How Do I Selectively Use Radiation to Benefit the Rectal Cancer Patient?

PROF DR ALAA KANDIL
PROFESSOR & CHAIRMAN
DEPARTMENT OF CLINICAL ONCOLOGY
ALEXANDRIA SCHOOL OF MEDICINE
Basic Facts:

- 2nd & 3rd most common cancer in females & males.
- 1.4 million new case and 694000 deaths.
- Lowest rates in Africa & South Central Asia.
Principles:

**Surgery** is the cornerstone in management

However,
## Crude Local Recurrence Rates with Surgery Alone

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients</th>
<th>Local Recurrence Rate</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC (Mobile)²</td>
<td>235</td>
<td>34%</td>
<td>5 years (minimum)</td>
</tr>
<tr>
<td>NSABP R-01³</td>
<td>184</td>
<td>25%</td>
<td>5.3 years (mean)</td>
</tr>
<tr>
<td>MRC (Fixed)⁵</td>
<td>140</td>
<td>46%</td>
<td>5 years (minimum)</td>
</tr>
<tr>
<td>GITSG 7175⁷</td>
<td>58</td>
<td>24%</td>
<td>6.7 years (median)</td>
</tr>
<tr>
<td>Norwegian (Tveit et al)¹⁵</td>
<td>72</td>
<td>30%</td>
<td>4 years (minimum)</td>
</tr>
<tr>
<td>Stockholm II¹⁶</td>
<td>285</td>
<td>27%</td>
<td>8.8 years (median)</td>
</tr>
<tr>
<td>Stockholm I¹⁷</td>
<td>425</td>
<td>23%</td>
<td>4.4 years (median)</td>
</tr>
<tr>
<td>EORTC¹⁸</td>
<td>228</td>
<td>31%</td>
<td>6.3 years (median)</td>
</tr>
<tr>
<td>Swedish Rectal Cancer Trial¹⁹</td>
<td>585</td>
<td>27%</td>
<td>5 years (minimum)</td>
</tr>
</tbody>
</table>
### Studies Demonstrating a Local Recurrence Advantage with the Addition of Radiation to Surgery in Stage II/III Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Local Recurrence Rates</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Surgery + Radiation</td>
</tr>
<tr>
<td>MRC-mobile²</td>
<td>34%</td>
<td>21%</td>
</tr>
<tr>
<td>NSABP R-01³</td>
<td>25%</td>
<td>16%</td>
</tr>
<tr>
<td>NSABP R-02⁴</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>MRC-fixed⁵</td>
<td>46%</td>
<td>36%</td>
</tr>
<tr>
<td>CCCG metaanalysis⁵</td>
<td>22%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Early-stage disease, defined as T1-2N0, is usually treated with surgery alone.
Locally advanced disease, defined as stage II/III disease, requires initial clinical staging with pelvic MRI and endoscopic rectal ultrasound (ERUS) evaluation to determine the extent of disease and nodal involvement.
Staging provides critical information

1- The likelihood of achieving a complete resection (R0)
2- The likelihood of sparing the rectal sphincter and thereby maintaining fecal continence.
Cuthbert Dukes 1932: Nodes as a prognostic factor

- system predicted **prognosis** and became a gold standard: Three-year survival after surgery was 80%, 73% and 7% for A, B and C respectively.
Preoperative Magnetic Resonance Imaging Assessment of Circumferential Resection Margin Predicts Disease-Free Survival and Local Recurrence: 5-Year Follow-Up Results of the MERCURY Study

MURCERY Trial:

**CONCLUSION:**

- High resolution magnetic resonance imaging accurately predicts whether the surgical resection margins will be clear or affected by tumour.

- *This technique can be reproduced accurately in multiple centres to predict curative resection and warns the multidisciplinary team of potential failure of surgery, thus enabling selection of patients for preoperative treatment.*
Reduced Circumferential Resection Margin Involvement in Rectal Cancer Surgery: Results of the Dutch Surgical Colorectal Audit

Lieke Gietelink, MD; Michel W.J.M. Wouters, PhD; Pieter J. Tanis, PhD; Marion M. Deken, MD; Martijn G. ten Berge, MD; Rob A.E.M. Tollenaar, MD, PhD; J. Han van Krieken, MD, PhD; and Mirre E. de Noo, PhD; on behalf of the Dutch Surgical Colorectal Cancer Audit Group

