increased rate of Duke’s A or B tumor)


German Trial

- 823 patients
- stage T3, T4 or node-positive disease
- randomized to receive either preoperative or postoperative chemoradiotherapy

Results

- Significant shift toward earlier TNM stages (8% vs 0% with complete histopathologic response P<.001)
- Increased sphincter preservation (39% vs 19%, P=.004)

14 randomized controlled trials comparing preoperative radiotherapy plus surgery vs. surgery alone

Improved overall mortality (OR 0.84 CI 0.72-0.98, P=.03) (NNT = 25) 12

**Improved cancer-related mortality** (OR 0.71, CI 0.61-0.82, P<.001) (NNT=13)

Decreased local recurrence (OR 0.49 CI 0.38-0.62 P<.001) (NNT=10)

Does everyone need an operation?

- Unpublished data from Brazil
- Increased traditional neo-adjuvant treatment from radiation plus 2 rounds of 5FU-leucovorin to radiation plus 6 rounds 5FU-leucovorin

Results

- 65% complete clinical response requiring no immediate surgery
- 97% rate of sphincter presentation
- No increased toxicity

General Surgery News March 2011
Benefits of Radiation

- Decreased rate of local recurrence
- Tumor downstaging
- Increased rate of sphincter preservation
- Possible improvement in overall survival
Recommendations

- American Society of Colon and Rectal Surgeons:
  - Adjuvant chemoradiation should be offered to patients with Stage II and III rectal cancers.

- National Comprehensive Cancer Network Clinical Practice Guidelines:
  - Combined-modality therapy consisting of surgery, radiation therapy, and chemotherapy is recommended for most patients with Stage II or Stage III rectal cancer.
References