Image Guided Adaptive Brachytherapy (IGABT) for Cervical Cancer.

Uncertainties in dose reporting

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Outline

Uncertainties
Dose Reporting

Background:
– Procedure in Utrecht

1. Geometrical uncertainties:
   – intra/inter application variation

2. Combination External Beam and Brachy

3. Same dose parameters ➔ same dose distribution??

Utrecht Treatment Cervical Cancer
MR guided adaptive RT

<table>
<thead>
<tr>
<th>39.6 Gy EBRT</th>
<th>19.2 Gy PDR-BT</th>
<th>5.4 Gy EBRT</th>
<th>19.2 Gy PDR-BT</th>
<th>10-14 Gy EBRT</th>
</tr>
</thead>
</table>
| External Beam IMRT
  • 25 x 1.6 Gy (44.3 Gy_Eq.)
| Cisplatin
| Brachytherapy
  • two applications
  • Pulsed Dose Rate (PDR)
  (or 4xHDR)
  • 32 pulses of 60 cGy
  • 1 pulse/hour

• MR guided treatment planning optimization according to GEC-ESTRO recommendations

Utrecht Applicator
Nucletron Veenendaal
**GEC-ESTRO recommendations:**

**Target definition**

**Reporting Dose Volume parameters**

DVH analysis: aims and constraints on total dose: EBRT + Brachytherapy

DVH analysis based on EQD2 with:

\[ \frac{\alpha}{\beta} \text{ (target)} = 10 \text{ Gy} \]
\[ \frac{\alpha}{\beta} \text{ (OAR)} = 3 \text{ Gy} \]
\[ T_{1/2} = 1.5 \text{ h} \]

Dose volume parameters:
- target: D90 and D100
- OAR: D2cc

Haie-Meder et al. Radiat Oncol 2005
Pötter et al. Radiat Oncol 2006

**Optimization**

in Utrecht:
- aim:
  \[ D_{90} \text{ HR-CTV} \geq 84 \text{ Gy}_{10} \]
- constraints:
  \[ D_{2cc} \text{ bladder} < 90 \text{ Gy}_{3} \]
  \[ D_{2cc} \text{ rect/sigm/bowel} < 75 \text{ Gy}_{3} \]

**Uncertainties**

- anatomical
- geometrical
  - registration between CT and MR
  - Organ motion and deformation
- physical
  - QA of both EB and BT
- combining dose distributions and dose parameters
- biological
  - dose rate, α/β, repair half time \( T_{1/2} \)
- clinical
  - scoring tumour response, scoring toxicity
Geometrical dose uncertainties Organ motion planning versus irradiation

- Intra application:
  - PDR during 32 hours
  - HDR: planning and irradiation 2-3 h later
- Inter application

Results of some (small) investigations:

- Study in 2008 PDR
  - second MR on day 2 of PDR
- Data pooling from 6 institutes
- Study PDR patients 2011
- Study HDR patients 2011

Study Intra-application in Utrecht 2008
An example: high decrease rectum

- 9 patients /18 applications
- MR during PDR on day 2 of application
- Average time interval between MR acquisitions 22.0 (SD 2.5) hour

<table>
<thead>
<tr>
<th>HR-CTV</th>
<th>bladder</th>
<th>rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>D90 EQD2 Gy</td>
<td>-0.2</td>
<td>2.0</td>
</tr>
<tr>
<td>D2 bladder</td>
<td>0.6</td>
<td>3.9</td>
</tr>
<tr>
<td>D2 rectum</td>
<td>0.0</td>
<td>3.9</td>
</tr>
</tbody>
</table>

On average differences limited, but variation can be large

note: sensitive to contouring
Different methods used for reporting of variations in single institution publications:
- total EQD2 (EBRT+BT), EQD2 for BT, physical dose changes for BT, single plan vs. multiple plans, etc.
- For direct comparison, raw data were collected and analysed using a common method.
  Nesvadl et al. Radiother Oncol 2012 abst ESTRO Barcelona
Comparison
Intra-application 2008 and Intra-application 2011

Message: be aware!
Message: Rather big uncertainties in rectum/sigmoid dose during 31 hours of PDR

Strong rationale to change to more HDR

no X-ray image, no contrast in rectum
MR scanning directly after application
Result: Empty rectum at planning MR, increase of gas during treatment

MR at department

In Shielded Treatment Room
HDR system secured

Application on MR table

Imaging workflow HDR patients.

