Emerging Paradigms in the Treatment of Localized Rectal Cancer

Christopher Willett, MD
Duke Cancer Institute

Case Presentation

• 65 year old man in good health developed rectal bleeding and narrowing of stools
• Rigid sigmoidoscopy
• Pelvic MRI
• Colonoscopy/Abdominal and Thoracic Imaging
Rigid sigmoidoscopy

- 7 cm from anal verge
- Bulky and nearly circumferential
- Bx- MD Adenoca

MRI Axial Image
MRI Sagittal Image

Audience Polling Results

Treatment Recommendations: Next Step?

1. Total Mesorectal Excision
2. FOLFOX Chemotherapy
3. US Style ChT/RT (50.4 Gy with capecitabine)
4. Above --> FOLFOX (6 cycles)
5. Short Course Radiation Therapy (25 Gy in 5 Fractions)
Pre- and Post- Radiation Therapy and Chemotherapy

Audience Polling Results

Treatment Recommendations: Next Step?

1. Total Mesorectal Excision
2. Transanal Excision
3. Careful observation with Surgery reserved for Salvage
4. Brachytherapy application

56% 17% 22% 4%
TOTAL MESORECTAL EXCISION

Distal resection margin after TME is about 2cm above dentate line.

Pathology of Resected Specimen

ypT0N1 (1/15 sampled mesorectal LN)
Paradigms in Treatment of Resectable Rectal Cancer

- Short Course vs. Long Course
- Neoadjuvant ChT ± RT
- Cure and Organ Preservation without Surgery
Rectal Cancer: Short-Course (SC) vs Long-Course (LC) Radiation

**European SC: 25 Gy/5Fx**
- Immediate Surgery
- No Δ in Preop Stage
- Lower Cost
- Excellent Compliance
- ? Less Acute Toxicity

**U.S. LC: 50.4 Gy + ChT**
- Delayed Surgery
- Improved Path Resp Rates
- More Tumor Regression
- Sphincter Preservation
- ? Improved Late Effects
- ? Watch and Wait

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**Phase III Trials: SC vs LC**

2. TROG (2012)
4. Polish II (2016)
Polish Preoperative Phase III Trial

T3,4

50.4 Gy/5-FU/LV → Surg (median 78 d)
5 Gy x 5 → Surg (median 8 d)

- 316 Pts with T3-4 Resectable Distal Cancers
- No Involvement of the Sphincter
- Total mesorectal excision (TME) Only for Distal Tumors
- No Central QA

Bujko et al: Radiother Oncol 2004

Polish Trial: Results

<table>
<thead>
<tr>
<th>Preoperative Schedule</th>
<th>Path CR (%)</th>
<th>Sphincter Preservation Rate (%)</th>
<th>LF (%)</th>
<th>4 yr OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Gy (155 Pts)</td>
<td>1</td>
<td>61</td>
<td>9</td>
<td>67.2</td>
</tr>
<tr>
<td>50.4 Gy + 5-FU (157 Pts)</td>
<td>16*</td>
<td>58</td>
<td>14.2</td>
<td>66.2</td>
</tr>
</tbody>
</table>

Bujko et al: BJS 2006
Polish Trial: Results

<table>
<thead>
<tr>
<th>Preoperative Schedule</th>
<th>Acute G3-4 Toxicity (%)</th>
<th>Compliance (%)</th>
<th>Late Toxicity (%)</th>
<th>Severe Late Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Gy (155 Pts)</td>
<td>3.2*</td>
<td>97.9*</td>
<td>28.3</td>
<td>10.1</td>
</tr>
<tr>
<td>50.4 Gy + 5-FU (157 Pts)</td>
<td>18.2</td>
<td>69.2</td>
<td>27</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Bujko et al: BJS 2006

TROG Trial

<table>
<thead>
<tr>
<th>Pelvic RT</th>
<th>Resection</th>
<th>Adjuvant chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>25 Gy/5 fx/ 5d</td>
<td>within 1 wk</td>
</tr>
<tr>
<td>LC</td>
<td>50.4 Gy/28 fx/ 5w3d + 5FU C 225 mg/m²/day 7d/wk</td>
<td>in 4 - 6 wk</td>
</tr>
</tbody>
</table>

