NEWER RADIATION (3 D - CRT, IMRT, IGRT) TECHNIQUES FOR CERVICAL CANCERS (COMMON PELVIC TUMORS)

Umesh Mahantshetty, DMRT, MD, DNBR

Associate Professor, Radiation Oncology
Convener: Urology Disease Management Group
Member: GYN Disease Management Group
TATA MEMORIAL HOSPITAL, MUMBAI, INDIA

GYN GEC – ESTRO RESEARCH NETWORK MEMBER & TEACHING FACULTY
GEC – ESTRO COMMITTEE MEMBER

26th-27th April 2014 ICRO TC, Shimla
Learning Objectives

• To understand the principles of Newer External (XRT) Radiation Technique Planning

• Dosimetric and Clinical Outcome of Newer XRT Techniques in Cervical Cancers

• Practical implementation of Newer RT Techniques
NEWER RADIATION TECHNIQUES FOR COMMON PELVIC TUMORS

• Introduction and principles of newer XRT

• Dosimetric and Clinical Outcome of Newer XRT Techniques in Pelvic Tumors
  - 3 D - CRT
  - IMRT
  - Volumetric Arc IMRT: Rapid Arc/ Tomotherapy
  - IGRT / Adaptive Radiotherapy

• Pelvic tumors and newer XRT techniques
  - Cervical Cancer
    - Prostate Cancer
    - Bladder Cancer
    - Ano-Rectal Cancer........
Conventional XRT Techniques

• 2D treatment – conventional EBRT

• AP/PA or 4 field Box (Radiological boundaries)

• Ensures that you do not miss anything in pelvis
  – Tumor / Target / PTV

• However, also results in significant normal tissue doses:
  – Rectum
  – Bladder
  – Sigmoid
  – Small bowel
  – Bone marrow......

• Newer XRT Techniques evolved
Rationale for Newer XRT Techniques

Optimal Target Identification & definition

Optimal Treatment delivery

Newer Imaging modalities: CT, MRI, PET-CT, SPECT – CT etc.,

Newer Delivery techniques: IMRT, VMAT, Rotational etc.,
Basic Principles

Of

Newer External Radiation (Teletherapy) Techniques

Conventional XRT
Conformal XRT
IMRT

Conventional RT Beam
Uniform Beam Intensity
squares / rectangles

Conformal RT Beam
Uniform Beam Intensity

IMRT Beam
Non-Uniform Beam Intensity

Complex Planning Process
3D CRT / IMRT PLANNING PROCESS

Patient Immobilization → Imaging → Contour Target Volume and Normal Structure

Set up & Simulation

Contour Target Volume and Normal Structure → IMRT

IMRT

Labor – Intensive
Team Approach

Select Beam Geometry and Energy → Plan Evaluation & Approval

Forward or Inverse Plan Optimization

Plan Evaluation & Approval → Patient Set up

Patient Dose Verification → Patient Position Verification

Machine Quality Assurance → Patient Set up → Patient Treatment

Verification and QA

Treatment delivery
Comparison of treatment plans AP-PA vs four field box

14 patients with cervical cancer

Van de Bunt et al 2006
Intensity Modulated Radiation Therapy (IMRT)

- 3-D Treatment Planning
  - Targets and Normal Tissues Identified Explicitly: Imaging modalities
- Multiple Beam Angles, Beamlet Collimation
  - Highly Conformal Dose Distributions
- Inverse Treatment Planning Algorithms
  - Plans Optimized to Meet Specified Objectives
- > 20 Dosimetric Studies Showing Advantages of IMRT
- > 20 Outcomes studies Showing Reduced Toxicity, Comparable Tumor Control
3D CRT

High dose regions of rectum & bladder are reduced significantly
Conformal RT Vs IMRT

Four field box
15 MV

7 coplanar equally spaced beams, 6/15 MV
CRT Vs IMRT

14 patients with cervical cancer, IMRT: 7 beams, 10 MV

Gain of IMRT is organ sparing!

