RECTAL CANCER:

Adjuvant Therapy

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Overview

Indications for adjuvant therapy

Preoperative

Postoperative

New Advances
Epidemiology

• Approximately 40,000 new US cases of rectal ca in 2012
  – 23,000 men; 17,000 women

• Estimated that 52,000 people will die from colorectal ca in 2012 in US

• Colorectal ca ranked as 3<sup>rd</sup> leading cause of US cancer death in 2012 for men and women, 2<sup>nd</sup> overall

• Incidence is decreasing, mortality has decreased by >35% from 1990 to 2007
  – May be due to earlier diagnoses, better treatment modalities
Anatomy

• Rectum begins at the rectosigmoid junction around level S3 vertebra.
• Rectum extends cephalad from the dentate or pectinate line for about 12-15 cm where it becomes sigmoid
• 5 cm segments-lower, middle, upper thirds
  – Upper third of the rectum is ~ 12 to 16 cm from the anal verge and is above the peritoneal reflection
  – Lower third 0-6 cm from anus
Anatomy

• Peritoneal investment
  – **Upper 1/3 Rectum**: Anteriorly and both sides
  – **Middle 1/3 Rectum**: Anteriorly
  – **Lower 1/3 Rectum**: None

↓ No serosal barrier for invasive cancers

<table>
<thead>
<tr>
<th>Upper 1/3 Rectum</th>
<th>Middle 1/3 Rectum</th>
<th>Lower 1/3 Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteriorly and both sides</td>
<td>Anteriorly</td>
<td>None</td>
</tr>
</tbody>
</table>
Lymphatics and Spread

- Tumors above anorectal ring
  - Upper 2/3 Rectum
    - Superior rectal vessels => IMA nodes
  - Lower 1/3 Rectum
    - IMA nodes
    - Middle rectal vessels => internal iliac nodes
  - Tumors extending into anal canal
    - Inferior rectal vessels => external iliac nodes

- Upper/Mid rectum
  - Liver mets most common
- Lower rectum/anal canal
  - Lung mets
Lymphatics and Spread

• Thus, cover the
  – perirectals, presacral, obturators, internal iliacs
  – external iliacs in cases of T4 lesions
Staging

**Primary Tumor (T)**

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolic or perirectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum
- **T4b** Tumor directly invades or is adherent to other organs or structures

**Regional Lymph Nodes (N)**

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1–3 regional lymph nodes
  - **N1a** Metastasis in one regional lymph node
  - **N1b** Metastasis in 2–3 regional lymph nodes
  - **N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** Metastasis in 4 or more regional lymph nodes
  - **N2a** Metastasis in 4–6 regional lymph nodes
  - **N2b** Metastasis in 7 or more regional lymph nodes

**Distant Metastasis (M)**

- **M0** No distant metastasis
- **M1** Distant metastasis
  - **M1a** Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
  - **M1b** Metastases in more than one organ/site or the peritoneum
<table>
<thead>
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<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<th>MAC*</th>
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<tr>
<td>I</td>
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<td>M0</td>
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<tr>
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<td>M0</td>
<td>A</td>
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<td>B</td>
<td>B2</td>
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<td>M0</td>
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<tr>
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<td>B</td>
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<td>C</td>
<td>C1</td>
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<td>N2a</td>
<td>M0</td>
<td>C</td>
<td>C1</td>
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<td>III B</td>
<td>T3–T4a</td>
<td>N1/N1c</td>
<td>M0</td>
<td>C</td>
<td>C2</td>
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<td>C</td>
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<td>M0</td>
<td>C</td>
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<td>Any T</td>
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<td>M1b</td>
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~ 5 yr OS

I: 80-95%

II: 50-90%

III: 30-60%

IV: <5%
Endoscopic ultrasound of a rectal carcinoma  Endoscopic ultrasonography showing a rectal carcinoma. The normal hypoechoic boundary of the muscularis propria is expanded and irregular (arrow), indicative of tumor infiltration into the perirectal tissue. Ultrasonographic staging as a T3 cancer was confirmed by surgical pathology. Courtesy Dennis J Ahnen, MD.
Rectal cancer  Endoscopic ultrasound image of a rectal cancer with involvement of perirectal lymph node (arrow). Courtesy of Gavin C Harewood, MD and Mauritius J Wiersema, MD.
## Accuracy of staging exams

