GYNECOLOGIC BRACHYTHERAPY 2
CONFLICT OF INTEREST STATEMENT

- Chen: NIH research grant
- Damato:
  - 2015 Elekta travel grant on electromagnetic tracking
  - 2016 Consulting work for Augmenix, Inc.
- Kirisits: nothing to disclose
- Mourtada: Elekta, Royalty recipient, CT/MR Shielded Applicator
GYN TARGETING $CTV_{HR} / CTV_{IR}$

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LEARNING OBJECTIVES

- Understand basics of ICRU 89 target concept
- Learn how to optimize implant geometries and dwell times to cover the target volumes with appropriate dose
Findings at time of diagnosis

**Dimensions (cm):**
- Width: 7
- Thickness: >5
- Height: >5
- Vaginal inv.: 0.5 (right fornix)

Findings at time of brachytherapy

**Dimensions (cm):**
- Width: 3.5
- Thickness: 2
- Height: 2
- Vaginal inv.: 0

Fig. 5.1
ICRU 89
ICRU/GEC-ESTRO report 89
Target volume concepts

**High Risk CTV:**
GTV at time of brachytherapy
In all cases includes:
- GTV + whole cervix
- Presumed tumour extension in adjacent tissues
  - Clinical assessment
  - Residual grey zones on MRI

**Intermediate Risk CTV:**
GTV at time of diagnosis
In all cases includes:
- HR-CTV
- Integrates initial GTV
SAFETY MARGINS:
1-1.5 cm cranially
0.5 cm antero-posteriorly
1 cm laterally
Overview of adaptive target concept in cervix cancer

ICRU/GEC ESTRO report 89
Figs. 5.9, 5.10, 5.11
Stage IB2
FROM PLANNING AIMS TO PRESCRIPTION

Traditional concepts:

“when prescribing to a target, the prescription dose is the planned dose to cover this target as completely as possible.”

or

prescription to a 100% isodose which is “to cover” the target volume”
Need for common terminology according to ICRU reports on proton treatment and IMRT

• **Planning aim dose**
  – Set of dose and dose/volume constraints for a treatment

• **Prescribed dose**
  – Finally accepted treatment plan (which is assumed to be delivered to an individual patient)

• **Delivered dose**
  – Actually delivered dose to the individual patient
Need for common terminology according to ICRU reports on proton treatment and IMRT

Example:
Previously: $4 \times 7 \text{ Gy} \sim 84 \text{ Gy EQD2}$ prescribed, $D_{90}$ was mean $93 \text{ Gy}$

Planning aim was to deliver $4 \times 7 \text{ Gy} \sim 84 \text{ Gy}$, $D_{2\text{cm}^3}$ for rectum, sigmoid $< 70 \text{ Gy EQD2}$, bladder $< 90 \text{ Gy EQD2}$

Prescribed dose was mean $93 \text{ Gy} \pm 13 \text{ Gy (1SD)}$ EQD2 to $D_{90}$ HR CTV

Delivered dose? Depending on variations and uncertainties
Level 2 - Advanced standard for reporting
All that is reported in level 1 plus:

3D delineation of volumes (on volumetric images with applicator and on clinical diagrams):

- $\text{GTV}_{\text{res}}$
- $\text{CTV}_{\text{HR}}$
- $(\text{CTV}_{\text{IR}}$ if used for prescription)$
- With maximum width, height, thickness and with volume

ICRU 89
Level 2 - Advanced standard for reporting
All that is reported in level 1 plus:

Dose reporting for defined volumes:

- $D_{98\%}$, $D_{90\%}$, $D_{50\%}$ for $CTV_{HR}$
- ($D_{98\%}$, $D_{90\%}$ for $CTV_{IR}$ if used for prescription)
- $D_{98\%}$ for $GTV_{res}$
- $D_{98\%}$ for pathological Lymph nodes

ICRU 89
Dose effect $CTV_{HR}$, $GTV$, and $CTV_{IR}$

Analysis for stage II and III

Tanderup et al 2016
Local failures in regard to brachytherapy target volumes

data available in 53 patients (66%)

Inside $\text{CTV}_{HE}$: 51%

Inside $\text{CTV}_{LR}$: 17%

Inside HR & IR-CTV: 30%

Not related: 2%

Schmid et al. ESTRO 2017
EMBRACE II

RChTh + BT in < 50 days

EBRT   | Chemotherapy | Brachy

<table>
<thead>
<tr>
<th>week 1</th>
<th>week 2</th>
<th>week 3</th>
<th>week 4</th>
<th>week 5</th>
<th>week 6</th>
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</table>

MRI guided adaptive brachytherapy (IGABT)

GTV_{res} \quad D_{95} \gg 95\text{Gy}

CTV_{in} \quad D_{95} \gg 90\text{Gy}

Bladder \quad D_{2cm} = 76\text{Gy} (<80\text{Gy})

Rectum \quad D_{2cm} = 61\text{Gy} (<65\text{Gy})

Sigmoid \quad D_{2cm} = 61\text{Gy} (<70\text{Gy})

~ 60 GY \quad CTV_{in} \quad D_{95} \gg 60\text{Gy}

Nodal CTV-E based on Risk Group

Residual GTV-T, Adaptive HR CTV-T, IR CTV-T
EMBRACE II - dose prescription protocol