Van de Bunt et al 2006
Dosimetric Studies of IMRT

Bladder

Roeske IJROBP 2000

Bowel

Georg Radiother Oncol 2006

Rectum

Ahmad IJROBP 2005

Bone Marrow

Mell IJROBP 2008
Clinical Studies of IMRT

Less Acute GI Toxicity  Less Late GI Toxicity  Less Hematologic Toxicity

Mundt et al. IJROBP 2002  Mundt et al. IJROBP 2003  Brixey et al. IJROBP 2002
3-Year Outcomes with IMRT

Pelvic Failure

Overall Survival

Hasselle et al. IJROBP 2011
3 D Conformal to IMRT in Cervical Cancers

• Optimize more dose to tumor (Simultaneous boost)
  – Increase tumor control rates mainly nodes
• Optimize dose to normal tissue
  – Decrease the normal tissue toxicities
• Other Advantages
  – Post operative pelvic radiation
  – Extended field radiation to treat para-aortic nodes
1. Post Operative IMRT in GYN Cancers

Fig. 2. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the upper pelvis. The small bowel and PTV are shaded in orange and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.
CRT Vs IMRT

• Generated treatment plans with 4 -11 equally spaced, coplanar, 6 and 18 MV photon beams
• Results: better dose conformity up to 9 beams
• Consistent with Bortfeld et al and Söderström et al (more than 7-9 fields does not improve dose conformity)
• Slightly better PTV coverage with 6 MV
• Compared four field box with 9-field, 6 MV IMRT

Roeske et al IJROBP 2000
IMRT – Intensity Modulated RadioTherapy
INTERTECC IMRT constraints

Normal tissue requirements for IMRT (hard constraints):

● Bowel (outermost extend of loops): $V_{45\text{Gy}} \leq 250 \text{ cc}$; maximum dose $< 110\%$
● Rectum: maximum dose $< 110\%$
● Bone Marrow: $V_{10\text{Gy}} < 90\%; V_{20\text{Gy}} < 75\%$
● Bladder: maximum dose $< 110\%$
● Femoral Head: maximum dose $< 110\%$
● Functional Bone Marrow (Substudy 3 only): mean dose $< 25 \text{ Gy}$;
IMRT Vs VMAT

8 patients with ca. cervix

IMRT

VMAT (Rapid Arc)

five coplanar equally spaced fields, 6 MV

360° arc rotation, 10 beam angles 6 MV

Cozzi et al R&O 2008
IMRT Vs VMAT (Rapid Arc)

8 patients with ca. cervix

Cozzi and TMH et al R&O 2008

<table>
<thead>
<tr>
<th>Organ</th>
<th>Parameter</th>
<th>Objectives</th>
<th>IMRT</th>
<th>RapidArc</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum-PTV</td>
<td>Mean (Gy)</td>
<td>&lt;45</td>
<td>42.5</td>
<td>36.3</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>$V_{40\text{Gy}}$ (%)</td>
<td>Minimise</td>
<td>78.7</td>
<td>51.5</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>$D_{2%}$ (Gy)</td>
<td>&lt;47.5</td>
<td>50.9</td>
<td>51.1</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>$D_{50%}$ (Gy)</td>
<td>&lt;30</td>
<td>44.1</td>
<td>38.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Bladder-PTV</td>
<td>Mean (Gy)</td>
<td>&lt;42</td>
<td>36.6</td>
<td>30.3</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>$V_{40\text{Gy}}$ (%)</td>
<td>Minimise</td>
<td>40.5</td>
<td>20.2</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>$D_{2%}$ (Gy)</td>
<td>&lt;47.5</td>
<td>47.8</td>
<td>46.9</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>$D_{50%}$ (Gy)</td>
<td>&lt;35</td>
<td>36.6</td>
<td>29.0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Cozzi and TMH et al R&O 2008
Beam On time (excluding the gantry reposition / reprogram time)

- RA IMRT: 245 ± 17 MU
- IMRT: 479 ± 63 MU

Shorter delivery time, at least by a factor 2!
HELICAL TOMOTHERAPY: IMRT with Mega Voltage CT Imaging

STATE-OF-THE-ART IMAGE GUIDED RADIATION THERAPY

Initial Experience: Useful in Challenging Sites like Extended field, CSI, TBI, Dose escalation protocols, multiple targets
IMRT vs HT
5 patients with endometrial cancer, postoperative

