Addressing Long-Term Side Effects after Treatment for Anal Cancer

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Treatment Options

• Surgery
  – Abdominoperineal resection (APR)
    • Removal of wide area of perianal skin, anal sphincter, rectum, ischiorectal fat, levator sling, perirectal & superior hemorrhoidal LN’s
  – Local excision
Treatments Options

- Combined Modality Therapy
  - Nigro Study (Dis Colon Rectum, 1974)
    - 3 pts w/ SCC of anal canal treated with pre-op RT to 30 Gy + concurrent 5-FU/MMC had path CR at surgery

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Combined Therapy for Cancer of the Anal Canal:
A Preliminary Report*

Norman D. Nigro, M.D.,† V. K. Vaitkevicius, M.D.,† Basil Considine, Jr., M.D.§

From Wayne State University, School of Medicine, Detroit, Michigan

In comparison with adenocarcinoma of the rectum, anal cancer is uncommon.² According to Morson,³ one squamous-cell can-

There are causes for the low cure rates even beyond the biologic characteristics of the neoplasm itself. The anatomic features
Anal Cancer

• Nigro protocol reported in 1973

• 2013: Still using Mitomycin C, 5-FU, pelvic RT

• What have we achieved in 40 years?
Rising Incidence of Anal SCC
<table>
<thead>
<tr>
<th>TN Category</th>
<th>No. Pts</th>
<th>Local-Regional TF(#)</th>
<th>5yr(%)</th>
<th>Distant Metastasis TF(#)</th>
<th>5yr(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2N0</td>
<td>302</td>
<td>50</td>
<td>19</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>T3N0</td>
<td>115</td>
<td>25</td>
<td>22</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>T4N0</td>
<td>31</td>
<td>13</td>
<td>50</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>T2N1-3</td>
<td>95</td>
<td>37</td>
<td>40</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>T3N1-3</td>
<td>47</td>
<td>27</td>
<td>58</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>T4N1-3</td>
<td>25</td>
<td>14</td>
<td>64</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Gunderson LL et al., ASTRO 2013
SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL: PATTERNS AND PREDICTORS OF FAILURE AND IMPLICATIONS FOR INTENSITY-MODULATED RADIATION TREATMENT PLANNING

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180 patients

→

45 locoregional persistence or failure

→

28 local-only

7 local and regional

10 regional only
IMRT plan for Anal Cancer
Results

- The two RT groups did not differ significantly in outcomes

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>CRT</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>2 yr OS</td>
<td>92%</td>
<td>89%</td>
<td>0.92</td>
</tr>
<tr>
<td>2 yr LRFS</td>
<td>88%</td>
<td>81%</td>
<td>0.19</td>
</tr>
<tr>
<td>2 yr DMFS</td>
<td>83%</td>
<td>88%</td>
<td>0.53</td>
</tr>
<tr>
<td>2 yr CFS</td>
<td>96%</td>
<td>91%</td>
<td>0.50</td>
</tr>
</tbody>
</table>

- When outcomes compared using the adjustment of the propensity score analysis, still no difference
- Mean duration of RT treatment was 41.5 days for IMRT and 41.4 days for 3DCRT, despite higher median RT dose for IMRT
- Longer RT duration was associated with worse tumor control: every 10 days of delay resulted in a 31% increase in LR rate.

DasGupta, Radiother Oncol, 2013
## RTOG 0529: Dose-Painted IMRT vs. RTOG 9811

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>0529 (n=52)</th>
<th>9811-MMC-arm (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Morbidity#</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>≥ Grade 3 GI/GU AE</td>
<td>22*</td>
<td>36*</td>
</tr>
<tr>
<td>≥ Grade 3 skin AE</td>
<td>20*</td>
<td>47*</td>
</tr>
<tr>
<td>Endpoint&amp;</td>
<td>2y-%</td>
<td>2y-%</td>
</tr>
<tr>
<td>Local-Regional Failure</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Colostomy Failure</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Disease-Free Survival</td>
<td>77</td>
<td>71</td>
</tr>
<tr>
<td>Colostomy-Free Survival</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>Distant Failure</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

*Kachnic L, Int J Rad Oncol Bio, 2013*
# Chemoradiation with Capecitabine

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Treatment</th>
<th>CR</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Glynne-Jones 2008</td>
<td>31</td>
<td>RT: 50.4 Gy Capecitabine 825 mg/m² bid M-F weekly Mitomycin C 12 mg/m²</td>
<td>77%</td>
<td>Compliance with CT 68%, RT 81%</td>
</tr>
<tr>
<td>Eng C ASCO 2009</td>
<td>20</td>
<td>RT: 45-59 Gy Capecitabine 825 mg/m² bid M-F weekly Oxaliplatin 50 mg/m² weekly</td>
<td>90%</td>
<td>Omission of CT in week 3 and 6 due to toxicity</td>
</tr>
</tbody>
</table>
MSKCC Approach

Capecitabine 825 mg/m² BID M-F

Mitomycin 10 mg/m²

RT: 45/50 Gy IMRT

Boost 6 Gy
Why are we worried about delivery of pelvic radiotherapy?

