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 morbidities

- Appreciate ongoing and future investigations aimed at individualizing therapy
Anal Cancer
Background

- Anal cancer is fairly rare – much less common than cancer of the colon or rectum\(^1\)
  - In 2018, approximately 8,580 individuals (5,620 women and 2,960 men) were diagnosed with anal cancer\(^2\)
  - 1,160 estimated deaths (680 women and 480 men)\(^2\)

- The number of new anal cancer cases has been rising for many years\(^1\)

- Anal cancer is **exclusively an HPV-driven disease**\(^3\); however, its low prevalence among other GI cancers (2.5%) makes specialization in this tumor rare

- Anal cancer is an area of relatively limited clinical research focus

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Patient Evaluation

- Sexual history & HPV/HIV risk
- PE for tumor extent, sphincter function, groins
- Females: full gynecologic examination with Pap (other HPV disease)
- Male: full GU examination with Pap if high risk
- 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
## Anal Cancer Staging – AJCC TNM 8th Edition 2018

<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>
<tr>
<td>T4</td>
<td>Locally invasive*</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)

<table>
<thead>
<tr>
<th></th>
<th>Disease-free Survival</th>
<th></th>
<th>Time to Colostomy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR</td>
<td>95% CI</td>
<td>P</td>
<td>Adjusted HR</td>
</tr>
<tr>
<td>Male</td>
<td>1.38</td>
<td>1.05-1.81</td>
<td>0.02</td>
<td>0.97</td>
</tr>
<tr>
<td>cLN+</td>
<td>2.66</td>
<td>2.04-3.46</td>
<td>&lt;.0001</td>
<td>1.03</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>1.5</td>
<td>1.14-1.97</td>
<td>0.004</td>
<td>1.85</td>
</tr>
</tbody>
</table>

NCCN Current Anal Cancer Treatment Guidelines Demonstrate *Limited Therapeutic Options*

<table>
<thead>
<tr>
<th>Localized Cancer</th>
<th>Metastatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-FU + Mitomycin + RT</strong></td>
<td></td>
</tr>
<tr>
<td>Continuous-infusion 5-FU 1000 mg/m²/d IV days 1–4 and 29–32</td>
<td></td>
</tr>
<tr>
<td>Mitomycin 10 mg/m²/d IV bolus days 1 and 29</td>
<td></td>
</tr>
<tr>
<td>Concurrent radiotherapy (now IMRT)</td>
<td></td>
</tr>
</tbody>
</table>

| **5-FU + Cisplatin**  |
| Continuous-infusion 5-FU 1000 mg/m²/d IV days 1–5 |
| Cisplatin 100 mg/m² IV day 2 |
| Repeat every 4 weeks |

| +/- Capecitabine + Mitomycin + RT  |
| Capecitabine 825 mg/m² PO BID, Monday – Friday, on each day that RT is given, throughout the duration of RT (typically 28 treatment days) |
| Mitomycin 10 mg/m² days 1 and 29 |
| Concurrent radiotherapy (IMRT) |
| or |
| Capecitabine 825 mg/m² PO BID days 1–5 weekly × 6 weeks |
| Mitomycin 12 mg/m² IV bolus day 1 |
| Concurrent radiotherapy (IMRT) |
IRCI/EORTC/ECOG EA2133: InterAACT1st Line Met SCCA of the Anal Canal to Establish a Standard

Arm A

Cisplatin 75 mg/m² day 1 + 5FU 1000 mg/m² infusion/24 hours/4 days q28 days

Arm B

Carboplatin (AUC = 5) + Paclitaxel (weekly) q21 days

- Treatment for 6M and cont at the discretion of the investigator
- Substratification: HIV+/HIV-, HPV status, and prior XRT
- CT scans: q3M
- N=100/Closed October 2017