<table>
<thead>
<tr>
<th></th>
<th>Transrectal ultrasound</th>
<th>CT</th>
<th>MRI</th>
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<tbody>
<tr>
<td><strong>T stage</strong></td>
<td>80-95%</td>
<td>65-75%</td>
<td>75-85%</td>
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<tr>
<td><strong>N stage</strong></td>
<td>70-75%</td>
<td>55-65%</td>
<td>60-65%</td>
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</tbody>
</table>

Up-to-date
Management

• Primary treatment modality => surgery
• Local recurrence rates ranged from 20% to 50% even with “curative” resections
• Goal is to remove gross and microscopic dz with negative proximal, distal, and circumferential margins
• Previously 5cm distal margin sought => now 2cm distal margin considered acceptable except in poorly differentiated lesions => increased functional preservation
Management

• So for early stage lesions (T1) with no adverse features
  – Local (Transanal) Excision
Management

- Transanal Excision/Transanal Endoscopic Microsurgery
  - cT1,N0
  - <3cm
  - Well to moderately differentiated
  - <8cm from verge
  - <30% rectal circumference
  - Require negative (>3mm) deep and mucosal margins
  - If high grade, +margins, +LVSI, +PNI => more radical resection
Management

• Steele et al. (CALGB 89-84)
  – Phase I-II, 177 pts with T1-T2 tumors ≤4cm, <10cm from verge, <40% circumference, at least 2mm deep margin
  – T1 => transanal excision + observation
  – T2 => adjuvant CRT [5-FU (d1-3, 29-31) + 54Gy/30F]
  – 6 yr OS 85-87%, LF 4% (T1), 14% (T2)

Management

- Russell et al. (RTOG 89-02)
  - Phase II, same eligibility criteria as CALGB 89-84
  - T1 lesions ≤ 3cm, >3mm margins, well to moderately differentiated, no LVSI, normal CEA => observed after surgery
  - T1 with poor risk features, T2-T3N0 => adjuvant CRT [5FU + 50-65Gy]
  - 5yr OS 78%, LF 4% (T1), 16% (T2), 23% (T3)

Management

• More advanced dz not meeting criteria for local excision
  – Invasive surgery
    • LAR vs. APR
      – TME regardless
Management

• Abdominoperineal Resection (APR)
  – For more distal lesions
  – Involves removal of entire rectum and anus with construction of permanent colostomy
  – Designed to excise anal canal with a wide circumferential margin
• Low Anterior Resection (LAR)
  – For lesions in upper 2/3 rectum
  – Recommend 4-5cm distal margin, 2cm minimum
  – Coloanal anastomosis with mobilization of splenic flexure to anastamose unirradiated bowel
  – Preservation of sphincter tone
• Either way, obtain wide radial margins!
Management

- Total Mesorectal Excision (TME)
  - Sharp dissection along plane separating visceral from parietal pelvic fascia with complete en bloc removal of rectum and surrounding rectal mesentery
  - Proper dissection should include **15 perirectal and pelvic LNs**
  - Should be done regardless of type of transabdominal surgery
Management

• Neoadjuvant Therapy?
  – Radiation vs.
  – Chemotherapy vs.
  – Chemoradiation

• Adjuvant Therapy
Management

• Postoperative RT

  – Advantage
    • Pathologic staging avoids overtreatment of some patients
    • Patients receive definitive surgical treatment
Management

• Postoperative RT
  – Disadvantage

  • Higher Local recurrence rate than preoperative therapy
  • Higher acute and chronic toxicity
  • Lack of sphincter preservation
  • Possible need to include perineal scar
Summary Postoperative RT

- 5 randomized trials of adjuvant RT without chemotherapy
- No randomized trial has demonstrated a survival advantage to postoperative RT
- Two randomized trials have demonstrated a statistical improvement in local control
  - NSABP RO 1 16% vs 25% p = .06
  - MRC 21% vs 34% p = .001
Management

• Preoperative Irradiation

  – Short course (SC) 25Gy / 5 fractions

  – Long course (LC) 50.4 Gy / 28 fractions
Management

• Swedish Rectal Cancer Trial, 1997: does preop RT improve LR/OS?
  – 1168 pts with resectable rectal cancer for which surgery planned
    • Surgery alone
    • Preop RT+ Surgery
  – RT => 25Gy/5F over 1 week
    • CTV covered anal canal, primary tumor, mesorectal/presacral/internal iliac LNs, lumbar LNs up to superior border L5, obturator LNs
    • Given via 3F prone or 4F box supine/prone
  – Surgery
    • (APR vs. LAR) performed within 1 week after completing RT
    • not standardized to total mesorectal excision
    • 908 pts had curative surgeries (negative margins)