HDR: 2 applications, with 2 fractions each

Application1 BT1
Fraction1
MRplan
match on applicator
contours of MRplan on MRpreRad
contours of MRplanBT1 on MRBT2
OK? OK?
irradiation opt planBT1
≥10 MR scans
HDR workflow: Illustration

**MRplan BT3**
- Visual inspection: OK? > irradiation
- if not OK > adept plan

**MRpreRad BT4**
-Contours back to master

**DVH analysis in BPS**
- OK? > irradiation
- if not OK > adept contours

D2cc rectum 4.2 ➔ 5.8 Gy

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**HDR Intra-application variation**

- **5 patients**
- **Difference DVH parameters**
  - MRplan and MRpreRad (3-4 hour):
    - very small for HR-CTV
    - on average increase in rectum:
      - SD for rectum 3 Gy EQD2, for bladder 5 Gy EQD2.
- **Difference MRpreRad and MRpostRad**
  - small

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**Learning phase!**

- the more you see, the more you can control!
Summary Geometric Uncertainties

- can be around 20% for OAR
- can change due to change in workflow
  - necessary for each center to investigate for themselves!
- can be better controlled for HDR, especially with MR scans just prior to irradiation
  - But still remain
  - And contouring ....

Outline Uncertainties Dose Reporting

1. Geometrical uncertainties: intra/inter application variation

2. Combination External Beam and Brachy
   - EB node boost

3. Same dose parameters ⇒ same dose distribution??

Dose summing EB and BT

In GEC-ESTRO recommendations:
Underlying assumption is that targets and OAR receive full EB dose.

- HR-CTV: \(25 \times 1.8 \text{ Gy} \equiv 44.3 \text{ Gy}_{\text{EQD2}}\)
- OAR: \(25 \times 1.8 \text{ Gy} \equiv 43.2 \text{ Gy}_{\text{EQD2}}\)

Total dose received from combined EB and BT:

- HR-CTV:
  \(D_{90} = 44.3 + D_{90}(\text{BTfraction1}) + D_{90}(\text{BTfraction2}) \text{ Gy}_{\text{EQD2}}\)

- OAR: worst case scenario:
  \(D_{2cc} = 43.2 + D_{2cc}(\text{BTfraction1}) + D_{2cc}(\text{BTfraction2}) \text{ Gy}_{\text{EQD2}}\)

⇒ “Adding parameters” Method

Is this a valid approximation?
"Adding 3D dose distributions" Method

CT + 3D dose IMRT

MR + 3D dose Brachy

Register underlying CT and MRI datasets

αβ and T1/2 tumour & OAR, defined on MRI

Compute 3D EQD2 and add voxel-by-voxel

Combined DVH

Illustration of combined EQD2 dose distributions

A

B

C

with node boost

with parametrium boost

Van de Kamer et al. Radiother Oncol 2010

Difference between Parameter Adding and 3D dose distribution Adding

for 5 patients:
differences between methods in %
only with boosts

Van de Kamer et al. Radiother Oncol 2010
EBRT + Brachy + EBNodeBoost
Dosimetric interaction

dose of EB boost to HR-CTV → reporting D90 to HR-CTV

prescription dose of EBboost → Brachy dose to 'pathological' lymph nodes

1. what is dose contribution from node boost to HR-CTV?
2. what is dose from brachy to nodes?

Dosimetric interaction study

• 15 consecutive (EMBRACE) patients receiving an EB boost to enlarged lymph nodes

• for these 15 patients
  • 1) we estimated dose from Node Boost to HR-CTV
  • 2) we determined dose from Brachy to nodes

Part 1: 15 patients with EB node boost: contribution to D90 HR-CTV

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR-CTV volume [cc]</th>
<th>D90 HR-CTV due to boost</th>
<th>D90 HR-CTV due to boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>32.7</td>
<td>94.1</td>
<td>1.0</td>
</tr>
<tr>
<td>#2</td>
<td>15.9</td>
<td>93.4</td>
<td>0.6</td>
</tr>
<tr>
<td>#3</td>
<td>91.3</td>
<td>86.1</td>
<td>1.6</td>
</tr>
<tr>
<td>#4</td>
<td>29.3</td>
<td>89.9</td>
<td>0.7</td>
</tr>
<tr>
<td>#5</td>
<td>19.5</td>
<td>89.5</td>
<td>0.3</td>
</tr>
<tr>
<td>#6</td>
<td>33.0</td>
<td>85.0</td>
<td>0.3</td>
</tr>
<tr>
<td>#7</td>
<td>115.0</td>
<td>91.6</td>
<td>0.6</td>
</tr>
<tr>
<td>#8</td>
<td>26.7</td>
<td>97.2</td>
<td>0.2</td>
</tr>
<tr>
<td>#9</td>
<td>18.6</td>
<td>89.7</td>
<td>0.5</td>
</tr>
<tr>
<td>#10</td>
<td>26.0</td>
<td>93.3</td>
<td>0.1</td>
</tr>
<tr>
<td>#11</td>
<td>22.3</td>
<td>89.7</td>
<td>0.3</td>
</tr>
<tr>
<td>#12</td>
<td>39.7</td>
<td>92.7</td>
<td>0.6</td>
</tr>
<tr>
<td>#13</td>
<td>52.5</td>
<td>91.1</td>
<td>0.8</td>
</tr>
<tr>
<td>#14</td>
<td>24.1</td>
<td>95.6</td>
<td>0.3</td>
</tr>
<tr>
<td>#15</td>
<td>44.3</td>
<td>90.7</td>
<td>0.3</td>
</tr>
</tbody>
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avg 39.4 90.3 0.6
SD 28.1 3.0
min 15.9 86.1 0.1
max 115.0 97.2 1.6

conclusion:
at our institute, currently the contribution is low.

