The Evolving Role of Radiation Therapy for Localized Lower GI Cancers

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Disclosures

- UpToDate™
- EPIC™
- INSYS Therapeutics
- NCI Funding (NRG Oncology, SWOG)
Learning Objectives

- Demonstrate knowledge of the evidence-based rationale for the use of definitive chemoradiation in localized anal canal cancer and preoperative chemoradiation for localized rectal cancer.

- Understand the novel strategies, including IMRT for anal cancer and the selective use of radiation in rectal cancer, to optimize treatment outcomes and reduce treatment-related morbidity.

- Appreciate ongoing and future investigations aimed at individualizing therapy.
Anal Cancer
## Risk Factors

<table>
<thead>
<tr>
<th>HPV (16, 18, 31, 33, 35)</th>
<th>Chronic immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple sexual partners</td>
<td>• HIV (anal SCC <em>not</em> AIDS-defining)</td>
</tr>
<tr>
<td>• Anal intercourse</td>
<td>• After solid-organ transplantation: dx at earlier age</td>
</tr>
<tr>
<td>• Sexual activity at young age</td>
<td></td>
</tr>
<tr>
<td>• Condyloma, AIN/ASIL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cigarette smoking</th>
<th>Correlated with duration and ppd</th>
</tr>
</thead>
</table>
Patient Evaluation

- Sexual history & HPV/HIV risk
- PE for tumor extent, sphincter function, groins
- Females: full gynecologic examination with Pap (other HPV disease)
- CBC, LFTs, renal fxn, HIV status
- Flexible sigmoidoscopy/colonoscopy with biopsy; p16 on path
- Abd-pelvic CT scan & chest x-ray; PET/CT
- FNA of suspicious groin nodes

<table>
<thead>
<tr>
<th>T1</th>
<th>≤ 2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>2-5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 5 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N1a</th>
<th>inguinal, mesorectal, or internal iliac lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1b</td>
<td>external iliac nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>external iliac nodes + N1a</td>
</tr>
</tbody>
</table>

* e.g. involving vagina, urethra, or bladder

Direct invasion of the rectal wall, peri-rectal skin, subcutaneous tissues, or sphincter muscles does not count as T4
## Prognostic Factors (RTOG 98-11)

Ajani et al: J Clin Oncol, 27:1116-21, 2009

<table>
<thead>
<tr>
<th>Disease-free survival</th>
<th>Time to colostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR</td>
</tr>
<tr>
<td>Male</td>
<td>1.38</td>
</tr>
<tr>
<td>cLN+</td>
<td>2.66</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Treatment Overview

- Anal margin
  - ~ skin cancer
  - surgical excision or radiation alone

- Adenocarcinoma
  - ~ rectal cancer

- SCCA of the anal canal
  - T1 tumors, local excision or radiation alone
  - T2 and above: chemoradiation therapy with curative intent
  - APR salvage for local recurrence
Wayne State/Nigro Regimen

- 28 pts; single institution study
- RT: 30 Gy in 15 fx via AP/PA fields to the pelvis, medial inguinal LN and anal canal
- Chemo: 5FU (1000 mg/m²/day) x 4 days + MMC (single 15 mg/m² bolus)
- APR planned; 5/6 initial pts had no residual tumor at APR; APR was then reserved as salvage
- Overall, 86% (24/28) clinical CR to chemo-RT
- Follow-up series OS₅ 67%; CFS₅ 59%
## Role of Chemotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Grade 4/5 Acute AEs</th>
<th>LC</th>
<th>CFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKCCCR¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>585</td>
<td></td>
<td>39%</td>
<td>61%</td>
<td>58%*</td>
</tr>
<tr>
<td>RT/5FU/MMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65%*</td>
</tr>
<tr>
<td>EORTC²</td>
<td></td>
<td></td>
<td>39%</td>
<td>40%</td>
<td>65%*</td>
</tr>
<tr>
<td>RT</td>
<td>110</td>
<td></td>
<td>58%</td>
<td>72%</td>
<td>72%*</td>
</tr>
<tr>
<td>RT/5FU/MMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 87-04³</td>
<td></td>
<td></td>
<td>7%</td>
<td>64%**</td>
<td>58%**</td>
</tr>
<tr>
<td>RT/5FU</td>
<td>310</td>
<td></td>
<td>23%</td>
<td>83%**</td>
<td>64%**</td>
</tr>
<tr>
<td>RT/5FU/MMC</td>
<td></td>
<td></td>
<td></td>
<td>65%**</td>
<td>67%**</td>
</tr>
</tbody>
</table>

