Rectal Cancer

To Radiate or not to radiate?

Dr. Corinne Doll
Radiation Oncologist
Tom Baker Cancer Centre
Calgary, Alberta

Q: Should rectal cancer RT/CRT decisions be based solely on stage?
Q: Can RT/CRT be omitted in some T3N0 cases?

Objectives

- Clinical cases
- Overview of rationale for RT/CRT
- Brief review of literature of results of neoadjuvant therapy based on tumour features and location
Clinical scenario: Presentation

- 47 yo male, Mr. T
  - Otherwise healthy
- Presents with 3 month history bowel problems
  - Decrease calibre stool $\rightarrow$ BRBPR
  - Tenesmus

Clinical scenario: Work-up

- Rectal mass at 5 cm from anal verge
- Sigmoidoscopy
  - Rectal mass extending from 5 cm above anal verge, to approx 10 cm
- Biopsy $\rightarrow$ adenocarcinoma
Patient case #2:
Mr. D

- 48 yo male
- Married, healthy
- Intermittent BRBPR x 4 months, FIT test positive

Work-up: MRI

7.5 cm
Patient case #2: Mr. D

- Examined
  - No palpable rectal mass
- Referred
  - Scope/biopsy
    - adenocarcinoma, upper rectum at 11 cm
- MRI – 3 cm tumour, upper rectum,
  - T3, N0, CRM not threatened (>5mm)

Same staging investigations

- CT abdomen and pelvis
- CT chest or CXR
- Complete colonic exam
- CEA
- MRI pelvis (high resolution)
  - T, N stage
  - CRM assessment

CCO Guidelines, Jan 2014
Management?

Goals of therapy

- Reduce local recurrence
- Maximize safety/minimize toxicity
  - QOL
- Prolong survival
- Preserve function (if possible)
Complete TME is key

- To achieve pelvic control, an R0 resection is essential
- Complete TME (grade 3), Quirke et al 2009
- <pelvic recurrences
  - Metastatic disease becoming a more predominant issue

Table 1: Histopathological grading of the quality and completeness of the mesorectum in a total mesorectal excision specimen

<table>
<thead>
<tr>
<th>Mesorectum</th>
<th>Defects</th>
<th>Coosing</th>
<th>CRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Intact, smooth</td>
<td>None</td>
<td>Smooth, regular</td>
</tr>
<tr>
<td>Nearly complete</td>
<td>Moderate bulk, but irregular</td>
<td>No visible muscularis propria</td>
<td>Moderate</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Little bulk and very irregular</td>
<td>Down to muscularis propria</td>
<td>Moderate--marked</td>
</tr>
</tbody>
</table>

Rectal cancer: adjuvant therapy selection – how to choose?

- Movement to preoperative therapy in the 1990s, many path variables no longer easily assessed
  - all patients with cT3 and/or N+ rectal cancer offered preoperative CRT
- The most common preoperative imaging techniques in the 1990s were transrectal ultrasound and CT
- This has led to both underuse and overuse of preoperative therapy
Neoadjuvant chemoradiotherapy

Pros

- “Downstage” disease
- Enhances sphincter sparing
- Less toxic than post-op
- Fewer anastomotic complications?
- Better outcomes?

Cons

- Pathologic staging not available
  - May be overtreating some?
- Delays primary surgery
- Toxicity
  - Radiation/CRT induced complications

The RT

- Dose/fractionation
  - Long: 45 Gy +/- 5.4 Gy boost/25-28#
  - Short: 5 Gy x 5#

- Pelvis
  - 4-field, occ IMRT
Pelvic RT

- To reduce risk of local relapse
  - By approximately 50%
- Not without risks
  - Loss of fertility
  - Radiation enteritis/cystitis
  - Delayed wound healing
  - Bone changes
  - (Second malignancies)
- Location of primary tumour can determine toxicity

Rectum anatomy – location

- Upper rectum
  - ≥10 cm -15 cm
- Mid rectum
  - ≥5-10 cm
- Low rectum
  - <5 cm
The Chemo

- Oral capecitabine
- Infusional 5-FU

Chemotherapy with RT

- To enhance local control, improve survival
- Not without risks
  - GI
    - NVD
    - mucositis
  - Hematologic
  - DPD deficiency - yikes!
T3 Rectal cancer – CRM matters