Study PIs UK - Rao, US - Eng

Objective: Identify best chemotherapy backbone to build for biologic development
1) Primary endpoint: RR
2) Secondary endpoints: PFS, OS, correlatives, and QOL, etc.
Localized Treatment Overview

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

- Adenocarcinoma
  - ~ rectal cancer

- SCCA of the anal canal
  - T1 tumors: local excision, radiation alone or chemoradiation
  - 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/m$^2$/day) x 4 days + MMC (single 15 mg/m$^2$ 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 chemoRT
- Follow-up series OS$_5$ 67%; CFS$_5$ 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 RT</td>
<td>585</td>
<td></td>
<td>39%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>RT/5FU/MMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58%*</td>
</tr>
<tr>
<td>EORTC² RT</td>
<td>110</td>
<td></td>
<td>39%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>RT/5FU/MMC</td>
<td></td>
<td></td>
<td>58%</td>
<td>72%</td>
<td>65%*</td>
</tr>
<tr>
<td>RTOG 87-04³ RT</td>
<td>310</td>
<td></td>
<td>7%</td>
<td>64%**</td>
<td>65%**</td>
</tr>
<tr>
<td>RT/5FU</td>
<td></td>
<td>23%</td>
<td>64%**</td>
<td>58%**</td>
<td></td>
</tr>
<tr>
<td>RT/5FU/MMC</td>
<td></td>
<td></td>
<td>83%**</td>
<td>64%**</td>
<td>67%**</td>
</tr>
</tbody>
</table>

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

Sequelae of Conventional Nonconformal ChemoRT

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

**Chronic:**
- Anal incontinence/fibrosis (5-15\%)
- Vaginal stenosis (30-80\%)
- Small bowel obstruction (5-10\%, but increases over time)
- Hip fracture (10-15\%; more common in women)
- Sexual dysfunction

Strategies to Decrease Morbidity

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

- MMC 10 mg/m²
- 5FU 1g/m²
- Cisplatin 75 mg/m²
- RT: 45 Gy
- Boost 10-14 Gy

- T3/4; N+, T2 with RD

Endpoints

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

- **Secondary**: overall worst AEs
Primary Endpoint

<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

## 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**

## 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

2D RT

<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>

*5FU, MMC arm

RTOG 0529: Phase II 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 fxfs over 5.5 weeks
T3N0 or T4N0: 54 Gy tumor; 45 Gy elective nodes in 30 fxfs over 6 weeks
N+: 50.4 Gy < 3 cm or 54 Gy > 3 cm in 30 fxfs over 6 weeks

T2 and above *HIV pts eligible

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 cGy x 28 = 5040 cGy
- Elective Nodal PTV: 150 cGy x 28 = 4200 cGy
T3/T4 or N+ IMRT Prescription

Single 30-fraction course, dose-painted:

- Primary PTV: $180 \text{ cGy} \times 30 = 5400 \text{ cGy}$
- Elective Nodal PTV: $150 \text{ cGy} \times 30 = 4500 \text{ cGy}$
- Nodal Positive PTV:
  - $\leq 3 \text{ cm} \ 168 \text{ cGy} \times 30 = 5040 \text{ cGy}$
  - $> 3 \text{ cm} \ 180 \text{ cGy} \times 30 = 5400 \text{ cGy}$
CT Simulation

- Supine (thin) or Prone
- Belly Board / Bowel Compression if Prone
- Aquaplast / Vac-loc Bag (or equivalent) if Supine
- Full Bladder; Empty Rectum
- Oral (SB follow through) +/- i.v. Contrast
- Anal marker/Wire Distal Extent of Disease; Consider Vaginal Marker
- ≤ 3mm Slice Thickness
- Use Multiple Fields
## Normal Tissue Constraints