**Acute toxicity**
- Acute proctitis
- Diarrhea
- Tenesmus
- Rectal urgency
- Thrombocytopenia
- Leukopenia
- Dysuria
- Enteritis

**Late effects**
Late Effects of Pelvic Radiotherapy

- Gastrointestinal complications
- Sexual dysfunction
- Decreased bone density
Late Radiation Enteropathy: Etiology

- Indirect injury to less mitotically-active vascular endothelial and connective tissue cells
- Progressive occlusive vasculitis
- Fibrosis & adhesions
Late Radiation Enteropathy: Symptoms

- Variable latency
  - average 2-3 yrs, range 6 mos-25 yrs
- Abdominal cramping
- Alternating diarrhea/constipation
- Malabsorptive symptoms
- Rectal bleeding
- SBO
- Intestinal perforation
- 50% report QOL affected by GI symptoms

Andreyev J, Lancet Oncol, 2007
Radiation Enteritis/Enteropathy: Risk Factors

- Radiation Dose
- Volume of bowel irradiated
- Fractionation schedule
- Combined chemotherapy
- Patient factors
- Pre-existing vascular disease (DM, CVD)
- Prior abdominal surgery
Recommendations

• Lactose-free diet
• Adjust fiber (Metamucil)
• BRAT diet
• Probiotics
• Flagyl
• Oral steroids?
• Bowel Rest
Late Effects: Bone Density

- Osteopenia
- Insufficiency fractures
  - 7% in rectal cancer patients
  - Sacrum, pubic rami, femoral neck

Kim HJ, IJROBP, 2012
Recommendations

• Vitamin D (check baseline Vit D levels)
• Calcium
• Exercise!
• Bone density scan (every 2 years in women)
• Referral to endocrinologist or OB-GYN for medical management
Late Effects: Sexual Dysfunction

**Women**
- Early menopause
- Infertility
- Vaginal stenosis

**Men**
- Infertility
- Hypogonadism

Hermann, IJROBP, 2006; Marijnen, JCO, 2005
Vaginal Stenosis

• Vaginal stenosis after pelvic radiotherapy (RT) can significantly impair long-term quality of life

• Studies have evaluated the incidence of vaginal stenosis in women with gynecologic malignancies

• Limited data in women with gastrointestinal (GI) cancers
Vaginal Dilators (VD)

- VD have been recommended after pelvic RT to reduce vaginal stenosis
- No standard practice
  - 3x/week for ~10 minutes
- Mechanism of action not well established
- Associated with poor level of adherence
Prospective Study of Vaginal Dilator Use Following Pelvic Radiotherapy for Gastrointestinal Malignancies

Ethel Law, RN
Elyn Riedel, MA
Ashlyn Tom, BA
Jung Jun Ho, PhD
Joanne Kelvin, RN
Bridgette Thom, MS
Karyn A. Goodman, MD, MS
Objectives

• To determine adherence and efficacy of vaginal dilator use as measured by ability to return to pre-RT vaginal dilator size at 12 months among women treated with pelvic RT

• To evaluate the incidence of vaginal stenosis in women with GI cancers
Baseline Evaluation

- Maximum size of dilator that could be easily inserted into the vagina
- Provided vaginal dilator kit and fact card
- Explained how to complete diaries (vaginal dilator use & symptoms)
- Reviewed use of vaginal moisturizers & lubricants

Post-RT Intervention

- Patients instructed to use 3x/week
- Initiate use at 4 weeks post-RT / 6 weeks post-surgery

Data Collection

- Post-RT follow-up visits: 1, 3, 6, 12 months
  - Vaginal dilator size and vaginal symptoms with use
- Self-report diaries: monthly
  - Adherence - (3x/wk) x 52 wks = 156x/year
  - Vaginal dilator size and symptoms
New Directions
Viral Etiology of Anal Cancer

- >80% anal cancer are associated with high-risk type of HPV (16 and 18)
- Viral proteins E6 and E7 mediate oncogenic transformation of squamous epithelia
- Goal
  - Develop therapeutic HPV vaccine
Immunogenicity of HPV

- Most immunocompetent individuals will eventually clear HPV
- Clearance correlates with development of specific CD4 T-cell immunity to HPV E2 and E6 proteins
- Naturally occurring systemic humoral responses are difficult to detect
  - Ab to E7 can be detected in people with invasive cancer, but not with early stage disease

Trimble and Frazer, Lancet Oncol, 2009
Prophylactic Vaccines

• Prophylactic vaccines (Gardasil) have been FDA approved, but no therapeutic effects on pre-existing HPV infections or lesions
• Primarily target L1 capsid protein and induce antibody response
• T-cell response is required to address established infection or HPV-associated lesion
Therapeutic Vaccines

• Therapeutic vaccines are in development
  – DNA vaccines
  – Generate cellular immunity against HPV-infected cells
  – Targeting E6 and E7 antigens
Conclusions

• Early identification of potential effects on GI tract, sexual function, and bone density
• Interventions to reduce impact on quality of life
  – Vit D, calcium, exercise
  – Vaginal dilators, referral to sexual health clinic
• New treatment options to reduce impact of chemotherapy and radiotherapy
  – Immunotherapy
• PREVENTION!!!
  – Prophylactic vaccines
THANK YOU!