Role of IMRT in the Treatment of Gynecologic Malignancies

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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.
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.

Highly efficacious and well tolerated in most patients.
IMRT Rationale

- RT → 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
- ↑ dose in “high risk” pts, e.g. node+ disease
- An alternative (or replacement) for conventional brachytherapy
Goals

- To discuss the current status of IMRT treatment planning for gynecologic patients receiving whole-pelvic IMRT.
- To describe emerging areas of research and development in the use of IMRT for gynecologic patients.
Treatment Planning Process

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-IMRT
Immobilization

- Patient in supine position
- Immobilized using alpha cradles indexed to the treatment table
Immobilization

- Others favor the prone position
- Data from the U Iowa suggest ↑dosimetric benefits to the prone position (Adli et al. Int J Radiat Oncol Biol Phys 2003;57:230-238)
- However, may not be possible in patients treated with pelvic-inguinal IMRT

Schefter T, Kavanagh B. Cervical Cancer: Case Study IMRT: A Clinical Perspective 2005

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Planning CT Scan

- Scan extent: L3 vertebral body to 3 cm below ischial tuberosities
- Typically use 3 mm slice thickness
- Larger volumes used only if treating extended field whole abdomen or pelvic-inguinal IMRT
Oral, IV and rectal contrast are commonly used.
Bladder contrast is not needed.
IV contrast is important to delineate vessels which serve as surrogates for lymph nodes.
A vaginal marker is also placed.
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
  - Parametria 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

Bladder

CTV

Small bowel

Large bowel

Rectal wall

definitive RT

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P Georg, MD – Med University Vienna
3D Visualization of the CTV
PTV Considerations

- Organ motion in the inferior portion of the CTV due to differential filling of the bladder and rectum
- Set-up uncertainty
- Appropriate expansion remains unclear; various reports ranging from 0.5 – 1.5 cm
- At Univ of Chicago, we use a 1 cm expansion
- Less is known about normal tissues
- Other centers (e.g., MD Anderson) routinely expand normal tissues
Organ Motion

- A concern in the region of the *vaginal cuff*
- Two approaches are being studied at our institution to address this:
  - IGRT
  - 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
Comparison of CT Scans

Week 3 scan

Treatment planning scan

Small bowel

Bladder

Rectum

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“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 → PTV_{ITV}
Illustration of ITV

Small Bowel

Bladder

Integrated Target Volume (ITV)

MD Anderson

Jhingran A, et al. Endometrial Cancer: Case Study
IMRT: A Clinical Perspective BC Decker 2005

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Treatment Planning

- 7-9 co-axial beam angles (equally spaced)
- Most centers use 6 MV
- Comparative plans of 6 vs. 18 MV show little or no difference
- However, 18 MV associated with higher total body doses
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)
Gyne IMRT - Input DVHs

Small bowel input DVH based on NTCP data

- PTV
- Bladder
- Rectum
- Small Bowel
- Tissue
### IM-WPRT Plan Optimization

#### Current PTV-Specific Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Acceptable</th>
<th>Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformity</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>PTV Coverage</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>

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NTCP Analysis
Gynecologic IMRT Patients

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

- **Conventional Pelvic RT**
- **IMRT**
IMRT Isodose Distribution

PTV

100%

70%
An Alternative Delivery Option: Solid Modulators

- Linac not equipped with MLC
- MLC carriage limitations result in “split” fields (i.e., 9 fields → 18 fields)
- Lower monitor units (MUs) associated with solid modulators
“Split” Fields

- MLC carriage limitation require some large fields to be split into 2 or 3 smaller modulated fields
- Most GYN-IMRT fields are “split”. Thus, 9 gantry positions will result in 18+ treatment fields
Example Modulator

1 inch screws

14 cm

14.5 cm

14 cm

Gantry = 280

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Comparison DVHs
Modulator + MLC

![Graph showing dose-volume histograms for different organs and structures with annotations for Bladder, Bladder-dec, Rectum, Rectum-dec, PTV, PTV-dec, Small Bowel, Small Bowel-dec, Bone Marrow, and Bone Marrow-dec.]

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Clinical Experience

- Between 2/00 and 7/06, >200 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

- Monitored weekly for *acute* side effects
- Worst toxicities were graded on a 4-point scale
  - 0 = none
  - 1 = mild, no medications required
  - 2 = moderate, medications required
  - 3 = severe, treatment breaks, hospitalizations
- Toxicity evaluated in a matched cohort of previous gynecology patients treated with conventional pelvic RT
- Balanced in terms of age, site, radiation dose, chemotherapy and brachytherapy
Acute GI toxicity
IM-WPRT vs. WPRT

P = 0.002


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On multivariate analysis controlling for age, chemo, stage and site, IMRT remained statistically significant \((p = 0.01; \text{OR} = 0.16, 95\% \text{ confidence interval} 0.04, 0.67)\)
What about tumor control?