- Norwegian Rectal Cancer Group
  - 1,676 pts with T3 rectal cancer + TME, without pre-op RT
  - Multivariate analysis: CRM status and LN status assoc with local recurrence, distant mets, and OS
    - 5-year local rec 19.4% with CRM ≤ 1mm vs 11.1% with CRM >3mm
    - Recommend pre-op MRI and pre-op CRT for tumours with mrf ≤ 3mm

MRC CR07 – CRM status matters

<table>
<thead>
<tr>
<th></th>
<th>Preoperative RT (n = 674) (%)</th>
<th>Selective Postoperative CRT (n = 678) (%)</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year local recurrence</td>
<td>4.4</td>
<td>10.6</td>
<td>0.39 (0.27-0.58)</td>
</tr>
<tr>
<td>3-year disease-free survival</td>
<td>77.5</td>
<td>71.5</td>
<td>0.76 (0.62-0.94)</td>
</tr>
<tr>
<td>3-year overall survival</td>
<td>80.3</td>
<td>78.6</td>
<td>0.91 (0.73-1.13)</td>
</tr>
<tr>
<td>3-year LR by CRM Involved</td>
<td>13.8</td>
<td>20.7</td>
<td>0.64 (0.25-1.64)</td>
</tr>
<tr>
<td>Uninvolved</td>
<td>3.3</td>
<td>8.9</td>
<td>0.36 (0.23-0.57)</td>
</tr>
<tr>
<td>3-year LR by tumor position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10-15 cm</td>
<td>1.2</td>
<td>6.2</td>
<td>0.19 (0.07-0.47)</td>
</tr>
<tr>
<td>&gt;15-10 cm</td>
<td>5.0</td>
<td>9.8</td>
<td>0.50 (0.28-0.90)</td>
</tr>
<tr>
<td>&gt;20 cm</td>
<td>4.8</td>
<td>10.4</td>
<td>0.45 (0.23-0.88)</td>
</tr>
<tr>
<td>3-year LR by plane of dissectiona</td>
<td></td>
<td></td>
<td>P = .0039</td>
</tr>
<tr>
<td>Muscularis propria</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Intramesorectal</td>
<td>4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mesorectal</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

MRC CR07/NCTC-CTG-CO16 Study of Preoperative Short-Course Radiotherapy Compared with Selective Postoperative CRT

*Compared with preoperative RT as baseline.

HRs not provided.

LR worse with CRM involved; worse in selective post-ops
LR lowest for upper rectal cancers; worse in selective post-ops
MRI: imaging advanced

- High-resolution MRI
  - opportunity to identify relevant variables preoperatively
  - Allows potentially more selective use of preoperative therapies
- Better than ERUS for evaluation of distance from tumour to mesorectal fascia
  - Mercury study, 92.5% positive correlation with T-stage

MRI

- CRM assessment
  - has important prognostic value re: local/distant recurrence
- Nodal involvement inside and outside the mrf
- Depth of penetration thru muscularis propria
- Extramural venous invasion
- Can assist surgical decisions – plane of surgery
Usefulness of old TNM T3 subclassification?

<table>
<thead>
<tr>
<th>TNM</th>
<th>Stage</th>
<th>Extension to</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 N0 M0</td>
<td>0</td>
<td>Carcinoma in situ, intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td>T1 N0 M1</td>
<td>I</td>
<td>Submucosa</td>
</tr>
<tr>
<td>T2 N0 M0</td>
<td>I</td>
<td>Muscularis propia</td>
</tr>
<tr>
<td>T3 N0 M0</td>
<td>IIA</td>
<td>Subserosa/perirectal tissue</td>
</tr>
<tr>
<td></td>
<td>Substaging&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>&lt;1 mm</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>1–5 mm</td>
</tr>
<tr>
<td></td>
<td>T3c</td>
<td>5–15 mm</td>
</tr>
<tr>
<td></td>
<td>T3d</td>
<td>15+ mm</td>
</tr>
<tr>
<td>T4 N0 M0</td>
<td>IIIB</td>
<td>Perforation into visceral peritoneum (b) or invasion to other organs (a)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>T1–2 N1 M0</td>
<td>IIIA</td>
<td>1–3 regional nodes involved</td>
</tr>
<tr>
<td>T3–4 N1 M0</td>
<td>IIIB</td>
<td>1–3 regional nodes involved</td>
</tr>
<tr>
<td>T1–4 N2 M0</td>
<td>IIIC</td>
<td>24 regional nodes involved</td>
</tr>
<tr>
<td>T1–4 N1–2 M1</td>
<td>IV</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

NB: based on TNM 5 and pre-treatment MRI (and/or histopathologic classification). NOT validated/incorporated in TNM versions 6 and 7.