<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Representative Constraints (RTOG 0529[33] and UK NICE Guidance for IMRT[35])</th>
</tr>
</thead>
</table>
| Small Bowel         | V45Gy < 20cc  
                              | V35Gy < 150cc  
                              | V30Gy < 200cc  |
| Femoral Heads (L & R) | V44Gy [%] ≤ 5    
                              | V40Gy [%] ≤ 35  
                              | V30Gy [%] ≤ 50  |
| Bladder             | V50Gy [%] ≤ 5    
                              | V40Gy [%] ≤ 35  
                              | V35Gy [%] ≤ 50  |
| Genitalia           | V40Gy [%] ≤ 5    
                              | V30Gy [%] ≤ 35  
                              | V20Gy [%] ≤ 50  |
| Large Bowel         | V45Gy < 20cc  
                              | V35Gy < 150cc  
                              | V30Gy < 200cc  |
| Bone Marrow         | V50Gy [%] ≤ 5    
                              | V40Gy [%] ≤ 35  
                              | V30Gy [%] ≤ 50  |
PTVp_5040
PTVn_4200

T2N0 Disease

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
Yellow CTVn_4200
Red CTVp_5040

Atlases:
Myerson; Red J 2009
Ng; Red J 2012
Muirhead; Clin Oncol 2014

Elective nodal coverage =
Internal iliac, external iliac, mesorectal, presacral, & inguinal
Rectum is target.
Methods/Results

- Survival analyzed via Kaplan-Meier; failure endpoints with cumulative incidence methods; endpoints were measured from study entry
- 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 \( (P < 0.0001) \)

63 patients accrued; 52 evaluable

Acute Toxicity: 0529 vs. 98-11

- Grade 2+ GI/GU: RTOG 9811 vs. RTOG 0529 (p=0.5)
- Grade 3+ GI/GU: RTOG 9811 vs. RTOG 0529 (p=0.0052)
- Grade 2+ Skin: RTOG 9811 vs. RTOG 0529 (p=0.10)
- Grade 3+ Skin: RTOG 9811 vs. RTOG 0529 (p<0.0001)
- Grade 2+ Hem.: RTOG 9811 vs. RTOG 0529 (p=0.032)
- Grade 3+ Hem.: RTOG 9811 vs. RTOG 0529 (p=0.29)
## Long-term Outcomes

Median follow-up all pts 0529 = 7.9 years (0.02-9.2)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RTOG 0529 (n=52)</th>
<th>RTOG 9811-MMC Arm (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Events</td>
<td>5y-% (95% C.I.)</td>
</tr>
<tr>
<td>Local-regional Failure</td>
<td>8</td>
<td>16 (7, 27)</td>
</tr>
<tr>
<td>Colostomy Failure*</td>
<td>6</td>
<td>10 (4, 20)</td>
</tr>
<tr>
<td>Distant Failure</td>
<td>11</td>
<td>16 (7, 27)</td>
</tr>
<tr>
<td>Disease-free Survival</td>
<td>19</td>
<td>70 (56, 81)</td>
</tr>
<tr>
<td>Colostomy-free Survival</td>
<td>17</td>
<td>74 (59, 84)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>16</td>
<td>76 (61, 86)</td>
</tr>
</tbody>
</table>

- *In 0529, 5 out of 6 colostomies were performed for local-regional failures
- In 9811, colostomies were performed for:
  - Disease - 26/38; Treatment complications - 10/38; Both - 2/38

## Late Sexual Function

Definitely, Probably, or Possibly Related to Protocol Treatment (n=51)

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients by Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Sexual Function</strong></td>
<td>2</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>0</td>
</tr>
<tr>
<td>Libido Decreased</td>
<td>1</td>
</tr>
<tr>
<td>Menses Irregular</td>
<td>0</td>
</tr>
<tr>
<td>Reproduction</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal Stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal Discharge</td>
<td>0</td>
</tr>
<tr>
<td>Vulvovaginal Dryness</td>
<td>2</td>
</tr>
</tbody>
</table>

NCI CTCAE version 3

RTOG 0529 Conclusions

- Chemoradiation using DP-IMRT for anal canal cancer provides comparable long-term efficacy, with reduced acute morbidity, as compared to non-conformal radiation delivery.