Management

• Swedish Rectal Cancer Trial, 1997
  – At 5 years
    • Preop RT significantly improved LR (11% vs. 27%)
      – In curative surgeries, 9% vs. 23%
    • Preop RT significantly improved OS (58% vs. 48%)
  – At 13 years
    • Preop RT significantly improved LR (9% vs. 26%)
    • Preop RT significantly improved OS (38% vs. 30%)
  – Criticisms
    • No standardization to TME, high LR rate for surgery arm
    – Set the standard for many following European studies with 25Gy/5F

Management

- Swedish Rectal Cancer Trial Toxicities, 13 year update
Management

- Swedish Rectal Cancer Trial Toxicities, 13 year update

<table>
<thead>
<tr>
<th>Specific Diagnosis</th>
<th>ICD-9 Diagnostic Codes</th>
<th>No RT (No.)</th>
<th>RT (No.)</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>Gastric ulcer</td>
<td>531A-X</td>
<td>8</td>
<td>7</td>
<td>0.78</td>
<td>0.28 to 2.15</td>
<td>.63</td>
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<tr>
<td>Duodenal ulcer</td>
<td>532A-X</td>
<td>7</td>
<td>5</td>
<td>0.60</td>
<td>0.19 to 1.90</td>
<td>.39</td>
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<tr>
<td>Fistulas</td>
<td>537E, 565B, 569C, 596B, 619B</td>
<td>5</td>
<td>9</td>
<td>1.56</td>
<td>0.52 to 4.67</td>
<td>.42</td>
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<td>Inguinal hernia</td>
<td>550X-552A</td>
<td>10</td>
<td>3</td>
<td>0.26</td>
<td>0.07 to 0.96</td>
<td>.04</td>
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<td>Incision hernia</td>
<td>552C-553X</td>
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<td>24</td>
<td>1.52</td>
<td>0.79 to 2.94</td>
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<tr>
<td>Paralytic bowel</td>
<td>560B</td>
<td>8</td>
<td>16</td>
<td>1.85</td>
<td>0.79 to 4.32</td>
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<tr>
<td><strong>Bowel obstruction</strong></td>
<td><strong>560D-X</strong></td>
<td><strong>20</strong></td>
<td><strong>42</strong></td>
<td><strong>1.88</strong></td>
<td><strong>1.10 to 3.20</strong></td>
<td><strong>.02</strong></td>
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<td>Constipation</td>
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<td>33</td>
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<td>0.96 to 3.09</td>
<td>.07</td>
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<td>1.73</td>
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<td>14</td>
<td>4.04</td>
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<td>Abdominal pain</td>
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<td>44</td>
<td>1.92</td>
<td>1.14 to 3.23</td>
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</tr>
</tbody>
</table>

NOTE. Specific disease diagnosis with fewer than 10 admissions are not presented in the table.
Abbreviations: ICD, International Classification of Diseases; RR, relative risk; RT, preoperative radiation therapy; No RT, surgery alone.
Fig 5. Proportion of patients free of late admissions (> 6 months) owing to bowel obstruction. Comparison of patients treated with different radiation techniques.
FIGURE 38-2. Treatment fields after a low anterior resection for a T3N1M0 rectal cancer 8 cm from the anal verge. In this example, the distal border is at the bottom of the obturator foramen and the perineum is blocked. Since the tumor was a T3, the anterior field is at the posterior margin of the symphysis pubis (to treat only the internal iliac nodes).

FIGURE 38-3. Treatment fields after a low anterior resection for a T4N1M0 rectal cancer 8 cm from the anal verge. In this example, the distal border is at the bottom of the obturator foramen and the perineum is blocked. Since the tumor was a T4, the anterior field is at the anterior margin of the symphysis pubis (to include the external iliac nodes).
FIGURE 38-4. Treatment fields after an abdominoperineal resection for a T3N1M0 rectal cancer 2 cm from the anal verge. In this example the distal border is extended to include the perineal scar. Since the distal border is being extended only to include the scar, the remaining normal tissues can be blocked.