Main eligibility criteria:
- localized adenocarcinoma of the rectum
- ultrasound or MRI staged clinical T3NanyM0

Ngan et al: J Clin Oncol 2012
Compliance

- Short Course (25 Gy/5 Fxs): 100%
- Long Course (50.4 Gy/28 Fxs): 93%
- Concurrent 5-FU: 84% (within 10% of prescribed dose)
- Adjuvant ChT: 85% Short Course and 86% Long Course

Ngan et al: J Clin Oncol 2012

Three-year LR rates between SC and LC were not statistically significantly different

No differences in rates of distant recurrence, relapse-free survival, overall survival

Comparison of QOL has become a clinically important issue in assessing their relative merits
Stockholm III Rectal Cancer Trial

25 Gy (1 week – immediate surgery [IS])

25 Gy (4-8 weeks – delayed surgery [DS])

50 Gy (4-8 weeks - delayed surgery [DS])

303 Pts. “Resectable”

Pettersson et al: British J Surgery 2010

Stockholm III: Preliminary Results

<table>
<thead>
<tr>
<th></th>
<th>p CR (%)</th>
<th>APR (%)</th>
<th>Severe Acute Toxicity (%)</th>
<th>Anastomotic Leak (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Gy (118 pts) IS</td>
<td>0.8</td>
<td>30</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>25 Gy (120 pts) DS</td>
<td>12.5</td>
<td>33.3</td>
<td>4.2</td>
<td>11</td>
</tr>
<tr>
<td>50 Gy (65 pts) DS</td>
<td>5.0</td>
<td>20</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Pettersson et al: British J Surgery 2010
Stockholm III: Interim Results

<table>
<thead>
<tr>
<th></th>
<th># Pts.</th>
<th>pCR (%)</th>
<th>Dworak G 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 Gy IS</td>
<td>234</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>25 Gy DS</td>
<td>228</td>
<td>11.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Pettersson et al: British J Surgery 2015

Swedish Rectal Cancer Trial: Late Toxicity

Birgisson et al: British J Surgery 2008
Bowel Function of TME Trial Patients 14 Years Post-Treatment

<table>
<thead>
<tr>
<th>Low Anterior Resection Syndrome</th>
<th>Preoperative RT + TME (n=118)</th>
<th>TME (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>55.9</td>
<td>35.5</td>
</tr>
<tr>
<td>Minor</td>
<td>19.5</td>
<td>25.0</td>
</tr>
<tr>
<td>None</td>
<td>24.6</td>
<td>39.5</td>
</tr>
</tbody>
</table>

Chen et al: Clinical Colorectal Cancer 2015

Long-term Quality of Life Analysis

- **Primary objective**
  - To compare long-term quality of life (QOL) between short course and long course preoperative radiotherapy for rectal cancer

- **Eligibility criteria**
  - Participants of the TROG 01.04 trial
  - Completed a baseline QOL
  - Completed at least one other QOL at or after 12 months

Endpoints

- Changes from baseline of nine QOL scales were nominated, prior to data analysis, as the major endpoints
  - global health status/QoL
  - sexual functioning
  - sexual enjoyment
  - micturition
  - gastrointestinal tract
  - male sexual problems
  - constipation
  - diarrhea
  - defecation problems

- An area-under-curve (AUC) statistic (from 12 to 60 months) was used to assess the major endpoints


Results

Global Health Status/QOL

Gastro-intestinal Tract

AUC analysis indicated there was little difference in global health status between arms. Mean diff = -2.5
P = 0.33 [95% CI: -7.48 to 2.48]

Difference in mean QOL = 3.3
P = 0.13 [95% CI: -0.96 to 7.48]

**Results**

**Sexual functioning**

Sexual functioning by time by arm (from LMM)

Difference in mean QOL = -0.3  
P = 0.93 [95% CI: -6.26 to 5.70]

**Sexual enjoyment**

Sexual enjoyment by time by arm (from LMM)

Difference in mean QOL = -2.8  
P = 0.67 [95% CI: -15.54 to 9.98]