- Rates of severe long-term effects were very low; comparisons to 98-11 are limited due to the different toxicity scoring systems (0529 NCI CTCAE; 98-11 RTOG/EORTC).

- DP-IMRT has become the platform for the next generation of locally advanced anal trials.
Strategies to Improve Outcome in Localized Disease Have Failed

- Adjuvant chemotherapy: RTOG 98-11\(^1\), UK ACT II\(^2\)
- Increased radiation doses: ACCORD 3\(^3\)
- EGFR inhibition: AMC 045/ECOG 3205\(^4\)

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>
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<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>

**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**

- **R**

  - **n = 940**

- **No Maintenance**

- **1st R endpoint:** 5% increase in cCR with CDDP
- **2nd R endpoint:** 3Y progression-free survival 25% to 17.5% decrease with maintenance 5FU/CDDP
- **Median follow-up 5.1 years**

---

### Outcomes

<table>
<thead>
<tr>
<th>ACT II 1st Randomization</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>

<table>
<thead>
<tr>
<th>2nd Randomization</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 3Y (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>

ACCORD 03 (T2>4cm-4 Nx M0)

Primary Endpoint CFS

n = 307

### Five Year Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CDDP/5FU/ CRT low RT dose</th>
<th>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

### AMC 045 & ECOG 3205 Ph II 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>

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 reports describe 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 & if still + then at 8 weeks post CRT; if disease persistent but regressing – monitor monthly; 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 for persistent disease OK to do 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
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 - ? maintenance immunotherapy post CRT
  - 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%
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
### Rectal Cancer Staging – AJCC TNM 8th Edition 2018

<table>
<thead>
<tr>
<th>T1</th>
<th>submucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>pericolic fat</td>
</tr>
<tr>
<td>T4</td>
<td>locally invasive*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N1a</th>
<th>1 node</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1b</td>
<td>2-3 nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastases</td>
</tr>
<tr>
<td>N2a</td>
<td>4-6 node</td>
</tr>
<tr>
<td>N2b</td>
<td>7+ nodes</td>
</tr>
</tbody>
</table>

- *T4a - penetrates through the visceral peritoneum
- *T4b - directly invades or is adherent to other organs or structures

Direct invasion of sphincter muscles does not count as T4
### Rectal Cancer Staging – AJCC TNM 8th Edition 2018

**Distant Mets**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>none</td>
</tr>
<tr>
<td>M1a</td>
<td>metastasis to one site or organ is identified without peritoneal metastasis</td>
</tr>
<tr>
<td>M1b</td>
<td>metastasis to two or more sites or organs is identified without peritoneal metastasis</td>
</tr>
<tr>
<td>M1c</td>
<td>metastasis to the peritoneal surface is identified alone or with other site or organ metastases</td>
</tr>
</tbody>
</table>
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 13 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>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 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>

RT significantly improves LR over TME alone

Dutch CKVO Ano-Rectal Dysfunction

Fig 1. Bowel function in eligible patients at risk without a stoma. RT, radiotherapy; TME, total mesorectal excision.

Short Course Pre-op RT Discussion

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
Phase III Preop vs. Postop Chemoradiation

- **Intergroup 0417**
  - 53 Pts; Closed Early Secondary to Poor Accrual

- **NSABP R-03**
  - Scheduled to Accrue 900 Pts; Closed at 200; Underpowered to Answer Survival Endpoints

- **German CAO/ARO/AIO-94 Study**
German Rectal Cancer Group CAO/ARO/AIO-94
Study Established Preop CRT, TME & Postop 5FU for T3/T4, N+ Localized Rectal Cancer

EUS Stage II/III

N=823; Primary Endpoint OS

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>Gd 3-4 late toxicity</td>
<td>14</td>
<td>24</td>
<td>0.01</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>

