ASTRO Refresher- Lower GI Cancers

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Disclosures

• Illumina- Advisory Board
• Novartis- Research Support
Goals

• To understand the clinical problem of locally advanced rectal cancer
• To evaluate the data supporting the use of preoperative regimens for rectal cancer
• To review the care recommendations for anal cancer
• To discuss CT-based target definitions.
A 70 yo gentleman presents with rectal bleeding. Sigmoidoscopy shows a lesion 8 cm from the anal verge. Biopsy shows moderately differentiated adenocarcinoma. CT chest/abdomen/pelvis shows the rectal tumor and no metastatic disease. Colonoscopy shows no other lesions.

A. Chemoradiation
B. Endorectal ultrasound
C. Pelvic MRI
D. Endorectal ultrasound or Pelvic MRI
Rectal Cancer - The Problem

- Colon Cancer
  - Stage III patients
    - Distant relapse risk
      - 60% with surgery alone
      - 40% with fluoropyrimidine-based chemotherapy
    - Local relapse (anastomotic)
      - 3-5%
Rectal Cancer

• Why is it different than colon cancer?
• Local recurrence rates are much higher and very morbid.
• Location
  – Pelvis is small
  – Hard to get negative margins
  – Much harder operation…
Historical Local Recurrence Rates: The Swedish Trial

Median F/U – 13 year

Folkesson et al. JCO 2005:23;5644-5650
Is Rectal Cancer Actually Different?

Sites of recurrence in all patients and those with single site relapse

<table>
<thead>
<tr>
<th>Site</th>
<th>All sites n (%)</th>
<th>Single site n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>77 (69)</td>
<td>59 (69)</td>
</tr>
<tr>
<td>Liver</td>
<td>22 (20)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>NRLN</td>
<td>12 (11)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Bone</td>
<td>8 (7)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Brain</td>
<td>5 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>5 (4)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

D. Liska, et al. ASCO 2010
## Mutation by site

<table>
<thead>
<tr>
<th>Mutation</th>
<th>All Colorectal (n=184)</th>
<th>Rectal (n=50)</th>
<th>Colon (n=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>65 (35%)</td>
<td>17 (34%)</td>
<td>48 (36%)</td>
</tr>
<tr>
<td>NRAS</td>
<td>7 (4%)</td>
<td>6 (12%)</td>
<td>1 (sigmoid, 0.7%)</td>
</tr>
<tr>
<td>BRAF</td>
<td>16 (9%)</td>
<td>1 (2%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>23 (13%)</td>
<td>6 (12%)</td>
<td>18 (13%)</td>
</tr>
<tr>
<td>PIK3CA/KRAS</td>
<td>11 (6%)</td>
<td>4 (8%)</td>
<td>7 (5%)</td>
</tr>
</tbody>
</table>

Russo AL, et al.  
ASCO 2011
How to Improve Local Failure

- Better surgery
  - Total Mesorectal Excision
  - Node dissection
- Adjuvant Therapy
  - Pre-operative Therapy
  - Post-operative Therapy
Circumferential Margin and Local Recurrence

• At 5 years, 90% (95% CI 84-96) of patients with negative margins had no local failure, versus 22% (95% CI 6-38), log rank p < .001

Thanks to David Sher

Total Mesorectal Excision (TME)

- Removal of the entire rectal mesentery, including that distal to the tumor, as an intact unit
- Direct visualization of the avascular plane between the mesorectum and the surrounding tissues
- Precise dissection in an areolar plane along the visceral fascia that envelopes the rectum and its mesentery
- Posterior, distal, and lateral mesorectum is excised out to hypogastric plexuses (preserved)
- Anteriorly, Denonvilliers fascia and peritoneal reflection are also excised.
## TME Historical Results

<table>
<thead>
<tr>
<th>Series</th>
<th>Stage</th>
<th>No.</th>
<th>RT</th>
<th>%LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cawthorn, 1990</td>
<td>T1-3,N+</td>
<td>122</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>McFarlane, 1993</td>
<td>T3 or N+</td>
<td>135</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>Enker, 1995</td>
<td>T3 or N+</td>
<td>204</td>
<td>33%</td>
<td>6%</td>
</tr>
<tr>
<td>Arbman, 1996</td>
<td>T1-3, N+</td>
<td>128</td>
<td>3</td>
<td>7%</td>
</tr>
</tbody>
</table>
Pre-operative vs. Post-operative Therapy

• Approach 1 – Post-operative radiation
  – Surgical resection
  – If T3/4 and/or N1/2 -> post-operative chemoradiation -> chemotherapy

• Approach 2 – Pre-operative radiation
  – U/S / MRI T3/4 cancer or clinical T4
  – Pre-operative therapy -> surgery -> chemotherapy
Post-operative Therapy: Who needs treatment?

T3 or greater Or N+

Select Post-operative Studies

• GITSG 7175
  – 4-arm trial: 1. obs 2. RT 3.5FU/MeCCNU 4. Chemo-RT
  – Survival benefit at 8 years for CHEMO-RT with chemo reducing DM (20% v 30%) and RT decreasing LR(16% v 25%)

• NSABP R-01
  – 3-arm trial 1. obs 2. RT alone 3. 5FU/MeCCNU/vincristine
  – Chemo improved 5 yr OS (60 v 37%);
  – RT decreased LR (16% v 25%) but no OS impact

• NSABP R-02
  – Chemo v. chemo-RT (complicated gender specific design)
  – RT decreased LR (8% v 13%) but no OS impact
  – 5FU/LV better than MOF
Post-operative Therapy Summary

• Post-operative radiation therapy improves local control, but not survival
• Chemotherapy improves survival, consistent with colon cancer data
• Currently recommended for T3/4 or N+ tumors
• # nodes, type of surgery, CRM status important
Advantages of Preoperative Treatment

- Tumor Can Be Clearly Defined
- Less Normal Tissue Irradiated = Less Toxicity
- Downstaging
- Increased Resectability (Especially T4 Tumors)
- Enhanced Sphincter Preservation
- New Era of Novel Agents - RT Combinations
Disadvantages of Preoperative Treatment

- Overtreating Pts with Early Stage or Undetected Metastatic Disease
- Loss of prognostic information of nodes
- Staging Dependent:
  - CT
  - MRI
  - EUS
Work up for preoperative patients

- **H+P**
  - Rectal exam - Location, size, tethered, circumferential, ulcerated, sphincter tone
- **Full Colonoscopy**
  - Synchronous primaries in up to 5%
- **CT C/A/P**
  - Liver mets
  - Lung mets/nodal mets also common
- **CEA**
- **Basic labs**
- **Tumor staging**
Pre-operative Tumor Assessment

65-75% accuracy in tumor staging; 55-65% accuracy in mesorectal LN staging

80-95% accuracy in tumor staging; 70-75% accuracy in mesorectal LN staging

75-85% accuracy in tumor staging; 60-65% accuracy in mesorectal LN staging
Is it a rectal cancer?