FIGURE 38-5. Treatment fields following an abdominoperineal resection for a T4N1M0 rectal cancer 2 cm from the anal verge. In this example, because the tumor was a T4, the anterior field is at the anterior margin of the symphysis pubis (to include the external iliac nodes). Since the distal border is being extended only to include the scar and external iliac nodes, the remaining normal tissues can be blocked.
Management

- Dutch CKVO 95-04: does preop RT improve LR/OS when TME is performed?
  - 1861 pts with resectable rectal cancer randomized to
    - Total Mesorectal Excision
    - Preop RT + Total Mesorectal Excision
  - RT => 25Gy/5F over 1 week
    - Upper border lower than in Swedish study
  - Surgery standardized to TME followed by APR/LAR
    - followed RT within 1 week

Management

• Dutch CKVO 95-04
  – At 2 years
    • Preop RT significantly improved local recurrence (2.4% vs. 8.2%)
    • Preop RT did NOT improve distant recurrence
    • Preop RT did NOT improve OS (82% vs. 81.8%)

  – At 10 years,
    • Preop RT significantly improved local recurrence (5% vs. 11%)
    • Preop RT did NOT improve OS
    • Preop RT significantly improved survival in Stage III pts with negative circumferential margins (50% vs. 40%)

  – Thus, neoadjuvant RT beneficial even when TME performed

Meta analysis preoperative therapy
Management

• Preoperative RT (short course)
  – Most trials demonstrate a decrease in LR
  – In 5 of 12 randomized trials this decrease reached statistical significance
  – Swedish Trial is the only study demonstrating a survival advantage for RT alone
  – Two meta analyses revealed a decrease in LR with RT
  – One meta analyses demonstrated a survival advantage
Management

So what about chemotherapy?
Management

• NSABP R-01: does adjuvant chemo or RT improve DFS/OS?
  – 555 pts with Dukes B/C lesions s/p curative resection (APR vs. LAR with negative margins) randomized to
    • Observation
    • MOF chemo (5-FU, semustine, vincristine) 21-42 days after surgery x8c q10wks
    • RT 46-47Gy via AP/PA fields w/ possible boost to 51-53Gy via laterals
      – L5/S1 sup, 1cm lateral to pelvic brim, inf covered perineum/bottom of obturator foramen in LAR pts OR 3cm below anastamosis
  – At 5 years, adjuvant chemo significantly improved DFS (42% vs. 30%-%) and OS (53% vs. 43%), but this difference only seen in men
  – At 5 years, trend towards increase in DFS with adjuvant RT but no improvement in OS

• NSABP R-02: does adding RT to CTX improve DFS/OS?
  – 694 pts with Dukes B/C lesions s/p resection randomized to
    • Chemo (MOF) alone (males)
    • Chemo (5-FU/LV) alone (males)
    • Chemo (5-FU/LV) alone (females)
    • Chemo (5-FU/LV) + RT (males)
    • Chemo (5-FU/LV) + RT (females)
    • Chemo (MOF) + RT (males)
  – RT was 4F box sup L5/S1, inf perineum vs. bottom obt foramen, 1cm lateral to pelvic brim, 45Gy/25F +/- boost to 50.4Gy
  – At 5 years, adjuvant RT did not improve DFS or OS in combination with chemo though it did decrease locoregional relapse from 13% to 8%
  – 5-FU/LV had significant benefit in DFS (55% vs. 47%) vs. MOF but not OS at 5 years in men.

Management

- GITSG 7175: does adjuvant CTX, RT, or chemoRT improve recurrence rates or survival?
  - 227 pts with Dukes B2/C lesions s/p curative resection randomized to
    - Observation
    - Chemotherapy
    - RT
    - ChemoRT

Table III

<table>
<thead>
<tr>
<th>Details of protocol therapy.</th>
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</table>

(2) **Chemotherapy alone**
- Intravenous 5-FU 325 mg/m² days 1-5
- Oral semustine (methyl-CCNU) 130 mg/m² day 1
- Intravenous 5-FU 375 mg/m² days 36-40
- Ten-week cycle, modified if hematological toxicity, repeated for 18 months

(3) **Radiotherapy alone**
- Institutional preference
  - 4000 cGy in 4-4.5 weeks
  - or
  - 4800 cGy in 5-5.5 weeks
- Treatment given 5 days a week with parallel opposed fields using beams of greater than 1 MeV to volume in Fig. 1. Typical field size 15 x 20 cm. Prescription point at midplane. The perineum was required to be included

(4) **Combined modality**
- 4400 Rad in 4.5-5.5 weeks. Other details as in (3) above
- Intravenous 5-FU 500 mg/m² days 1-3 and last 3 days of radiotherapy
- Five weeks after radiotherapy, intravenous 5-FU 300 mg/m² days 1-3 and oral methyl-CCNU 130 mg/m² day 1. Thereafter, chemotherapy as in (2) above.