<table>
<thead>
<tr>
<th></th>
<th>$D_{90%\text{CTV}<em>{\text{HR}}\text{EQD2}</em>{10}}$</th>
<th>$D_{98%\text{CTV}<em>{\text{HR}}\text{EQD2}</em>{10}}$</th>
<th>$D_{98%\text{GTV}\text{EQD2}_{10}}$</th>
<th>$D_{98%\text{CTV}<em>{\text{IR}}\text{EQD2}</em>{10}}$</th>
<th>Point A $\text{EQD2}_{10}$</th>
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<tr>
<td><strong>Planning Aims</strong></td>
<td>&gt; 90 Gy &lt; 95 Gy</td>
<td>&gt; 75 Gy</td>
<td>&gt; 95 Gy</td>
<td>&gt; 60 Gy</td>
<td>&gt; 65 Gy</td>
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<tr>
<td><strong>Limits for Prescribed Dose</strong></td>
<td>&gt; 85 Gy</td>
<td>-</td>
<td>&gt; 90 Gy</td>
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<td>-</td>
</tr>
</tbody>
</table>
IIIb, 8 cm width, insufficient response (11/99)

no adaptation of application technique
intracavitary approach only

Optimization with Tandem/ring only

HR CTV
D90%: 69 Gy

Diagnosis

recurrence
9 months after treatment

Brachytherapy
Application technique and patterns of tumor regression
Combined intracavitary interstitial applicators

Utrecht

Aarhus

The Vienna Applicator
When is a combined intracavitary interstitial applicator necessary?
How to decide when to use combined intracavitary interstitial applicator?

Practical approaches:

1. Pre-implant planning with applicator in situ
2. Pre-implant planning without applicator
3. Intraoperative assessment with TRUS
Preplanning with applicator in situ
Preplanning without applicator in situ
Preplanning with intraoperative TRUS
Applicator for distal parametrical disease

The Vienna II Applicator

Berger D et al. unpublished data
Dose per fraction Brachytherapy

$CTV_{HR}$:
$D_{90\%} = 5.2\text{Gy} \quad V_{100\%} = 68\%$

$GTV$:
$D_{90\%} = 12\text{Gy}$

Standard without needles
Dose per fraction brachytherapy

$CTV_{HR}$:
$D_{90}\% = 8.1\text{Gy} \quad V_{100\%} = 96\%$

$GTV$:
$D_{90} = 14\text{Gy}$

Optimized with needles
Spatial dose distribution
Limitations

DVH parameters

Spatial dose distribution (Hot spots / Cold spots)

Dwell time distribution to take into account
  not contoured structures
  parametrial tissue
  vagina
  nerves
  vessels
  ureter
Manual optimization
Inverse optimization
Manual plan
Inverse planning without spatial dis.
Summary

- Understand basics of ICRU 89 target concept
- Learn how to optimize implant geometries and dwell times to cover the target volumes with appropriate dose
GYN ORGANS AT RISK

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LEARNING OBJECTIVES

- Review relevant organs-at-risk and their dose constraints
- Discuss contouring uncertainties and image modalities
- Reviewing volumes-at-risk
ORGANS-AT-RISK AND MORBIDITY

- Rectum and Sigmoid:
  - Telangiectasia in small volumes → bleeding
  - Dose to the overall wall → continence

- Bladder:
  - Trigone/neck → urgency/incontinence
  - Dose to overall wall → frequency

- Vaginal stenosis, ulcerations, adhesions
ORGANS-AT-RISK: BASIC CONCEPTS

- Brachy-related morbidity typically associated with small volumes receiving high doses

- Focus on absorbed dose to the very small (0.1 cm$^3$) and small (2 cm$^3$) volumes

- Dose to very small and small volumes are significantly different: different morbidity patterns
Fig. 6.4
ICRU 89
### Organs-at-Risk: Typical Constraints

#### Brachytherapy (fx)

<table>
<thead>
<tr>
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<th>1</th>
<th>2</th>
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<th>4</th>
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<tr>
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<td>7.00</td>
<td>7.00</td>
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<tr>
<td>D90</td>
<td>7.30</td>
<td>7.50</td>
<td>7.00</td>
<td>7.30</td>
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<td>Rectum D2cc</td>
<td>4.00</td>
<td>4.10</td>
<td>3.50</td>
<td>3.50</td>
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<tr>
<td>Bladder D2cc</td>
<td>6.00</td>
<td>7.50</td>
<td>5.00</td>
<td>6.00</td>
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<tr>
<td>Sigmoid D2cc</td>
<td>3.60</td>
<td>3.70</td>
<td>3.80</td>
<td>3.20</td>
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<tr>
<td>Bowel D2cc</td>
<td>4.20</td>
<td>2.50</td>
<td>4.50</td>
<td>3.80</td>
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#### Brachytherapy (EQD2)

<table>
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<td>Rectum D2cc</td>
<td>5.6</td>
<td>5.8</td>
<td>4.6</td>
<td>4.6</td>
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<tr>
<td>Bladder D2cc</td>
<td>10.8</td>
<td>15.8</td>
<td>8.0</td>
<td>10.8</td>
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<tr>
<td>Sigmoid D2cc</td>
<td>4.8</td>
<td>5.0</td>
<td>5.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Bowel D2cc</td>
<td>6.0</td>
<td>2.8</td>
<td>6.8</td>
<td>5.2</td>
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</table>