Uncertainty in D90 HR-CTV small

but...rigid registration
**Part 2: Contribution Brachy to total dose lymph nodes**

- 15 patients from Utrecht UMCU
  - 2 fractions PDR
- 27 patients from Pittsburgh UPCI
  - 5 fractions HDR

- For each brachy fraction:
  - Contouring of enlarged lymph nodes
  - DVH analysis in BPS D90 pLNN
    - physical dose D90 in cGy
    - physical dose D90 in percentage PD
    - biologically weighted D90 in EQD2 Gy

Van den Bosch et al. *Radiother Oncol* 2012 abst ESTRO Barcelona

<table>
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<th>Volume HR-CTV (cm$^3$)</th>
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<td>4.9</td>
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* PDR data were recalculated as if given by HDR in 4 fractions of 7 Gy and scaled for OAR constraints.

Van den Bosch et al. *Radiother Oncol* 2012 abst ESTRO Barcelona

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Van den Bosch et al. *Radiother Oncol* 2012 abst ESTRO Barcelona
**Results:** D90 nodes for different nodal regions

<table>
<thead>
<tr>
<th>Anatomical nodal regions</th>
<th>D90 (Gy EQD2)</th>
<th>TRAK/Dose (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UMCU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UMCU HDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D90 brachy to be taken into account for prescribing EB node boost</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion**

IGABT: individualized dosimetry of pelvic nodal disease highly recommended.
Outline Uncertainties Dose Reporting

• Geometrical uncertainties: intra/inter application variation
• Combination External Beam and Brachy
• Same dose parameters $\Rightarrow$ same dose distribution??
  – planning study tandem/ovoid applicator

Planning study Tandem/Ovoid centers

<table>
<thead>
<tr>
<th>Center(s)</th>
<th>2x PDR, 2x HDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>4 EMBRACE patients from Utrecht database</td>
</tr>
<tr>
<td></td>
<td>small (19.5cc), medium (31.9 and 33.8cc), large (68cc)HR-CTV with 0, 2, 3, 6 needles contoured according GEC-ESTRO recommendations</td>
</tr>
<tr>
<td>3 treatment plans</td>
<td>created by each centre</td>
</tr>
<tr>
<td>Standard (Std)</td>
<td>Optimized without needles (Opt-IC)</td>
</tr>
<tr>
<td>Optimized with needles (Opt-IC/IS)</td>
<td>(3 centers)</td>
</tr>
</tbody>
</table>

Aim: D90 HR-CTV > 85 Gy EQD2
Constraints OARs:
- bladder D2cc < 90 Gy EQD2
- rectum/sigmoid/bowel D2cc < 75 Gy EQD2

Nomden et al. Radiother Oncol 2012

Comparison of...

• Dose parameters D90 HR-CTV and D2cc OARs
• Dwell time distribution
• Spatial Dose distribution
Clinical route

Applicator insertion

Imaging

Contouring

Applicator reconstruction

Treatment planning

Dose delivery

Treatment planning

Applicator insertion

Imaging

Contouring

Applicator reconstruction

Treatment planning

Dose delivery

Results  Dose parameters

Two patients

![Graph showing dose parameters for small and large volume patients.](image)
Results Dose parameters
Two patients

Dose distribution map

Dwell time distribution

Centres different choices
Dose distribution maps: Standard plan

Example of patient 4 with large HR-CTV

Centre 1 PDR
Centre 2 PDR

Centre 1: more dose to tip tandem
Centre 2: more dose to ovoids

Distance maps of 85 Gy α/β iso-dose contour

Dose distribution centre 2
more conformal to HR-CTV
less dose to OAR (incl vagina)

Dose distribution maps:
Example of patient 4 with large HR-CTV

• MR guided optimised plans, same anatomy, same goals, similar DVH parameters:
  • different 3D dose distributions
    → other doses in non-reported regions, e.g. vaginal dose
    → soft constraints
    high dose regions etc
    use of needles
    asymmetry
    SLP

• Difficult to compare treatments based on only few parameters

Learned from discussion:
Practise changing studies!
General conclusion

• Geometrical uncertainties: intra/inter application variation
  – using HDR and imaging just prior to treatment provides the best control

• Combination External Beam and Brachy
  – compute D90 EQD2 from brachy to nodes

• Same dose parameters ➔ same dose distribution?
  – keep in mind the 3D dose distribution, not only the values of DVH parameters

Uncertainties are here to stay, but …

• registration studies like EMBRACE help us to recognize and deal with them.
  E.g. now vaginal dose reporting to correlate with vaginal toxicity

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  • Ann Nulens (Leuven)
  • Remy Naul (UMC)
  • Mirjam Laman (UMC)
  • Marljin Ketelaars (UMC)
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