Management

• GITSG 7175
  – At 9 years, adjuvant **CRT significantly improved**
    • OS from 27% to 54%
    • Recurrence rate from 55% to 33%
    • LF rate from 25% to 10%
  when compared to the surgery + observation arm
  – More severe toxicity with combined modality treatment
    • 61% with CRT
    • 31% with chemo
    • 18% with RT
  – Criticisms
    • Underpowered, 5-FU given by bolus with semustine (carcinogenic), unequal randomization, no ITT analysis
Management

Fig. 3. Disease-free survival by treatment arm.

Fig. 4. Actuarial survival by treatment arm.
Management

- Krook et al. (NCCTG 79-47-51): does adding CTX to RT improve recurrence rates or survival?
  - 204 pts with T3-T4 or N1-N2 disease s/p APR vs. LAR randomized to
    - RT [45-50.4Gy]
    - Sequential chemoRT [semustine/5-FU > 5-FU/RT > semustine/5-FU]
  - RT via 4F box, inf border covered perineum with 1.5-2cm margin for APRs, 3-5cm below anastomosis vs. bottom of obturator foramen for LARs ⇒ 45Gy/25F + 5.4Gy boost if initial tx tolerated

Management

• Krook et al. (NCCTG 79-47-51)
  – ChemoRT – RT same as in other arm
    • Single oral dose semustine 130mg/m², 5-FU given via bolus 300mg/m²/day d1-5, 400mg/m²/day x5 days starting d36, RT started d64, 5-FU given via bolus dose of 500 mg/m² during 1st three days of 5th week of RT, followed by single oral dose of semustine 100mg/m² one month after RT with 5-FU 300mg/m²/day x5 days, followed by 5-FU 400mg/m²/day x5 days.
  – Basically semustine + 5-FUx2 => 5-FU+RT => semustine + 5-FUx2
  – At 5 years
    • CRT significantly reduced recurrence (63% vs. 42%)
    • CRT significantly improved OS (55% vs. 40%)
    • CRT reduced recurrence by 34%, local recurrence by 46%, distant mets by 37%, cancer deaths by 36%, and overall deaths by 29%
Management

• NSABP R-01
  – Adjuvant chemo improves DFS/OS in men
  – Adjuvant RT trended toward improving recurrence rate
• NSABP R-02
  – Adjuvant RT decreased locoregional recurrence
  – Adjuvant RT did not improve DFS/OS
• GITSG 7175
  – Adjuvant CRT improves LR, recurrence, and OS vs. observation
• NCCTG 79-47-51
  – Adjuvant CRT improves LR, DFS, DMFS, OS
Management

• So adjuvant therapy is good
  – Chemo definitely improves OS
  – RT at least improves LR
  – Adjuvant chemoRT is the way to go, at least for Stage II/III

• What about the chemo?
Management

- O’Connell et al. (NCCTG 86-47-51)
  - 660 pts with TNM Stage II or III lesions s/p resection randomized to
    - Systemic FU + RT w/ concomitant bolus FU
    - Systemic FU + RT w/ concomitant PVI FU
    - Systemic FU/semustine + RT w/ concomitant bolus FU
    - Systemic FU/semustine + RT w/ concomitant PVI FU
  - RT
    - 45Gy/25F + 5.4Gy boost + additional 3.6Gy boost if no SB in field
    - 4F technique, sup 1.5cm above sacral promontory, inf 3-5cm below anastomosis if LAR/included perineal scar if APR, at least 1.5cm lateral to widest bony margin

Figure 1. Schedule of Chemotherapy and Radiation Therapy for Rectal Cancer.

Bolus denotes the administration of fluorouracil by rapid intravenous injection, and PVI its administration by protracted venous infusion. Fluorouracil was given in a dose of 500 mg per square meter of body-surface area on days 1 to 5 and days 36 to 40 and 450 mg per square meter on days 134 to 138 and days 169 to 173. Semustine was given in a dose of 130 mg per square meter on day 1 and 100 mg per square meter on day 134. Radiation therapy began on day 64; the total dose was 4500 cGy. For other details of therapy, see the Methods section.
Management

• O’Connell et al. (NCCTG 86-47-51)
  – PVI 5-FU significantly decreased LR (47% vs. 37%) and DM (40% vs. 31%) in comparison to bolus 5-FU during RT
  – Similar difference seen in pts who did not receive semustine
  – At 4 years, PVI 5-FU improved OS (70% vs. 60%) vs. bolus 5-FU
  – PVI 5-FU also increased time to relapse
  – No significant benefit seen with semustine
Management

• What about neoadjuvant therapy though?