#### Total EQD2 (Gy)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Brachy</th>
<th>Total</th>
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<tr>
<td>Prescription</td>
<td>44.3</td>
<td>39.7</td>
<td>83.9</td>
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<tr>
<td>D90</td>
<td>44.3</td>
<td>41.9</td>
<td>86.2</td>
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<tr>
<td>Rectum</td>
<td>43.2</td>
<td>20.5</td>
<td>63.7</td>
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<td>Bladder</td>
<td>43.2</td>
<td>45.4</td>
<td>88.6</td>
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<tr>
<td>Sigmoid</td>
<td>43.2</td>
<td>18.8</td>
<td>62.0</td>
</tr>
<tr>
<td>Bowel</td>
<td>43.2</td>
<td>20.7</td>
<td>63.9</td>
</tr>
</tbody>
</table>

< 75 Gy  
< 90 Gy  
< 75 Gy
3D ORGANS-AT-RISK: REPORTING

- Level 1:
  - Bladder and rectum contouring
  - D0.1cm³ and D2cm³
  - Recto-vaginal reference point

- Level 2: Level 1 +
  - Sigmoid and bowel (adjacent)
  - Upper vagina points
3D ORGANS-AT-RISK: REPORTING

Level 3: Level 2 +
- Vagina contouring
- Vaginal reference length/volume
- Bladder sub-volumes (neck, wall, etc)
- Anus
- “Remaining Volume”
MR OR CT

Bladder
HR-CTV
Rectum

Viswanathan,
IJROBP 2007
Table 3. Volume and dose to organs at risk after importing to Plato, normalized to 7 Gy/fraction

<table>
<thead>
<tr>
<th>OARs</th>
<th>MRI</th>
<th>CT</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (cm³)</td>
<td>62.5 ± 31.6</td>
<td>84.5 ± 57.5</td>
</tr>
<tr>
<td>D₀.₁cm³</td>
<td>7.5 ± 1.0</td>
<td>6.5 ± 1.5</td>
</tr>
<tr>
<td>D₁cm³</td>
<td>6.1 ± 0.6</td>
<td>5.5 ± 1.4</td>
</tr>
<tr>
<td>D₂cm³</td>
<td>5.6 ± 0.6</td>
<td>5.0 ± 1.2</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (cc)</td>
<td>45.3 ± 15.3</td>
<td>62.8 ± 16.8*</td>
</tr>
<tr>
<td>D₀.₁cm³</td>
<td>5.0 ± 0.9</td>
<td>5.0 ± 1.1</td>
</tr>
<tr>
<td>D₁cm³</td>
<td>4.2 ± 0.7</td>
<td>4.2 ± 0.9</td>
</tr>
<tr>
<td>D₀₂cm³</td>
<td>3.9 ± 0.7</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>Sigmoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (cc)</td>
<td>36.5 ± 25.2</td>
<td>29.8 ± 16</td>
</tr>
<tr>
<td>D₀.₁cm³</td>
<td>5.5 ± 1.1</td>
<td>5.5 ± 1.9</td>
</tr>
<tr>
<td>D₁cm³</td>
<td>4.5 ± 0.9</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>D₂cm³</td>
<td>4.0 ± 0.8</td>
<td>3.9 ± 1.4</td>
</tr>
</tbody>
</table>

Abbreviations: \( D₀.₁cm³ \) = dose to 0.1 cm³; \( D₁cm³ \) = dose to 1 cm³; \( D₂cm³ \) = dose to 2 cm; other abbreviations as in Table 1. * \( p < 0.01 \).
CONTOURING UNCERTAINTIES

- Intra- and inter-fraction variations may be significant, in particular for sigmoid, bowel and bladder.

- “Assumption of static hotspots” dictate conservative summation of D0.1cm$^3$ and D2cm$^3$ dose.
CONTOURING UNCERTAINTIES

- Contouring uncertainties may be important if affecting the organ walls close to the applicator.

- Contouring practice also important:
  - Organ wall contouring
  - Rectum/Sigmoid junction
CONCLUSION - OAR

- $D_{2cm^3}$ (and $D_{2cm^3}$) most important metrics in brachytherapy

- Summation of metrics among fractions despite intra- and inter- fraction uncertainties

- MRI and CT both acceptable for OAR contouring
ACHIEVING GYN OPTIMIZATION GOALS

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Chief of clinical physics
Helen F. Graham Cancer Center
Christiana Care Health System
Newark, Delaware
LEARNING OBJECTIVES

- Review the basic elements needed to achieve optimal plans for intracavitary GYN brachytherapy.
- Realize the limitations and pitfalls to avoid when using available TPS tools.
3D-based HDR Treatment Planning

- Reconstruct implant via CT/MR
- Contour target/OARs
- Define dose-volume objectives
- Define dose points (ICRU 38 reporting)
  - A and B points
  - Bladder and Rectal points
- Select dwell positions
- Optimize dwell time relative weights
OPTIMIZATION ROAD MAP

- A set of dose–volume constraints must be defined \textit{prior} to the optimization of dwell positions and dwell times,
- Adaptive approach for each fraction since tumor volume is changing
- New plan for each fraction is needed
- Account for dose distributions from previous brachytherapy and/or external-beam fractions.
Level 1: *Minimum standard for reporting*