• Based on being above or below the peritoneal reflection
• Some studies use 15 cm from anal verge
• Can be difficult to know for sure
Commonly used preoperative strategies

- **Short course radiation only**
  
  5 Gy x 5 (1 week) $\rightarrow$ 1 week $\rightarrow$ Surgery $\rightarrow$ Chemotherapy if node +

- **Full course chemoradiation**
  
  45-50.4 Gy x 1.8 Gy/fx (5+ weeks) with fluoropyrimidine-based chemo $\rightarrow$ 4-7 weeks $\rightarrow$ Surgery $\rightarrow$ Fluoropyrimidine-based chemotherapy
Pre-operative Therapy in the Pre-TME era: The Swedish Rectal Trial

- surgery vs RT → surgery
- phase III, 1987-1990, 1168 pts
- all resectable tumors at initial evaluation
- RT: 25 Gy, 5 Gy/fx
- surgery: LAR or APR, within 1 week from RT completion

NEJM 1997; 336: 980-987
### The Swedish Rectal Trial: Results

<table>
<thead>
<tr>
<th></th>
<th>RT→S</th>
<th>S only</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR5</td>
<td>11%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS5</td>
<td>58%</td>
<td>48%</td>
<td>0.004</td>
</tr>
<tr>
<td>CSS9</td>
<td>74%</td>
<td>65%</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Does pre-operative radiation improve upon TME?

The Dutch Study

Operable Rectal Cancer (1805 pts)

- 25 Gy in 5 Fx + TME (897 pts)
- TME Only (908 pts)

## Dutch Study: Results

<table>
<thead>
<tr>
<th></th>
<th>RT→S</th>
<th>S Only</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR2</td>
<td>2.4%</td>
<td>8.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS2</td>
<td>82.0%</td>
<td>81.8%</td>
<td>0.84</td>
</tr>
<tr>
<td>DM2</td>
<td>14.8%</td>
<td>16.8%</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Dutch Study: Conclusions

- Local control is excellent with TME
- Even with TME, pre-operative radiation therapy improves local control
- Radiation therapy does not impact survival
- Study does not address impact of modern chemotherapy
Clinically operable adenocarcinoma of the rectum <15cm from anal verge; no metastases

n = 1350

PRE

Pre-operative RT 25Gy / 5F

Surgery

Pathology

SEL POST

Surgery

Pathology

CRM-ve

No CRT

CRM+ve

Post-op CRT 45Gy / 25F + concurrent 5FU

Adjuvant chemotherapy given as per local policy
Local recurrence (ITT)

Total Events 3 yr LR

- **PRE**
  - 674 events
  - 27 local recurrences
  - 4.4%

- **SEL POST**
  - 676 events
  - 72 local recurrences
  - 10.6%

HR (95% CI) = 0.39 (0.27-0.58) p = 0.000004
Disease free survival (ITT)

HR(95% CI) = 0.76 (0.62-0.94) p=0.013
Subset analysis (Local recurrence)
(no. events/no. entered)

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM Status</td>
</tr>
<tr>
<td>CRM +ve 5/61 13/81</td>
</tr>
<tr>
<td>CRM –ve 19/563 54/561</td>
</tr>
<tr>
<td>p=0.351</td>
</tr>
<tr>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distance of distal tumour extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5cm 11/229 23/217</td>
</tr>
<tr>
<td>&gt;5-10cm 15/345 30/337</td>
</tr>
<tr>
<td>&gt;10-15cm 1/95 18/112</td>
</tr>
<tr>
<td>p=0.02</td>
</tr>
<tr>
<td>p=0.02</td>
</tr>
<tr>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I 4/192 4/143</td>
</tr>
<tr>
<td>Stage II 3/173 19/222</td>
</tr>
<tr>
<td>Stage III 18/260 44/282</td>
</tr>
<tr>
<td>p=0.598</td>
</tr>
<tr>
<td>p=0.004</td>
</tr>
<tr>
<td>p=0.002</td>
</tr>
</tbody>
</table>

PRE better  SEL POST better
MRC CR 07: Conclusions

- Preoperative RT reduces local recurrences in the setting of modern chemotherapy
- Preoperative RT improves DFS at 3 years compared to a selective postoperative approach
Preoperative Chemoradiation for Clinical T3

- Allows greater interaction of drug-radiation
- Allow for more downstaging
- Convert APR to a Sphincter Preserving Operation
- Complete Pathologic Responses 10-20%

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Gy</th>
<th>S-P%</th>
<th>LC%</th>
<th>Act OS%</th>
<th>Bowel Fx%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagman</td>
<td>16</td>
<td>50.4</td>
<td>77</td>
<td>100 (5 y)</td>
<td>64 (5 y)</td>
<td>85% gd-excel</td>
</tr>
<tr>
<td>Rouanet</td>
<td>27</td>
<td>60</td>
<td>78</td>
<td>93 (crude)</td>
<td>83 (2 y)</td>
<td>NA</td>
</tr>
<tr>
<td>Mohiuddin</td>
<td>52</td>
<td>45-60</td>
<td>NA</td>
<td>86 (crude)</td>
<td>85 (5 y)</td>
<td>90% acceptable</td>
</tr>
<tr>
<td>Bosset</td>
<td>60</td>
<td>45</td>
<td>58</td>
<td>92 (5 y)</td>
<td>60 (5 y)</td>
<td>acceptable</td>
</tr>
</tbody>
</table>

German Study

• ALL PATIENTS HAD TME

• Pre-op
  – RT – 50.4 Gy with 3 or 4 field
  – Chemo – 5FU CI 1000 mg/m^2/d over 5 days wk 1,5

• Post-op
  – RT – 55.8 Gy (50.4 Gy with 3 or 4 field with 5.4 Gy bst to tumor bed)
  – Chemo – 5FU CI 1000 mg/m^2/d over 5 days wk 1,5

• Adjuvant Chemo – 4 cycles bolus 5FU (500 mg/m^2/d (5 times weekly every four wks)
  – Pre-op – to start 4 weeks after surgery
  – Post-op – to start 4 weeks after chemo-RT
### Table 2. Compliance with the Protocol and Protocol Violations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative Chemoradiotherapy</th>
<th>Postoperative Chemoradiotherapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomly assigned — no.</td>
<td>421</td>
<td>402</td>
<td>0.12</td>
</tr>
<tr>
<td>Included in full analysis population — no.</td>
<td>405</td>
<td>394</td>
<td>0.05</td>
</tr>
<tr>
<td>Requested change in treatment group — no.</td>
<td>9</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Included in treated population — no.</td>
<td>415</td>
<td>384</td>
<td></td>
</tr>
<tr>
<td>Received full dose of radiotherapy — no. (%)</td>
<td>380 (92)</td>
<td>206 (54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received full dose of chemotherapy — no. (%)</td>
<td>369 (89)</td>
<td>193 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Did not receive chemoradiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I disease</td>
<td>NA</td>
<td>71 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other reason†</td>
<td>1 (&lt;1)</td>
<td>39 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received radiotherapy with modification</td>
<td>19 (5)</td>
<td>31 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Received chemotherapy with modification — no. (%)</td>
<td>23 (6)</td>
<td>26 (7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Protocol violations — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>13 (3)</td>
<td>33 (9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>15 (4)</td>
<td>49 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing data — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2 (&lt;1)</td>
<td>4 (1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7 (2)</td>
<td>6 (2)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Better Compliance with Pre-op
Pathological Findings