  – Radiation vs. Chemoradiation
Management

• Gerard et al. (FFCD 9203): does preop CRT improve LR/OS over preop RT?
  • 733 P pts with resectable T3-4, NxM0 rectal adenoca accessible to DRE randomized to
    – Preop RT
    – Preop CRT
  • RT – 45Gy/25F, 3-4F box technique, sup border at sacral promontory or 1cm below for distal lesions, inf border 4-5cm distal to tumor or verge, lateral borders 1.0 cm lateral to widest bony margin, entire thickness of sacral bone included, general field sizes were 14x13cm post, 14x12cm lat
  • CTX – given concurrently, first cycle given d1-5: LV 20mg/m² prior to 5-FU 350mg/m² bolus 1 hr prior to RT; second cycle given d29-33
  • Surgery - 3-10 weeks after preop RT/CRT, APR vs. LAR, TME recommended, 2cm distal margin required in sphincter-saving surgery
  • Adjuvant CTX – Pts in both arms received 4c q4wks after RT/CRT

Management

- Gerard et al. (FFCD 9203)
  - 5 year LR significantly lower with CRT vs. RT (8.1% vs. 16.5%)
  - 5 year OS did not differ (67%)
  - Grade 3-4 acute toxicity significantly more frequent with CRT (14.6% vs. 2.7%); no difference in sphincter preservation

  Thus, preop CRT recommended in resectable T3-T4 cancers in mid-distal rectum for improvement in LR despite moderate increase in acute toxicity

- Criticisms
  - TME not standard
  - Bolus 5-FU instead of continuous infusion
Management

- Bosset et al. (EORTC 22921): does preop CRT improve LR/OS over preop RT?
  - 1011 pts with cT3-4 resectable rectal cancer randomized to
    - Preop RT
    - Preop CRT
    - Preop RT + Postop CTX
    - Preop CRT + Postop CTX
  - RT: 45Gy/25
  - CTX: LV 20mg/m\(^2\)/d + 5-FU 350mg/m\(^2\) given x5d 1\(^{st}\) and 5\(^{th}\) week of RT
  - Surgery: 3-10 weeks after preop RT/CRT, APR vs. LAR, TME recommended after 1999
  - Adjuvant CTX: 3-10 weeks after surgery, 4c q3wks, same drugs

Management

- Bosset et al. (EORTC 22921)
  - No difference in 5 year OS, 65%.
  - At 5 years, recurrence rates were
    - Preop CRT: 8.7%
    - Postop CTX: 9.6%
    - Preop CRT/Postop CTX: 7.6%
    - No CTX (Preop RT only): 17.1%

- Overall conclusion:
  - Adding 5-FU-based CTX preop/postop does not effect survival
  - CTX does significantly improve local control (preop or postop)
Management

• But the older studies supported adjuvant CRT
• And these more recent ones support neoadjuvant CRT

• What do we use?
Management

- Sauer et al. (German Rectal Cancer Trial): does neoadjuvant CRT or adjuvant CRT better improve LR/OS?
  - 823 pts with cT3-4 or N+ resectable rectal cancer randomized to
    - Preop CRT
    - Postop CRT
  - Preop: 50.4Gy/28F via 3F-4F box technique with 5-FU 120hr CI
    1000mg/m²/d given wk1+5 of RT, followed by 4c bolus 5-FU
    500mg/m²/d x5d q4wks four weeks after surgery.
  - Surgery: TME + APR/LAR, intended surgery assessment
    recorded, surgery to occur 6 weeks after preop therapy.
  - Postop: 4-6 weeks after surgery, same regimen as preop except
    for additional 5.4Gy boost to tumor bed, and that adjuvant 5-FU
    bolus therapy followed 4 weeks after CRT

Management

- Sauer et al. (German Rectal Cancer Trial)