Dose reporting
- TRAK
- Point A dose
- Recto-vaginal reference point dose
- $D_{0.1cm^3}, D_{2cm^3}$ for the bladder, rectum

Level 2: *Advanced standard for reporting*
All that is reported in level 1 plus

Dose reporting for defined volumes
- $D_{98\%}, D_{90\%}, D_{50\%}$ for the CTV$_{HR}$
- $(D_{98\%}, D_{90\%})$ for the CTV$_{IR}$ if used for prescription
- $D_{98\%}$ for GTV$_{res}$
- $D_{98\%}$ for pathological lymph nodes

Dose reporting OARs
- Bladder reference-point dose
- $D_{0.1cm^3}, D_{2cm^3}$ for the sigmoid
- $D_{cm^3}$ for the bowel
- Intermediate- and low-dose parameters for the bladder, rectum, sigmoid, and bowel (e.g., $V_{15\ Gy}, V_{25\ Gy}, V_{35\ Gy}, V_{45\ Gy}$, or $D_{98\%}, D_{50\%}, D_{2\%}$)
- Vaginal point doses at level of sources (lateral at 5 mm)$^a$
- Lower and mid-vagina doses (PIBS, PIBS $\pm$ 2 cm)$^a$

$^a$Surrogate points for volumetric vaginal-dose assessment.
Key Ingredients for optimal GYN HDR plans

- Pre-defined Dose/Volume constraints
- Dwell positions/weights optimization
- Applicator Placement Relative to target and OARs
- Applicator Selection
APPLICATOR SELECTION/PLACEMENT

- Selection of applicator type is critical to achieve the optimal plan, basic physics laws must be considered.
  - Learn your source and applicator dose properties
- Applicator geometry in relation to target volumes and organs at risks (OARs) must be evaluated
  - Volumetric images, CT scouts, or orthogonal films
OPTIMIZE APPLICATOR SELECTION

• Tandem/Ovoid
  – standard pear shaped distribution
  – Covers upper vagina
• Tandem/Ring
  – narrower dose distribution
  – Covers anterior and posterior lip of cervix
• Tandem/Cylinder
  – Very narrow distribution
  – Covers length of vagina
• Interstitial
  – large volume of disease, sidewall, lower vagina

courtesy A. Viswanathan
CERVICAL/UPPER VAGINAL VOLUME

Tandem and ovoid

Tandem and ring

courtesy A. Viswanathan
Dose Distribution around Shielded Ovoids

TG-43 (no shields)  TG-186 (shields modeled)
OPTIMIZE SYSTEM GEOMETRY

• Optimal placement of the applicators in the uterus and vagina.
• Optimal placement of the radioactive sources in applicators
• Pear-shaped dose distribution
  ➢ high dose to the cervical and paracervical tissues
  ➢ reduced dose to the bladder and rectum
• HR-CTV shaped dose distribution (ICRU89)
• Pear-shaped and HR-CTV hybrid dose distribution
Lateral View of Optimized Applicator Placement

- Tandem - 1/3 of the way between S1 – S2 and the symphysis pubis
- The tandem - midway between the bladder and S1 - S2
- Marker seeds should be placed in the cervix
- Ovoids should be against the cervix (marker seeds)
- Tandem should bisect the ovoids
- The bladder and rectum should be packed away from the implant

MD Anderson, Houston, TX
AP View of Optimized Applicator Placement

- The ovoids should fill the vaginal fornices, add caps to increase the size of the ovoids if necessary.
- The ovoids should be separated by 0.5 to 1.0 cm, admitting the flange on the tandem.
- The axis of the tandem should be central between the ovoids.

MD Anderson, Houston, TX
Example of Poor Applicator Placement

MD Anderson, Houston, TX
DWELL POSITIONS & WEIGHTS ITERATIVE PLANNING

- Start the optimization process with **standardized loading patterns** for the active dwell positions
  - This would achieve reproducible and controlled absorbed dose distributions
  - Normalize to Point A
  - Then in an iterative process, the dwell positions and dwell times are adjusted
  - until an acceptable compromise between target coverage and OAR constraints is achieved.
Optimization Tools (Oncentra)

- Manual dwell weights
  - For T&O and T&R starting point (classical LDR rules)
- Geometrical Optimization: on distance or volume
  - Vaginal cylinder w one channel (on distance)
  - Syed interstitial (on volume)
- Graphical Optimization:
  - add final touches with a fine “brush”
- IPSA (Inverse Planning Simulated Annealing)
- HIPO (Hybrid Inverse Planning Optimization)
  - requires use of volumetric constraints, but allows setting optimization priorities to the target and OAR.
Manual dwell weights (relative)

- Ideal for T&O and T&R loading to mimic classical loading described by Fletcher to obtain the Pear shape 100% dose cloud

- Start with general guideline, but watch for hot/cold spots
  - Tandem loading (mgRa eq): 15 10 10 (1 0.67 0.67)
  - Ovoids loading (mgRa eq): 10 10 (0.67, 0.67)

Note: Manually changing dwell weights and dwell times changes the dose distribution, ignoring the previously prescribed dose. Therefore, use this option carefully!
## Mimic Ra-226 tube source active length

### Tandem Loading Rules (Sources) Assumptions: mHDR source (3.6mm AL)/ 5mm step size

<table>
<thead>
<tr>
<th>Active Length</th>
<th>Source Configuration</th>
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<tr>
<td>7.5mg &lt; A ≤ 15mg</td>
<td>½ source (15mm)</td>
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<tr>
<td>Range: 5mg &lt; A ≤ 7.5mg</td>
<td>1 source (10mm)</td>
</tr>
<tr>
<td>A ≤ 2.5mg</td>
<td>½ source (5mm)</td>
</tr>
</tbody>
</table>

### Fletcher Rules:
- Tandem activity 4 to 6 mgRaeq/cm
- Use spacers to achieve this linear intensity, if required.
Remember the Fletcher Rule of activity per unit length to avoid hot/cold spots

![Ideal](image1)

![Hot](image2)
Remember the Fletcher Rule of activity per unit length to avoid hot/cold spots.

