Background

- RT has a long history in the treatment of gynecologic malignancies, notably cervical and endometrial cancer
- The 1st gynecology patient was treated with RT a century ago

IMRT for Gynecologic Malignancies: The University of Chicago Experience

Bulent Aydogan, PhD
The University of Chicago

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

- Potential toxicities due to the treatment of considerable volumes of normal tissues
  - Small bowel → diarrhea, SBO, enteritis, malabsorption
  - Rectum → diarrhea, proctitis, rectal bleeding
  - Bone Marrow → ↓WBC, ↓platelets, anemia
  - Pelvic Bones → Insufficiency fractures, necrosis
- Reduction in the volume of normal tissues irradiated with IMRT may thus ↓risk of acute and chronic RT sequelae
**Gynecologic IMRT flow chart**

- Patient selection
- Simulation - Prone vs. Supine: Type of immobilization
- Target and Tissue Delineation - Multiple imaging modalities
- Treatment Planning/Optimization - Number of beams/orientation
- Plan Evaluation - High conformity vs. dose homogeneity
- Quality Assurance - Verification of calculated dose
- Treatment Delivery/Verification - Verification scheme / IG
- Imaging for treatment assessment - Tumor response / Adaptive approach

**Patient Selection**

- 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

Mull LK, Roachke J, Munch AJ. Gynecologic Tumors/ Overview Chapter 23 IMRT: A Clinical Perspective BC Decker, Toronto 2005
Others favor the prone position.
Data from the U Iowa suggest dosimetric benefits with the prone position.

*Adli et al. Red J 2003;57:230-238

Simulation

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)

Note: Not possible in patients treated with pelvic-inguinal IMRT (frog-leg position)

Target Definition

- **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 and Normal Tissues

Postoperative RT: PTV

Definitive RT: CTV and Normal Tissues

P Georg, MD – Med University Vienna
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

Consistency with contouring helps with DVH interpretation and outcome studies

- Rectum: Outer wall (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 (EASY TO CONTOUR THE BONE)
  - 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

Expand CTV → PTV

- To account for setup uncertainty and organ motion
- Appropriate expansion remains unclear
  - Various expansions have been used for Gyn 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
- Immobilization: Alpha cradle under legs and upper body with arms above head*
- Measured setup position using image-registration interface (Balter, et al.)

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


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)
- Now we simply avoid tight CTV volumes and use a 1 cm CTV→PTV expansion
  - Produces very generous volumes around the vaginal cuff

Organ Motion

- Using this approach, no failures in the vaginal cuff have been seen in patients treated with adjuvant IM-PRT at our institution (>100 pts treated)
- Nonetheless, tighter volumes could result in toxicity
- Tighter margins are also needed if higher than conventional doses are used

MD Anderson’s “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 (InTV) is drawn on the full bladder scan (encompassing the cuff and parametria on both scans)
- InTV is expanded by 0.5 cm → PTV_{InTV}
Normal Tissue Changes and Organ Motion

Week 3 scan  Treatment planning scan

Bladder and Rectal Volumes

DVH Comparisons - Bladder

DVH Comparisons - Rectum
**IMRT Planning and delivery at the University of Chicago**

- Initial phase are completed with CORVUS planning system
- Currently we use Varian Eclipse and Pinnacle
- 7-9 co-axial beam angles (equally spaced)
- 120 Leaf MLC using
- step-and-shoot mode on a Varian 2100 Ex

**IM-WPRT Plan Optimization**

- 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**

- 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)

**Current PTV-Specific Criteria**

<table>
<thead>
<tr>
<th>Conformity</th>
<th>Acceptable</th>
<th>Unacceptable</th>
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</thead>
<tbody>
<tr>
<td>PTV Coverage</td>
<td>Good &gt; 98%</td>
<td>Poor &lt; 98%</td>
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</table>

**Hot Spots**

<table>
<thead>
<tr>
<th>Location</th>
<th>Acceptable</th>
<th>Unacceptable</th>
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</thead>
<tbody>
<tr>
<td>Within CTV or GTV</td>
<td>Edge of PTV</td>
<td></td>
</tr>
<tr>
<td>Preferably within GTV</td>
<td>Rectal or bladder walls in ICB region</td>
<td></td>
</tr>
<tr>
<td>Magnitude (&lt;10% or 110% dose)</td>
<td>&gt;20% (110% dose)</td>
<td></td>
</tr>
<tr>
<td>0% (115% dose)</td>
<td>&gt;2% (115% dose)</td>
<td></td>
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</table>

**Cold Spots**

<table>
<thead>
<tr>
<th>Location</th>
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<th>Unacceptable</th>
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<tbody>
<tr>
<td>Edge of PTV</td>
<td>Within CTV or GTV</td>
<td></td>
</tr>
<tr>
<td>Magnitude (&lt;1% of the total dose)</td>
<td>&gt;1% of the dose</td>
<td></td>
</tr>
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</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.

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 (SBvol100%).


NTCP Analysis of Gynecologic IMRT Patients

Isodose Distribution Comparison
**IM-WPRT Planning Studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Bowel</th>
<th>Bladder</th>
<th>Rectum</th>
</tr>
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<tbody>
<tr>
<td>Roeske</td>
<td>150%</td>
<td>123%</td>
<td>123%</td>
</tr>
<tr>
<td>Ahamad</td>
<td>↓40-63%*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Chen</td>
<td>↓70%</td>
<td>↓**</td>
<td>↓**</td>
</tr>
<tr>
<td>Selvaraj</td>
<td>↓51%***</td>
<td>↓31%***</td>
<td>↓66%***</td>
</tr>
</tbody>
</table>

*dependent on PTV expansion used

**Quality Assurance**

Prior to (and throughout) treatment, rigorous QA is essential
**QA**
- Dose verification
  - Ion chamber, diode arrays, film, or MU calculation.
- Verify setup accuracy on day 1 and then weekly with orthogonal x-ray films.
- Role of daily CBCT is still not clear.
- Special QA problem is that field sizes may exceed MLC travel limits.
  - Fields must be split into ≥ 2 carriage movements.

Kamath S et al. Med Phys 2004;31:3314

**Impact of Tumor Regression in Cervical Cancer Patients**
- 14 cervical cancer pts
- MRI before RT and after 30 Gy
- 46% ↓GTV


**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

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)

Chronic GI Toxicity

Excellent Pelvic Control Rates

Cervical Cancer
Kochanski J, Mundt AJ. ASCO (2004) 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
Knab B, Mundt AJ. ASTRO (2004) 31 stage I-III endometrial cancer pts 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.

Future Directions

- Bone marrow sparing IMRT
- IGRT and adaptive radiotherapy in GYN-IMRT
- IMRT as a replacement of or complimentary to brachytherapy

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.
- 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.
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