Abstract

**Background:** The circumferential resection margin (CRM) is a significant prognostic factor for local recurrence, distant metastasis, and survival after rectal cancer surgery. Therefore, availability of this parameter is essential. Although the Dutch total mesorectal excision trial raised awareness about CRM in the late 1990s, quality assurance on pathologic reporting was not available until the Dutch Surgical Colorectal Audit (DSCA) started in 2009. The present study describes the rates of CRM reporting and involvement since the start of the DSCA and analyzes whether improvement of these parameters can be attributed to the audit. **Methods:** Data from the DSCA (2009–2013) were analyzed. Reporting of CRM and CRM involvement was plotted for successive years, and variations of these parameters were analyzed in a funnel plot. Predictors of CRM involvement were determined in univariable analysis and the independent influence of year of registration on CRM involvement was analyzed in multivariable analysis. **Results:** A total of 12,669 patients were included for analysis. The mean percentage of patients with a reported CRM increased from 52.7% to 94.2% (2009–2013) and interhospital variation decreased. The percentage of patients with CRM involvement decreased from 14.2% to 5.6%. In multivariable analysis, the year of DSCA registration remained a significant predictor of CRM involvement. **Conclusions:** After the introduction of the DSCA, a dramatic improvement in CRM reporting and a major decrease of CRM involvement after rectal cancer surgery have occurred. This study suggests that a national quality assurance program has been the driving force behind these achievements. (J Natl Compr Canc Netw 2015;13:1111–1119)
Radiotherapy and surgical resection are **standard components** of therapy for patients with stage II/III carcinoma of the rectum.
Total Mesorectal Excision (TME):

- Removal of peri-rectal tissues involving lateral & circumferential margins of mesorectal envelop.
Neoadjuvant Therapy
The objectives of neoadjuvant Therapy

1-optimization of disease-free survival (DFS) overall survival (OS)
2-minimizing toxicity from RT and chemotherapy
3-eliminating local recurrence.
Neoadjuvant Therapy: The German Study: A Shifting Concept

Design of the German Cancer Society’s CAO/ARO/AIO-94 Randomized Trial

- Adenocarcinoma of the rectum
- Ultrasound T3, T4 or node positive
- Distal edge of tumor within 16 cm of anocutaneous line
- Deemed resectable by LAR or APR with R0 resection likely
- No evidence of metastatic disease

**RANDOMIZE**

**pT1-2 N0 Patients**
- Observation
- Surgery

**Arm 1**
- Within 4 Weeks of Surgery
  - Radiation: 1.8 Gy/day to 50.4 Gy to pelvis using 3 or 4 fields followed by a boost of 5.4 Gy in 1.8 Gy fractions to the tumor bed
  - 5-FU: 1000 mg/m²/day continuous infusion for 120 hours on first and fifth week of radiation therapy
  - 5-FU: 500 mg/m²/day bolus for 5 consecutive days every 4 weeks x 4 cycles

**Arm 2**
- Radiation: 1.8 Gy/day to 50.4 Gy to pelvis using 3 or 4 fields
- 5-FU: 1000 mg/m²/day continuous infusion for 120 hours on first and fifth week of radiation therapy

**4-6 Weeks After Completion of Chemoradiation**
- Surgery

---

**A**

Cumulative incidence of local recurrence (%)

- Preoperative chemoradiotherapy: 13%
- Postoperative chemoradiotherapy: 6%

No. at Risk:
- Preoperative chemoradiotherapy: 397 368 312 250 190 133 97
- Postoperative chemoradiotherapy: 384 351 299 240 184 135 85

P = 0.006

**B**

Cumulative incidence of distant recurrence (%)

- Preoperative chemoradiotherapy: 38%
- Postoperative chemoradiotherapy: 46%

No. at Risk:
- Preoperative chemoradiotherapy: 397 330 382 226 171 116 86
- Postoperative chemoradiotherapy: 384 316 267 214 162 123 77

P = 0.84

---

Preoperative Multimodality Therapy Improves Disease-Free Survival in Patients With Carcinoma of the Rectum: NSABP R-03

Journal of Clinical Oncology 27, no. 31 (November 1 2009) 5124-5130.
Patients with clinical T3 or T4 or node-positive rectal cancer were randomly assigned to preoperative or postoperative chemoradiotherapy. Chemotherapy consisted of fluorouracil and leucovorin with 45 Gy in 25 fractions with a 5.40-Gy boost within the original margins of treatment. In the preoperative group, surgery was performed within 8 weeks after completion of radiotherapy. In the postoperative group, chemotherapy began after recovery from surgery but no later than 4 weeks after surgery. The primary end points were disease-free survival (DFS) and overall survival (OS).
T3/4 or N+

5-FU CRT + Surg vs ...