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**Male sexual problems**

Male sexual problems by time by arm (from LMM)

Difference in mean QOL = -2.1  
P = 0.73 [95% CI: -13.83 to 9.72]


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Female sexual problems was not analysed due to lack in response to this question (n=11)
Results

**Diarrhea**

Difference in mean QOL = 6.2

P = 0.17 [95% CI: -2.59 to 15.03]

**Constipation**

Difference in mean QOL = 1.7

P = 0.65 [95% CI: -5.66 to 9.10]


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Results

**Micturition**

Difference in mean QOL = -1.4

P = 0.52 [95% CI: -5.86 to 2.97]

**Defecation problems**

Difference in mean QOL = 3.0

P = 0.34 [95% CI: -3.16 to 9.09]

Conclusion

Assuming >10 points difference in QOL is clinically important, during the period from 12-60 months following registration for the trial, in patients alive and without having relapsed, results suggest that:

- There is no important difference between SC and LC for global health status, constipation, sexual functioning, micturition, GIT, and defecation;

- Possible important differences have not been ruled out in:
  - diarrhoea [95% CI: -2.59 to 15.03]
  - sexual enjoyment [95%: -15.54 to 9.98] and
  - male sexual problems [95% CI: -13.83 to 9.72].

Resectable Rectal Cancer: SC vs. LC

- Similar rates of local control, distant metastases, and overall survival
- Similar rates of late (intermediate time) toxicity
- Similar impact on QOL (intermediate time)
- Watch late effects with SC (> 5years!) – Swedish and TME trials (no comparable data – Long Course)
- Time after treatment is important for tumor regression.
Survival data from randomised clinical trials: Adjuvant chemotherapy vs. Observation

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Adjuvant chemotherapy arm</th>
<th>Observation arm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22921</td>
<td>10-year OS</td>
<td>( n = 506 ) 51.8%</td>
<td>( n = 505 ) 48.4%</td>
<td>0.32</td>
</tr>
<tr>
<td>I-CNR-RT Italian trial</td>
<td>5-year OS (in resected patients only)</td>
<td>( n = 296 ) 69%</td>
<td>( n = 294 ) 70%</td>
<td>0.77</td>
</tr>
<tr>
<td>PROCTOR SCRIPT</td>
<td>5-year OS</td>
<td>( n = 216 ) 79.2%</td>
<td>( n = 221 ) 80.4%</td>
<td>0.77</td>
</tr>
<tr>
<td>CHRONICLE</td>
<td>3-year DFS</td>
<td>( n = 54 ) 72.5%</td>
<td>( n = 59 ) 71.3%</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Boustani et al: Clinical Onc 2016
Survival data from randomised clinical trials: 5-fluorouracil (5-FU)- or oxaliplatin-based adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>5-FU-based adjuvant chemotherapy</th>
<th>Oxaliplatin-based adjuvant chemotherapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETACC 6 (phase III)</td>
<td>3-year DFS</td>
<td>$n = 547$ 74.5%</td>
<td>$n = 547$ 73.9%</td>
<td>0.78</td>
</tr>
<tr>
<td>CAO/ARO/AIO-04 (phase III)</td>
<td>3-year DFS</td>
<td>$n = 637$ 71.2%</td>
<td>$n = 628$ 75.9%</td>
<td>0.038</td>
</tr>
<tr>
<td>ADORE (phase II)</td>
<td>3-year DFS</td>
<td>$n = 149$ 62.9%</td>
<td>$n = 146$ 71.6%</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Boustani et al: Clinical Onc 2016

European/Scandinavian Treatment Algorithm of SC and LC

Low Risk
- T1-3(< 5mm): Mid/Upper Rectum
- T1-3(Superficial): Distal Rectum
- N0
- Extramural Vascular Invasion: No
- MRF: Clear
- Risk of LR <10%

Intermediate Risk
- T3(>5mm)
- T4(Posterior vaginal wall)
- Or
- N1/2
- Extramural Vascular Invasion: Yes
- MRF: clear (>1 mm)
- Risk of LR 10-20%