Sphincter Preservation

Sphincter preservation rate in 194 patients with low-lying tumors declared by the surgeon prior to randomization to require an APR:

Preop: 39% (43/109)
Postop: 19% (17/85)

(P = 0.004)
Ten Year Recurrence

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

CAO/ARO/AIO-94 Comments

- Potential for Overtreating with Preop CRT:
  - pT1-2 N0 Disease Was Found in 18% of Postop Patients

- Difficult to Administer Postop Therapy:

<table>
<thead>
<tr>
<th></th>
<th>Preop (%)</th>
<th>Postop (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed RT</td>
<td>92</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Completed CT</td>
<td>89</td>
<td>50</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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

n=1608
Primary Endpoint: LRR
*TME Not Mandated

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)

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
pCR Rates (%)

Pathologic Complete Response

- 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)

P = 0.14
P = 0.42

* No significant fluoropyrimidine by oxaliplatin interaction

Primary Endpoint: Local-Regional Control

5-FU vs. Cape

No Oxali vs. Oxali

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><strong>Diarrhea (3/4)</strong></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-GI002 (TNT) Schema
Non-comparative Experimental Arms (PI George)

Current accrual = 174/174 as of 2/14/18

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 + Pembrolizumab → Surgery

FOLFOX x 8 → ?? → Surgery

Primary Endpoint: Reduction in NAR Score
NCT02921256

Coming soon

NRG - GI002 (TNT) Schema
Non-comparative Experimental Arms (PI George)

Current accrual = 174/174 as of 2/14/18

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 + Pembrolizumab → Surgery

FOLFOX x 8 → ?? → Surgery

Primary Endpoint: Reduction in NAR Score
NCT02921256

Coming soon
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
Endpoints

Primary = 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

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

\[ NAR = [5 \ pN - 3 (cT - pT) + 12] \div 2 \div 9.61 \]

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

- Low Score Reference, p < 0.0001
- Int Score HR=1.53 (1.00-2.33)
- High Score HR=4.48 (3.03-6.63)

Years from Surgery: 0, 1, 2, 3, 4, 5, 6, 7

Survival Rates:
- 0.0, 0.2, 0.4, 0.6, 0.8, 1.0

Overall Survival:
- 92.4%
- 88.8%
- 68.4%
Strategies to Reduce Morbidity in Locally Advanced Rectal Cancer

- Selective Use of Radiation
- Watch & Wait
- IMRT
Sequelae of CRT with 5FU or Cape

- **Acute:**
  - Anorectal dysfunction (frequency & urgency)
  - GI (grade 2+ > 30%)
  - GU (frequency & dysuria)
  - 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>I</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>IIC</td>
<td>T4bN0M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2N1 / T1N2a</td>
<td>5-10%</td>
<td>80%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4aN1 / T2-3N2a / T1-2N2b</td>
<td>10-15%</td>
<td>60%</td>
</tr>
<tr>
<td>IIIIC</td>
<td>T4aN2a / T3-4aN2b / T4bN1-2</td>
<td>15-20%</td>
<td>40%</td>
</tr>
<tr>
<td>IVA</td>
<td>M1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>M1b</td>
<td></td>
<td></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
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
Organ Preservation ‘Watch & Wait’

- Organ preservation in patients with rectal adenocarcinoma is a highly appealing management approach.

- It remains poorly understood how these results translate when attempted in a diverse practice setting; therefore not yet available for a prospective cooperative group trial.