German Trial
n=823
Local Recurrences (10y) pre CRT vs post CRT
7% vs 10%
(p=.04)
Overall Survival (10y)
60% vs 60%
(n.s.)

French Trial
n=762
Local Recurrences (10y) pre CRT vs pre RT
8% vs 16%
(p<.05)
Overall Survival (10y)
68% vs 67%
(n.s.)

EORTC Trial
n=1011
Local Recurrences (10y) pre CRT vs pre RT
12% vs 22%
(p<.001)
Overall Survival (10y)
51% vs 49%
(n.s.)

Sauer et al., J Clin Oncol 2012
Gerard et al., J Clin Oncol 2006
Bosset et al., Lancet Oncol 2014
**T1-3 Nany**

5x5 Gy + Surg vs Surg alone

**Swedish Trial**

- n=1168
- Local Recurrences @ 13 years
  - 9% vs 26% (p<.001)

- Overall Survival (13y)
  - 38% vs 30% (p=.008)

  Fokesson et al., J Clin Oncol 2005

**Dutch Trial**

- n=1861
- Local Recurrences @ 10 years
  - 5% vs 11% (p<.001)

- Overall Survival (10y)
  - 48% vs 49% (n.s.)

  van Gijn et al., Lancet Oncol 2011

**British Trial**

- n=1350
- Local Recurrences @ 5 years
  - 5% vs 12% (p<.001)

- Overall Survival (5y)
  - 70% vs 68% (n.s.)

  Sebag-Montefiore et al., Lancet 2009
Where do we come from?

T1-3 Nany
5 x 5 Gy + immediate surgery

T3/4 or cN1-2
5-FU CRT + delayed surgery
<table>
<thead>
<tr>
<th></th>
<th>Polish Trial</th>
<th>5x5 Gy</th>
<th>CRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Tox (Grade 3-4, %)</td>
<td>3</td>
<td>18</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>pCR (%)</td>
<td>1</td>
<td>16</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRM + (%)</td>
<td>13</td>
<td>4</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Sphincter Preservation (%)</td>
<td>61</td>
<td>58</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Local Recurrences (4y, %)</td>
<td>11</td>
<td>16</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Overall Survival (4y, %)</td>
<td>67</td>
<td>66</td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Late Tox (Grade 3-4, %)</td>
<td>10</td>
<td>7</td>
<td></td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Med. F/U: 48 months

Bujko et al., Radiother Oncol 2004
Buiko et al., Br J Surg 2006
Pietrzak et al. Radiother Oncol 2007
<table>
<thead>
<tr>
<th></th>
<th>Trans-Tasman</th>
<th>5x5 Gy</th>
<th>CRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Tox (Grade 3-4; %)</td>
<td>2</td>
<td>28</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ypT0 (%)</td>
<td>1</td>
<td>15</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sphincter Preservation (%)</td>
<td>63</td>
<td>69</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Local Recurrences (3y, %)</strong>*</td>
<td><strong>7.5</strong></td>
<td><strong>4.4</strong></td>
<td></td>
<td><strong>0.24</strong></td>
</tr>
<tr>
<td>Overall Survival (5y, %)</td>
<td>74</td>
<td>70</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Late Tox (Grade 3-4, %)</td>
<td>5.8</td>
<td>8.2</td>
<td></td>
<td>0.53</td>
</tr>
</tbody>
</table>

*< 5 cm from AV: 6/48 vs 1/31 pts (p = 0.21)

Ngan SY et al., J Clin Oncol 2012
European Model of Stratification
based on MRI risk categorization
Where are we now?