9 equally spaced coplanar 6 MV fields

<table>
<thead>
<tr>
<th>Organ</th>
<th>Parameter</th>
<th>IMRT</th>
<th>HT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel</td>
<td>$V_{20Gy}$(%)</td>
<td>63</td>
<td>64</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>$V_{40Gy}$(%)</td>
<td>20</td>
<td>19</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>$V_{50Gy}$(%)</td>
<td>9</td>
<td>8</td>
<td>ns</td>
</tr>
<tr>
<td>Rectum</td>
<td>$V_{20Gy}$(%)</td>
<td>97</td>
<td>98</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>$V_{40Gy}$(%)</td>
<td>64</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$V_{50Gy}$(%)</td>
<td>27</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Bladder</td>
<td>$V_{20Gy}$(%)</td>
<td>89</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$V_{40Gy}$(%)</td>
<td>38</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>$V_{50Gy}$(%)</td>
<td>17</td>
<td>14</td>
<td>-</td>
</tr>
</tbody>
</table>

HT decrease integral dose to OAR
HT increase integral dose normal tissue

Yang et al Acta Oncol 2010
3. Active Bone Marrow as a potential OAR

- Dose Volume Constraints: PET based Active marrow and correlation with HT toxicity
- Potential for aggressive Chemo-radiation protocols
- Studies ongoing: MR sequences, FLT- PET etc..

Mell IJROBP 2011

Umesh IJGC Oct. 2012
Active Bone Marrow as a potential OAR

- FDG PET based definition of active bone marrow
- Active BM: > Mean SUV muscle value (INTERTECC STUDY)

- Functional BM constraints:
  - V10Gy < 90% (Mell group, San Diego, INTERTECC study)
  - V20Gy < 75% (Mell group, San Diego, INTERTECC study)
  - V40Gy < 40% (Mahantshetty, Tata Memorial, IJGC 2012)

Liang et al, IJROBP 2013
PET-CT Based IMRT: Outcome

Table 2. Distribution of recurrences for the IMRT, non-IMRT, and total groups

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>IMRT</th>
<th>Non-IMRT</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>39 (28.9%)</td>
<td>139 (43.8%)</td>
<td>178</td>
<td>0.036</td>
</tr>
<tr>
<td>Pelvic</td>
<td>11 (8.1%)</td>
<td>33 (10.4%)</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>21 (15.6%)</td>
<td>78 (24.6%)</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>7 (5.2%)</td>
<td>28 (8.8%)</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

Grigsby et al., IJROBP 2010
PET-CT Based IMRT: Toxicities

ACUTE toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>8 (38.1%)</td>
<td>2 (9.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GU</td>
<td>5 (23.8%)</td>
<td>2 (9.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>1 (4.8%)</td>
<td>2 (9.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>6 (28.6%)</td>
<td>3 (14.3%)</td>
<td>4 (19.0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

LATE toxicities: Grade 3 or more GI and GU toxicities

<table>
<thead>
<tr>
<th>Complication</th>
<th>IMRT group</th>
<th>Non-IMRT group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectovaginal fistula</td>
<td>2</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Vesicovaginal fistula</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Large bowel obstruction</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Cystitis, Grade 4</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Rectal ulcer</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Ureteral stricture</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Rectal stricture</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Proctitis, Grade 4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusion: Cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy.

Grigsby et al., IJROBP 2010
### Webtable 4

**Acute GI and hematological toxicities are significantly low with IMRT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Endpoint</th>
<th>IMRT group</th>
<th>Non-IMRT group</th>
<th>p</th>
<th>Strength of endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mundt (2001)</td>
<td>15/25</td>
<td>G2 acute GI toxic effects, %</td>
<td>53.4</td>
<td>96</td>
<td>0.001†</td>
<td>Cii</td>
</tr>
<tr>
<td>Mundt (2002)</td>
<td>40/35</td>
<td>No or only infrequent antidiarrhoeal medication, %</td>
<td>73.3</td>
<td>20</td>
<td>0.001†</td>
<td>Cii</td>
</tr>
<tr>
<td>Mundt (2003)</td>
<td>36/30</td>
<td>G2 acute GI toxic effects, %</td>
<td>60</td>
<td>91</td>
<td>0.002†</td>
<td>Cii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No or only infrequent antidiarrhoeal medication, %</td>
<td>75</td>
<td>34</td>
<td>0.001†</td>
<td>Cii</td>
</tr>
<tr>
<td>Mundt (2003)</td>
<td></td>
<td>Chronic GI toxic effects, %</td>
<td>11.1</td>
<td>50.0</td>
<td>0.001†</td>
<td>Cii</td>
</tr>
<tr>
<td>Brixey (2002)</td>
<td>36/88</td>
<td>≥G2 WBC toxic effects⁴, %</td>
<td>31.2</td>
<td>60</td>
<td>0.08</td>
<td>Cii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥G2 ANC toxic effects⁴, %</td>
<td>15.3</td>
<td>23.5</td>
<td>0.58</td>
<td>Cii</td>
</tr>
<tr>
<td>Chen (2007)</td>
<td>33/35</td>
<td>≥G2 Haemoglobin toxic effects⁴, %</td>
<td>15.2</td>
<td>35.2</td>
<td>0.22</td>
<td>Cii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-year locoregional control, %</td>
<td>93</td>
<td>94</td>
<td>0.9606</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute GI toxic effects (G0/G1/G2/G3), %</td>
<td>64/12/24/0</td>
<td>20/23/57/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G1-G2 combined acute GU toxic effects, %</td>
<td>30</td>
<td>60</td>
<td>0.022†</td>
<td>Cii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute haematological toxic effects, %</td>
<td>NA</td>
<td>NA</td>
<td>0.724</td>
<td>Cii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic GI toxic effects, %</td>
<td>6</td>
<td>34</td>
<td>0.002†</td>
<td>Cii</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic GI toxic effects, %</td>
<td>9</td>
<td>23</td>
<td>0.231</td>
<td>Cii</td>
</tr>
</tbody>
</table>

