Integration of IMRT and Brachytherapy in the Treatment of Cervical Cancer

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Advancements- Radiation Therapy

- Major advancements in RT planning and delivery in recent years
- Particularly true with external beam RT
- Growing implementation of intensity modulated (IMRT) and image-guided RT (IGRT)

Mell LK, Mundt et al. IMRT Use in the USA-2004 Cancer 2005;104:1296-303
Gynecology Has Lagged Behind

- In 2002 Survey, only 15% of IMRT users had treated a gynecology patient
- Most treated head/neck and prostate cancers

Mell LK, Mundt AJ
Survey of IMRT Use in the United States
Cancer (2003)
Gynecology Has Lagged Behind

- And Gynecologic Brachytherapy remains prescribed to a point!
- Unlike all other tumor sites where treatment is prescribed to a volume
- Unbelievable in the Year 2007
Fortunately Change is in the air….

- Latest IMRT Survey-
  - Gynecology 4th most common site treated

- Most rapidly growing site

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>85%</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>80%</td>
</tr>
<tr>
<td>CNS Tumors</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Gynecology</strong></td>
<td><strong>35%</strong></td>
</tr>
<tr>
<td>Breast</td>
<td>28%</td>
</tr>
<tr>
<td>GI</td>
<td>26%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>20%</td>
</tr>
<tr>
<td>Lung</td>
<td>22%</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>16%</td>
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<tr>
<td>Lymphoma</td>
<td>12%</td>
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</tbody>
</table>

Change will continue

- Residents now receive training in gynecologic IMRT

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
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<tbody>
<tr>
<td>Head and Neck</td>
<td>92%</td>
</tr>
<tr>
<td>Prostate</td>
<td>81%</td>
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<tr>
<td>CNS Tumors</td>
<td>56%</td>
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<tr>
<td>Pediatrics</td>
<td>38%</td>
</tr>
<tr>
<td>Gynecology</td>
<td>24%</td>
</tr>
<tr>
<td>Recurrent/Palliative</td>
<td>24%</td>
</tr>
<tr>
<td>Breast</td>
<td>21%</td>
</tr>
<tr>
<td>GI</td>
<td>21%</td>
</tr>
<tr>
<td>Lung</td>
<td>15%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7%</td>
</tr>
</tbody>
</table>

Malik, Mundt et al. Survey of Resident Education in IMRT
Promising IMRT Reports

- Numerous dosimetric studies demonstrate superiority of IMRT planning in Gynecology patients
  

- Promising preliminary outcome studies
  
## Clinical Outcome Studies--Cervical Cancer

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>FU</th>
<th>Stage</th>
<th>DFS</th>
<th>Pelvic Control</th>
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</thead>
<tbody>
<tr>
<td><strong>Intact Cervix</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kochanski</td>
<td>44</td>
<td>23 m</td>
<td>I-IIA</td>
<td>81%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IIB-IIIB</td>
<td>53%</td>
<td>67%</td>
</tr>
<tr>
<td>Beriwal</td>
<td>36</td>
<td>18 m</td>
<td>IB-IVA</td>
<td>51%</td>
<td>80%</td>
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<tr>
<td><strong>Postoperative Cervix</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kochanski</td>
<td>18</td>
<td>21 m</td>
<td>I-II (node+)</td>
<td>79%</td>
<td>94%</td>
</tr>
<tr>
<td>Chen</td>
<td>35</td>
<td>35 m</td>
<td>I-II (node+)</td>
<td>NS</td>
<td>93%</td>
</tr>
</tbody>
</table>

Chen et al. *Int J Radiat Oncol Biol Phys* 2001;51:332
Prospective Trials Underway

- **RTOG 0418**
  - Phase II trial
  - Post-operative IMRT in cervical and endometrial cancer

- **Tata Hospital (India)**
  - Phase III trial
  - IMRT versus conventional RT in stage IIB cervical cancer
Moving to 3D image-based brachytherapy planning

Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology

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Radiotherapy Oncology 2006:78:67-77
IMRT and Brachytherapy

- Unfortunately, IMRT and brachytherapy have long been cast as “foes”
- Endless debates, Point-Counterpoints in journals and meetings

Could IMRT Replace Brachytherapy in the Treatment of Cervical Cancer?