NCCN Guidelines Rectal Cancer (Version 1/2016)

Preoperative Short-Course RT:

Option for T3 or N+; not recommended for T4

„Evaluation ... should be in a multidisciplinary setting, with a discussion of the need of downstaging and the possibility of long-term toxicity.“

*Practical Radiation Oncology, in press 2016*
Radiation + Chemotherapy are **MANDATORY** in Neoadjuvant Therapy:

<table>
<thead>
<tr>
<th>Trial/Preoperative Treatment</th>
<th>RT Total Dose</th>
<th>% pCR</th>
<th>% 5-year LR</th>
<th>% SPS</th>
<th>% 5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22921</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>45 Gy (1.8 Gy)</td>
<td>5.3</td>
<td>17.1</td>
<td>52.8</td>
<td>65</td>
</tr>
<tr>
<td>Chemo-RT*</td>
<td>45 Gy (1.8 Gy)</td>
<td>14</td>
<td>8.7</td>
<td>55.3</td>
<td>65</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>.0016</td>
<td>.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FFCD 9203</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>45 Gy (1.8 Gy)</td>
<td>3.7</td>
<td>16.5</td>
<td>51.7</td>
<td>66.6</td>
</tr>
<tr>
<td>Chemo-RT</td>
<td>45 Gy (1.8 Gy)</td>
<td>11.7</td>
<td>8</td>
<td>52.6</td>
<td>67.8</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.05</td>
<td>NR</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Polish Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>25 Gy (5 Gy)</td>
<td>1</td>
<td>NR</td>
<td>61</td>
<td>NR</td>
</tr>
<tr>
<td>Chemo-RT</td>
<td>50.4 Gy (1.8 Gy)</td>
<td>16</td>
<td>NR</td>
<td>58</td>
<td>NR</td>
</tr>
<tr>
<td>P value</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>GRECCAR 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT alone</td>
<td>63 Gy (1.8 Gy)</td>
<td>NR</td>
<td>NR</td>
<td>83</td>
<td>NR</td>
</tr>
<tr>
<td>Chemo-RT</td>
<td>45 Gy (1.8 Gy)</td>
<td>NR</td>
<td>NR</td>
<td>86</td>
<td>NR</td>
</tr>
<tr>
<td>P value</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Gastrointest Cancer Res 1:49-56. ©2007 by International Society of Gastrointestinal Oncology
Neoadjuvant Therapy:
The Use of Capecitabine:

R-04 SCHEMA
Adenocarcinoma of the Rectum Amenable to Surgical Resection Located < 12 cm From the Anal Verge

STRATIFICATION
- Gender
- Clinical Tumor Stage (Stage II [T3.4 No]; Stage III [T1.4 N1.2])**
- Intent for Type of Surgery (sphincter saving; non-sphincter saving)

RANDOMIZATION

Group 1
5-FU 225 mg/m²/day by continuous infusion for 5 days per week on days of planned RT + Pelvic RT**

Group 2
5-FU 225 mg/m²/day by continuous infusion for 5 days per week on days of planned RT + Oxaliplatin 50 mg/m² IV weekly x 5 concurrently with RT + Pelvic RT**

Group 3
Capecitabine 825 mg/m² po BID 5 days per week throughout RT + Pelvic RT**

Group 4
Capecitabine 825 mg/m² po BID 5 days per week throughout RT + Oxaliplatin 50 mg/m² IV weekly x 5 concurrently with RT + Pelvic RT**

Surgery***
Neoadjuvant Therapy: 
Adding Oxaliplatin:

**Table 1. Phase III trials adding oxaliplatin to preoperative fluorouracil-based chemoradiotherapy in stage II and III rectal cancer**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Preoperative treatment</th>
<th>Surgery</th>
<th>Postoperative treatment</th>
<th>First results/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD 12 [6]</td>
<td>RT 45 Gy + capecitabine</td>
<td>TME</td>
<td>Postoperative CT alone</td>
<td>pCR 14 versus 19% (n.s.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/4 toxicity increased</td>
</tr>
<tr>
<td>STAR-01 [7**]</td>
<td></td>
<td></td>
<td></td>
<td>3/4 toxicity increased</td>
</tr>
<tr>
<td>NSABP R-04 [8]</td>
<td></td>
<td></td>
<td></td>
<td>3/4 toxicity increased</td>
</tr>
<tr>
<td>CAO/ARO/AIO-04 [9]</td>
<td>RT 50.4 Gy + capecitabine + oxaliplatin</td>
<td>TME</td>
<td>5-FU versus</td>
<td>pCR 13 versus 17% (P = 0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4 toxicity not increased</td>
</tr>
<tr>
<td>PETACC 6</td>
<td>RT 50.4 Gy + 5-FU + oxaliplatin</td>
<td>TME</td>
<td>5-FU + oxaliplatin</td>
<td>Accrual completed</td>
</tr>
<tr>
<td></td>
<td>RT 45 Gy + capecitabine</td>
<td>TME</td>
<td>Capecitabine versus</td>
<td></td>
</tr>
</tbody>
</table>