- Preliminary data suggests that our IMRT patients have a low rate of pelvic failure.
- Majority of recurrences within the GTV; only 1 in the CTV in uninvolved nodes.
- None of the stage IB-IIA cervix or stage IB-IIIB endometrial patients relapsed in the pelvis.
- However, longer follow-up and more patients needed to truly evaluate the impact of IMRT on tumor control.
Future Directions

- Bone marrow sparing IMRT
- IGRT and adaptive radiotherapy in gynecologic IMRT
- IMRT as a replacement of brachytherapy
Gynecologic IMRT
Bone Marrow Sparing Approach

- Focus is on the small bowel and rectum
- Additional important pelvic organ is the bone marrow
- 40% total BM is in the pelvis (within the WPRT fields)
- ↓pelvic BM dose may ↑tolerance of concurrent chemotherapy and the chemotherapy at relapse
Increased Dose Conformity with IMRT Reduces Volume of Pelvic Bone Marrow Irradiated
Grade $\geq 2$ WBC Toxicity
WPRT versus IM-WPRT Patients

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BM-Sparing IMRT

- Dosimetric analysis of factors associated with acute hematologic toxicity
- 37 cervical cancer pts treated with IM-pelvic RT plus CDDP (40 mg/m²/week)
- **Major predictors** of hematologic toxicity:
  - Total pelvic BM V-10 and V-20
  - Lumbar sacral spine V-10
- **Not** volume of the iliac crests

A Bone Marrow Primer for Physicists

- Two types of marrow:
  - Red Marrow – Active
  - Yellow Marrow - Inactive
- Nearly 40-50% of red marrow is located in the pelvis.
- Distribution of red marrow depends on age and sex.
- With age, conversion of red to yellow marrow occurs.
Use Tc-99m sulfur colloid SPECT imaging to define active bone marrow

SPECT/CT Fusion

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Bone Marrow Sparing

- Patients treated using IM-WPRT have a demonstrated reduction in AHT compared to patients treated with WPRT.
- Further improvements may be achieved by incorporating BM into the planning process.
- Functional BM imaging may have an important role for identifying areas of active BM.
- Future investigations are being designed to determine if functional BM imaging can reduce hematologic toxicities in these patients.
Many cervical tumors rapidly shrink during RT (especially with concomitant chemotherapy)

- Tight margins (CTV-to-PTV expansions) early on may be too large by the end of treatment
Impact of Tumor Regression in Cervical Cancer Patients

- 14 cervical cancer pts
- MRI before RT and after 30 Gy
- 46% ↓ GTV

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IGRT/Adaptive RT

- IGRT techniques (cone beam CT) may allow plans to be adapted as tumors respond

- ↑ Bladder and rectal sparing

- No changes made in coverage of the parametrial tissues

- Also allow management of organ motion

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Tumors
Shrink
Plan Adapts

Bladder

Rectum

Week 1

Tumor

Prescription
Isodose

Week 3

Bladder

Rectum

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IGRT/Adaptive RT

- University of California San Diego: Clinical trial in gynecology patients assessing
  - Feasibility of on-board imaging (cone beam CT) to improve delivery of IMRT plans
  - Impact of adapting treatment plans to tumor response
Can IMRT Replace ICB?

- IMRT has been used to reduce volume of normal tissues irradiated
- In selective sites (e.g., head and neck, prostate), IMRT has been used to deliver higher than conventional doses
- Can the same paradigm be applied to cervical cancer?
Early stage endometrial cancer treated with whole pelvic RT and vaginal (cylinder) HDR

Goal: Use vaginal cylinder-type immobilization device and IMRT
Comparison of HDR vs. IMRT

HDR

IMRT

Comparison of HDR vs. IMRT

HDR

PTV

Rectum

Bladder

IMRT

PTV

Rectum

Bladder

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**IMRT vs. HDR**

- Maximum rectal doses lower with IMRT vs. HDR (89% vs. 143%, \( p < 0.05 \))
- Mean rectal doses in IMRT also lower than HDR (14.8% vs. 21.4%, \( p < 0.05 \))
- IMRT also resulted in lower maximum bladder doses (66.2% vs. 74.1%, \( p < 0.05 \))
- Plans provided comparable coverage to the PTV with IMRT plans resulting in less dose heterogeneity

B Aydogan, PhD – Univ of Chicago
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*
- Few 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
References