IMRT for Gynecologic Malignancies: The University of Chicago Experience

Bulent Aydogan, PhD
John C. Roeske, PhD
The University of Chicago
RT in Gynecologic Tumors

- Typically a combination of external beam whole pelvic RT (WPRT) and intracavitary brachytherapy (ICB)
- WPRT is used to treat the primary tumor/tumor bed plus the regional lymphatics
- ICB is used to boost the primary tumor/tumor bed safely to high doses
Gynecologic RT

- Highly efficacious and well tolerated in most patients
- Excellent pelvic control particularly in early stage cervical and endometrial cancer
- Adjuvant RT improves outcome of women with high risk features following surgery
GYN-IMRT Rationale

- RT $\rightarrow$ potential toxicities due to the treatment of considerable volumes of normal tissues
  - Small bowel $\rightarrow$ diarrhea, SBO, enteritis, malabsorption
  - Rectum $\rightarrow$ diarrhea, proctitis, rectal bleeding
  - Bone Marrow $\rightarrow$ ↓WBC, ↓platelets, anemia
  - Pelvic Bones $\rightarrow$ Insufficiency fractures, necrosis

- Reduction in the volume of normal tissues irradiated with IMRT may thus ↓risk of acute and chronic RT sequelae
Gynecologic IMRT
Practical Issues

- Simulation
- Target and Tissue Delineation
- Treatment Planning
- Delivery and Quality Assurance
Patient Selection

- Most gynecology patients can be treated with IMRT
- Poor candidates
  - Uncooperative patients
  - Unable to tolerate ↑time on the table
- Markedly obese patients not ideal
  - Inability to capture entire external contour
  - Difficulties with daily setup
- Dosimetric benefits may be less in the obese*

Simulation and CT Scanning

- Patients in supine position
- Immobilized using a customized device
- Patient scanned from L2 to below ischial tuberosities
- Oral, IV and rectal contrast
Immobilization

- Immobilized supine
- Upper and lower body alpha cradles indexed to the table

Mell LK, Roeske J, Mundt AJ. Gynecologic Tumors: Overview Chapter 23 IMRT: A Clinical Perspective BC Decker, Toronto 2005

MD Anderson

Jhingran A, et al. Endometrial Cancer: Case Study (Chapter 23.2) IMRT: A Clinical Perspective 2005

JCR – 7/2005
Planning CT Scan

Scan extent:
L2 vertebral body to 3 cm below the ischial tuberosities

Thin slice thickness, e.g. 3 mm

Larger volumes only used if treating extended field, whole abdomen or pelvic-inguinal IMRT
Contrast Administration

Helps delineate normal and target tissues

Oral, rectal and IV contrast
Bladder contrast not needed

IV contrast is important (vessels serve as surrogates for nodes)
*With experience, IV contrast less needed

A vaginal marker is also placed (be careful not to distort)
Target Definition

- Clinical target volume (CTV) drawn on axial CT slices
- CTV components depend on the pathology
- In all patients:
  - Upper ½ of the vagina
  - Parametrial tissues
  - Pelvic lymph nodes regions (common, internal and external iliacs)
- In cervical cancer and endometrial cancer patients with positive cervical involvement, include the presacral region
CTV – Upper Slice
CTV – Middle Slice

- Bowel
- External Iliac artery
- External Iliac vein
- Iliac muscle
- Psoas Muscle
- Piriform Muscle
- Rectum

Mell, Roeske, Mundt, Gynecologic Tumors, IMRT: A Clinical Perspective, BC Decker 2005
3D Visualization of the CTV
Normal Tissues

- Normal tissues delineated depends on the clinical case.
- In most cases, include:
  - Small bowel, rectum, bladder
- In patients receiving concomitant or sequential chemotherapy, include the bone marrow.
- Others include the femoral heads.
- Kidneys and liver included only if treating more comprehensive fields.
Normal Tissues

- Be consistent with contouring
  - Helps with DVH interpretation
- Rectum: Outer wall ?mm (anus to the sigmoid flexure)
- Small bowel: Outermost loops from the L4-5 interspace
  - Include the colon above the sigmoid flexure as well in the “small bowel” volume
- Bone marrow: Intramedullary space of the iliac crests
  - Stop at the top of the acetabulum
  - Note that this approach ignores marrow in other pelvic bones
Small Bowel