  - No significant difference in OS at 5 years

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuv CRT</th>
<th>Adjuv CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Relapse, ss</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Acute G3-4 Toxicity, ss</td>
<td>27%</td>
<td>40%</td>
</tr>
<tr>
<td>Sphincter-Sparing Surgery, ss</td>
<td>39%</td>
<td>19%</td>
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</table>
Management

- Sauer et al. (German Rectal Cancer Trial)

<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>
</tbody>
</table>
Management

• Sauer et al. (German Rectal Cancer Trial)
  – Only 8% of the pts with preop CRT had a pCR
  – 92% patients received full dose of preop RT vs. 54% postop RT
  – 89% pts received full dose of preop CTX vs. 50% postop CTX
German Trial: Conclusions

- Pre-op CRT improves LR, toxicity, compliance
- Pre-op improves sphincter preservation
  - More than doubled in those felt to require APR pre-tx
- OS equivalent
- Pre-op CRT should be standard option for patients with T3, T4, or N+ disease

Lancet 2009
Pre- vs. Post-op CRT

• Phase III. 1,350 patients with resectable rectal CA
  – 80 centers, 4 countries
• Randomized to short-course pre-op RT (25 Gy/5fx) + surgery vs. surgery + selective post-op chemoRT (45 Gy and 5-FU)
  – restricted to patients with involvement of the circumferential resection margin.

Lancet 2009

Pre- vs. Post-op CRT

• Reduction in LR for pre-op RT vs. selective post-op chemoRT (4.4% vs. 10.6%).
  – No difference in OS.

Confirmed benefit of neoadjuvant radiation.
Pre-op vs. Post-op CRT

- RTOG 94-01
  - Closed early due to poor accrual
- NSABP R-03
  - Closed early due to poor accrual
- German trial
  - Results reported in NEJM, 2004
- MRC CR07/NCIC-CTG C016
  - Lancet 2009
Short vs long course neoadjuvant therapy

• Trans Tasman radiation oncology group 01.04

• T3No-N2Mo 12 cm verge

• SC 5Gy x5fx 3-7 days surgery 6 courses adjuvant chemotherapy 5FU 425mg/M2 X 5days

• LC 1.8 Gy x 28fx with PVI 5FU 225 mg/M2

• Surgery 4-6 weeks followed 4 courses adjuvant chemotherapy
Short vs long course neoadjuvant therapy

- RT same fields in both arms but reduced at 45Gy to include gross disease with a 2 cm margin
Short vs long course neoadjuvant therapy

N = 326 patients

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>LR 3 YR</th>
<th>OS 5YR</th>
<th>LR</th>
<th>DISTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>163 SC</td>
<td>1.0%</td>
<td>7.5%</td>
<td>74%</td>
<td>6/48</td>
<td></td>
</tr>
<tr>
<td>163 LC</td>
<td>15%</td>
<td>4.4%</td>
<td>70%</td>
<td>1/31</td>
<td></td>
</tr>
</tbody>
</table>

P < .001  P = .24  P = .62  P = .21
Short vs long course neoadjuvant therapy

• 3 Year LR rates were not statistically different between SC and LC therapy
• LC therapy may be more effective in reducing LR in distal tumors.
• No difference in OS or relapse free survival
When may surgery be omitted?

- Wait and see approach Maas et al
  T4
  T3 involvement of mesorectum and/or 3+ nodes
  Neoadjuvant Rx
  50.4Gy/28 fx with capecitibine 825 mg/m² Bid
  If node + oxaliplatin 130mg/m² and capecitibine 1000mg/m² Bid for 6 3 week cycles
  Response evaluated at 6 – 8 weeks
When may surgery be omitted?

• Evaluation
  – MRI T2
  – Diffusion weighted MRI

If both negative for disease

Endoscopy and biopsy
When may surgery be omitted?

- 2004 – 2012
  192 patients Rx neoadjuvant
  mean follow-up 25 +/- 19 mo
  21/192 CR
  20/192 CR at TME

- CR at TME
  1 death surgical complications
  1 metastatic disease
  No local failures
When may surgery be omitted?

• 2004 – 2012 192 patients Rx neoadjuvant
  mean follow-up 25+/- 19 mo
  21/192 CR 20/192 CR at TME

• CR
  1 endoluminal recurrence
  at 22 mo salvaged transanal excision
When may surgery be omitted?