High Risk
- T4
- N0/1/2
- MRF: involved
- Risk of LR > 20%

Preoperative
- SC EBRT
- TME
- Adjuvant ChT

Preoperative
- EBRT/ChT
- TME
- Adjuvant ChT

Smith and Garcia-Aguilar: J Clin Oncol 2015
Neoadjuvant Chemotherapy for Resectable Rectal Cancer

• 3 Small single arm phase II trials
• 1 Retrospective report (abstract only)
• 1 Pilot study

MSKCC cT3N0

• Pooled analysis 6 high volume centers
• 188 cT3N0 by EUS/MRI
• CRT-> Surgery

• Results
  – 22% pathologically positive mesorectal LN
  – Many patients understaged by preoperative imaging

Guillem et al: J Clin Oncol 2008
Japanese Single Arm Trial

- 2001-2004, RT availability limited in Japan + ‘toxicity unfavorable’
- 26 patients, T3-4 N0-2, mid/lower rectum
- IFL chemo x 2 cycles

-R0: 100%
-downstaging in 58%
-pCR: 1 patient
-5y DFS: 74%
-5y OS: 84%

Ishii et al: Eur J Surg Oncol 2010

Rectal Cancer: Neoadjuvant Chemotherapy

GEMCAD 0801 Trial

- 46 pts with CS II-III Rectal Ca
- 4 cycles capecitabine + oxaliplatin + bevacizumab → Surgery
- 44 Pts Surgery: All R0 Resection, 20% pCR
- AnastomoticLeaks: 13%; G5 Toxicity: 3 pts.

Fernandez-Martos, The Oncologist 2014
Japanese Phase II Trial

- CAPOX plus bev prior to TME
- 32 patients, poor-risk per MRI
  - R0: 90%
  - downstaging in 37%
  - pCR: 13%
  - post-op complications: 43% (attributed to bev? anastomotic leakage, perforation)

Uehara et al: Jpn J Clin Oncol 2013

MSKCC Retrospective

- Pts receiving chemo alone because of suspected metastatic disease, contraindications/refusal of XRT
- 20 patients, 6 rectal
- FOLFOX +/- bev
  - overall pCR 35%

Rectal patients n=6:
- pCR: 3 patients
- tumor regression: 5 patients

Cercek et al: JCO 2010; 28(15S) abst 3511
MSKCC Pilot Study

- Clinical stage II/III rectal
- non-T4 tumors
  - Sphincter-sparing candidates (LAR with TME)
  - Nonthreatened CRM by MRI
- FOLFOX+ bev x 6
- 32 patients (2 had preop XRT)
  - R0: 100%
  - downstaging in 100%
  - pCR: 25%
  - 4y local recurrence: 0%
  - 4y DFS: 84%
  - 4y OS: 91%

Schrag et al: J Clin Oncol 2014

PROSPECT

Preoperative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

An Alliance Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

clinicaltrials.gov NCT01515787
Inclusion Criteria

- Biopsy proven rectal adenocarcinoma
- Tumor tissue located at **5-12 cm** from the anal verge
- Candidate for sphincter sparing surgery
- ECOG Performance Status 0, 1 or 2
- Surgeon is TME credentialed
- Baseline Clinical staging: T2N1, T3N0, T3N1
  - Physical exam by primary surgeon
  - Proctoscopy
  - MRI or ERUS (MRI preferred)
  - CT scan of Chest/Abdomen/Pelvis

clinicaltrials.gov NCT01515787

Study Schema

“Standard Arm”

FOLFOX x 6

TME

FOLFOX x 8

“Selective Arm”

FOLFOX x 2

TME

FOLFOX x 6

Response >20%

RANDOMIZE 1:1

Response <20%

clinicaltrials.gov NCT01515787
Caution with Neoadjuvant Chemotherapy

- Inclusion relies on imperfect preoperative imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Chemoradiotherapy (N=415)</th>
<th>Postoperative Chemoradiotherapy (N=384)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathological finding (%)</td>
<td>Complete response</td>
<td>8</td>
</tr>
<tr>
<td>TNM stage</td>
<td>I</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>6</td>
</tr>
</tbody>
</table>