Ideal

Cold

15-11-10, 12.5/12.5

15-11-5, 12.5/12.5
Watch for the vaginal surface dose as well
Geometrical Optimization: On Distance

- Takes the dose contribution of dwell positions in all catheters into account.
- Influence of the distant catheter(s) on the dose in the current point (dwell position in the current catheter) is small.
- The optimization provides a ‘tight’ dose around each catheter while still attempting to fill in the spaces to cover the desired volume.
# Vaginal Cylinder
## GO-Distance Optimization

17 active positions
2.5 mm source step size
Dose point type: Axis

<table>
<thead>
<tr>
<th>Pos</th>
<th>X (mm)</th>
<th>Y (mm)</th>
<th>Z (mm)</th>
<th>Abs. Dose (cGy)</th>
<th>Rel. Dose (%)</th>
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<td>186.4</td>
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</table>
Graphical Optimization

- Drag and Drop function for isodose lines in order to optimize the dose distribution
- Based on adjustment of individual “dwell weights/times”, reflected in the table on screen
- Adjustable behaviour: from Global to Local correction
Graphical manual tool - Interstitial Tandem and Ring
CAUTION WHEN USING GRAPHICAL OR INVERSE PLANNING METHODS

- Inverse optimization and graphically assisted dose distribution shaping should be performed *with care* as the spatial distribution of over-dosed and underdosed spots within the treated volume is often changed substantially compared with the manual iterative procedure!
New inverse planning technology for image-guided cervical cancer brachytherapy: Description and evaluation within a clinical frame

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Cervix

ABSTRACT

Purpose: To test the feasibility of a new inverse planning technology based on the Hybrid Inverse treatment Planning and Optimisation (HIPO) algorithm for image-guided cervical cancer brachytherapy in comparison to conventional manual optimisation as applied in recent clinical practice based on long-term intracavitary cervical cancer brachytherapy experience.

Materials and methods: The clinically applied treatment plans of 10 tandem/ring (T/R) and 10 cases with additional needles (T/R + N) planned with PLATO v14.3 were included. Standard loading patterns were manually optimised to reach an optimal coverage with 7 Gy per fraction to the High Risk CTV and to fulfil dose constraints for organs at risk. For each of these patients an inverse plan was retrospectively created with Oncentra GYN v0.9.14. Anatomy based automatic source activation was based on the topography of target and organs. The HIPO algorithm included individual gradient and modification restrictions for the T/R and needle dwell times to preserve the spatial high-dose distribution as known from the long-term clinical experience in the standard cervical cancer brachytherapy and with manual planning.

Results: HIPO could achieve a better target coverage (V100) for all T/R and 7 T/R + N patients. Changes in the shape of the overdose volume (V200/400) were limited. The D2cc per fraction for bladder, rectum and sigmoid colon was on average lower by 0.2 Gy, 0.4 Gy, 0.2 Gy, respectively, for T/R patients and 0.6 Gy, 0.3 Gy, 0.3 Gy for T/R + N patients (a decrease from 4.5 to 4 Gy per fraction means a total dose reduction of 5 Gy EQD2 for a 4-fraction schedule). In general the dwell times in the additional needles were lower compared to manual planning. The sparing factors were always better for HIPO plans. Additionally, in 7 T/R and 7 T/R + N patients all three D0.1cc, D1cc and D2cc for vagina wall were lower and a smaller area of vagina was covered by the reference dose in HIPO plans. Overall loading times in the tandem, the ring and the needles, as well as dose distribution, were largely preserved with adaptations performed due to specific topographical variations, in particular in lateral and caudal directions.

Conclusions: Inverse planning based on the HIPO algorithm can produce treatment plans for cervical cancer brachytherapy which are comparable to plans based on manual optimisation as applied in clinical practice. It is essential to take into account the spatial dose distribution in addition to the DVH-based constraints. The proposed inverse planning concept is feasible for improving the therapeutic ratio and limiting substantial high-dose regions around needles.

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Create a pseudostructure from the Rx isodose surface of the manually optimized plan and then using that in conjunction of the dose received by OARs and the maximization of dose to target while preserving the general shape of the pear-shape Rx isodose surface.