- ++ Toxicity & -- Compliance.
- Did not improve:
  1. R₀ RR.
  2. pCR.
  3. Sphincter Preservation
Neoadjuvant Therapy: Adding EGFR/VEGF Inhibition:

No Significant Added Benefit over Chemotherapy & Higher G 3 & 4 Adverse Events.
Neoadjuvant Therapy:  
Indications:

1. T3 – T4 Lesions

2. Depth of Extramural Invasion:
   - T3 lesions (>5 mm) \(\rightarrow\) ++ LN involvement \(\rightarrow\) Higher Cancer Specific Mortality (54% Versus 85%).
   - Selection of high risk T3 for treatment.
   - Approved outside US.

3. T1 – 2 lesions with Positive Nodes.

4. Low situated lesions.

5. Invasion of mesorectal fascia.
Neoadjuvant Therapy: Treatment Outcome:

- **pCR**
  - ypT_0N_0

- **Complete Response**
  - 15 – 30%.
  - Small & Less Advanced Lesions
  - 10 – 12 Weeks.

- **cCR**
  - Involution to flat scar.
  - DRE & Endoscopy.
  - Imaging:
    - Endorectal US
    - PET-CT
    - MRI.

Neoadjuvant Therapy: Treatment Outcome in Relation to pCR: German Study:
Neoadjuvant Therapy:  
Impact of Pathological CR:

**Can we Avoid Surgery?**

British Journal of Surgery 2012; 99: 918–928
Predicting Pathologic CR: Questions & Debates:

- **DRE**: Under estimation.
- **CT and ERUS**: Residual disease & nodes ($y_pT0 \rightarrow LN\ +ve = 2 – 9\%$)
- **Timing of Assessment**: 6 or 12 or 6 & 12 months?
- **CEA**: Cutoff Point = 2.7 ng/ml at 4 or 8 weeks?
- **Diffusion Weighted MRI**: Higher sensitivity and specificity.
- **Full Thickness Excision Biopsy**.
- **PET CT Scan**: 6 and 12 months.
- **Molecular Signature**: 33 & 54 genes signatures.

Can we Avoid Surgery?

Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer


See accompanying editorial on page 4604; listen to the podcast by Dr Kachnic at www.jco.org/podcasts
Can Surgery be Avoided After Preoperative Chemoradiation for Rectal Cancer in the Era of Organ Preservation? Current Review of Literature

Sheema Chawla, MD,* Alan W. Katz, MD, MPH,† Stephen M. Rauh, MD,‡ and John R. T. Monson, MD, FRCS, FACS§

Abstract: Approximately 10% to 25% of patients have a pathologic complete response after neoadjuvant chemoradiation. There is a compelling argument for attempting to avoid surgery in carefully selected groups of patients. Although nerve-preserving surgical techniques are now standard, the rates of urinary and sexual dysfunction are significant. Also, although sphincter function and quality of life among patients undergoing an ultra-low anterior resection is acceptable, results are poorer than expected and may be disabling. Trials of omission of surgery for selected patients with complete response after preoperative chemoradiation, otherwise known as “Watch and Wait,” have shown favorable long-term results. We review the current literature on accepted standards of care and identify areas of controversy and important ongoing clinical studies aiming to resolve these issues.