Sauer et al: NEJM 2004

Chemotoxicity

Second cancer
- 5.5% FOLFOX4 group
- 6.1% LV5FU2 group

Andre et al: J Clin Oncol 2009
Intensification of Neoadjuvant Treatment

- Chemotherapy → LC → Surgery
- SC or LC → Chemotherapy → Surgery

Royal Marsden: Neoadjuvant Chemotherapy + RT/Chemotherapy

105 pts: “poor risk” rectal ca:
- Capecitabine + oxaliplatin (12 wks)
- 45 Gy with capecitabine
- TME (6 wks)
- Capecitabine (12 wks)

Chau et al: Lancet Oncol 2010
**Royal Marsden: Neoadjuvant Chemotherapy + RT/Chemotherapy**

- ChT not completed: 12/105 (11%)
- 5 Deaths During Neoadjuvant ChT
- MR scan: 74% RR after ChT
- TME: 95/105 (90%)
- pCR: 21/105 (20%)

Chau et al: Lancet Oncol 2010

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**GCR-3: Ph II Preop Trial**

- **High Risk Rectal Ca** 108 pts
  - CapOx/RT → TME
  - → 4 Cyc CapOx
  - 71%: Adjuvant ChT
  - 4 Cyc CapOx → RT/ChT → TME
  - 96%: Neoadjuvant ChT


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### Spanish GCR-3 Trial Results

<table>
<thead>
<tr>
<th>Neoadjuvant Tx</th>
<th>R0 Rate (%)</th>
<th>pCR Rate (%)</th>
<th>5 yr LF / DM (%)</th>
<th>5 yr OS/ DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChT/RT TME 4 Cycles CapOx (n=52)</td>
<td>87</td>
<td>13</td>
<td>2 / 21</td>
<td>78 / 64</td>
</tr>
<tr>
<td>4 Cycles CapOx Ch/RT TME (n=56)</td>
<td>86</td>
<td>14</td>
<td>5 / 23</td>
<td>75 / 62</td>
</tr>
</tbody>
</table>


### Polish II: Ph III Trial

**Fixed cT3or cT4**

515 pts

5 Gy x 5 mFOLFOX x 3 Surgery

50 Gy + FU/Leu ± Oxal Surgery

### Polish II Trial Results

<table>
<thead>
<tr>
<th>Neoadjuvant Tx</th>
<th>R0 Rate (%)</th>
<th>pCR Rate (%)</th>
<th>LF / DM (%)</th>
<th>3 yr OS/ DFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Gy x 5 FOLFOX4 x 3 Surgery n=264</td>
<td>77</td>
<td>16</td>
<td>22 / 30</td>
<td>73* / 53</td>
</tr>
<tr>
<td>50.4 Gy+FU/Leu ± Oxal Surgery n=215</td>
<td>71</td>
<td>12</td>
<td>21 / 27</td>
<td>65* / 52</td>
</tr>
</tbody>
</table>


### Polish II Trial Results

<table>
<thead>
<tr>
<th>Neoadjuvant Tx</th>
<th>G3/4 Toxicity Rate (%)</th>
<th>Toxic Deaths (%)</th>
<th>Postop Toxicity (%)</th>
<th>Late Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Gy x 5 FOLFOX 4 x 3 Surgery n=264</td>
<td>23</td>
<td>16</td>
<td>29</td>
<td>20</td>
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<td>50.4 Gy+FU/Leu ± Oxal Surgery n=215</td>
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<td>12</td>
<td>25</td>
<td>22</td>
</tr>
</tbody>
</table>

Rapido Trial
Locally Advanced Rectal Cancer

Randomisation

Experimental arm B:
5x5 Gy short course RT
6 cycles CAPOX
TME surgery

Standard arm A:
Chemoradiotherapy
TME surgery
8 cycles CAPOX

Nilsson et al: BMC Cancer 2013

Adding mFOLFOX after Neoadjuvant Chemoradiation: Multi-site Phase II Study

292 Patients with Rectal Cancer:
• Clinical Stage II (T3-4, N0) or III (any T, N1-2)
• Cancers within 12 cm of the anal verge
• Local Staging: EUS or MRI
• Accrued Patients from 2004-2012