CR rate – 8%
About 10% downstaging

<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>Histopathological finding (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete response</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>6</td>
<td></td>
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</table>
Type of Surgery

<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>Type of resection (%)</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Low anterior, intersphincteric</td>
<td>69</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Abdominoperineal</td>
<td>26</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Greater rate of sphincter preservation in group preoperatively felt to need APR.
Gr. 3-4 Side Effects (by actual treatment)

<table>
<thead>
<tr>
<th>Type of Toxic Effect</th>
<th>Preoperative Chemoradiotherapy (N=399)</th>
<th>Postoperative Chemoradiotherapy (N=237)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>Hematologic effects</td>
<td>6</td>
<td>8</td>
<td>0.27</td>
</tr>
<tr>
<td>Dermatologic effects</td>
<td>11</td>
<td>15</td>
<td>0.09</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>27</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Long-term</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal effects†</td>
<td>9</td>
<td>15</td>
<td>0.07</td>
</tr>
<tr>
<td>Strictures at anastomatic site</td>
<td>4</td>
<td>12</td>
<td>0.003</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>2</td>
<td>4</td>
<td>0.21</td>
</tr>
<tr>
<td>Any grade 3 or 4 toxic effect</td>
<td>14</td>
<td>24</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Fewer Gr. 3-4 toxicities in pre-op group
Overall Survival

![Graph showing overall survival rates for preoperative and postoperative chemoradiotherapy with corresponding no. at risk values.](image-url)
Disease-free Survival

![Graph showing disease-free survival rates over time for different treatment groups.](image)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Preoperative chemoradiotherapy</th>
<th>Postoperative chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>397</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>331</td>
<td>314</td>
</tr>
<tr>
<td></td>
<td>280</td>
<td>259</td>
</tr>
<tr>
<td></td>
<td>224</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td>169</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>73</td>
</tr>
</tbody>
</table>

**P-value:** 0.32
Local Recurrence

A

Cumulative Incidence of Local Recurrence (%)

- Preoperative chemoradiotherapy
- Postoperative chemoradiotherapy

No. at Risk
Preoperative chemoradiotherapy
397 368 312 250 190 133 97
Postoperative chemoradiotherapy
384 351 290 240 184 135 85

P = 0.006
Distant Recurrence

![Graph showing the cumulative incidence of distant recurrence with different lines for preoperative and postoperative chemoradiotherapy, along with numbers at risk at different months.]

- Preoperative chemoradiotherapy:
  - No. at Risk: 397, 330, 382, 226, 171, 116, 86

- Postoperative chemoradiotherapy:
  - No. at Risk: 384, 316, 267, 214, 162, 123, 77

P = 0.84
Why is this study so important?

- Very well designed trial
- Modern, conventional pre-op regimen
- TME surgery
- Modern chemotherapy
Interesting Findings

• Improved Local Control - Compliance issue?
  – Local control doesn’t look different than Dutch control arm

• 18% overstaged in post-op arm
  – Fits with 80% accuracy
  – Needs better staging

• 8% pCR rate in pre-op arm
German Study: Conclusions

- Pre-op improves local control
  - Compliance issue
- Pre-op has higher rates of sphincter preservation
- Pre-op is better tolerated
- Pre-op may overtreat by 20%
- No difference in DM, DFS, OS
- PREOPERATIVE THERAPY IS THE STANDARD OF CARE
NSABP R03
Pre-op vs Post-op ChemoRT

267 patients
Stage II/III

Which agents?

• 5-FU or capecitabine
• +/- oxaliplatin
X-ACT:
The role of capecitabine in the adjuvant colon ca

Twelves C, et al. NEJM
2005;352:2696-2704
Capecitabine versus 5-FU Chemoradiation

- 401 stage II/III rectal cancer randomized to receive either pre or postoperative ("sandwich") therapy with either:
  - Cape 1650 mg/M2 d1-38 + 50.4 Gy, Cape x 4 or 5 cycles
  - 5-FU 225 mg/M2 CI for adjuvant or 1000 mg/M2 CI d1-5, d29-33 for neoadjuvant, bolus 5-FU d1-4 x 4 cycles

- Toxicity:
  - Capecitabine: greater PPE, proctitis, diarrhea and fatigue
  - 5-FU: greater alopecia and leukopenia

# Neoadjuvant Capecitabine versus 5-FU Chemoradiation

<table>
<thead>
<tr>
<th></th>
<th>Cape</th>
<th>5-FU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR (%)</td>
<td>26</td>
<td>21</td>
<td>.56</td>
</tr>
<tr>
<td>R0 (%)</td>
<td>95.8</td>
<td>91.9</td>
<td>1.0</td>
</tr>
<tr>
<td>pCR (%)</td>
<td>13.5</td>
<td>5.4</td>
<td>.16</td>
</tr>
<tr>
<td>ypT0-2 (%)</td>
<td>53.9</td>
<td>39.2</td>
<td>.07</td>
</tr>
<tr>
<td>ypT3-4 (%)</td>
<td>46.1</td>
<td>60.8</td>
<td></td>
</tr>
<tr>
<td>LR (%)</td>
<td>6.1</td>
<td>7.2</td>
<td>.7795</td>
</tr>
<tr>
<td>Distant mets (%)</td>
<td>18.8</td>
<td>27.7</td>
<td>.0367</td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>19.3</td>
<td>28.2</td>
<td>.038</td>
</tr>
<tr>
<td>DFS 5y (%)</td>
<td>67.8</td>
<td>54.1</td>
<td>.035</td>
</tr>
<tr>
<td>OS-5y (%)</td>
<td>75.7</td>
<td>66.6</td>
<td>&lt;.001non-inf</td>
</tr>
</tbody>
</table>

MOSAIQ: The role of oxaliplatin in the adjuvant colon ca

STAR-01 Trial: 
Role of Oxaliplatin in Rectal Cancer

- 747 patients with T3/4±N+ rectal cancer 12 cm from anal verge randomized to
  - 5-FU 225 mg/M2/d, 50.4 Gy +/- oxaliplatin 60 mg/M2 x6
  - Surgery 6-8 weeks after CRT