• Conclusion
  – A wait and see approach may be feasible in select patients achieving a CR to neoadjuvant therapy although follow-up is short
  – In almost every case bowel function was better in patients managed with observation
  – Efforts should be made to maximize CR to neoadjuvant therapy
  – Aggressive imaging may underestimate CR to neoadjuvant treatment
Maximizing response to neoadjuvant therapy

• STAR – 01 Phase III Trial
  – 747 patients T3/T4 N1/N2 Mid to lower rectum
    – 50.4 Gy + 5FU 225 mg/m²/d
    – 50.4 Gy + 5FU 225 mg/m²/d + oxaliplatin 60 mg/m² weekly X 6
Maximizing response to neoadjuvant therapy

- STAR – 01 Phase III Trial
  - Grade 3 – 4 toxicity  24% vs 8%  
  - APR  20% vs 18%
  - Path complete response  16% vs 16%
Maximizing response to neoadjuvant therapy

• STAR – 01 Phase III Trial
  
  – Addition of oxaliplatin had no effect on the response of the primary tumor
  – 5FU remains the standard of care
  – Data is not mature enough to determine a survival benefit
Phase III

T3-4, N+ Rectal CA
TME rectal surgery
ALL PRE-OP
n=1,606

Group 1:
5-FU + XRT

Group 2:
5-FU + oxaliplatin + XRT

Group 3:
Xeloda + XRT

Group 4:
Xeloda + oxaliplatin + XRT

Capecitabine = 825 mg/m² PO BID
5-FU = 225 mg/m²/day continuous infusion
Oxaliplatin = 50 mg/m² weekly x 5

[Note: enrollment on post-surgical adjuvant trial is “encouraged”]
R0 4 Preliminary Results

- Capecitabine Noninferior to 5-FU with Improved Toxicity Profile in Rectal Cancer
- “Administration of capecitabine with preoperative radiotherapy achieved similar rates to continuous infusion 5-FU for surgical downstaging, sphincter-saving surgery, and complete pathologic response,”
- No advantage for oxaliplatin in improving local response rates
Conclusion

• Neoadjuvant CRT is indicated for:
  – T3/T4 rectal Ca as defined by TRUS or MRI
  – Distal lesions not amenable to excision
  – Invasion or close proximity to mesorectum
  – T1/T2 node + disease

• Best neoadjuvant treatment has not been established
  – Oral capecitibine may be substituted for 5FU
  – No advantage to oxaliplatin
  – New agents ie irinotecan, cetuximab
Conclusion

• Surgical resection remains the standard of care
• Despite the lack of phase III data, patients undergoing neoadjuvant CRT should receive post surgical 5FU based adjuvant chemotherapy
• Technique matters in RT delivery. Newer techniques including IMRT and theoretically proton therapy may allow for dose escalation with the goal of sphincter preservation and decreased toxicity
Which of the following trials demonstrated an improvement in survival for patients receiving preoperative radiation therapy for rectal cancer?

- A. German Rectal Cancer Study Group
- B. Swedish Rectal Cancer
- C. Dutch CKVO
- D. NSABP R-01

Correct answer is B. RATIONALE: The only randomized trial that has shown a survival benefit for preoperative radiotherapy was the Swedish Trial. The German and Dutch trials did not show a survival benefit. NSABP R-01 evaluated postoperative treatment.
174. According to the German Rectal Cancer Study Group (Sauer) trial, what was the pathologic complete response rate to preoperative chemoradiation for patients who have rectal cancer?

- A. 08%
- B. 18%
- C. 28%
- D. 38%

Correct answer is A. RATIONALE: The German trial is one of the most important recent studies on rectal cancer. The pathologic complete response (CR) rate was reported. REFERENCE: Sauer, et al. New England Journal of Medicine (NEJM). 2004;351:1731-40.
Based on the German Rectal Cancer Study, which of the following outcomes in patients with rectal cancer was significantly improved by preoperative chemoradiation versus postoperative chemoradiation?

- A. Pelvic control
- B. Overall survival
- C. Distant metastatic rate
- D. Postoperative wound complications

Correct answer is A. RATIONALE: Preoperative chemoradiotherapy, as compared with postoperative chemoradiotherapy, improved local pelvic control in patients with rectal cancer. It also was associated with reduced toxicity, but it did not improve overall survival. REFERENCE: New England Journal of Medicine (NEJM). 2004;351:1731-40.
In a T4 rectal cancer which of the following lymph node groups need to be covered by a pelvic RT field?

A  External iliac 
B  Presacral 
C  Internal iliac 
D  All the above 

Answer  D