CONCLUSIONS: The TSO can be added with minimal planning time increase but with the potential of dramatic and systematic reductions in OAR D_{2cc} and in some cases with concurrent increase in target dose coverage. These single-fraction modifications would be magnified over the course of four to five intracavitary insertions and may have real clinical implications in terms of decreasing both acute and late toxicities. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.
CONCLUSIONS

- Overall understanding of the radiotherapy course, including EBRT and clinical goals, should be realized since each HDR fraction is adaptive and may be tailored to achieve optimal outcomes.
- Several tools are available to achieve GYN optimization goals, strength and pitfalls should be realized by the planner.
- Optimization should be performed with caution
  - evaluate spatial dose distribution, not just DVH parameters
EXTRA SLIDES
OPTIMIZATION DOSE POINTS

The following types can be defined to help the optimizer:

- Axis dose points
- Catheter dose points
- Basal dose points
- Target dose points
- Patient points
From ICRU 38

Manchester System (1932)

Figure 3.3. The Manchester system. Assuming three intra-uterine sources of 15 mg, 10 mg, 10 mg radium each and 20 mg for each intra-vaginal ovoid, the total activity of 75 mg (1 mm Pt filtration) would deliver a TRAK rate of 469 μGy h⁻¹. After an application of 6 days (144 h), the TRAK would be 67.5 mGy and a source-mass × duration of 10.800 mg h (ICRU, 1985; Meredith, 1967).
EMBRACE
(International Study on MRI-Guided Brachytherapy in Locally Advanced Cervical Cancer)

- Recommends volumetric optimization should start from Point A plan, i.e. a standard loading pattern.
- A completely new volumetric, conformal optimization plan is not recommended such as a pure inverse optimization plan.

GEOMETRICAL OPTIMIZATION: VOLUME

• The distance of the active dwell positions in the other catheters to the current active dwell position determine the relative weight in that dwell position.

• That is why ≥ 2 catheters are required for geometrical optimization on volume. Limits are imposed on total dwell times per catheter.

• The catheter on which the current dwell position is located is not included in the calculation.

• In this way, weighting of each catheter dwell position is primarily influenced by the active dwell positions on other catheters, therefore filling in the spaces to cover the desired volume.
Volume Optimization on Target points
GYN I - GYN RADIOBIOLOGY

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LEARNING OBJECTIVES

Understand the radiobiological aspects of GYN brachytherapy & their potential clinical implications.

- Dose delivery characteristics
- Relevant radiobiological models
- Key radiobiological features
- Potential clinical implications
DOSE-DELIVERY CHARACTERISTICS

- Intracavitary (mostly) and/or interstitial source placement
- High dose gradients in tumor & normal organs
- Efficacy established historically with LDR delivery
- Modern treatments are mostly delivered in HDR
- Often given in combination with EBRT

→ Variations in dose rate, fractionation, dose distribution, treated volume, and treatment duration can significantly affect the treatment response
- **Biologically effective dose (BED)**

\[
BED_{total} = \sum_i BED_i^0 - \frac{\ln 2}{\alpha T_d} (T_{total} - T_k)
\]

- EBRT treatment \((n\ \text{fractions with dose}\ d\ \text{per fraction})\):

\[
BED_{EBRT}^0 = n d \cdot \left(1 + \frac{d}{(\alpha/\beta)}\right)
\]

- Brachytherapy treatment \((\text{each fraction of dose}\ D)\) :

\[
BED_{BT}^0 = D \left\{1 + \frac{2D}{(\alpha/\beta)(\mu t)^2} (e^{-\mu t} + \mu t - 1) \right\}
\]

\[
\mu = \ln 2 / \tau \quad (\tau:\ \text{repair half-time})
\]
BIOLOGIC EFFECT MODELING

- Equivalent dose in 2-Gy fractions (EQD2)

\[ EQD2 = \frac{BED}{1 + \frac{2}{(\alpha / \beta)}} \]

(Assumes same treatment time)

- The total dose in 2 Gy fractions that would produce the same level of cell kill as the given schedule

- It can be compared with clinical experiences established with administering 2 Gy fractions

- More intuitive quantity for physicians

- Recommended by GEC-ESTRO & ABS for dose reporting
DOSE DELIVERY @ CONSTANT DOSE RATE

- Clinical scenarios:
  - Intracavitary LDR brachytherapy using $^{137}$Cs source ($T_{1/2}$ of 30 yrs) for cervical cancer
    - e.g., total dose: 80 Gy to Point-A in two fractions
    - Dose rate at Point-A: ~ 0.53 Gy/h, total treatment last 144 hrs
    - Dose rate: ~constant per fraction due to long $T_{1/2}$
  - Intracavitary HDR using $^{192}$Ir source ($T_{1/2}$ of 74 days) for GYN malignances.
    - Total dose: variable in multiple fractions
    - Dose rate at prescription point: ~ 12 – 50 Gy/h, treatment last from minutes to < 1 h per fraction
    - Dose rate: ~constant per fraction due to short treatment time
DOSE DELIVERY @ CONSTANT DOSE RATE

- The BED model

\[
BED = D \left[ 1 + \frac{D}{(\alpha / \beta)} \left( e^{-\mu T} + \mu T - 1 \right) \right] - \gamma \frac{T - T_k}{\alpha}
\]

- \( G(T) \) – dose protraction factor

- RE – relative effectiveness

Recall the basic assumptions:

- Constant dose rate = \( D/T \)
- For uniform dose distribution or dose at a point of interest
- Radiobiological properties by five parameters (\( \alpha, \beta, \mu, \gamma, T_k \))
- Mono-exponential repair kinetics
- Uniform proliferation rate
  - This model captures the influence of only 2 “R”s of radiobiology, i.e., repair & repopulation, on the dose rate effect
  - In absence of these 2 “R”s, \( BED = D \left[ 1 + \frac{D}{(\alpha / \beta)} \right] \), no dose rate effect
MODEL PARAMETERS