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**Mercury: Identification of good prognosis stage I/II/III rectal ca pts: surgery alone?**

| TABLE 3. Outcomes for MRI-predicted Good Prognosis Patients and Effect of Univariate and Multivariate Analysis Local Recurrence, 5-year Overall Survival and Disease-free Survival |
| MERCURY—MRI-predicted Good Prognosis Patients | Local Recurrence | 5-Year Overall Survival | 5-Year Disease-free Survival |
| Total patients (n = 122) | 3.3% | 68.2% (95% CI: 60.3%–76.0%); 84.7% (95% CI: 76.0%–92.4%) |
| Tumor height (cm) | 2.20 (0.4–24.3) | 0.02 | **1.15 (1.044–1.257)** | 0.004 |
| Type of operation (AP) | No events | 1.28 (0.040–3.317) | 0.79 | 1.00 (0.596–1.816) | 0.99 |
| Age (y) | 0.85 (0.4–2.0) | 0.80 | 1.00 (0.59–1.8) | 0.97 |
| Sex (male) | 0.85 (0.125–2.724) | 0.20 | 1.10 (0.585–2.146) | 0.88 |

Hypothesis: optimal MRI staging enables identification of a group of stage II and III patients with good prognosis rectal cancer and therefore the ability to avoid the need for pre-operative therapy.

Tumour height ≤ 5 cm vs > 5 cm was not associated with LR or DFS on multivariate analysis. Age and APR were associated with worse OS.

Low local recurrence rates in MRI-defined T3a/b, regardless of nodal status and location of tumour.

Taylor et al, Ann Surg 2011
Tumour location and benefit from RT or CRT

- Upper rectal tumours vs other
  - not bound by physical limitations of mid-lower tumours low in pelvis
  - Technically less challenging to get clear margins
  - Provided CRM not at risk, do these patients really benefit from neoadjuvant RT or CRT....?

Local recurrence in rectal cancer with neoadjuvant and adjuvant therapy

<table>
<thead>
<tr>
<th>Trial (year results published)</th>
<th>Design</th>
<th>N</th>
<th>Upper rectal ca subset, distance from anal verge (cm), %</th>
<th>Follow-up (months)</th>
<th>Treatment</th>
<th>Local recurrence, overall</th>
<th>Local recurrence, effect, upper rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish Rectal Cancer Trial (1997)</td>
<td>RCT</td>
<td>1168</td>
<td>&gt;11 (27)</td>
<td>60</td>
<td>Neo short course RT vs surgery alone</td>
<td>11% vs 27% (p=0.001)</td>
<td>NS p=0.30</td>
</tr>
<tr>
<td>Dutch TME Trial (2001)</td>
<td>RCT</td>
<td>1861</td>
<td>10.1-15 (30)</td>
<td>24</td>
<td>Neo short-course RT (standard TME) vs surgery alone</td>
<td>2.4% vs 8.2% (p=0.001) 10-year 5% vs 11% (p=0.001)</td>
<td>NS p=0.17</td>
</tr>
<tr>
<td>German Rectal Cancer Study Group (2004)</td>
<td>RCT</td>
<td>799</td>
<td>&gt;10 (15)</td>
<td>60</td>
<td>Neo long course RT + chemo vs x6 long course RT + chemo</td>
<td>6% vs 13% (p=0.006)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Adapted from Popek et al, Clin Colorec Ca 2012
Valentini et al, JCO 2011

- “Nomograms for Predicting Local Recurrence, Distant Metastases, and Overall Survival for Patients With Locally Advanced Rectal Cancer on the Basis of European Randomized Clinical Trials”
- Purpose: develop accurate models and nomograms to predict local recurrence, distant metastases, and survival for patients with locally advanced rectal cancer treated with long-course CRT followed by surgery