<table>
<thead>
<tr>
<th>Path Stage</th>
<th>FU-XRT N=368 (%)</th>
<th>FUOx XRT N=368 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0N0</td>
<td>60 (16)</td>
<td>57 (16)</td>
<td>.94</td>
</tr>
<tr>
<td>Diameter</td>
<td>26 (1-100)</td>
<td>24 (2-80)</td>
<td></td>
</tr>
<tr>
<td>CRM+</td>
<td>6</td>
<td>4</td>
<td>.13</td>
</tr>
<tr>
<td>M1</td>
<td>11 (3)</td>
<td>2 (0.5)</td>
<td>.014</td>
</tr>
</tbody>
</table>

STAR-01 Toxicity

• Increased toxicity but manageable

<table>
<thead>
<tr>
<th></th>
<th>FU/RT (379)</th>
<th>FU/Ox/RT (353)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>8</td>
<td>24</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>15</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Rad dermatitis</td>
<td>2</td>
<td>5</td>
<td>.038</td>
</tr>
<tr>
<td>Gr 2-3 neurosensory</td>
<td>.5/0</td>
<td>36/1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Rx related deaths</td>
<td>.3 (1)</td>
<td>.6 (2)</td>
<td></td>
</tr>
</tbody>
</table>

courtesy of L Blaszkowsky
ACCORD 12/0405 PRODIGE 2: Role of Oxaliplatin in Rectal Cancer

- 584 patients with T3, T4, N0-2 rectal cancer randomized to
  - capecitabine 800 mg/M2 BID and 45 Gy in 25 fx or
  - capecitabine 800 mg/M2/BID 5 of 7d, oxaliplatin 50 mg/M2/week and 50Gy in 25 fx

<table>
<thead>
<tr>
<th></th>
<th>Cape-45 %</th>
<th>CapOx-50 %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>98</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>RT full dose</td>
<td>99%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Sphinct pres</td>
<td>73</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>pCR</td>
<td>14</td>
<td>19</td>
<td>0.11</td>
</tr>
<tr>
<td>N0 + few cells</td>
<td>30</td>
<td>41</td>
<td>0.008</td>
</tr>
<tr>
<td>CRM 0-1/0-2mm</td>
<td>12/19</td>
<td>7/9</td>
<td>0.21/.017</td>
</tr>
</tbody>
</table>

courtesy of L Blaszkowsky

## ACCORD Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Cape45 (293)</th>
<th>CapOx 50 (291)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Gr 3-4</td>
<td>11</td>
<td>25</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gr 3-4 diarrhea</td>
<td>3</td>
<td>13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gr 3-4 heme</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Gr 2 PPE</td>
<td>&lt;1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gr 2 Peripheral neurop</td>
<td>.4</td>
<td>5</td>
<td>&lt;.002</td>
</tr>
</tbody>
</table>


courtesy of L Blaszkowsky
Neoadjuvant 5-FU + Oxaliplatin Chemoradiation: CAO/ARO/AIO-04

- 637 patients with locally advanced rectal cancer randomized to:
  - 5-FU 1000 mg/M2/d d1-5 and 29-32 + 50.4 Gy, TME, then 5-FU 500 mg/M2 d1-5 x 4 cycles
  - 5-FU 250 mg/M2/d d1-14 and 22-35 + oxaliplatin 50 mg/M2 days 1, 8, 22, 29 + 50.4 Gy, TME, then mFOLFOX6 (100 mg/M2) x 8 cycles
- Primary endpoint is disease free survival

# Neoadjuvant 5-FU + Oxaliplatin Chemoradiation: CAO/ARO/AIO-04

<table>
<thead>
<tr>
<th></th>
<th>5-FU (N=624)</th>
<th>FUOx (N=613)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr3/4 tox (%)</td>
<td>22</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>GI Gr 3/4 (%)</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Neuro Gr 2/3 (%)</td>
<td>&lt;1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mesorectal plane (%)</td>
<td>74</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>LAR (%)</td>
<td>66</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>APR (%)</td>
<td>23</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Complication (%)</td>
<td>42</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>R0 (%)</td>
<td>92</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>pCR (%)</td>
<td>12.8</td>
<td>16.5</td>
<td>.045</td>
</tr>
</tbody>
</table>

**NSABP R-04**

- 1608 patients with resectable Stage II/III rectal cancer randomized to preoperative 5-FU CI or capecitabine ± oxaliplatin with 5040-5580 cGy
- TME not mandated
- Questions asked:
  - Is cape non-inferior
  - Is addition of oxaliplatin superior

<table>
<thead>
<tr>
<th></th>
<th>FU</th>
<th>Cape</th>
<th>No Oxali</th>
<th>Oxali</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR (%)</strong></td>
<td>18.8 (16-21.8)</td>
<td>22.2 (19.2-25.5)</td>
<td></td>
<td></td>
<td>.12</td>
</tr>
<tr>
<td><strong>pCR (%)</strong></td>
<td>19.1 (16-22.6)</td>
<td>20.9 (17.7-24.5)</td>
<td></td>
<td></td>
<td>.46</td>
</tr>
<tr>
<td><strong>GI tox gr3/4 (%)</strong></td>
<td>6.8</td>
<td>15.4</td>
<td></td>
<td></td>
<td>.0001</td>
</tr>
</tbody>
</table>

NSABP R-04

- Capecitabine is similar to 5-FU CI:
  - Surgical downstaging
  - Sphincter preservation
  - pCR
- No improvement with addition of oxaliplatin but increase in GI toxicity
- No difference in surgical complications
- Too early for local recurrence, DFS and OS
# Oxaliplatin Neoadjuvant Trials

<table>
<thead>
<tr>
<th></th>
<th>STAR-01</th>
<th>ACCORD</th>
<th>CAO/ARO/AIO-04</th>
<th>NSABP R-04</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conclusions</strong></td>
<td>pCR 16% in both arms</td>
<td>pCR 14v19% (NS), ox</td>
<td>pCR 12.8v16.5% No incr tox</td>
<td>pCR 19v21% Ox more toxic</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>66% admin</td>
<td>59% dose modified</td>
<td>80v 85% full dose</td>
<td>?</td>
</tr>
<tr>
<td>pre-op</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Full dose RT</strong></td>
<td>97 v 90%</td>
<td>100 v 87%</td>
<td>95 v 94%</td>
<td>?</td>
</tr>
<tr>
<td>ypN+</td>
<td>28 v 26%</td>
<td>30 v 28%</td>
<td>28 v 30%</td>
<td>29.5 v 29%</td>
</tr>
<tr>
<td><strong>CRM≤1mm (%)</strong></td>
<td>-</td>
<td>13 v 8%</td>
<td>6 v 5%</td>
<td>-</td>
</tr>
</tbody>
</table>

Does how we give 5FU matter?
Interpreting the control arms

- Wk 1,5 1000 mg/m2 96 hr
  - Sauer 2004- pCR = 8%
  - Hofheinz 2011- pCR = 5.4%
  - Roedel 2011- pCR = 12.8%

- Daily CI infusion (~225 mg/m2 throughout)
  - Aschele 2009- pCR = 16%
  - Roh 2011 - pCR = 18.8%
  - Russo (MGH) 2011 – pCR = 21%
Why do we care about pCR?