*3-yr; **5-yr; purple denotes statistically significant

¹UKCCCR, Lancet 1996; ²Bartelink, JCO 1997; ³Flam, JCO 1996
Sequelae of Conventional Nonconformal ChemoRT

- **Acute:**
  - Anorectal dysfunction (frequency & urgency)
  - Dermatitis (grade $\frac{3}{4} > 50\%$)
  - Heme morbidity (grade $\frac{3}{4} > 50\%$), neutropenic sepsis
    - 6 chemotherapy-related deaths in UKCCCR study
    - 4 deaths in the RTOG/ECOG study

- **Chronic:**
  - Anal incontinence/fibrosis (5-15\%)
  - Vaginal stenosis
  - Small bowel obstruction (5-10\%, but increases over time)
  - Hip fracture (10-15\%; more common in women)
  - Sexual dysfunction

UKCCRC: Lancet 348:1049-54, 1996;
Strategies to Maintain Outcomes and Decrease Morbidity

- Substitution of MMC: RTOG 98-11
- Technical improvements in RT: IMRT (RTOG 0529)
RTOG 98-11 (T2-4 Nx M0; no HIV)

RT: 45 Gy

Boost 10-14 Gy

Cisplatin 75 mg/m²
5FU 1g/m²

MMC 10 mg/m²
5FU 1g/m²

T3/4;N+, T2 with RD
Boost 10-14 Gy

T3/4;N+, T2 with RD

Ajani et al: Jama 299 (16), 1914-21, 2008
Study Endpoints

- Primary: 5-year DFS increase from 63 to 73% (n=682)

- Secondary: overall worst AEs
## RTOG 98-11: Outcomes

<table>
<thead>
<tr>
<th>5-Year Rates</th>
<th>CDDP/5FU – RT/CDDP/5FU n=320 (%)</th>
<th>RT+MMC/5FU n=324 (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free Survival</td>
<td>54</td>
<td>60</td>
<td>0.17</td>
</tr>
<tr>
<td>Local Relapse</td>
<td>33</td>
<td>25</td>
<td>0.07</td>
</tr>
<tr>
<td>Colostomy</td>
<td>19</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>19</td>
<td>15</td>
<td>0.14</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>70</td>
<td>75</td>
<td>0.10</td>
</tr>
</tbody>
</table>

**MEDIAN f/u 2.5 years**

### RTOG 98-11: Five Year Outcomes

<table>
<thead>
<tr>
<th>5-Year Rates</th>
<th>CDDP/5FU – RT/CDDP/5FU n=320 (%)</th>
<th>RT+MMC/5FU n=324 (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free Survival</td>
<td>57.8</td>
<td>67.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Local Relapse</td>
<td>26.4</td>
<td>20</td>
<td>0.087</td>
</tr>
<tr>
<td>Colostomy</td>
<td>17.3</td>
<td>11.9</td>
<td>0.074</td>
</tr>
<tr>
<td>Distant Mets</td>
<td>18.1</td>
<td>13.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>70.7</td>
<td>78.3</td>
<td>0.026</td>
</tr>
</tbody>
</table>

**MEDIAN f/u = 5 years**

Gunderson et al: JCO 30 (35), 4344-51, 2010
# RTOG 98-11: Toxicity

<table>
<thead>
<tr>
<th>Acute Toxicity</th>
<th>RT/5FU/MMC</th>
<th>Induction 5FU/CDDP → RT/5FU/CDDP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3/4 hematologic</td>
<td>61%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G3/4 non-hematologic</td>
<td>74%</td>
<td>74%</td>
<td>NS</td>
</tr>
<tr>
<td>Worst overall</td>
<td>87%</td>
<td>83%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Similar rates of severe long-term side effects: 11% vs. 10%