Valentini et al, Rectal cancer nomograms

- All data (N = 2,795) from five major European clinical trials for rectal cancer were pooled and used to perform an extensive survival analysis and to develop multivariate nomograms based on Cox regression
- The variables: sex, age, clinical tumor stage, tumor location, radiotherapy dose, concurrent and adjuvant chemotherapy, surgery procedure, and pTNM stage
Valentini et al, Rectal cancer nomograms

### Table 1. Characteristics of the Five European Randomized Trials (n = 3,488) for Training the Prediction Models

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Accrual</th>
<th>No. of Patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Organization for Research and Treatment of Cancer (EORTC 22921)</td>
<td>Preoperative RT</td>
<td>Tumour location (high best) predicts for distant control and overall survival</td>
<td>1993-2003</td>
<td>1,011</td>
<td>Bossert et al.</td>
</tr>
<tr>
<td></td>
<td>Preoperative CRT</td>
<td>No history of cancer</td>
<td>1993-2003</td>
<td>1,011</td>
<td>Bossert et al.</td>
</tr>
<tr>
<td></td>
<td>Preoperative CRT = postoperative CRT</td>
<td>Age &lt; 85 years</td>
<td>1993-2003</td>
<td>1,011</td>
<td>Bossert et al.</td>
</tr>
<tr>
<td></td>
<td>Preoperative CRT + postoperative CRT</td>
<td>Tumour within 15 cm of the anorectal verge</td>
<td>1993-2003</td>
<td>1,011</td>
<td>Bossert et al.</td>
</tr>
<tr>
<td>French (Fédération Francophone de Cancérologie Digestive, FCCD)</td>
<td>Preoperative RT</td>
<td>Age &lt; 75 years</td>
<td>1993-2003</td>
<td>733</td>
<td>Gérard et al.</td>
</tr>
<tr>
<td></td>
<td>Preoperative CRT</td>
<td>WHO performance index 0-1</td>
<td>1993-2003</td>
<td>733</td>
<td>Gérard et al.</td>
</tr>
<tr>
<td>German (Gastrointestinal Group of the German Cancer Society)</td>
<td>Preoperative CRT</td>
<td>Age &lt; 75 years</td>
<td>1996-2002</td>
<td>829*</td>
<td>Sauer et al.</td>
</tr>
<tr>
<td>Polish</td>
<td>Preoperative RT</td>
<td>Age &lt; 75 years</td>
<td>1999-2002</td>
<td>512*</td>
<td>Bulat et al.</td>
</tr>
<tr>
<td></td>
<td>(5 cycles of 5 Fu)</td>
<td>No history of cancer</td>
<td>1999-2002</td>
<td>512*</td>
<td>Bulat et al.</td>
</tr>
<tr>
<td></td>
<td>Preoperative CRT</td>
<td>Age &lt; 75 years</td>
<td>1995-2001</td>
<td>579</td>
<td>CSNSG et al.</td>
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<tr>
<td></td>
<td>(5 cycles of 5 Fu)</td>
<td>WHO performance index 0-2</td>
<td>1995-2001</td>
<td>579</td>
<td>CSNSG et al.</td>
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<tr>
<td>Italian</td>
<td>Preoperative CRT</td>
<td>Age &lt; 75 years</td>
<td>1995-2001</td>
<td>579</td>
<td>CSNSG et al.</td>
</tr>
<tr>
<td></td>
<td>Preoperative CRT + postoperative CRT</td>
<td>Tumour within 15 cm of the anorectal verge</td>
<td>1995-2001</td>
<td>579</td>
<td>CSNSG et al.</td>
</tr>
</tbody>
</table>