**IMRT=intensity-modulated radiotherapy. GI=gastrointestinal. Cii=quality of life in relation to treatment-induced toxic effects. WBC=white-blood-cell count. ANC=absolute neutrophil count. D=indirect surrogates including disease-free survival, progression-free survival, tumour response, local control, and locoregional control. GU=genitourinary. Strength of endpoint of each study was classified according to the modified Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine PDQ. *Assessed in the subgroup of patients that received combined chemotherapy. †Statistically significant.**

[http://oncology.thelancet.com Published online April, 2008 Webtable 4](http://oncology.thelancet.com)
# IMRT & CERVICAL CANCERS

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Endpoints</th>
<th>IMRT group</th>
<th>Non-IMRT group</th>
<th>p</th>
<th>Strength of endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manoh (2001)*</td>
<td>15</td>
<td>25</td>
<td>G2 acute GI tract effects, %</td>
<td>53</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>Manoh (2001)*</td>
<td>40</td>
<td>35</td>
<td>No or only infrequent anti-diarrheal medication, %</td>
<td>73</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Manoh (2003)*</td>
<td>36</td>
<td>30</td>
<td>Chronic GI tract effects, %</td>
<td>11</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Braye (2002)†</td>
<td>36</td>
<td>38</td>
<td>a G1/WGC tract effects*, %</td>
<td>31</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>Chen (2004)‡</td>
<td>33</td>
<td>35</td>
<td>a G1 Hemoglobin tract effects*, %</td>
<td>15</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-year locoregional control, %</td>
<td>93</td>
<td>9</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute GI tract effects (G1/G2/G3/G4/G5), %</td>
<td>64/12/24/40</td>
<td>20/34/57/70</td>
<td>0.00002†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G3-G5 combined acute GI tract effects, %</td>
<td>36</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute G1 tract effects (G1/G2/G3/G4/G5), %</td>
<td>70/18/22/40</td>
<td>40/34/26/40</td>
<td>0.00002†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G3-G5 combined acute G1 tract effects, %</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute haemorrhagic tract effects, %</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic GI tract effects, %</td>
<td>6</td>
<td>34</td>
<td>23</td>
</tr>
</tbody>
</table>

IMRT: Intensity modulated radiotherapy. G: grade. CI: confidence interval. QA: quality of life in relation to nausea-related toxic effects. WBC: white blood cell count. ANC: absolute neutrophil count. GI: gastrointestinal. †: indirect surrogates including disease-free survival, progression-free survival, tumour response, local control, and locoregional control. CI: confidence intervals. Strength of endpoint of each study was classified according to the modified Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine (PCAC). *Assessed in the subgroup of patients that received combined chemotherapy. ‡Statistically significant.