- Typical values used in model calculations for GYN
  - $\alpha/\beta = 10$ Gy for tumor
    - $= 3$ Gy for bladder, rectum, sigmoid, and small bowel
  - $\tau = 1.5$ h for tumor (with large uncertainty)

  - Impact of model parameter uncertainty/variation on model prediction can be assessed by varying the values over a reasonable range
  - Using a consistent parameter set is good for maintaining reporting consistency and inter-comparability
DOSE DELIVERY @ CONSTANT DOSE RATE

\[ RE = 1 + \frac{D}{(\alpha / \beta)} \left( \frac{2}{(\mu T)^2} \left( e^{-\mu T} + \mu T - 1 \right) \right) \]

\[ RE = 1 + \frac{D}{(\alpha / \beta)} \]

\( T \to 0 \)

No repair (\( \mu \to 0 \)):

\( RE = 1 \)

\( T \to \infty \)

Instant repair (\( \mu \to \infty \))

(repair half-time (\( t_{1/2} \)) = 1.5 h, \( \gamma = 0.0 \), \( D = 60 \) Gy)

- Relative effectiveness of dose increases with increasing dose rate
DOSE DELIVERY @ CONSTANT DOSE RATE

\[ RE = 1 + \frac{D}{(\alpha / \beta)} \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1) \]

\[ RE = 1 + \frac{D}{(\alpha / \beta)} \]

\( (t_{1/2} = 1.5 \text{ h}, \gamma = 0.0, D = 60 \text{ Gy}) \)

- Altering dose rate has a greater influence on late-reacting (e.g., typical normal) tissues than for early reacting tissues (e.g. typical tumors)
DOSE DELIVERY @ CONSTANT DOSE RATE

\[ RE = 1 + \frac{D}{(\alpha / \beta) (\mu T)^2} \left( e^{-\mu T} + \mu T - 1 \right) \]

\[ \text{Surrogate for potential therapeutic gain} \]

\[ \frac{RE(\alpha/\beta = 10 \, \text{Gy})}{RE(\alpha/\beta = 3 \, \text{Gy})} \]

\( T \to 0: \)
\[ = (1 + 60/10)/(1 + 60/3) \]
\[ = 1/3 \]

\( (t_{1/2} = 1.5 \, \text{h}, \gamma = 0.0, D = 60 \, \text{Gy}) \)

– Consistent with the general philosophy favoring dose protraction while cautioning against using small number of high doses/dose rate
The observations made so far are based on 3 key assumptions:

1) The $\alpha/\beta$ of tumor is greater than irradiated normal tissues
2) There is no cell proliferation
3) Normal tissues receives the same dose as the tumor

A change in these assumed conditions may lead to a different conclusion, for example

- The advantage of dose protraction on therapeutic gain diminishes for tumors with $\alpha/\beta \leq$ those of normal tissues (e.g., prostate Ca)

- Additional normal tissue sparing achievable in an HDR treatment could potentially improve the therapeutic ratio of the HDR technique to the level of LDR treatment
MULTI-FRACTION HDR VS. LDR FOR CERVIX

- LDR reference treatment
  - 60 Gy in 72 hours
  - $\alpha/\beta = 10$ Gy for tumor & 3 Gy for rectum, $\tau = 1.5$ h, no repopulation
  - Rectum receive 80% of prescription dose ($f = 0.8$)

\[
BED = f \cdot D \left[ 1 + \frac{f \cdot D}{(\alpha/\beta)} \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1) \right]
\]
- $BED_{\text{tumor}}$ (LDR) = 81.0 Gy
- $BED_{\text{rectum}}$ (LDR) = 92.8 Gy

- HDR using 6 fractions with matching tumor BED

\[
BED = 6 \cdot f \cdot d \left[ 1 + \frac{f \cdot d}{(\alpha/\beta)} \right] = 81.0 \text{ Gy}
\]
- $d = 7.6$ Gy ($f = 1.0$)
- $BED_{\text{rectum}} = 111.6$ Gy ($f = 0.8$)

- Additional sparing needed to achieve LDR $BED_{\text{rectum}}$

\[
BED = 6 \cdot f \cdot d \left[ 1 + \frac{f \cdot d}{(\alpha/\beta)} \right] = 92.8 \text{ Gy}
\]
- $f = 0.72$

- An extensive analysis by Brenner & Hall for fractionated HDR and LDR brachytherapy of the cervix also reached a similar conclusion

CONCLUSION

Radiobiological principles and models are useful to help understand the:

- general trends
- potential clinical issues

In GYN brachytherapy

A good understanding of model assumptions and limitations is needed to achieve more fruitful use
COMBO WITH EBRT

Christian Kirisits, Ph.D.
Professor, Medical University of Vienna
Vienna, Austria
LEARNING OBJECTIVES

- To understand the impact of different external beam and brachytherapy contributions on dose and volume
- To learn which situations cause high uncertainties when adding dose parameter
- To follow recommendations for appropriate methods to combine external beam and brachytherapy dose
Various patterns of response guided adaptive CTV Radiobiology: Time-dose pattern