- Dip small bowel contour into concave CTV
- ↑ Conformity reducing small bowel dose

Jhingran A, et al.
MD Anderson
Endometrial Cancer: Case Study
Chapter 23.2
IMRT: A Clinical Perspective BC Decker
2005
Bone Marrow

Contour the intramedullary canal of the Crests
Alternatively, contour the outer surface of the iliac crests (certainly faster!)
Treatment Planning

- Expand CTV → PTV
  - To account for setup uncertainty and organ motion
- Appropriate expansion remains unclear
- Various expansions have been used for Gyne IMRT ranging from 0.5 to 1.5 cm
- At the U of Chicago, we use 1 cm
- Less is known about normal tissue motion, so we don’t expand the normal tissues
- Other centers, e.g. MD Anderson, routinely expand normal tissues
Setup Uncertainties

- Digitized weekly setup films of 50 patients. These patients were immobilized using upper and lower alpha cradles.
- Measured setup position using image-registration interface (Balter, et al.)
- Compared digitized images to DRR’s representing patient planning position
- Recorded setup uncertainties in AP, LR, and SI directions


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Measured Setup Uncertainties

- Immobilization: Alpha cradle under legs and upper body with arms above head*

\[
\begin{align*}
\sigma_{LR} & = 3.2 \text{ mm} \\
\sigma_{SI} & = 3.7 \text{ mm} \\
\sigma_{AP} & = 4.1 \text{ mm}
\end{align*}
\]

* Analysis of 50 patients treated with IM-WPRT
Organ Motion

- A concern in the region of the vaginal cuff
- Two approaches are being studied at our institution to address this:
  - IGRT (Varian OBI unit)
  - Vaginal immobilization
- Now we simply avoid tight CTV volumes and use a 1 cm CTV→PTV expansion
  - Produces very generous volumes around the vaginal cuff
Using this approach, no failures in the vaginal cuff have been seen in patients treated with adjuvant IM-PRT at our institution (>80 pts treated).

Nonetheless, tighter volumes could result in ↓ toxicity.

Tighter margins are also needed if higher than conventional doses are used.
“Integrated Target Volume”

- A creative solution to the organ motion problem developed at MDAH?
- Two planning scans: one with a full and one with an empty bladder
- Scans are then fused
- An *integrated target volume* (ITV) is drawn on the *full* bladder scan (encompassing the cuff and parametria on both scans)
- ITV is expanded by 0.5 cm $\rightarrow$ PTV_{ITV}
Normal Tissue Organ Motion

- Small bowel
- Bladder
- Rectum

Week 3 scan

Treatment planning scan
Bladder and Rectal Volumes

Week

Rectum
Bladder
IMRT Planning at the University of Chicago

- CORVUS (Version 5.0) planning system (Nomos)
- User specifies: dose-volume constraints of tumor, individual organs; number of fields and gantry angle
- Produces 3D, IM dose distribution
- Uses simulated annealing to produce fluence maps
Treatment and Delivery

- 7-9 co-axial beam angles (equally spaced)
- 80 or 120 Leaf MLC using step-and-shoot mode on a Varian 2100 CD
Treatment Planning

- Prescription dose: 45-50.4 Gy
  - 45 Gy in pts receiving vaginal brachytherapy
  - 50.4 Gy if external beam alone
- 1.8 Gy daily fractions
  - Given inherent inhomogeneity of IMRT
  - Avoids hot spots > 2 Gy
- “Dose painting” (concomitant boosting) remains experimental
  - Potentially useful in pts with high risk factors (positive nodes and/or margins)
Increasing number of planning systems now commercially available

Despite inherent differences, no one system appears superior

Acceptable gynecologic IMRT plans have been produced on all major planning systems
Treatment Planning

- Input parameters are next entered for the PTV and normal tissues
- Optimal input parameters not known
- Derived iteratively
- Differ from one system to another
- Priority should be given to coverage of the PTV (over sparing of normal tissues)
- Strive for $\geq 97\%$ PTV coverage
Gyne IMRT - Input DVHs

Dose (Gy)