Key Words: rectal cancer, organ preservation, neoadjuvant chemoradiation

(Am J Clin Oncol 2015;38:534–540)
<table>
<thead>
<tr>
<th>References (Institution)</th>
<th>Patients Treated</th>
<th>Follow-up (mo)</th>
<th>cCR (n [%])</th>
<th>Locoregional Failure</th>
<th>Disease-free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr-Gama et al&lt;sup&gt;16&lt;/sup&gt; (Brazil)</td>
<td>265</td>
<td>57</td>
<td>71 (26.8)</td>
<td>2/7 (2.8%)</td>
<td>83% (5 y)</td>
<td>88% (5 y)</td>
</tr>
<tr>
<td>Habr-Gama et al&lt;sup&gt;18&lt;/sup&gt; (Brazil)</td>
<td>361</td>
<td>60</td>
<td>99 (27.4)</td>
<td>5/99 (5%)</td>
<td>85% (5 y)</td>
<td>93% (5 y)</td>
</tr>
<tr>
<td>Habr-Gama et al&lt;sup&gt;19&lt;/sup&gt; (Brazil)</td>
<td>360</td>
<td>NS</td>
<td>99 (27.5)</td>
<td>6/9 (6%)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Habr-Gama et al&lt;sup&gt;20&lt;/sup&gt; (Brazil)</td>
<td>173</td>
<td>65</td>
<td>67 (39)</td>
<td>8/173 (4.6%)</td>
<td>72% (5 y)</td>
<td>96% (5 y)</td>
</tr>
<tr>
<td>Maas et al&lt;sup&gt;22&lt;/sup&gt; (The Netherlands)</td>
<td>192</td>
<td>35 ± 23 (Mean)</td>
<td>21 (11)</td>
<td>1/21 (5%)</td>
<td>89% (2 y)</td>
<td>100% (2 y)</td>
</tr>
<tr>
<td>Dalton et al&lt;sup&gt;23&lt;/sup&gt; (England)</td>
<td>49</td>
<td>26</td>
<td>12 (24)</td>
<td>Biopsy negative: all NED</td>
<td>88% (2 y)</td>
<td>96% (2 y)</td>
</tr>
<tr>
<td>Smith et al&lt;sup&gt;24&lt;/sup&gt; (MSKCC)</td>
<td>265</td>
<td>28</td>
<td>32 (12)</td>
<td>Biopsy positive: 2/6 distant failure</td>
<td>88% (2 y)</td>
<td>96% (2 y)</td>
</tr>
</tbody>
</table>

cCR indicates clinical complete response; CRT, chemoradiation; MSKCC, Memorial Sloan-Kettering Cancer Center; NED, no evidence of disease; NS, not stated.
There may be patients with a pCR after neoadjuvant therapy who *may be* candidates for a “watch-and-wait” approach—thus avoiding surgery—which is the subject of current clinical investigation.
Watch and wait approach to rectal cancer: A review

Marcos E Pozo, Sandy H Fang

Table 1  Watch and wait protocol surveillance schedule (adapted from Habr-Gama et al(101))

<table>
<thead>
<tr>
<th>Assessment of complete response</th>
<th>Initial assessment</th>
<th>First year</th>
<th>Second year</th>
<th>Third year and after</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE</td>
<td>10 wk</td>
<td>Every 1-2 mo</td>
<td>Every 3 mo</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>CEA</td>
<td>10 wk</td>
<td>Every 1-2 mo</td>
<td>Every 3 mo</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>Endoscopic assessment</td>
<td>10 wk</td>
<td>Every 1-2 mo</td>
<td>Every 3 mo</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>MRI</td>
<td>10 wk</td>
<td>If 1st assessment normal with cCR, then every 6 mo</td>
<td>Every 6 mo</td>
<td>Every 6 mo</td>
</tr>
</tbody>
</table>
Neoadjuvant Therapy: Problems with Current Practice:

- CRT 5.5 Weeks
- 6 wks
- TME 1 – 2 weeks
- 4-6 wks
- Adjuvant Cth

- 18 weeks
- Delayed.
- Reduced.
- Omitted

- CRT
- Neoadjuvant Chemoth.
- TME

- Total Neoadjuvant Therapy Paradigm.
  - Better down-staging.
  - Better pCR.
  - Higher R_0 Resection Rates.

Adopted from Deborah Schrag’s Presentation at 2015 ASCO Annual Meeting
The Art of Today:

- Radical resection remains the cornerstone in management regardless the achieved response.
- The identification of patients with pCR is challenging, however, patients should be informed about watch and wait strategy.
- Data showed higher incidence of relapse during the 1st year then becoming comparable to those following radical surgery → intensive follow up during the 1st year.
- Adoption of MDT should be encouraged.
- The need for more clinical trials is highly appreciated.
Conclusion

*Preoperative* chemoradiotherapy, compared with postoperative chemoradiotherapy, *significantly improved* DFS and showed a trend toward improved OS.