- Key is follow-up with rigorous imaging (pelvic MRI).
# Select Organ Preservation Series

<table>
<thead>
<tr>
<th>Published:</th>
<th>First Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Number of Centers Treating Patients</th>
<th>Total Radiation Dose</th>
<th>Rate of NOM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Habr-Gama et al.</td>
<td>2004</td>
<td>265</td>
<td>1</td>
<td>5040 cGy</td>
<td>26.8%</td>
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<tr>
<td></td>
<td>Habr-Gama et al.</td>
<td>2013</td>
<td>70</td>
<td>1</td>
<td>5400 cGy</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Maas M et al.</td>
<td>2011</td>
<td>21</td>
<td>1 (MSKCC)</td>
<td>5040 cGy</td>
<td>NR</td>
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<tr>
<td></td>
<td>Smith et al.</td>
<td>2012</td>
<td>32</td>
<td>1 (MSKCC)</td>
<td>5600 cGy</td>
<td>NR</td>
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<tr>
<td></td>
<td>Appelt et al.</td>
<td>2015</td>
<td>55</td>
<td>1</td>
<td>6000 cGy, IMRT + 5 Gy brachy boost</td>
<td>78%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accruing:</th>
<th>NCT</th>
<th>Status</th>
<th>Design</th>
<th>Total Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>02008656</td>
<td>Accruing</td>
<td>Phase II</td>
<td>5600 cGy</td>
</tr>
</tbody>
</table>
On-going Watch & Wait Trial (NCT 02008656)

Stage II & III

n = 300

CAPOX/FOLFOX x 6 → 50.4 Gy + 5FU/LV

50.4 Gy + 5FU/LV

CAPOX/FOLFOX x 6

No, Surgery

Yes, Watch & Wait

cCR

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%

Acute Toxicity: 3D vs. IMRT (BMC)

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

Rectal Conformal Planning

CT Simulation

- Supine (thin) or Prone
- Belly Board / Bowel Compression if Prone
- Aquaplast / Vac-loc Bag (or equivalent) if Supine
- Full Bladder; Empty Rectum
- Oral (SB follow through) +/- i.v. Contrast
- Anal Marker; Consider Vaginal Marker
- ≤ 3mm Slice Thickness
- Use Multiple Fields
- Consider IMRT for Select Cases (small bowel issues, T4, anal canal involvement)
Target Definition

CTV: Elective nodal regions

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

PTV: 5-7 mm around CTV if perform daily IGRT; 1 cm if not
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 $\leq$ 45 Gy; small bit sb 50.4 Gy

- **IMRT Plan – Final Tumor Dose of 50 Gy in 25 Fractions (Dose Painted)**
  - 5-field static plan or 270 VMAT
  - 45 Gy to PTV45 for elective pelvis
  - 50 Gy to PTV rectal tumor and adjacent positive nodes
Rectal Case on TNT Trial

- 45 year old male who presents with 1 month history of hematochezia
- Colonoscopy reveals a 3 x 4 cm sessile non-obstructing mass in the distal rectum within a few centimeters of the anal verge
- Path revealed moderately differentiated adenocarcinoma
Work-up

- CEA was 2.7
- CT chest/abd/pelvis showed no evidence of distant metastases
- MRI pelvis reveals rectal tumor encompassing the levator ani insertion. Above the levator ani, the tumor invades the muscularis propria but does not extend beyond. Two subcentimeter LNs noted. cT2N1.
- DRE tumor felt starting at levator
- Based on current tumor location/size, would require APR
Enrolled in NRG GI-002 trial

Received neoadjuvant FOLFOX x 8 cycles, followed by neoadjuvant chemoradiation with concurrent capecitabine

Post treatment flexible sigmoidoscopy showed no visible lesion; clinical complete response

Given response, patient now felt to be eligible for sphincter-preserving surgery with LAR and coloanal anastomosis

Final pathology showed no residual adenocarcinoma and 14 benign lymph nodes ypT0N0(0/14)
Radiation Therapy Plan

Prone, belly board, VMAT, 270 arcs, 6MV, two sequential plans per protocol, PTV_4500 and PTV_5040
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 ongoing and developing studies are evaluating moving outback chemo upfront, novel radiosensitizers and risk-based treatments (selective use of RT and watch & wait) in an attempt to optimize outcomes while minimizing morbidities