Percent Volume

PTV
Bladder
Rectum
Small Bowel
Tissue

0 10 20 30 40 50

0 10 20 30 40 50

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Treatment Planning

- Alternatively, use “tuning” structures to force conformity to the shape of the PTV sparing normal tissues.
- Input constraints are entered for these structures.
- More limited constraints are entered for the normal tissues, e.g. maximum dose.
Tuning Structures

- An anterior structure (AVOID) to reduce dose to the small bowel
- A SHELL around the PTV to force conformity
  - First a 0.5 cm expansion is made on the PTV (GAP)
  - The SHELL is then a 2 cm expansion around the GAP
- A posterior structure (Rectum-PTV) to reduce the dose to the rectum
Treatment Planning

- Generate *several* plans per patients
- Evaluate each plan:
  - Qualitatively (slice-by-slice evaluation of conformity and hot/cold spots)
  - Quantitatively (evaluate DVHs of PTV and normal tissues)
- No consensus on plan acceptability
  - ≥95%, ≥97%, ≥98% coverage???
  - Cold spots should be small in magnitude and preferably on the periphery of the PTV
# IM-WPRT Plan Optimization

## Current PTV-Specific Criteria

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conformity</strong></td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>PTV Coverage</strong></td>
<td>&gt; 98%</td>
<td>&lt; 96%</td>
</tr>
<tr>
<td><strong>Hot Spots</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Within CTV</td>
<td>Edge of PTV</td>
</tr>
<tr>
<td></td>
<td>Preferably within GTV</td>
<td>Rectal or bladder walls in ICB region</td>
</tr>
<tr>
<td>Magnitude</td>
<td>&lt;10% (110% dose)</td>
<td>&gt;20% (110% dose)</td>
</tr>
<tr>
<td></td>
<td>0% (115% dose)</td>
<td>&gt;2% (115% dose)</td>
</tr>
<tr>
<td><strong>Cold Spots</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Edge of PTV</td>
<td>Within CTV or GTV</td>
</tr>
<tr>
<td>Magnitude</td>
<td>&lt;1% of the total dose</td>
<td>&gt;1% of the dose</td>
</tr>
</tbody>
</table>
A more difficult question is *what* makes a normal tissue DVH acceptable.

IM-WPRT plans achieve better normal tissue DVHs than WPRT plans. But how good does a normal tissue DVH need to be?

The answer is not clear.
DVH Acceptance Criteria for Small Bowel

- Dosimetric analysis of acute GI toxicity in our Gyne IMRT pts was performed.
- On multivariate analysis, the strongest predictor of acute GI toxicity was the small bowel volume receiving the prescription dose or higher ($SB_{vol100\%}$).

Roeske et al.
NTCP Analysis?
Gynecologic IMRT Patients

\[
NTCP = \frac{1}{1 + \left( \frac{410}{V_{100}} \right)^{3.2}}
\]

Conventional Pelvic RT
IMRT
Conventional Isodose Distribution
IMRT Isodose Distribution

PTV

100%

70%

50
Rectum

Percent Volume

Conv

IMRT

Percent Dose

0 20 40 60 80 100 120

0 20 40 60 80 100 120
Absolute Volume (cc) of SBR Receiving 45 Gy

Patient Number

Conv
IMRT

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## IM-WPRT Planning Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Volume Receiving Prescription Dose</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Bowel</td>
</tr>
<tr>
<td>Roeske</td>
<td>↓50%</td>
</tr>
<tr>
<td>Ahamad</td>
<td>↓40-63%*</td>
</tr>
<tr>
<td>Chen</td>
<td>↓70%</td>
</tr>
<tr>
<td>Selvaraj</td>
<td>↓51%***</td>
</tr>
</tbody>
</table>

*dependent on PTV expansion used
**data not shown
***reduction in percent volume receiving 30 Gy or higher
Positioning

- All of our studies (set-up uncertainty, organ motion) are based on patients in the supine position.
- The *prone* position may offer some additional dosimetric sparing.