ICRU 89
General principles for assessment and reporting of physical and equieffective EBRT and brachytherapy dose (all reporting levels)

Physical dose and number of fractions is assessed for target, OARs, dose points:
• brachytherapy
• EBRT

Total equieffective dose (EQD2) is calculated according to the linear quadratic model through the following steps:
• Brachytherapy EQD2 for each fraction
• Total brachytherapy EQD2
• Total EBRT EQD2
• Accumulated total EBRT+brachytherapy EQD2*

*Based on current assumptions outlined in chapter 9

Reporting of radiobiological parameters:
\( \alpha/\beta \) values for tumour and OARs*
In addition \( T_{1/2} \) and recovery model for LDR and PDR treatments*
*At present: \( \alpha/\beta = 3 \text{ Gy} \) for late effects in OAR and 10 Gy for tumour, and \( T_{1/2} = 1.5 \text{ h} \)
Example

ICRU 89
## Example

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<th>1&lt;sup&gt;st&lt;/sup&gt; application</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; application</th>
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<tr>
<td>2 cm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.5</td>
<td>1.5</td>
<td>2.6</td>
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</table>

ICRU 89
Dose response studies

Dose response curve

Probability for vaginal stenosis G≥2

Bladder

Vagina

Dose to the ICRU rectal point in Gy (EQD2)

Various examples
Tanderup et al.
Fokdal et al.
Mazeron et al.
DVH for OAR

ICRU 89
Typical DVH curve for OAR from intracavitary BT. The curve is defined by 3 curves assuming an identical shape.
An increase of TRAK will result in an increase of the dose to the OAR. The shape of the new curve is stretched, the ratio of the two upper points on the DVH curve becomes larger. The impact on the low dose regions is smaller. The same ratio applies. The blue symbols are from the previous figure with lower dose to the OAR. The third point in the low dose region is not needed necessarily to describe the shape.
The orange curve could be the result of different external beam component or other treatment technique. The shape of the curve is completely changed. All three points on the DVH curve are needed to describe the difference to the two curves shown before.
45 Gy whole pelvis EBRT plus 4 fractions of HDR brachytherapy (total target dose 85 Gy EQD2)

ICRU 89, Chapter 8
45 Gy whole pelvis EBRT plus 15 Gy EBRT tumor boost plus 2 fractions of HDR brachytherapy (total target dose 85 Gy EQD2)

ICRU 89, Chapter 8
Combination of EBRT and BT

EB + Node Boost

2xF1 optimized PDR

2xF1 optimized PDR

courtesy Astrid de Leeuw / van de Kamer et al. Radiother Oncol 2010
Differences between two methods ‘adding 3D Distributions’ versus ‘adding Parameters’

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<th>Rectum</th>
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<td>with paraBoost</td>
<td>without</td>
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<tr>
<td>PDR avg</td>
<td>1.5%</td>
<td>9.1%</td>
<td>-0.5%</td>
</tr>
<tr>
<td>PDR SD</td>
<td>1.7%</td>
<td>6.2%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Is adding parameters a valid approximation?

Yes, provided no EB boost!

courtesy Astrid de Leeuw / van de Kamer et al. Radiother Oncol 2010
3 cm shielding after 30 Gy AP/PA
Filling the gap in central shielding: three dimensional analysis of the EQD2 dose in radiotherapy for cervical cancer with the central shielding technique
Tomoaki Tamaki, Tatsuya Ohno, Shin-ei Noda, Shingo Kato, Takashi Nakano

Isodose lines: (EQD$_2$)
- 100 Gy
- 90 Gy
- 80 Gy
- 70 Gy
- 60 Gy
- 50 Gy
- 40 Gy
- 30 Gy

Point A

see also Tamaki et al 2017

Calculation of DVH for several fractions

DVH rectum

Approximation
Worst case assumption

courtesy K Tanderup
Rectum wall DVH in EQD2
2.5 cm longitudinal shift of whole organ
Deformable registration

- Problem: fusing images (from different modalities), taken at different times in the treatment (before, during, after BT)
  I) Some organs move and change shape dramatically (sigmoid),
  II) insertion of applicator changes topography, ...
  Approximation by rigid registration fails.

- Aim: to register each voxel correctly with the corresponding voxel in a different image set in order to **evaluate the received radiation dose**.

- Currently, especially for the pelvic region and breast, it is theoretically not solved how tissue voxels can move, expand, and shrink.
Deviation when using deformable image registration to conventional DVH summation:

$$D_{2\text{cm}^3} = 0.4 \pm 0.3 \text{ Gy}_{\alpha\beta} (1.5\% \pm 1.8\%)$$

Else Stougård Andersen, Karsten Østergaard Noe, Thomas Sangild Sørensen, Søren Kynde Nielsen, Lars Fokdal, Mer...

**Simple DVH parameter addition as compared to deformable registration for bladder dose accumulation in cervix cancer brachytherapy**

More literature on deformable image registration for brachytherapy

Sabater et al. Dose accumulation during vaginal cuff brachytherapy based on rigid/deformable registration vs. single plan addition. Brachytherapy (2013)


SUMMARY

- To understand the impact of different external beam and brachytherapy contributions on dose and volume
- To learn which situations cause high uncertainties when adding dose parameter
- To follow recommendations for appropriate methods to combine external beam and brachytherapy dose