Rodel C, JCO, 2005
Significance of pCR
Results of pre-op arm in German Trial

![Graph showing Disease-Free Survival rates for different TRG groups over months, with data for No. at risk: 40, 229, 75, 24, 127, 41, 8, 39, 15, and 2, 3.]

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>5-Year Disease-Free Survival (%)</th>
<th>P</th>
<th>5-Year Distant Metastases-Free Survival (%)</th>
<th>P</th>
<th>5-Year Local Relapse-Free Survival (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grouped TRG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>86</td>
<td>.006</td>
<td>86</td>
<td>.009</td>
<td>100</td>
<td>.33</td>
</tr>
<tr>
<td>2 + 3</td>
<td>229</td>
<td>75</td>
<td></td>
<td>75</td>
<td></td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>0 + 1</td>
<td>75</td>
<td>63</td>
<td></td>
<td>66</td>
<td></td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>
EORTC who benefits from chemo

Fig 3. Kaplan-Meier curve of disease-free survival after surgery by adjuvant treatment and pathological down staging to ypT0-2. O, number of events; N, number of patients; CT, chemotherapy.
Response to Chemoradiation

- pCR may be a marker of CHEMO sensitivity or biology
- Alternatively, pCR may be a marker of better biology
- Efficacy of short course as well as lack of impact of response and LC in German trial suggest that pCR does not help local control in the setting of TME
Which Pre-operative Regimen: The Polish Study

Clinical T3 or T4 adenocarcinoma of the rectum

Randomize

1999-2002

n=316

n=155

5 Gy x 5 → surgery <7 days

n=157

50.4 Gy + 4-6 weeks → surgery

1. Rate of sphincter preservation
2. Survival
3. Local control
4. Late toxicity
5. Permanent stoma

End points:

Power calculation:
15% increase in sphincter sparing
Survival

Overall survival

Disease-free survival

<table>
<thead>
<tr>
<th>Time after randomization (years)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>155</th>
<th>135</th>
<th>125</th>
<th>110</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-course radiotherapy</td>
<td>157</td>
<td>145</td>
<td>125</td>
<td>110</td>
<td>56</td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>157</td>
<td>122</td>
<td>102</td>
<td>89</td>
<td>48</td>
</tr>
</tbody>
</table>
Local Failure

15.6%
10.6%

No. at risk
Short-course radiotherapy 146 125 118 100 46
Chemoradiation 149 136 116 98 53
Late Toxicity

No Difference

<table>
<thead>
<tr>
<th></th>
<th>Short-course radiotherapy (n = 138)</th>
<th>Chemoradiation (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small/large intestine†</td>
<td>7 (5.1)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Skin (non-healing perineal wound)</td>
<td>0</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Urether</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Nerves: motor function</td>
<td>3 (2.2)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Nerves: sensory function</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Nerves: pain</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Postoperative hernia requiring surgery</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Fracture of femoral neck</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Total complications</td>
<td>16 in 14 patients</td>
<td>13 in 10 patients</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. †The total number of patients does not include those for whom there were no data concerning severe late complications (six patients in the short-course radiotherapy group and eight in the chemoradiation group) or those who did not undergo tumour resection or died within 30 days of surgery (11 patients in the short-course radiotherapy group and eight in the chemoradiation group). †Of nine patients with severe complications from the small/large intestine, three had ileus, three had fistula and three had stenosis of the anastomosis.
TROG Randomized Trial

- Short course vs. Chemoradiation
  - Short Course 5 Gy x 5
  - Chemoradiation 50.4 Gy w CI 5FU 225 mg/m2
- Primary endpt – LR
  - Powered to detect 15% vs 5%
- Had to be MRI or U/S
- T3 Nx
- All patients received 4 cycles of FL (Mayo Clinic)

Ngan S, et al. ASCO 2010
Results

- 326 patients
- Median f/u 5.9 years
  - Primary endpt- LR-3- 7.5% (SC) vs. 4.4 (LC) NS
  - OS 5- 74% (SC) vs. 70% (LC)
  - No difference in late toxicity
Conclusions

• This study fixed a lot of the problems of the Polish Study
  – Preop staging
  – Standardized chemotherapy
• Continued to show no difference
Current Recommendations

45-50.4 Gy x 1.8 Gy/fx (5+ weeks) with fluoropyrimidine-based chemo → 4-7 weeks → Surgery

TME → Fluoropyrimidine-based chemotherapy (Typically FOLFOX)
Bellyboard

MODIFIED OPEN TABLE TOP:
Face mask and arm support increase patient comfort and setup reproducibility

Lateral XRT portal avoids small bowel

Duodenum

Rectum

Small bowel shift with patient in prone position
Radiation Fields
Radiation Plans
Anal Cancer

Historical Perspective

- Surgery (APR) is inadequate
  - associated with 40-70% 5 yr OS
- Chemoradiation is associated with high cure rate
  - Wayne State regimen: 5FU/MMC/XRT
    - First 3 patients had pCRs, follow up series with chemoRT (surgery reserved for post-therapy residual) → 5yr OS 67% and 5yr CFS 59%.
## Historical Perspective

Chemoradiation is better than radiation alone

<table>
<thead>
<tr>
<th>Study*</th>
<th>No. of Patients</th>
<th>Local Control</th>
<th>Overall Three-Year Survival</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Organization for Research and Treatment of Cancer</td>
<td>110</td>
<td>39</td>
<td>Radiation Therapy Alone</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58</td>
<td>Chemotherapy and Radiation Therapy</td>
<td>0.02</td>
</tr>
<tr>
<td>United Kingdom Coordinating Committee on Cancer Research</td>
<td>585</td>
<td>39</td>
<td>Radiation Therapy Alone</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61</td>
<td>Chemotherapy and Radiation Therapy</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Median follow-up was 42 months in both studies.\(^6,^{112}\)
Historical Perspective

- Mitomycin C
  - Not a potent radiosensitizer of tumor cells
  - Marginal, if any, activity as a single agent
  - Associated with chronic renal, pulmonary, and bone marrow toxicity

The First Question: Eliminate MMC?
RTOG 87-04/ECOG: 5-FU + RT vs. 5-FU + MMC + RT

<table>
<thead>
<tr>
<th>Arms</th>
<th>N</th>
<th>5-yr LR</th>
<th>5-yr CFS</th>
<th>5-yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/RT</td>
<td>145</td>
<td>36%</td>
<td>58%</td>
<td>50%</td>
</tr>
<tr>
<td>5-FU/MMC/RT</td>
<td>146</td>
<td>17%,(p&lt;0.001)</td>
<td>64%,(p=0.09)</td>
<td>67%,(p&lt;0.003)</td>
</tr>
</tbody>
</table>