RTOG 98-11 Conclusions

- Not a direct comparison between arms
- Difference in DFS, OS with 5 year follow-up in favor of standard arm
- Cumulative colostomy rate significantly worse in CDDP arm; ? delay in radiation with induction chemo ? different radiosensitization on two arms
- No overall toxicity savings in CDDP arm
- **Induction** chemotherapy is not of additional benefit
- Is CDDP inferior to MMC – cannot determine with 98-11
- From this trial - RT plus 5FU/MMC remains the standard of care for patients with anal canal carcinoma
RTOG 98-11 Acute Toxicity Anal Cancer

<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>Gl</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>

*5FU, MMC arm

RTOG 0529: Dose Painted IMRT

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

DP-IMRT – Real Time Review
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

Study Endpoints

- Primary: Reduce combined grade 2+ GI/GU toxicities by 15%, as compared to 98-11 5FU/MMC arm (n=59 pts)

- Secondary: all AEs vs. 98-11

- Secondary: feasibility (< 5 cases with major deviations)

- Secondary: two year outcomes
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
Results

- Total of 52 pts evaluable
- 81% required volume re-contouring (mesorectum #1 offender)
- On final review, only 3 cases with major violations on normal tissue (feasibility endpoint met)
- Median DP-IMRT duration 43 days (range 32-59) vs. 49 days (range 4-100) on the 5FU/MMC arm of 9811 ($P < 0.0001$)

Elective nodal coverage =
Internal iliac, external iliac, mesorectal, presacral, & inguinal
Rectum = target

Acute Toxicity: 0529 vs. 98-11

- Grade 2+ GI/GU: p=0.5
- Grade 3+ GI/GU: p=0.0052
- Grade 2+ Skin: p=0.10
- Grade 3+ Skin: p<0.0001
- Grade 2+ Hem.: p=0.032
- Grade 3+ Hem.: p=0.29
## Two Year Outcomes: 0529 vs. 98-11

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>0529 (n=52)</th>
<th>9811 - MMC Arm (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Events</td>
<td>2y-% (95% C.I.)</td>
</tr>
<tr>
<td>Local-Regional Failure</td>
<td>11</td>
<td>19 (8, 30)</td>
</tr>
<tr>
<td>Colostomy Failure</td>
<td>5</td>
<td>8 (0.4, 15)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>11</td>
<td>86 (73, 93)</td>
</tr>
<tr>
<td>Disease-Free Survival</td>
<td>13</td>
<td>77 (63, 86)</td>
</tr>
<tr>
<td>Colostomy-Free Survival</td>
<td>12</td>
<td>84 (71, 92)</td>
</tr>
<tr>
<td>Distant Failure</td>
<td>8</td>
<td>14 (4, 24)</td>
</tr>
</tbody>
</table>
RTOG 0529 Conclusions

- While preclinical chosen primary endpoint is negative, the use of IMRT significantly improved grade 3+ GI, dermatologic and grade 2 hematologic toxicity; significantly decreased the duration of CRT as compared to MMC arm of RTOG 98-11

- The use of IMRT is feasible amongst different U.S. centers, but requires much education

- Outcomes are at least comparable and may be better; long-term outcomes and patterns of failure are currently being prepared for ASTRO 2017
Strategies for Optimizing Outcomes in Locally Advanced Disease

- Intensification of therapy: UK ACT II (adjuvant chemo), ACCORD (higher dose RT), AMC 045/ ECOG 3205 (EGFR inhibitor)
## Advanced Stage Disease Associated with Poor Outcomes (Analysis of RTOG 98-11)