Table 4: Indicators of efficacy and toxic effects of comparative studies on IMRT for gynecological malignancies.
Table 4
Summary of studies on IMRT in locally advanced cervical cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Stage</th>
<th>C/T</th>
<th>LRR</th>
<th>DM</th>
<th>LRR + DM</th>
<th>Grade 3 or 4 GI toxicity</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidd et al.</td>
<td>135</td>
<td>IA2–IVA</td>
<td>NA</td>
<td>8.0%</td>
<td>15.6%</td>
<td>5.2%</td>
<td>6.0%</td>
<td>NA</td>
</tr>
<tr>
<td>Beriwal et al.</td>
<td>36</td>
<td>IB2–IVA</td>
<td>Yes</td>
<td>5.6%</td>
<td>25.0%</td>
<td>NA</td>
<td>5.6%</td>
<td>2-year: 65.0%</td>
</tr>
<tr>
<td>Chen study</td>
<td>109</td>
<td>IB2–IVA</td>
<td>Yes</td>
<td>4.6%</td>
<td>12.8%</td>
<td>9.2%</td>
<td>2.7%</td>
<td>3-year: 78.2%</td>
</tr>
</tbody>
</table>

Abbreviations: IMRT: intensity-modulated radiotherapy; C/T: chemotherapy; LRR: local recurrence rate; DM: distant metastasis; GI: gastrointestinal; OS: overall survival; NA: not available.
A Phase II Randomized Trial Comparing Intensity Modulated Radiation Therapy (IMRT) with Conventional Radiation Therapy in Stage IIB Carcinoma Cervix


Carcinoma Cervix Stage IIB (SQ / Adeno CA)

100 patients
Conventional External RT (40 Gy /20#)
+ ICA – HDR (7 Gy × 5#)
with Concomitant Chemo-radiation

100 patients
IMRT Pelvis (50 Gy/25#)
+ ICA – HDR (7 Gy × 5#)
with Concomitant Chemo-radiation

HYPOTHESIS: Pelvic IMRT

• Reduction in Acute and Late RT toxicity’s by 15-25% using pelvic IMRT
• Accrual Period: 5 years
• Power of detection: 80% (alpha error: 0.05)

TMH Study: Dec 2014 final analysis
IMRT vs IGBT, cervical cancer

Georg et al (IJROBP 71, 2008):

**Intracavitary & interstitial brachytherapy vs IMRT,**
9 patients, 45Gy/25fx + boost of 28Gy/4fx

**Brachytherapy:**
- Tandem and ring applicators ± needles
- High-risk CTV (Heie-Meder et al 2005)
- Manually optimised

**IMRT:**
- HR-PTV = HR-CTV + 3mm margin/5mm margin
- Inverse planning to give highest possible dose to HR-PTV while respecting dose constraints for the rectum and bladder
IMRT vs IGBT, cervical cancer

- For IMRT CTV-PTV margins is needed, i.e. a larger volume, compared to brachytherapy, has to be treated
- D90 for IMRT was lower compared to BT for most of the patients
- The volumes receiving intermediate doses (>60Gy) are much larger for IMRT
- The importance of very high central doses are most likely of major importance for the excellent local control obtained with brachytherapy

Advanced BT is superior to IMRT
Image Guided Radiation Therapy
IGRT

Image Guidance before treatment irrespective of type of Radiation

- IMAGE: The ability to image the treatment volume
- FUSION: Fuse the image to the treatment plan
- CORRECT: Align and make corrections
- TREAT: Then treat accurately

IDEAL SITUATION: All in real time, during a patient’s daily radiation session
Image Guided Radiation therapy (IGRT)
Imaging options before RT

- Linac based
- Linac modified
- Tomotherapy unit
- Cyberknife
• Set up error
• Organ motion
  – Bladder filling
  – Rectal filling
  – Intrauterine fluid
  – Tumor response
• Accuracy of CTV

Why?
Potential Benefits of IGRT

• Accuracy
• Tighter margins
• Dose escalation
• Decreased morbidity
• Increased tumor control

STILL INVESTIGATIONAL
Registration methods

• Registration on bony anatomy:
  
  – EPID (Electronic Portal Imaging Device)
    • MV
    • 2D

  – kV imaging (OBI – On Board Imaging)
    • kV
    • 2D

  – CBCT (Cone Beam CT) imaging
    • kV
    • 3D
EPIX (Electronic Portal Image Device)

Bony or marker match
CBCT on Newer Generation LA Unit

Correction protocol depending on the CTV-PTV margins
An example of Image Guided Radiation therapy (IGRT)
Image Guided Radiation Therapy (IGRT)
STUDY SCHEMA

Ideally daily
Practical
Approach:
Atleast 3-4
times 1st week
Apply
systematic
errors
Repeat in 2nd
week for
confirmation
Subsequently
2-3 times / randomly

Treatment planning- CT scan as per protocol described CT –MR fusion → contouring, 3DCRT/ IMRT ----planning for cancer cervix.