Substituting MMC with cisplatin: The Rationale for RTOG 9811

- Encouraging phase II results with the use of cisplatin, 5FU, and XRT

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Induction</th>
<th>cCR</th>
<th>CFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pieffert</td>
<td>80</td>
<td>Yes</td>
<td>94%</td>
<td>73%</td>
</tr>
<tr>
<td>Gerard</td>
<td>95</td>
<td>No</td>
<td>*9%</td>
<td>72%</td>
</tr>
<tr>
<td>Meropol</td>
<td>45</td>
<td>Yes</td>
<td>80%</td>
<td>78%</td>
</tr>
</tbody>
</table>
U.S. GI Intergroup RTOG 98-11
Schema

Stratifications
Gender
Clinical N
T size

Randomize

5-FU/Mitomycin 2 cycles
→ Radiation therapy 45 to 59 Gy
→ Any N-stage

5-FU/Cisplatin 2 cycles → 5-FU/Cisplatin 2 cycles
→ Radiation therapy 45 to 59 Gy

Primary Endpoint = DFS
n = 650
Initial Results

DFS- No Difference

OS- No Difference

Time to colostomy-

Ajani et al., Jama 299 (16), 1914-21, 2008.
Updated Results

Median f/u – 5.46 years

DFS- Significant Difference

OS- Significant Difference

Gunderson LL, et al. ASCO 2011
Authors’ Conclusions

1. RT+5FU/MMC has statistically better DFS & OS than RT+5FU/CDDP (5-yr DFS: 67.7 vs. 57.6%, p=0.0044; 5-yr OS: 78.2 vs. 70.5%, p=0.021)

2. RT+5FU/MMC has borderline statistical significance for CFS, LRF, and CF (p=0.053, 0.089 and 0.075)

3. Males, >5 cm tumor diameter, and clinical N+ cancer were independent poor prognosticators for DFS and OS

4. RT+5FU/MMC remains the standard of care for patients with anal canal carcinoma.

5. Potential strategies to improve outcomes:
   a) Treatment intensification: EBRT - IMRT dose escalation; chemo/targeted agents; earlier surgical salvage – PET based
   b) Individualized molecular-based treatment
What Happened?

DFS - Significant Difference

OS - Significant Difference
Why did the standard arm win?

- They were asking two questions
  - Substitution with cisplatin
  - Induction chemotherapy
Does Cisplatin matter?
ACT II UK Phase III Study

**Trial Design**

- Patients with confirmed primary epidermoid anal cancer
- Staged and biopsied by EVA & CT scan
- GFR >50 ml/min
- RANDOMISE

- 5-FU & MMC + Radiotherapy
- 5-FU & MMC + Radiotherapy
- 5-FU & CDDP + Radiotherapy
- 5-FU & CDDP + Radiotherapy
- No Maintenance Therapy
- Maintenance Therapy
- No Maintenance Therapy
- Maintenance Therapy
- 5-FU & CDDP

**Radiotherapy**
- 50.4 Gy in 28 fractions

**Synchronous Chemotherapy**
- 5-Fluorouracil 1000 mg/m² days 1-4 & 29-32 by 24 hour continuous infusion
- Mitomycin 12 mg/m² day 1 only, iv bolus or
- Cisplatin 60 mg/m² days 1 & 29 by iv infusion

**Maintenance Chemotherapy**
- Two courses 5-FU and Cisplatin
- 4 weeks after the end of primary chemoradiation repeated after 3 wks
- 5-Fluorouracil 1000 mg/m² days 1-4 and
- Cisplatin 60 mg/m² day 1 by iv infusion

**Current Status**
- Opened June 2001
- Target accrual 950 pts
- 01/01/2005: 380 patients entered
- Majority of UK radiotherapy centres (49/60) treating patients
- Closure of accrual - 2008

James R, et al. ASCO
2009
## ACT II: Recurrences

<table>
<thead>
<tr>
<th>Site of Initial Recurrence</th>
<th>MMC $n=472$</th>
<th>CDDP $N=468$</th>
<th>No Maintenance $N=446$</th>
<th>Maintenance $N=448$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local only</td>
<td>21 (4%)</td>
<td>28 (6%)</td>
<td>24 (5%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>18 (4%)</td>
<td>25 (5%)</td>
<td>24 (5%)</td>
<td>19 (4%)</td>
</tr>
<tr>
<td>Loco-regional &amp; Distant</td>
<td>11 (3%)</td>
<td>8 (2%)</td>
<td>7 (2%)</td>
<td>11 (3%)</td>
</tr>
</tbody>
</table>
Primary Endpoint - Decrease of Recurrence from 25% to 17.5% in Maintenance Arms.

**RECURRENCE-FREE SURVIVAL**
- 75% in maintenance arms vs. 75% in No maintenance arms @ 3 yrs
  - HRatio=0.94, 95% C.I. 0.72-1.24, \(P=0.67\)

**OVERALL SURVIVAL**
- 85% in maintenance arms vs. 84% in No maintenance arms @ 3 yrs
  - HRatio=0.81, 95% C.I. 0.57-1.13, \(P=0.21\)
Why did the standard arm win?

• They were asking two questions
  – Substitution with cisplatin
  – Induction chemotherapy
Could induction be worse for the patient?

- Combined analysis of 9811 and 8704
  - Compared 3 treatment groups
    - 5FU/MMC – 472
    - 5FU/cis – 320
    - 5FU alone – 145
Combined analysis 8704/9811

- Only two treatment variable significant on multivariate analysis
  - 5FU alone (HR 2.44, p <0.0001)
  - **ALL Treatment Duration > 53 days** (HR 1.96, P=0.0006)
Interpreting 9811

• Induction 5FU/Cisplatin followed by 5FU/Cisplatin/XRT is clearly inferior to the standard 5FU/MMC/XRT regimen

• Is 5FU/Cisplatin/XRT worse than 5FU/MMC/XRT?
  – Based on ACT II, probably not
  – However, with 9811, this question is unlikely to be asked again
Have we made progress?