<table>
<thead>
<tr>
<th>5-YR %</th>
<th>T2N0</th>
<th>T3N0</th>
<th>T4N0</th>
<th>T2N+</th>
<th>T3N+</th>
<th>T4N+</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>81</td>
<td>75</td>
<td>59</td>
<td>66</td>
<td>44</td>
<td>48</td>
<td>.0001</td>
</tr>
<tr>
<td>DFS</td>
<td>69</td>
<td>63</td>
<td>40</td>
<td>40</td>
<td>26</td>
<td>34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LRF</td>
<td>19</td>
<td>22</td>
<td>50</td>
<td>40</td>
<td>58</td>
<td>64</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DM</td>
<td>12</td>
<td>14</td>
<td>21</td>
<td>31</td>
<td>32</td>
<td>17</td>
<td>.0035</td>
</tr>
<tr>
<td>CF</td>
<td>10</td>
<td>14</td>
<td>20</td>
<td>9</td>
<td>23</td>
<td>17</td>
<td>.0147</td>
</tr>
</tbody>
</table>

From 98-11, Gunderson et al.: ASCO GI, 2010
ACT II UK (T1-4 Nx M0)

- Cisplatin 60 mg/m²
- 5FU 1g/m²

RT: 50.4 Gy

- MMC 12 mg/m²
- 5FU 1g/m²

RT: 50.4 Gy

n = 940

- 1st R endpoint: 5% increase in cCR with CDDP
- 2nd R endpoint: progression-free survival 25% to 17.5% decrease with maintenance 5FU/CDDP
- Median follow-up 5.1 years

## ACT II

### 1st Randomization

<table>
<thead>
<tr>
<th></th>
<th>RT+CDDP/5FU n=468 (%)</th>
<th>RT+MMC/5FU n=472 (%)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo. cCR</td>
<td>89.6</td>
<td>90.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Colostomy Rate 3Y</td>
<td>11.3</td>
<td>13.7</td>
<td>NS</td>
</tr>
<tr>
<td>G 3/4 Heme AE</td>
<td>16</td>
<td>26</td>
<td>0.001</td>
</tr>
<tr>
<td>G 3/4 Non-Heme AE</td>
<td>68</td>
<td>62</td>
<td>0.22</td>
</tr>
</tbody>
</table>

### 2nd Randomization

<table>
<thead>
<tr>
<th></th>
<th>CRT + CT n=448</th>
<th>CRT alone n=446</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free Survival 3 Y (73%/74% CDDP/MMC arm)</td>
<td>HR 0.95, 95% CI 0.75-1.21</td>
<td></td>
<td>0.70</td>
</tr>
</tbody>
</table>

ACT II Conclusions

- 5FU/MMC should remain standard of care
- CDDP appears no more effective than MMC
- Maintenance chemotherapy not effective
ACCORD 03 (T2>4cm-4 Nx M0)

Primary endpoint CFS

# ACCORD 03 (n=307) Five Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>2 CDDP/5FU/ CRT low RT dose</th>
<th>2 CDDP/5FU/ CRT high RT dose</th>
<th>CRT low RT dose</th>
<th>CRT high RT dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>78%</td>
<td>86%</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>Colostomy-free Survival</td>
<td>70%</td>
<td>82%</td>
<td>77%</td>
<td>73%</td>
</tr>
</tbody>
</table>

- No survival benefit of adjuvant CT or higher dose RT

Conroy et al: J Clin Oncol 2009; abstr 4033
### AMC 045 & ECOG 3205 Trials:
5FU, CDDP, Cetuximab + RT (IMRT Optional) - Three Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>AMC045</th>
<th>E3205</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>45 HIV +</td>
<td>61 (28 with induction CT)</td>
</tr>
<tr>
<td>Stage I/II/III</td>
<td>24%/42%/34%</td>
<td>5%/31%/64%</td>
</tr>
<tr>
<td>Completed Therapy</td>
<td>37 (82%)</td>
<td>49 (79%)</td>
</tr>
<tr>
<td>Grade 3+ Adverse Events</td>
<td>&gt; 50% (2 grade 5)</td>
<td>&gt; 50% (3 grade 5)</td>
</tr>
<tr>
<td>3 Y CFS (95% CI)</td>
<td>89% (74-96%)</td>
<td>75% (61-84%)</td>
</tr>
<tr>
<td>3 Y LRF</td>
<td>42%</td>
<td>23%</td>
</tr>
<tr>
<td>3 Y PFS (95% CI)</td>
<td>72% (56-84%)</td>
<td>68% (55-79%)</td>
</tr>
</tbody>
</table>