Kaled Alektiar, M.D.
Memorial Sloan Kettering Cancer Center

vs.

Arno J. Mundt, M.D.
University of Chicago

Journal Brachytherapy (January 2003)
Can IMRT Replace Brachytherapy in Cervical Cancer?

- Interesting question
- At best a purely academic question
- Given excellent efficacy and tolerance of modern brachytherapy, no need to replace it
- At best, IMRT could provide a potential fallback for patients unable or unwilling to receive brachytherapy
Is there any evidence that IMRT could replace brachytherapy?

- Multiple dosimetric studies suggest that an IMRT boost is feasible

- Clinical outcome data, however, is extremely limited
10 cervical cancer patients
MSKCC dose-volume constraints (prostate ca)
Median Total dose = 79 Gy
Higher doses possible with smaller margins
- 0.25 cm margin → 84 Gy+
Others propose using a **simultaneous integrated boost (SIB)**

Guerrero et al.
*Int J Radiat Oncol Biol Phys 2005;62:933*

- SIB approach
  - 45 Gy in 1.8 Gy fractions (pelvis)
  - 70 Gy in 2.8 Gy fractions (cervical tumor)
- Radiobiologically equivalent to 45 Gy pelvic RT + 30 Gy HDR (5 fractions)
- Better bowel and bladder sparing
- Shortening of overall treatment (5 weeks)
PET/MRI compatible applicator

- Localizes the cervix and positions the bladder and rectum on a daily basis
- Spatially registers the tumor and internal organs for planning and treatment
- HDR dose and fractionation schedule
- Better coverage of select tumors
12 gynecology pts (8 cervix cancers)
Unable to undergo brachytherapy
Treated with a 3DCRT boost
Re-planned using IMRT
Better normal tissue sparing using IMRT
Clinical Outcome Data

Molla (Spain)

• 16 patients (7 cervix cancer)
• Hypofractionated boost (dynamic arc, IMRT)
  • Intact disease 7 Gy x 2 (4-7 days between)
  • Postoperative 4 Gy x 5 (2-3 days between)
• 6-10 mm PTV margins
• Body stereotactic RT system
• Rectal balloon for internal immobilization
IMRT Boost

- Median follow-up 12.6 months
- 15/16 (93%) local control
- No grade ≥ 3 acute toxicity
- 1/16 (6%) grade ≥ 2 late GI/GU

Molla et al.
Fractionated stereotactic RT boost for gynecologic tumors: an alternative to brachytherapy?
A more interesting question

- Can IMRT and Brachytherapy be integrated?
- Timely given interest in Europe and the USA with 3D (image guided) brachytherapy
Benefits of Integration

- Numerous potential benefits
- “Repair” unacceptable brachytherapy implants
  - Feasible in Prostate Cancer
- Optimize parametrial boosts in locally advanced patients
- The list goes on…..
Greatest Benefit

Comprehensive Adaptive Treatment

Adaptive Image-Guided IMRT Integrated with Adaptive Image-Guided 3D Brachytherapy
Cervical Cancer

- Long been known that cervical cancers respond rapidly to treatment
- Particularly true with concomitant chemotherapy
- Significant response seen early on during external beam RT
- Response continues over brachytherapy course
14 patients
MRI before RT and at 30 Gy
46% reduction in GTV

Int J Radiat Oncol Biol Phys 2006;64:189
Cervix Cancer Regression-During External Beam

Beadle, Eifel (MD Anderson)
ASTRO 2006

16 cervical cancer patients
Weekly CT Scans
Cervix Cancer Regression-During Brachytherapy