Online matching- Daily pretreatment CBCT. Matching to Pelvic lymph nodes CTV/Vessels. documents shifts all directions (Set I).

Offline matching- Taking online set of shifts starting point, matching is done for CTV Primary, documents shifts (Set II).

Set I -set II values = surrogate organ motion.

Mid-MRI (T2 sequences) at end 3rd week (24-30)Gy.

Tumor regression- GTV contouring on both MRI → document tumor regression in all directions, volumetric regression.
Adaptive IGRT

• Organ Motion and tumor shrinkage
• Exciting possibilities in patients with Gynecologic Tumors
• Especially intriguing in Cervical Cancer where significant changes in tumor volumes occur during external beam RT
Organ motion

- Internal organ motion in pelvis significant.
  - Interfractional & interfractional motion.
- Bladder & Rectal filling - daily changes in OAR & Target position.
- Missing of target volumes while giving high precision conformal treatment.

Kerkhof E. M. et al.
Bladder & Rectal filling

Fig. 1. Planning CT showing bladder (yellow), CTV (red), and rectum (green) contours. Thick lines define contours from the planning day. Thin lines show the positions of the organs on different treatment days. Contours were generated after registration of bony anatomy.

Comparison of various online IGRT strategies: The benefits of online treatment plan re-optimization, Derek Schulze et al. Radiotherapy and Oncology 90 (2009) 367–376

ESTABLISH INSTITUTIONAL BLADDER FILLING AND RECTAL FILLING PROTOCOLS
Bladder protocol: 750-1000 ml over 15-20 minutes

Bladder filling (upto 300 ml) time after 45 minutes repeated every 15 min.

Volume assessed by serial Trans-Abdominal US

N = 46 patients

**Median filling time**

 wk1 | wk2 | wk3 | wk4 | wk5
---|---|---|---|---
 45 | 67.5 | 75 | 67.5 | 75

**Mean filling time**

 wk1 | wk2 | wk3 | wk4 | wk5
---|---|---|---|---
 57 | 67 | 66 | 66 | 69

*TMH Study (unpublished; submitted to Clin. Oncol. 2014)*
TMH STUDY
PET – CT and MR Correlation (N – 104 pts)

Upasani et al; IJGC 2012
Tumor Regression

- Regression of cervical cancer during EBRT approx. 60% - 80% of the pre therapeutic tumor volume.

- Often significant tumor regression during first 2-3 weeks of Radiotherapy.

![Image of tumor regression](image)

*Percent of Initial Cervical Volume during Chemoradiation* (Beadle et al, 2006)
On line Adaptive RT

STILL INVESTIGATIONAL
Prostate Cancers and Newer Radiation Techniques
## 3D-CRT v. IMRT: Dose Delivery

Prostate and Seminal Vesicles

<table>
<thead>
<tr>
<th>Organ</th>
<th>3D CRT Mean±SD</th>
<th>IMRT Mean</th>
<th>IMRT Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small field:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate:</td>
<td>74.0 ± 1.5</td>
<td>75.7</td>
<td>82.8</td>
</tr>
<tr>
<td>Seminal Vesicles:</td>
<td>50.0 ± 1.0</td>
<td>63.5</td>
<td>79.1</td>
</tr>
<tr>
<td><strong>Large field:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate:</td>
<td>50.0 ± 1.0</td>
<td>55.1</td>
<td>61.8</td>
</tr>
<tr>
<td>+ Boost:</td>
<td>70.0 ± 1.4</td>
<td>77.3</td>
<td>87.7</td>
</tr>
<tr>
<td>Nodes:</td>
<td>50.0 ± 1.0</td>
<td>54.2</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Steven Hancock, 2002
GU/GI Toxicity-Limited Fields

Maximum RTOG Toxicity Score

P = 0.05

Steven Hancock, 2002
GU or GI Toxicity

Maximum RTOG Score

Probability (%)

0 1 2 3

P = 0.002

Steven Hancock, 2002
CA Prostate

Daily CBCT
IMRT: Clinical Aims in Prostate Cancer

- Improve conformity: dose escalation
- Reduce high dose volumes in rectal wall & bladder
- Reduced small bowel dose in nodal therapy
IMRT: Prostate Cancer