Sparano et al: J Clin Oncol 2016 Epub
HIV and Anal Cancer Summary

- HIV+ patients tend to be male and present at a younger age
- No apparent difference in OS or CSS between HIV+ and HIV- patients treated with concurrent chemoRT
- Controversial, but decreased LC in HIV+ patients and increased acute toxicity
- IMRT appears to provide improved toxicity with excellent LC
- So treat the same as non-HIV with 5FU/MMC and IMRT unless CD4 count < 200; then consider 5FU/CDDP/RT
Follow-up after CRT

- Exam at 4 weeks & at 8 weeks post CRT; if disease persistent but regressing – monitor, biopsy NOT indicated at this time.

- If clinical suspicion of non-responding disease at 12 weeks – can still watch if moving in the right direction until 6 months per ACT II.

- Biopsy at persistent disease OK between 3-6 months; if still disease at 6 months, restage and if no met disease, consider APR.

- Progressive disease at any time = immediate biopsy and re-staging.

- PET at 3 months post CRT completion is good biomarker of response if insurance will allow.

- Vaginal dilator for women at one month post CRT completion.
Localized Anal Cancer: Summary & Conclusions

- Multidisciplinary treatment modality is imperative
- Chemoradiation with curative intent remains gold standard for previously untreated patients
  - 5-FU & MMC still recommended
  - RTOG 98-11/ACT II shows adjuvant chemotherapy of no benefit
  - ACCORD 03 shows that higher doses of RT of no benefit
  - IMRT now standard
- Challenges that remain:
  - Enhanced therapy for advanced disease
  - Reduced therapy for HPV+ early stage disease
Rectal Cancer
Risk of CRC

- General population: 5%
- Personal history of colorectal neoplasia: 15%–20%
- Inflammatory bowel disease: 15%–40%
- HNPCC mutation: 70%–80%
- FAP: >95%

Lifetime risk (%)
Patient Evaluation

- H & P, DRE (fixed - mobile - ulcerated – exophytic; distance from verge; anal tone; peri-rectal LAD; adjacent organ involvement)
- Chest X-ray (or CT chest) & abdominopelvic CT
- Full colonoscopy (synchronous disease in 5%)
- TRUS and/or pelvic MRI for local staging
- CBC (Hct), BUN/Cr, LFTs, CEA
Improved Local Failure in Rectal Cancer

Better Surgery
- Total Mesorectal Excision (TME)
- Adequate nodal dissection

Radiotherapy and/or Chemotherapy
- Pre-operative

- 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
Preoperative Radiation Alone

• 20 + Randomized Trials:
  • Majority Short Course Hypofractionated RT
  • All Decrease LR
  • Swedish Rectal Cancer Trial Showed Survival Advantage
  • Problem = Ano-rectal Morbidity & Late Effects
Swedish Rectal Cancer Trial (No TME)

1168 Resectable Rectal Cancers

25 Gy in 5 Fxs Surgery 1 Wk Later (RT→S)

Surgery (S)

Swedish Trial Outcomes 13 Years

<table>
<thead>
<tr>
<th></th>
<th>RT→ S</th>
<th>S Only</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>9%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>38%</td>
<td>30%</td>
<td>0.008</td>
</tr>
<tr>
<td>CSS</td>
<td>72%</td>
<td>62%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*N.B. Only trial to show survival advantage with RT alone.*

Dutch CKVO 95-04 TME Trial

1805 Operable Rectal Cancers

25 Gy in 5 Fxs TME 1 Wk Later (RT→S)

Total Mesorectal Excision Surgery (TME)

## Dutch CKVO 95-04 - Ten Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>RT→S</th>
<th>S Only</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>5.1%</td>
<td>11.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>47.6%</td>
<td>48.8%</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>24.9%</td>
<td>28.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Surgery +/- Short Course Preop Radiation: Local Recurrence