Garcia-Aguilar et al: Lancet Oncology 2015
### Trial Protocol

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous infusion + radiotherapy</td>
<td>Rest</td>
<td>mFOLFOX6 (two cycles)</td>
<td>Rest</td>
</tr>
<tr>
<td>Rest</td>
<td>Total mesorectal excision</td>
<td>Total mesorectal excision</td>
<td>Total mesorectal excision</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from start of chemoradiation to surgery (weeks)</td>
<td>14·2 (4·3)</td>
<td>17·1 (2·9)</td>
<td>21·0 (2·7)</td>
<td>25·2 (4·0)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0·0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| Time from end of chemoradiation to surgery (weeks) | 8·5 (4·2) | 11·1 (2·9) | 15·4 (2·6) | 19·3 (4·2) |
| p value | 0·0001 |

### Surgical Results

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=60)</th>
<th>Group 2 (n=67)</th>
<th>Group 3 (n=67)</th>
<th>Group 4 (n=65)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from start of chemoradiation to surgery (weeks)</td>
<td>14·2 (4·3)</td>
<td>17·1 (2·9)</td>
<td>21·0 (2·7)</td>
<td>25·2 (4·0)</td>
<td>0·0001</td>
</tr>
<tr>
<td>Time from end of chemoradiation to surgery (weeks)</td>
<td>8·5 (4·2)</td>
<td>11·1 (2·9)</td>
<td>15·4 (2·6)</td>
<td>19·3 (4·2)</td>
<td>0·0001</td>
</tr>
<tr>
<td>Sphincter-saving surgery</td>
<td>46 (77%)</td>
<td>50 (75%)</td>
<td>50 (75%)</td>
<td>44 (68%)</td>
<td>0·68</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>38/46 (83%)</td>
<td>43/50 (86%)</td>
<td>47/50 (94%)</td>
<td>38/43 (88%)</td>
<td>0·33</td>
</tr>
<tr>
<td>Resection with negative margins</td>
<td>59 (98%)</td>
<td>67 (100%)</td>
<td>64 (96%)</td>
<td>64 (100%)</td>
<td>0·089</td>
</tr>
<tr>
<td>Number of nodes examined</td>
<td>12 (2–31)</td>
<td>14 (2–30)</td>
<td>13 (2–30)</td>
<td>11 (1–47)</td>
<td>0·20</td>
</tr>
<tr>
<td>Pelvic fibrosis</td>
<td>2·4 (1·7)</td>
<td>3·9 (2·6)</td>
<td>4·4 (2·4)</td>
<td>3·9 (2·4)</td>
<td>0·0001</td>
</tr>
<tr>
<td>Technical difficulty</td>
<td>4·6 (2·7)</td>
<td>4·9 (2·8)</td>
<td>5·1 (2·5)</td>
<td>4·8 (2·4)</td>
<td>0·80</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>200 (50–1200)</td>
<td>225 (25–1500)</td>
<td>200 (50–1000)</td>
<td>150 (0–1000)</td>
<td>0·62</td>
</tr>
</tbody>
</table>

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### Surgical Complications

<table>
<thead>
<tr>
<th>Grading</th>
<th>Group 1 (n=60)</th>
<th>Group 2 (n=67)</th>
<th>Group 3 (n=67)</th>
<th>Group 4 (n=65)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Pts.</td>
<td># of events</td>
<td># of Patients</td>
<td># of events</td>
<td># of patients</td>
</tr>
<tr>
<td>None</td>
<td>36 (60%)</td>
<td>NA</td>
<td>41 (61%)</td>
<td>NA</td>
<td>44 (66%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>11 (18%)</td>
<td>16</td>
<td>12 (18%)</td>
<td>18</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (7%)</td>
<td>6</td>
<td>10 (15%)</td>
<td>12</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Grade 3a</td>
<td>2 (3%)</td>
<td>2</td>
<td>1 (1%)</td>
<td>2</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Grade 3b</td>
<td>5 (8%)</td>
<td>6</td>
<td>2 (3%)</td>
<td>2</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Grade 4a</td>
<td>2 (3%)</td>
<td>2</td>
<td>1 (1%)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Garcia-Aguilar et al: Lancet Oncology 2015