• After multiple randomized trials, MMC/5FU/RT remains the standard of care

• In spite of the success and generally favorable prognosis, there are questions regarding over/undertreatment based on stage
  – Did we abandon surgery too early for high risk disease?
  – Are we overtreating low risk disease?
# U.S. GI Intergroup RTOG 9811

## Relapse by TN Category

<table>
<thead>
<tr>
<th>TN Category</th>
<th>No. Pts</th>
<th>Local-Regional</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TF(#) 5yr(%)</td>
<td>TF(#) 5yr(%)</td>
</tr>
<tr>
<td>Node Neg.</td>
<td>448</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N0</td>
<td>302</td>
<td>50 19</td>
<td>31 12</td>
</tr>
<tr>
<td>T3N0</td>
<td>115</td>
<td>25 22</td>
<td>12 14</td>
</tr>
<tr>
<td>T4N0</td>
<td>31</td>
<td>13 50</td>
<td>5 21</td>
</tr>
<tr>
<td>Node Pos.</td>
<td>167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2N1-3</td>
<td>95</td>
<td>37 40</td>
<td>22 31</td>
</tr>
<tr>
<td>T3N1-3</td>
<td>47</td>
<td>27 58</td>
<td>12 32</td>
</tr>
<tr>
<td>T4N1-3</td>
<td>25</td>
<td>14 64</td>
<td>4 17</td>
</tr>
</tbody>
</table>

P-value: <0.0001 0.0035

Gunderson L, et al. ASTRO 2010
What about very early cancers?

- 21 patients
  - Dysplasia with microinvasion
  - T1 with close/involved margins
  - T2 with close/involved margins

Hatfield P, et al. IJROBP 2008;17:419-24
Conclusions

• 5FU/MMC remains the standard of care
  – Longer follow up now shows a survival benefit
  – The efficacy of cisplatin is confounded by the use of induction therapy

• In spite of successes, we have not significantly improved the efficacy of our regimens

• Further investigation is needed to individualize our care based on risk recurrence
Work Up

• Physical exam
  – Anal exam
  – Inguinal exam
• Biopsy
• CT C/A/P- WITH IV CONTRAST
• PET- may be useful, not approved
Figure 1. Dose-Volume Comparison

IMRT

Normal Tissue Structure

Courtesy Lisa Kachnic
RTOG 0529: Dose Painted IMRT in Anal Cancer (Kachnic, et al.)

Mitomycin-C 10 mg/m² IV bolus on days 1 & 29 IMRT

5-FU 1000 mg/m²/day by CI on days 1-4 & 29-32 IMRT

T2 and above
*HIV pts eligible
DP-IMRT

• T2N0: 50.4 Gy tumor; 42 Gy elective nodes in 28 fxs over 5.5 weeks

• T3N0 or T4N0: 54 Gy tumor; 45 Gy elective nodes in 30 fxs over 6 weeks

• N+: 50.4 Gy ≤ 3 cm or 54 Gy > 3 cm in 30 fxs over 6 weeks

Courtesy Lisa Kachnic
# RTOG 9811 Acute Toxicity

*5FU, MMC arm*

Ajani et al., Jama 299 (16), 1914-21, 2008

Courtesy Lisa Kachnic

<table>
<thead>
<tr>
<th>9811*</th>
<th>Gd 1</th>
<th>Gd 2</th>
<th>Gd 3</th>
<th>Gd 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heme</td>
<td>10%</td>
<td>23%</td>
<td>35%</td>
<td>26%</td>
</tr>
<tr>
<td>Derm</td>
<td>9%</td>
<td>35%</td>
<td>43%</td>
<td>5%</td>
</tr>
<tr>
<td>GI</td>
<td>17%</td>
<td>38%</td>
<td>32%</td>
<td>4%</td>
</tr>
<tr>
<td>GU</td>
<td>16%</td>
<td>19%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*2D RT*
Anal Anatomy for IMRT

- Gross Disease

- Nodal Areas at Risk:
  - inguinal
  - internal & external iliac
  - mesorectal (peri-rectal and presacral)
  - target volumes differ from GYN & GU
  - rectum and associated mesentary are target, not avoidance structures

Myerson, Kachnic et al., IJROBP 74: 824-30, 2009

Courtesy Lisa Kachnic
Methodology

- Three CTVs
  - CTVA: peri-rectal, pre-sacral, internal iliac
  - CTVB: external iliac
  - CTVC: inguinal
Indications

- Anal Cancer: CTVA + CTVB + CTVC
- Rectal Cancer: CTVA
  - + CTVB - if invasion of GYN/GU structures
  - + ?CTVC? - if invasion of anus or peri-anal skin - no consensus

Courtesy Lisa Kachnic
Recommendations: 
Upper Pelvis, CTVA CTVB

Upper Extent: 
sacral promentory/
bifurcation of ext/int iliacs

CTVA: 
~ 1 cm pre-sacral margin & ~ 1 cm around int iliac vessels
-Cephalad extent of peri-rectal coverage: top of rectum or 2 cm above tumor

CTVB: .7 to ~ 1 cm around ext iliac vessels

Courtesy Lisa Kachnic
**Recommendations:**

**Mid Pelvis, CTVA CTVB CTVC**

**CTVA:** include internal iliacs + at least the posterior portion of the obturator vessels

~ 1 cm anterior margin for bladder variability

**CTVB, C:** ~ 0.7 cm vascular margin--consider more anterolaterally

-external iliac to inguinal transition at ~ bottom of the obturator vessels (upper edge of superior pubic ramus)
-include all detectable LNs even if considered reactive

Courtesy Lisa Kachnic
Recommendations: Lower Pelvis, CTVA CTVC

Lower Extent of CTVA:
- Rectal Cancer: 2 cm caudad to disease or the pelvic floor, whichever is more caudad
- Anal cancer: 2 cm skin margin around verge plus 2 cm skin margin beyond any involved skin

Lower Extent of CTVC:
- 2 cm caudad to saphenous/femoral junction

Courtesy Lisa Kachnic
T2/N0 IMRT Dose Prescription

Single 28-fraction course, dose-painted:

- Primary PTV: $180 \text{ cGy} \times 28 = 5040 \text{ cGy}$
- Elective Nodal PTV: $150 \text{ cGy} \times 28 = 4200 \text{ cGy}$
T3/T4 or N+ IMRT Prescription

Single 30-fraction course, dose-painted:

- Primary PTV: 180 cGy x 30 = 5400 cGy
- Elective Nodal PTV: 150 cGy x 30 = 4500 cGy
- Nodal Positive PTV:
  - < 3 cm 168 cGy x 30 = 5040 cGy
  - > 3 cm 180 cGy x 30 = 5400 cGy

Courtesy Lisa Kachnic
Simulation

- Full bladder
- Prone on bowel displacement device (if can do daily OBI or equivalent)
- Anal marker & wire on distal edge of tumor if possible
- IV & oral contrast
- 2.5 to 5 mm CT slices

Courtesy Lisa Kachnic
Anal Cancer IMRT Planning Parameters & Dose Prescriptions

**GTV = Gross Tumor Volume**
- GTVA = gross primary anal tumor volume (exam, scope and radiology)
- GTV50 = all involved nodal regions containing macroscopic disease ≤ 3 cm
- GTV54 = all nodal regions containing macroscopic disease > 3 cm