- Swedish Trial, 5 yrs: 27%
- Dutch TME Trial, 5 yrs: 11%
Conclusions

- Short course preop RT decreases LR, even with meticulous TME
- TME decreases LR over non-TME resection
- Selective RT for CRM + margins was inferior to short course pre-op RT
- Notable late bowel effects
German Rectal Cancer Group CAO/ARO/AIO-94 Study Established Preop CRT, TME & Postop 5FU for T3/T4, N+ Localized Rectal Cancer

N=823; Primary Endpoint OS

## CAO/ARO/AIO-94 Five Year Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preop (%)</th>
<th>Postop (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gd 3-4 acute toxicity</td>
<td>27</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Gd 3-4 late toxicity</strong></td>
<td><strong>14</strong></td>
<td><strong>24</strong></td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Pathologic CR</td>
<td>8</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N+ (Downstaging)</td>
<td>25</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Pelvic recurrence</td>
<td>6</td>
<td>13</td>
<td>0.006</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>76</td>
<td>74</td>
<td>NS</td>
</tr>
<tr>
<td>Disease-free Survival</td>
<td>68</td>
<td>65</td>
<td>NS</td>
</tr>
</tbody>
</table>

Ten Year Recurrence (German Trial)

10-yr Local Recurrence: 7.1% (preop) vs. 10.1% (postop), p=.048

Strategies for Optimizing Outcomes in Locally Advanced Disease

- Addition of oxaliplatin to standard chemoradiation
- Other radiosensitizers
- US TNT (total neoadjuvant therapy) protocol
Impact of Oxaliplatin:
NSABP R-04 Phase III Preoperative

Stratify

- T2 vs. T3
- M vs. F
- SP vs. APR

Capecitabine (825 mg BID) 50.4 Gy

+ Oxaliplatin (50 mg/m2 qw)

CI 5-FU (225 mg/m2/d) 50.4 Gy

+ Oxaliplatin (50 mg/m2 qw)

n=1608
Primary Endpoint: LRR
*TME Not Mandated

R-04 Endpoints

- Primary Endpoint: 3-year local-regional control with 3 years of minimum follow-up.

- Secondary Endpoints:
  - Rate of pathologic CR
  - Number of pts undergoing sphincter-saving surgery
  - Disease free and overall survival
  - Quality of Life
  - Toxicity
  - Correlating genetic patterns and specific tissue biomarkers with response and prognosis
NSABP R-04 pCR Rates (%)

- **5-FU**: 17.8% (15.1-20.6)
- **Cape**: 20.7% (17.9-23.7)
- **No Oxali**: 17.8% (14.9-21.0)
- **Oxali**: 19.5% (16.5-22.8)

* No significant fluoropyrimidine by oxaliplatin interaction

NSABP R-04
Primary Endpoint: Local-Regional Control

5-FU vs. Cape

- 5-FU: 782 Pts, 95 L/R Recurrence
- Cape: 785 Pts, 97 L/R Recurrence
- HR = 1.00, 95% CI (0.75-1.32)
- P = 0.98

No Oxali vs. Oxali

- No Oxali: 641 Pts, 81 L/R Recurrence
- Oxali: 643 Pts, 76 L/R Recurrence
- HR = 0.94, 95% CI (0.67-1.29)
- P = 0.70

## NSABP R-04 Mortality & Adverse Events (%)

<table>
<thead>
<tr>
<th>Toxicity (Grade)</th>
<th>5-FU</th>
<th>Capecitabine</th>
<th>5-FU + Oxaliplatin</th>
<th>Capecitabine + Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (3+)</td>
<td>26.5</td>
<td>30.1</td>
<td>39.9</td>
<td>42.2</td>
</tr>
<tr>
<td>Diarrhea (3/4)</td>
<td>7</td>
<td>7</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Death (5)</td>
<td>0.3</td>
<td>1.3</td>
<td>0.3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

NSABP-R-04 Conclusions

- Capecitabine with preop RT achieved rates similar to CIV 5-FU for:
  - LR Failure – Primary Endpoint
  - pCR
  - DFS
  - OS