### Pathological Tumor Response

<table>
<thead>
<tr>
<th>Grading</th>
<th>Group 1 (n=60)</th>
<th>Group 2 (n=67)</th>
<th>Group 3 (n=67)</th>
<th>Group 4 (n=65)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path complete response</td>
<td>11 (18%)</td>
<td>17 (25%)</td>
<td>20 (30%)</td>
<td>25 (38%)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Partial response</td>
<td>44 (73%)</td>
<td>50 (75%)</td>
<td>46 (69%)</td>
<td>39 (60%)</td>
<td>..</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (8%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>..</td>
</tr>
</tbody>
</table>

Garcia-Aguilar et al: Lancet Oncology 2015
### Conclusions

- Increasing cycles of mFOLFOX6 after ChT/EBRT and before Surgery: ↑ in Path CR rates
- ↑ Response: without tumor progression, ↑ technical difficulties or surgical complications.
- Support efforts to shift systemic treatments into neoadjuvant setting
- Delivering Chemotherapy after EBRT/ChT: More effective at increasing pCR rates than before
- ? Higher proportion of patients for less invasive surgery or watch and wait approaches
Rectal Cancer: Organ Preservation

Papillon: Endocavitary Irradiation of “Early” Rectal Cancer (1951)

Papillon: Technique/Results

- 1951-1967: 123 Pts with minimum 5 yr follow-up
- 3-5 applications (2500-4000 R) with 50 kV unit over 4-6 weeks
- 84 Pts (68%) Disease free (>5 yrs)
- 14 pts (11%) Local Failure: 5 salvaged with surgery
- 9 pts (7%) Distant Metastases

Non-Operative Tx

- PMH: 229 pts
- RT alone (unresectable, medically unfit, refused surgery)
- Dose 40 Gy/10 fx to 60 Gy/30 fx
- mobile tumors: cCR 50%
- cCR mobile crude LF: 38%

Brierley et al: IJROBP 1995

Non-Operative Treatment of Rectal Cancer after RT/Chemotherapy (50.4 Gy/5-FU/LV)

• 360 pts with low rectal cancer
  – 99 pts (28%) with clinical complete response
  • OBSERVED
    – Mean follow-up 60 months
      » 7 systemic recurrences
      » 5 local recurrences
      » 1 systemic and local recurrence
      » 5 yr OS: 93%
      » 5 yr DFS: 85%

Habr-Gama et al: J of GI Surgery 2006
T3 Rectal Cancer

• 183 pts with distal rectal cancer (cT2-4, N 0/+)
  – 90 pts (49%) with clinical complete response at 8 weeks
    • Watch and Wait
      – Median follow-up 60 months
        » 5 yr Local RFS: 69% (28 LF)
        » Salvage therapy: 26/28 pts (4 LF)
        » 5 yr Local RFS: 94% (including salvage)
        » 5 yr Cancer Specific OS: 91%
        » 5 yr DFS: 68%

**MSKCC: Non-Operative Management (NOM)**

- 447 Pts (Stage I-III Rectal Ca): Neoadjuvant Tx (2006-2014)
- 73 Pts. Identified: cCR and NOM
- 72/369 Pts (20%): TME with pCR

Smith et al: ASCO GI Symposium 2015 (abstract 509)

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**MSKCC: Non-Operative Management Results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pt #</th>
<th>Local Regrowth</th>
<th>LR after resection</th>
<th>DM</th>
<th>DSS</th>
<th>OS</th>
<th>Rectal preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOM</td>
<td>73</td>
<td>19</td>
<td>0</td>
<td>9</td>
<td>69(91%)</td>
<td>67(71%)</td>
<td>56(72%)</td>
</tr>
<tr>
<td>TME/pCR</td>
<td>72</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>70(96%)</td>
<td>68(95%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Smith et al: ASCO GI Symposium 2015 (abstract 509)
MSKCC Non-Operative Management: Conclusions

- Highly selected pts (cCR) to Neoadjuvant Tx:
- NOM with surgical salvage of local tumor regrowth achieved local control in all pts.
- 4 yr oncologic outcome for NOM pts was comparable to pts with pCR after resection
- NOM does not compromise oncologic outcome and rectal preservation is achieved in a majority of patients.