**CTV = Clinical Target Volume**
- CTVA = GTVA and the anal canal with a 2.5 cm cranial-caudal and 1.5 cm radial (AP and lateral) expansion (except into bone or air)
- CTV42, CTV45 = uninvolved nodal coverage (mesorectum, presacral, inguinal, internal & external iliac to common bifurcation) plus 7 – 10 mm radial expansion for T2N0 and T3-4 or N+ disease, respectively
- CTV50.4, CTV54 = involved nodal regions containing ≤ 3 cm or > 3 cm, respectively, plus 1 to 1.5 cm expansion

**PTV = Planning Target Volume**
- 5-10 mm around the CTV in all directions to define each respective PTV; pull back under inguinal skin
- prescription isodose surface will encompass at least 90% of the primary and involved nodal PTVs, and at least 85% of the uninvolved nodal PTVs

Courtesy Lisa Kachnic
Normal Tissue Contouring Guidelines

**DP-IMRT Dose Constraints for Normal Tissues Listed in Order of Descending Priority**

<table>
<thead>
<tr>
<th>Organ</th>
<th>&lt; 5% exceed (Gy)</th>
<th>&lt; 35% exceed (Gy)</th>
<th>&lt; 50% exceed (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel*^</td>
<td>45 &lt; 20cc</td>
<td>35 &lt; 150cc</td>
<td>30 &lt; 200cc</td>
</tr>
<tr>
<td>Femoral heads*</td>
<td>44</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Iliac crest</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>External genitalia</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Bladder</td>
<td>50</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Large bowel^</td>
<td>45 &lt; 20cc</td>
<td>35 &lt; 150cc</td>
<td>30 &lt; 200cc</td>
</tr>
</tbody>
</table>

*assigned criteria for major and minor violations on the RTOG 0529 trial;  
^dose constraints based on cubic centimeters

Courtesy Lisa Kachnic
Prone. Ten modulated fields (nine gantry angles) with 6-MV photons. Red colorwash = anal tumor PTV prescribed to 54 Gy. Orange colorwash = positive 2 cm right inguinal node PTV prescribed 50.4 Gy. The elective nodal PTVs (purple and violet) were prescribed 45 Gy.
Dose Volume Histogram

Normal Volume

Dose (cGy)

Line Type

ROIs

Display

ROI

GTV

CTV54 anal tumor

PTVA

CTV 45 Mesorectum an

PTV 45 MESO

PET+ing node

CTV 50 x3cm node

PTV 50 ING node

CTV 45 ING nodes

PTV 45 ING

CTV 45 EXT Iliac

PTV 45 EXT

ROI Statistics

Line Type

ROI

Trial

Min.

Max.

Mean

Std. Dev.

% Outside Grid

% > Max

Generalize EUD

Bladder

LAK STUDY

3212.1

5682.1

4203.7

523.7

0.00 %

0.00 %

4199.62

Bowel LG

LAK STUDY

246.5

5409.3

2477.2

1554.8

0.00 %

0.00 %

2480.45

Bowel SM

LAK STUDY

260.9

5214.1

2090.9

1109.4

0.00 %

0.00 %

2099.46

Femur L

LAK STUDY

2304.4

5247.3

4118.8

457.2

0.00 %

0.00 %

4117.48

Femur R

LAK STUDY

2813.4

4685.6

4147.2

324.8

0.00 %

0.00 %

4148.34

GTV

LAK STUDY

5396.7

5331.1

5615.7

94.7

0.00 %

0.00 %

5615.32

PTV 50 ING node

LAK STUDY

3641.2

5509.6

5150.9

139.2

0.00 %

0.00 %

5155.79

Courtesy Lisa Kachnic
RTOG 0528
Acute Toxicity (CTCAE v 3.0)

Grade 2+ GI/GU
Grade 3+ GI/GU
Grade 2+ Skin
Grade 3+ Skin
Grade 2+ Hem.
Grade 3+ Hem.

p=0.437
p=0.067
p=0.008
p<0.0001
p=0.062
p=0.342

RTOG 9811  RTOG 0529

Courtesy Lisa Kachnic
Median RT duration 43 days (range 32-59) vs. 49 days (range 4-100) on the MMC arm of 9811 \( (P < 0.0001) \)

Treatment breaks due to toxicity needed in 49%, as compared to 61% on the MMC arm of 9811 \( (P = 0.10) \)

Median duration of treatment break due to toxicity = 0 days (range 0-12), as compared to 3 days (range 0-33) on the MMC arm of 9811 \( (P = 0.0037) \)

Courtesy Lisa Kachnic
Anal Recommendations

• Chemoradiation with 5FU/MMC
• Increasingly, IMRT is being used
  – Follow the 0529 guidelines for dose/contouring
• Most recurrences occur within 3 years
• Do not biopsy too early
• Do not send for APR too early
• Recognize T3/4 and node + have substantial recurrence rates
Thank You
Question 1

• A 70 yo gentleman presents with rectal bleeding. Sigmoidoscopy shows a lesion 8 cm from the anal verge. Biopsy shows moderately differentiated adenocarcinoma. CT chest/abdomen/pelvis shows the rectal tumor and no metastatic disease. Colonoscopy shows no other lesions
The next step is:

A- Chemoradiation
B- Endorectal ultrasound
C- Pelvic MRI
D- Endorectal ultrasound or Pelvic MRI
Question 2

- A patient is found to have a T3 N+ (MRI) rectal cancer. You have recommended chemoradiation.
The most appropriate concurrent chemotherapy is:

- A - 5FU/Oxaliplatin
- B - Capecitabine/Irinotecan
- C - Capecitabine
- D - 5FU/Mitomycin C
Question 3

• A patient presents with a T3N0 rectal cancer by ultrasound staging. She asks you to consider short course radiation therapy.
Based on randomized data, in comparing short course and standard chemoradiation:

- A: Standard chemoradiation is associated with better local control
- B: Standard chemoradiation is associated with greater sphincter preservation
- C: Short course radiation is more toxic
- D: There is no difference in local control
A patient is found to have a squamous cell carcinoma of the anal canal. She is found to have a 3 cm primary tumor and CT scans and physical exam show no nodal disease.
For this patient with T2N0M0 anal cancer, the most appropriate therapy is radiation with:

- A- No chemotherapy
- B- Concurrent 5FU alone
- C- 5FU/MMC
- D- Induction cisplatin/5FU followed by concurrent cisplatin/5FU
Question 5

- When added to neodjuvant radiation and fluoropyrimidin (5FU or capecitabine), the addition of oxaliplatin was associated with:
  - A- higher pathological complete response rate (pCR)
  - B- Better tolerance of radiation
  - C- More Gr 3 or greater toxicity
  - D- Better survival
A 70 yo gentleman presents with rectal bleeding. Sigmoidoscopy shows a lesion 8 cm from the anal verge. Biopsy shows moderately differentiated adenocarcinoma. CT chest/abdomen/pelvis shows the rectal tumor and no metastatic disease. Colonoscopy shows no other lesions.

A. Chemoradiation
B. Endorectal ultrasound
C. Pelvic MRI
D. Endorectal ultrasound or Pelvic MRI