- CTV
- SV
- Bladder
- Rectum
Tomotherapy

Before treatment

Institutional Correction protocol

After treatment
MVCT on Tomotherapy Unit
Radiation Doses (treatment time: 7-8 weeks)

Localized Prostate Cancer

► Low Risk: 3 D CRT / IMRT / Brachytherapy: 70 - 74 Gy
► Int Risk: 3 D CRT / IMRT +/- Brachytherapy: 74 - 76 Gy
► High Risk: 3 D CRT / IMRT +/- Brachytherapy: 74 - 80 Gy

Locally Advance Prostate Cancer

► Prostate only fields include Prostate + SV with margins
► Prostate + pelvic fields include Prost. + SV with margins and pelvic LN’s
► Doses: Prostate + SV: 74 - 78 Gy
       : Pelvic Nodes: 50 Gy (if positive: 55 - 60 Gy)

RT Doses > 74 Gy mandates a component of IMRT / IGRT
If brachytherapy: XRt doses: 50-55 Gy only

TMH EBM Guidelines 2010
Prostate IMRT: Prescription Doses

MSKCC:  
Dose to 98 ± 2% of CTV: 81. Gy  
Dose to 95% of PTV: 78. Gy

5% of Bladder > 83. Gy  
25-30% Rectum > 75.6 Gy  
Dose per fraction 1.8 Gy

2 yr risk of GI bleeding: 2% IMRT v. 10% 3D-CRT

Zelefsky et al. Radiother & Oncol 55:241
why hypo-fractionate?

Hypo-fractionation for CaP will:

- escalate dose biologically
- reduce acute sequelae
- keep same normal tissue late-effects
- reduce overall treatment course

Still not a standard of care
Organ-sparing intensity-modulated radiotherapy for anal cancer using the ACTII schedule: a comparison of conventional and intensity-modulated radiotherapy plans.

Brooks CJ¹, Lee YK, Aitken K, Hansen VN, Tait DM, Hawkins MA.

Abstract

AIMS: Conventional external beam radiotherapy for anal cancer is associated with a high rate of treatment-related morbidity. The purpose of this retrospective study was to compare the dosimetric advantages of three intensity-modulated radiotherapy (IMRT) plans with the conventional plan with regards to organs at risk avoidance delivering the ACTII schedule of 50.4 Gy in 1.8 Gy/fraction: 17 fractions for phase 1 and 11 fractions for phase 2.

MATERIALS AND METHODS: Ten anal cancer patients (T1-3 N0-3) treated with the conventional plan using four fields and conformal boost were identified. The phase 1 planning target volume (PTV) included tumour, anal canal and inguinal, peri-rectal and internal/external iliac nodes. Phase 2 included identifiable disease only. Three step-and-shoot IMRT plans were generated: IMRT1: phase 1 inverse-planned IMRT with two- to four-field conformal phase 2; IMRT2: both phase 1 and phase 2 inverse-planned IMRT; IMRT3: phase 1 IMRT and phase 2 forward-planned IMRT. All IMRT plans were then compared against the conventional plan on PTV coverage, small bowel, genitalia, femoral heads, bladder and healthy tissue dose volume information.

RESULTS: While achieving similar PTV coverage compared with the conventional plan, significant dose reductions were observed for IMRT plans in external genitalia, small bowel and healthy tissue. Reductions were also observed in the femoral heads and bladder.

CONCLUSIONS: IMRT significantly reduces the dose to organs at risk while maintaining excellent PTV coverage in anal cancer radiotherapy.
RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal.

Kachnic LA¹, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, Haddock MG, Rotman M, Parikh PJ, Safran H, Willett CG.

Abstract

PURPOSE: A multi-institutional phase 2 trial assessed the utility of dose-painted intensity modulated radiation therapy (DP-IMRT) in reducing grade 2+ combined acute gastrointestinal and genitourinary adverse events (AEs) of 5-fluorouracil (5FU) and mitomycin-C (MMC) chemoradiation for anal cancer by at least 15% compared with the conventional radiation/5FU/MMC arm from RTOG 9811.