Smith et al: ASCO GI Symposium 2015 (abstract 509)

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Clinical Complete Response

- **DRE**
  - flat mucosa
  - smooth induration / scar
  - no mass / nodule

- **Proctoscopy**
  - normal, flat mucosa
  - +/- pale scar
  - +/- telangiectasias
  - no ulceration
  - no luminal narrowing/stenosis

- **Imaging**
  - no detectable tumor or LNs
  - (imaging not standardized)

*Clinical assessment at 8 +/- 4 weeks after CRT—MSKCC Consensus Conference January 2014 (Smith JI, et al. Manuscript in preparation)
**Post-treatment follow-up**

**Typical surveillance and intervals:**

<table>
<thead>
<tr>
<th>Yr1</th>
<th>Yr2</th>
<th>Yr3-5</th>
<th>&gt;Yr5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td>q3m</td>
<td>q4m</td>
<td>q6m</td>
</tr>
<tr>
<td>DRE</td>
<td>q3m</td>
<td>q4m</td>
<td>q6m</td>
</tr>
<tr>
<td>Imaging</td>
<td>q6m</td>
<td>q6m</td>
<td>q6-12</td>
</tr>
</tbody>
</table>


---

**“Wait-and-See”**

- **Netherlands trial**
- 21 pts cCR after chemoradiotherapy prospectively followed
- 3 to 6 monthly MRI, endoscopy, and CT
- Mean f/u 25 months
- 1 LR undergoing surgical salvage; others disease free

Maas et al: J Clin Oncol 2011
“Wait-and-See”

- Conclusion: Wait-and-see with strict selection criteria, up-to-date imaging techniques and follow-up is feasible and results in promising outcomes

“Watchful Waiting”

- Danish Prospective Trial
- 55 pts cT2-3,N0-1 (1999-2013)
- Tx: 60 Gy IMRT + 5 Gy endorectal brachytherapy + tegafur-uracil
- 40 pts cCR after chemoradiotherapy prospectively followed
- 3 to 6 monthly MRI, endoscopy, and CT
- Median follow-up 23.9 months
- 9 LR undergoing surgical salvage; 3 DM
- G3 Bleeding – 3 pts and sphincter function – excellent

Appelt et al: Lancet Oncology 2015
“Wait-and-See” Trials

- MSKCC Randomized Phase II Trial
- Royal Marsden Hospital
- Instituto do Cancer do Estado de São Paulo (Randomized Phase II)
- CMT with > 80% regression: (OPERA) trial standard CRT (45 Gy + 5.4 Gy boost) versus (45 Gy) contact X-ray radiotherapy boost (UK-phase III)
- European expert panel-cCR pts should be given option

Summary

- Short Course vs. Long Course Treatment
- Neoadjuvant ChT ± RT
- Cure and Organ Preservation without Surgery
What is the Optimal Neoadjuvant Therapy for Clinical Stage II and III Rectal Cancer?

1. ChT Only (FOLFOX)
2. Long Course Radiation Therapy + Concurrent Fluoropyrimidine
3. Short Course Radiation Therapy
4. Radiation Therapy Followed by ChT (FOLFOX)

Randomized Trials Have Shown that Short Course Radiation Therapy:

1. Inferior DFS and OS Rates Vs. Long Course RT + ChT
2. Higher Acute and Late Complication Rates Vs. Long Course RT + ChT
3. Superior Quality of Life Vs. Long Course RT + ChT
4. Pathological CR Rates Depend on Time from Completion of Radiation Therapy
For Patients Having a Complete Clinical Response After Long Course RT + ChT: Next Step?

1. Total Mesorectal Excision
2. Transanal Excision
3. Observation with Careful Follow-up
4. Chemotherapy (FOLFOX)

48% 3% 36% 14%