- Oxaliplatin did not improve outcomes but added significant GI toxicity (diarrhea) and is therefore not indicated in combination with RT in the preop rectal setting

- Establishes capecitabine as a standard of care in the preop rectal setting

- Fully annotated tissue samples available for molecular studies
NRG GI-002 (TNT) Schema
Ph II Non-comparative experimental arms (PI George)

High Risk (distal, bulky, N2) Locally Advanced Rectal Cancer

- FOLFOX x 8 → XRT + Capecitabine → Surgery
- FOLFOX x 8 → XRT + Capecitabine + Veliparib → Surgery
- FOLFOX + x 8 → XRT + Capecitabine + ? → Surgery

Primary Endpoint: Reduction in NAR Score from 14.32 (contemporary studies) to 9.62; corresponds to a ~20% reduction of HR for death and 3-4% increase in 5 year OS; 87 per arm
Design/Eligibility

- Randomized phase II modular clinical trial platform in locally advanced rectal cancer
  - Distal (≤5cm from anal verge)
  - Bulky (<3mm pelvic side wall margin on imaging)
  - High risk of mets (N2 disease)
  - Not candidates at diagnosis for sphincter preservation

- Complete all therapy pre-op
- Test novel intensification hypotheses
TNT Endpoints

Primary = NAR Score

Secondary

• pCR
• Toxicity
• 3 year OS and DFS
  • Rate of negative circ margin
  • Rate of sphincter preservation/function/QOL
  • Rate of local recurrence
• Compliance
• Correlative molecular predictors of response and distant failure
Neoadjuvant Rectal (NAR) Score

Developed to include more relevant downstaging parameters than just pCR

\[
NAR = \left[5 \ pN - 3 (cT - pT) + 12 \right] \div 9.61
\]

Where

- \(cT\) in \{1, 2, 3, 4\},
- \(pT\) in \{0, 1, 2, 3, 4\},
- \(pN\) in \{0, 1, 2\}

Validated in NSABP R-04

Yothers et al. GI Cancer Symposium #384
Yothers et al: ASCO 2014 #3533
Overall Survival By NAR Score Group

Overall Survival

Years from Surgery

Low Score Reference, p < 0.0001

Int Score HR=1.53 (1.00-2.33)

High Score HR=4.48 (3.03-6.63)
Strategies to Reduce Morbidity in Locally Advanced Rectal Cancer

- Selective Use of Radiation
Sequelae of CRT with 5FU or Cape

- **Acute:**
  - Anorectal dysfunction (frequency & urgency)
  - GI (grade 2+ > 30%)
  - Heme (lower with CI 5-FU)
  - Hand/foot

- **Chronic:**
  - Anorectal dysfunction
  - F: Vaginal stenosis
  - M: Erectile dysfunction
  - Anastomotic stricture (4-10%)
  - Small bowel obstruction (5-15%, but increases over time)
  - Hip fracture (10-15%; more common in women)
Who Needs Pelvic Radiation?
Intergroup Pooled Analysis of Postop Trials: T & N Stage

- 3791 Pts from 5 Phase III Trials (NCCTG, INT, NSABP R01 + R02): Outcome Analyzed by T & N Stage and Treatment
  - Intermediate Risk: T1-2/N1 or T3N0
  - Moderate Risk: T1-2/N2, T3N1, T4N0
  - High Risk: T3N2, T4N1-2

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>TNM Stage</th>
<th>5-yr LR</th>
<th>5-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0</td>
<td>&lt;5%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>T2N0M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0M0</td>
<td>5-10%</td>
<td>80%</td>
</tr>
<tr>
<td>IIB</td>
<td>T4aN0M0</td>
<td>10-15%</td>
<td>60%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4bN0M0</td>
<td>5-10%</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T1-2N1 / T1N2a</td>
<td>5-10%</td>
<td>80%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1-2N2a / T1N2b</td>
<td>10-15%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>M1a</td>
<td>5-10%</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>10-15%</td>
<td>60%</td>
</tr>
</tbody>
</table>