### Table 2. Event-Free Rates at 5 and 10 Years for the Complete Randomized Pooled Data Set, Stratified for Each Variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>5 Years</th>
<th>10 Years</th>
<th>P</th>
<th>5 Years</th>
<th>10 Years</th>
<th>P</th>
<th>5 Years</th>
<th>10 Years</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis</td>
<td>Sex</td>
<td>.466</td>
<td>.128</td>
<td>&lt; .001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1,961</td>
<td>87.1</td>
<td>87.1</td>
<td>&lt; .001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>943</td>
<td>87.0</td>
<td>87.0</td>
<td>&lt; .001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age, years</td>
<td>&lt; .40</td>
<td>370</td>
<td>94.6</td>
<td>93.9</td>
<td>0.04</td>
<td>60.0</td>
<td>64.5</td>
<td>71.9</td>
<td>63.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-60</td>
<td>746</td>
<td>86.9</td>
<td>85.9</td>
<td></td>
<td>70.1</td>
<td>66.6</td>
<td>72.9</td>
<td>65.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 60</td>
<td>1,131</td>
<td>86.7</td>
<td>85.4</td>
<td></td>
<td>67.3</td>
<td>64.5</td>
<td>67.0</td>
<td>54.6</td>
</tr>
<tr>
<td></td>
<td>Age ≤ 70</td>
<td>540</td>
<td>89.8</td>
<td>87.4</td>
<td></td>
<td>72.8</td>
<td>68.3</td>
<td>88.8</td>
<td>46.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumour location</td>
<td>High</td>
<td>369</td>
<td>90.8</td>
<td>88.6</td>
<td></td>
<td>75.4</td>
<td>72.5</td>
<td>74.3</td>
<td>55.6</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>953</td>
<td>86.0</td>
<td>84.8</td>
<td></td>
<td>64.3</td>
<td>60.1</td>
<td>64.7</td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Med</td>
<td>1,401</td>
<td>86.2</td>
<td>85.4</td>
<td></td>
<td>70.9</td>
<td>68.1</td>
<td>71.5</td>
<td>69.8</td>
<td></td>
</tr>
</tbody>
</table>

Tumour location (high best) predicts for distant control and overall survival
- however, not independent factor in multivariate analysis as final predictors in the nomogram
Who should have pre-op CRT?

- Advanced tumours at *any location*:
  - “The ugly”
- T3, mrf + (CRM breached or threatened)
- T4;
- Sacral +
- Node + (esp lateral LN+)
Who doesn’t need pre-op CRT?

- “The good”
- T1/T2
- Mrf clear (CRM not threatened)
- N0
- Very low local recurrence rates, and high cure rates after TME surgery

What about the in-betweeners?

- T3, esp upper rectum
- Mrf clear (CRM not threatened, predicted ≥ 2mm)
- N0
Are there clearly distinguishable intermediate T3 groups who do not need RT?

- Based on MRI and clinical risk factors
- T3a/b, <4 mm extension into muscularis propria, CRM not threatened (predicted ≥ 2mm), cN0, M0
- Overall – chance of R0 resection and good quality in mesorectal plane, no shrinkage required

Glynne-Jones, 2014
Schrag et al, JCO 2014

- MSKCC07-021
- Single institution phase II trial
- Thirty-two patients with clinical stages II to III rectal cancer
- All were candidates for low anterior resection with total mesorectal excision (TME)

Patient flow diagram.
For selected patients with clinical stages II to III rectal cancer, neoadjuvant chemotherapy and selective radiation does not seem to compromise outcomes.

Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT), a randomized phase III trial to validate this experience, is now open in the US cooperative group network...
A phase II/III trial of neoadjuvant FOLFOX with selective use of combination XRT in locally advanced rectal cancer

- N1048: NCCTG through Alliance for Clinical Trials in Oncology “NCIC CRC7” – PROSPECT TRIAL
- Can RT be safely omitted in some patients and still achieve RO and good local control?
- **Eligibility:** clinical T2N1, T3N0, T3N1 (stage IIA, IIB, or IIIB) adenocarcinoma of the rectum where standard treatment recommendation would be combined modality neoadjuvant chemoradiation followed by curative intent surgical resection
  - Tumour >5 cm to 12 cm from anal verge; Tumour not within 3 mm of mrf on pre-op MRI or ERUS/pelvic CT
- **Objectives:** Primary Outcomes: Pelvic R0 resection rate (phase II) DFS (Phase III) Time to local recurrence (TLR)
## Summary

- Paucity of data evaluating outcomes of locally advanced upper rectal cancer, or location-based analyses, treated with and without neoadjuvant RT
- Adequate CRM appears to be the major variable shown to correlate with local recurrence rates in
  - Accurate pre-treatment staging is key
- Some patients with T3N0 rectal cancer may have little/no benefit with RT
  - Esp if CRM is not threatened
  - However, CRM status likely more important than location

## Summary…

- Re-think pre-op CRT for “all T3/4 and/or N+”
- Await results of CRC7/Prospect Trial for more definitive results
  - …update coming up!
- Weigh risks/benefits of CRT
  - Multidisciplinary discussion
  - Patient and tumour factors