METHODS AND MATERIALS: T2-4N0-3M0 anal cancer patients received 5FU and MMC on days 1 and 29 of DP-IMRT, prescribed per stage: T2N0, 42 Gy elective nodal and 50.4 Gy anal tumor planning target volumes (PTVs) in 28 fractions; T3-4N0-3, 45 Gy elective nodal, 50.4 Gy ≤ 3 cm or 54 Gy >3 cm metastatic nodal and 54 Gy anal tumor PTVs in 30 fractions. The primary endpoint is described above. Planned secondary endpoints assessed all AEs and the investigator’s ability to perform DP-IMRT.

RESULTS: Of 63 accrued patients, 52 were evaluable. Tumor stage included 54% II, 25% IIIA, and 21% IIIB. In primary endpoint analysis, 77% experienced grade 2+ gastrointestinal/genitourinary acute AEs (9811 77%). There was, however, a significant reduction in acute grade 2+ hematologic, 73% (9811 85%, P=.032), grade 3+ gastrointestinal, 21% (9811 36%, P=.0062), and grade 3+ dermatologic AEs 23% (9811 49%, P<.0001) with DP-IMRT. On initial pretreatment review, 81% required DP-IMRT replanning, and final review revealed only 3 cases with normal tissue major deviations.

CONCLUSIONS: Although the primary endpoint was not met, DP-IMRT was associated with significant sparing of acute grade 2+ hematologic and grade 3+ dermatologic and gastrointestinal toxicity. Although DP-IMRT proved feasible, the high pretreatment planning revision rate emphasizes the importance of real-time radiation quality assurance for IMRT trials.

Copyright © 2013 Elsevier Inc. All rights reserved.
A phase II trial of neoadjuvant IMRT-based chemoradiotherapy followed by one cycle of capecitabine for stage II/III rectal adenocarcinoma.


Abstract

PURPOSE: Neoadjuvant chemoradiation has become the standard treatment in locally advanced rectal cancer (LARC) and improves local control. This study explored the feasibility of an intensified chemoradiation treatment followed by one cycle of capecitabine before surgery for LARC.

METHODS AND MATERIALS: Patients with histologically confirmed, newly diagnosed, locally advanced rectal adenocarcinoma (cT3-T4 and/or cN+) located within 12 cm of the anal verge were included in this study. Patients received intensity-modulated radiation therapy (IMRT) to the pelvis (total dose 44 Gy in 20 fractions), as well as concurrent oxaliplatin (50 mg/m² d1 weekly) and capecitabine (625 mg/m² b.i.d. d1-5 weekly). One cycle of capecitabine (1000 mg/m² b.i.d. d1-14) was given two weeks after the completion of concomitant chemoradiation, and radical surgery was scheduled six weeks after chemoradiation.

RESULTS: Between October 2007 and November 2008, a total of 42 patients were enrolled in the study (median age 51 years; 31 male). Of these, 38 underwent surgical resection and 4 refused radical surgery because of almost complete primary tumor regression and complete symptom relief after neoadjuvant therapy. Fifteen patients underwent sphincter-sparing lower anterior resection. Six patients had a pathological complete response (pCR). The incidence of grade 3 hematologic, gastro-intestinal, and skin toxicities were 4.7%, 14.3%, and 26.2%, respectively. Grade 4 toxicity was not observed. Surgical complications (incisional infection within 2-3 weeks after surgery) were observed in 5 patients. Good responders (defined as TRG 3-4) had a significant difference in DFS (81.6% vs. 16.8%, respectively; p = 0.000) and OS (83.9% vs. 40.7%, respectively; p = 0.007) compared to those who were evaluated as TRG 1-2.

CONCLUSIONS: Our study indicates that neoadjuvant chemoradiation followed by one cycle of capecitabine before surgery has a good treatment efficacy, with only mild toxicities associated with chemoradiation and acceptable surgical complications. Treatment response was an early surrogate marker and correlated to oncologic prognosis.
Summary

• Newer RT techniques: Basic principles should be understood

• GYN Cancers: Teletherapy: Atleast box field 3D CRT
  - IMRT more for post-operative pelvic tumors
  - Brachytherapy is better than IMRT boost
  - IGRT: establish a proper protocol
  - Adaptive RT: Still Investigational

• Prostate Cancers: IMRT preferable with dose escalation

• Anal canal and Rectal Cancers: Evolving
Acknowledgements:

- Departments of Radiation Oncology & Medical Physics
- Department of Radio-diagnosis
- GYN Disease Management Group TMC
- Patients

THANK YOU