**Stage II: T3/T4, node-negative**

**Stage III: Node-positive**
**Hypothesis:** Treatment with neoadjuvant FOLFOX and selective use of preop 5FU-CRT for LARCs with curative intent sphincter sparing TME is not inferior to 5FU-CRT followed by surgery and FOLFOX
Eligibility

- Biopsy proven rectal adenocarcinoma at age 18+
- Tumor located at 5-12 cm from the anal verge
- Candidate for sphincter sparing surgery according to TME experienced surgeon
- Baseline Clinical staging: T2N1, T3N0, T3N1
  - Physical exam by primary surgeon
  - Proctoscopy
  - MRI or ERUS (MRI preferred)
  - CT scan of C/A/P
PROSPECT Endpoints

Primary Outcomes:
- Randomized Phase II Component; n = 366
  - R0 Resection Rate
  - Time to local recurrence (TLR)
- Phase III Component: Co-primary endpoints; n = 644
  - Time to local recurrence (TLR)
  - Disease free survival (DFS)

Secondary Outcomes:
- Pathologic complete response rate (CR)
- Overall survival
- Quality of life (QOL)
- Clinician and patient reported treatment toxicity – WILL INCLUDE PROCTCAE
- Molecular correlates of response to neoadjuvant therapy
Rectal Cancer - Radiation Techniques

CT Simulation

- Supine (thin) or Prone
- Belly Board / Bowel Compression if Prone
- Aquaplast / Vac-loc Bag (or equivalent) if Supine
- Full Bladder
- Oral (SB Follow Through) +/- i.v. Contrast
- Anal marker; consider vaginal marker
- ≤ 3mm Slice Thickness
- Use Multiple Fields
- Consider IMRT for Select Cases (nodal burden, small bowel issues)
Rectal Cancer – Target Definition

CTV: Elective nodal regions

- Standard: Peri-rectal, internal iliac, and superior hemorrhoidal (7 mm around vessels)
- For T4 tumors extending anteriorly: include external iliac
- For tumors invading anal canal: include inguinal and external iliac

PTV: 5 mm around CTV
Rectal Conformal Dose Constraints

- **3D Plan – Final Tumor Dose 50.4 Gy in 28 Fractions**
  - 45 Gy to pelvis in 25 fractions
    - Standard – 3-field if prone
    - External iliac coverage for T4 – 4-field may be needed
  - 5.4 Gy to boost tumor/mesorectum in 3 fractions – lats or 3-field
  - Femoral heads, small bowel < 45 Gy; small bit sb 50.4 Gy

- **IMRT Plan – Final Tumor Dose of 50 Gy in 25 Fractions (Dose Painted)**
  - 5-field + plan
  - 45 Gy to PTV45 for elective pelvis
  - 50 Gy to PTV rectal tumor and PTV positive nodes
RTOG 0822 Phase II Rectal IMRT Trial

cT3-4NxM0 or cTxN1-2M0
Preop for planned resection

Radiation + Chemo
capcitabine
± oxaliplatin

Adjuvant Chemo
FOLFOX

Surgery
LAR or APR

68 patients; 58 contoured correctly; grade 2 + GI toxicity was 52%

Hong et al: IJROBP 93: 29-36, 2015
Acute Toxicity: 3D vs. IMRT (BMC)

Figure 1. Grade 2 or higher acute toxicity (%): 3D-CRT vs. IMRT

- Overall: $P = 0.035$
- GI: $P = 0.077$
- Diarrhea: $P = 0.039$
- GU: $P = 0.503$
- Heme: $P = 0.160$
- Skin: $P = 0.991$

Localized Rectal Cancer: Summary & Conclusions

- US standard for stage II/III disease is long course preoperative CRT (50 Gy RT & cape), TME 6-10 weeks later and FOLFOX x 8

- Oxali in the preop mix has proven not to improve outcomes

- Current developing studies are evaluating moving outback chemo upfront, novel radiosensitizers and risk-based treatments (selective use of RT) in an attempt to optimize outcomes while minimizing morbidities