Lin, Grigsby (Washington University)
Int J Radiat Oncol Biol Phys 2007;67:91

- 11 cervical cancer patients
- $^{18}$F-FDG PET prior to first, middle and last HDR insertions
- Significant reduction in tumors

<table>
<thead>
<tr>
<th>Median Tumor Size</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Insertion</td>
</tr>
<tr>
<td>Mid/Last Insertion</td>
</tr>
</tbody>
</table>
New IGRT Technologies

- Response now easily assessed **daily** with in-room volumetric imaging

- Tomotherapy
- Varian Trilogy
- Elekta Synergy
- CT-on-Rails
- Etc....
Daily CBCT
Patient A
Adaptive IMRT

- Current work focused on using daily volumetric imaging to adapt IMRT phase

- Van de Bunt noted benefits of re-planning
  - Improves sparing of the rectum
  - If >30cc GTV reduction, re-planning improved sparing of the small bowel

- Daily imaging also addresses concerns of inter-fraction organ motion of the uterus
Adaptive IMRT

- Many hurdles need to be addressed
- Multiple software tools required
  - Automated Segmentation
    To address labor-intensive aspect of contouring
  - Deformable Registration
    To allow generation of cumulative DVHs
- Prospective clinical trials needed
  - How often?
  - Does it help?
  - Does it hurt?
Are Cone-Beam CT Images Adequate for Adaptive IG-IMRT?

- Sufficient for most patients
- Easier to deform planning CT → CBCT than vice versa
Potential Shortcut

- Deform intensity distributions
- “Intermediate way” to adapt
  - Conformally avoid bladder and rectum based on daily CBCT image
  - Addresses tumor shrinkage and inter-fraction organ motion

**Physics Contribution**

USE OF DEFORMED INTENSITY DISTRIBUTIONS FOR ON-LINE MODIFICATION OF IMAGE-GUIDED IMRT TO ACCOUNT FOR INTERFRACTIONAL ANATOMIC CHANGES

Radhe Mohan, Ph.D., Xiaodong Zhang, Ph.D. He Wang, Ph.D., Yixiu Kang, Ph.D., Xiaochun Wang, Ph.D., Helen Liu, Ph.D., K. Kian Ang, M.D., Deborah Kuban, M.D., and Lei Dong, Ph.D.

Department of Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX
Adapt to What?

Bladder

Tumor

Rectum

Week 1

Bladder

Tumor

Rectum

Week 3
Ultimate Goal

- Extend adaptation to include brachytherapy
- Re-planning based on deformed images
- Generation of true (cumulative) DVHs
Comprehensive Adaptive IMRT

- Many hurdles need to be addressed
- Deformation of an image with an applicator to one without one not a trivial task!
- Incorporation of other imaging modalities, e.g. PET, MRI
- Prospective clinical trials needed
  - How?
  - When?
  - Does it matter?
Comprehensive Adaptive RT

- Potential of this approach limited by computational power
- Research collaboration with the UCSD Supercomputer Center
- Image reconstruction, deformable registration, re-optimization performed in minutes
- Daily on-line adaptive IMRT may be a true possibility
On-Line Adaptive IMRT

Simulation

Planning

Patient Setup

Cone Beam CT

Treatment Delivery

New IMRT Plan

SDSC
The War Needs to End!

- No more debates!
- No more Point-Counterpoints!
- Devote energies instead to the integration of brachytherapy with IMRT
- Only then can the ultimate goal of comprehensive adaptive RT be possible
Gynecologic IMRT, Adaptive IGRT Team

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Steve Jiang, Ph.D.
Todd Pawlicki, Ph.D.
Lily Tang, Ph.D. (post-doc)
Amit Majumdar, Ph.D. (UCSD Super-Computer Center)
UCSD Radiation Oncology

- Cancer Center & current Rad Onc Department
- Department Expansion 2 Linacs
- Proton Treatment & Research Center