Quality Assurance
Treatment Delivery/QA

- At U Chicago:
  - Varian CL2100 CD accelerators
  - 120-leaf MLC
  - Automatic beam sequencing software.
  - Step and shoot mode

- All major delivery systems have been used successfully
  - Elekta, Siemens, Varian, Tomotherapy

- Alternatively, fabricated customized physical modulators could be used
  - Southeastern Radiation Products
    www.seradiation.com
No clear best delivery approach

Increasingly important factor, however, is **treatment duration**

- ↑ time → ↓ efficacy

Effort should be directed to minimize treatment duration

Joseph Deasy, Jack F. Fowler
Radiobiology of IMRT
Chapter 3
IMRT: A Clinical Perspective 2005
Treatment Delivery/QA

- Prior to (and throughout) treatment, rigorous QA is essential
- Verify setup accuracy on day 1 and then weekly with orthogonal x-ray films
- Special QA problem is that field sizes may exceed MLC travel limits
  - Fields must be split into $\geq 2$ carriage movements

Kamath S et al. Med Phys 2004;31:3314
Comparison of Ion Chamber with Calculation

\[ y = 0.990x \]

\[ R^2 = 0.995 \]
Independent MU Verification

- Use RadCalc Software (Lifeline Medical)*
- Uses a modified Clarkson integration algorithm to calculate dose to isocenter
- Program exploits rotational symmetry of scatter to make computation efficient

*MUVC code is licensed by the University of Chicago to Lifeline Medical
Comparison of Radcalc to Corvus

Mean = 1.4%, Standard deviation = 1.2%, N = 504

J. Haslam et al. Comparison of dose calculated by an intensity modulated radiotherapy treatment planning system and an independent monitor unit verification program.

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In our Gyne IMRT patients, we compared doses calculated by CORVUS and the RadCalc MUVC program.

- Lifeline Software, Inc., lifelinesoftware.com/

Mean disparity was 0.2% (standard deviation 1.1%)

Disparities ≥ 3% result in additional QA (ion chamber and film measurements)

Film Dosimetry
Clinical Experience

- Between 2/00 and 7/05, >150 women were treated with IM-WPRT in our clinic
- Most had cervical cancer, primarily stage IB
- Most underwent definitive RT and, in stages IB2-IIIB, concomitant cisplatin-based chemotherapy
- Endometrial cancer patients were treated following primary surgery
- ICB was administered in ~50% of women following IM-WPRT

Clinical Experience

- How do results compare to conventional treatments?
- Acute GI toxicities (Grade 2)
  - WPRT: 91%
  - IM-WPRT: 60% \( p = 0.002 \)
- Acute GU toxicities (Grade 2)
  - WPRT: 20%
  - IM-WPRT: 10% \( p = 0.22 \)

Acute GI toxicity in IM-WPRT Patients vs. WPRT

The bar chart compares the incidence of acute GI toxicity in IM-WPRT patients versus WPRT patients across different grades (0-3). The chart indicates that IM-WPRT patients experience higher toxicity than WPRT patients, with a significant difference in Grade 2 toxicity.
On multivariate analysis controlling for age, chemo, stage and site, IMRT remained statistically significant (\( p = 0.01 \); odds ratio 0.16, 95% confidence interval 0.04, 0.67)
Excellent Pelvic Control Rates

**Cervical Cancer**
34 stage I-II cervical cancer pts
   21 intact uterus, 13 postoperative
Median follow-up = 26.2 months
3-year actuarial pelvic control = **92%**

**Endometrial Cancer**
31 stage I-III endometrial cancer pts
   All treated postoperatively
Median follow-up = 24.1 months
3-year actuarial pelvic control = **100%**
Pelvic Control

- While encouraging, follow-up remains relatively short and the number of patients treated remains small.
- Only with longer follow-up and larger patient cohorts can more definitive statements be made.
- Cooperative groups (RTOG, GOG) are currently developing protocols to evaluate IMRT in gynecology patients.
Conclusions

- IMRT is a useful means of reducing the volume of normal tissues irradiated in gynecologic patients receiving WPRT
- Our initial evaluation indicate a significant reduction in GI toxicity relative to patients receiving conventional therapy
- Continued follow-up and critical evaluation are required to validate the long term merits of this approach
What about the negatives?

- IMRT results in higher volumes of normal tissue receiving lower doses
- Increased MUs result in higher total body doses
- Target and tissue delineation are time-consuming
- No guidelines exist regarding how targets should be contoured and plans optimized
- Long-term follow-up is not available assessing tumor control and unexpected sequelae
- Clinical data are available from only one institution and while prospective no randomized comparisons have been performed