Medical Aspects of Treatment Planning and Dose Constraints Based on Gyn GEC ESTRO/ICRU Recommendations

Richard Pötter
Outline for methodology of evaluation
dose-volume effects according GEC ESTRO Rec I/II
based on retrospective analyses (Evid. Level III/IV)

- DVH parameters for HR CTV (D90) and OAR (2 ccm)
  „simple“ integration of 3D EBRT (no CS) and BT
- Clinical endpoints: local failure, morbidity (prospective ass.)
- Material: mono-institutional series of consecutive patients
- Method: Prospective evaluation of clinical outcome
  3D assessment of failures and morbidity + link
- Results: links between DVH parameters and outcome
  CTV D90 and local control
  OAR 2 ccm and morbidity
- Conclusions and limitations
3D image based treatment planning: four major issues (Gyn GEC ESTRO Rec II)

1. Integration of EBT and Brachytherapy, Volumes + Biology
   - 3D based planning aims and D90 for CTV
   - 3D based planning aims and D 2 cc for OAR
   - 3D based clinical evaluation of treatment plan: prescription and reporting applying dose volume parameters for CTV and OAR
Stage IIB

EBRT 3D CRT Treatment Planning open field 45 Gy
Rectum DVH (EQD2) and clinical effects

EBRT: 45 Gy 3D CRT                45 + 15 Gy Boost to Tumour region
BT:   2 x 17.5 Gy PDR BT,        2 x 12 Gy PDR BT

EQD2 V(H) for Rectum af BT

e.g. 50% e0 31 ccm
or
2 ccm

EQD2 [Gy]

Vol (% e0 ccm)
**Results – DVH values / ICRU ref. points (Vienna)**

EBRT Dose to 50% of rectum: 43 Gy; total dose $D_{30cc}$ 50 Gy

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$D_{2cc}$</th>
<th>$D_{0.1cc}$</th>
<th>ICRU point dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>95 (±22) Gy$_{\alpha\beta3}$</td>
<td>162 (±75) Gy$_{\alpha\beta3}$</td>
<td>72 (±15) Gy$_{\alpha\beta3}$</td>
</tr>
<tr>
<td>Rectum</td>
<td>65 (±12) Gy$_{\alpha\beta3}$</td>
<td>86 (±27) Gy$_{\alpha\beta3}$</td>
<td>67 (±13) Gy$_{\alpha\beta3}$</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>62 (±12) Gy$_{\alpha\beta3}$</td>
<td>78 (±12) Gy$_{\alpha\beta3}$</td>
<td></td>
</tr>
</tbody>
</table>

**EQD2:** Biologically weighted to 2 Gy/fraction, $\alpha/\beta=3$ Gy

145 patients with individual MRI treatment plans. Georg et al. 2011 IJROBP
3D image based treatment planning: four major issues (Gyn GEC ESTRO Rec II)

• Integration of EBT and Brachytherapy, Volumes + Biology
• **3D based planning aims and D90 for CTV**
• 3D based planning aims and D 2 cc for OAR
• 3D based clinical evaluation of treatment plan: prescription and reporting applying dose volume parameters for CTV and OAR
3D based dose prescription CTV

„developed based on the past!“

Correlation of (institutional) tradition of dose schedules to 3D image based CTV dose distribution (HR CTV and/or IR CTV)*

Dose effect relationship in advanced cervix cancer for point A (e.g. Perez)

Point A dose prescription ~ (mean) HR CTV dose prescription**

Vienna experience:

45-50 Gy EBT + 4 x 7 Gy HDR BT (40 Gy EQD2)

total: ~ 85-90Gy+ α/β10,2Gyfr

variation (1s): +/- 20%


**Kirisits et al. IJROBP 2005, de Brabandere et al. R&O 2007; Lindegaard et al. IJROBP 2008
<table>
<thead>
<tr>
<th>Stage</th>
<th>Dose pt A</th>
<th>pelvic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB and IIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;2 cm)</td>
<td>70-80 Gy</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>(&gt;2 cm)</td>
<td>up to 85-90 Gy</td>
<td>25-37%</td>
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<tr>
<td>Stage IIB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonbulky</td>
<td>70 Gy</td>
<td>50%</td>
</tr>
<tr>
<td>bulky</td>
<td>&gt;80 Gy</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>&gt;80 Gy</td>
<td>30%</td>
</tr>
<tr>
<td>Stage III unilateral</td>
<td>up to 70 Gy</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&gt;70 Gy</td>
<td>35%</td>
</tr>
<tr>
<td>Stage III bilateral/bulky</td>
<td>&lt; 70 Gy</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>&gt;70 Gy</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&gt;85 Gy</td>
<td>35%</td>
</tr>
</tbody>
</table>

"Refinements in brachytherapy techniques are necessary to improve the present results" (Perez et al IJROBP 1998)
Linking DVH-parameters to clinical outcome

HR CTV/Tumour (45 Gy + 4x7 Gy BT, Vienna)

Analysis (n=141, FIGO: IB-IVA, median follow-up=51 months)

*D90 for the HR-CTV and probability of local control*

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**Entire population (n=141)**

- D90 HR CTV 90 Gy EQD2
  - >86% probability for local control
- D90 HR CTV 70 Gy EQD2
  - 65% probability for local control

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*Dimopoulos et al. IJROBP 2008*

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*Dimopoulos et al., R&O 2010*
Correlation between HR-CTV D90 and local control: NIRS

100%: tumor ≤ 4 cm

95.3%: tumor > 4 cm

HR-CTV D90 > 60 Gy\textsubscript{EQD2}

40.0%: tumor > 4 cm

HR-CTV D90 < 60 Gy\textsubscript{EQD2}

P = 0.001

HR-CTV D90 need more than 60 Gy\textsubscript{EQD2}

(WP 30 Gy + ICBT 5.8 Gy x 4 to HR-CTV)
Correlation between HR-CTV D90 and local control: Gunma University

**D90 ≥ 58 GyEQD2 (n=21)**

- 95%
- 70%

**D90 < 58 GyEQD2 (n=21)**

**Group 1:** tumor size < 4cm (n=13)  
**Group 2:** tumor size ≥ 4cm  
**Group 3:** tumor size ≥ 4cm  

**Group 1:** D90 ≥ 58 GyEQD2 (n=13)  
**Group 3:** D90 < 58 GyEQD2 (n=16)  

**p=0.0470**

**p=0.0884**

D90: 58GyEQD2  
WP 30Gy/15fr + ICBT5.5Gy x 4fr (HR-CTV D90)

(JSGO 48th Ohno et al.)
HR-CTV D90 – by center

88Gy ± 9Gy
Provisional comparison
DVH parameters & outcome
based on multi-centre experience

<table>
<thead>
<tr>
<th>Study</th>
<th>HR CTV D90 (Gy)</th>
<th>Bladder D2cc (Gy)</th>
<th>Rectum D2cc (Gy)</th>
<th>Sigmoid D2cc (Gy)</th>
<th>2y Local Control</th>
<th>2y G3-G4 BL+GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIC 3</td>
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<tr>
<td>Def EBRT+BT</td>
<td>73</td>
<td>70</td>
<td>61</td>
<td>58</td>
<td>79%(74)</td>
<td>1%(14)</td>
</tr>
<tr>
<td>n=201</td>
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<tr>
<td>EMBRACE</td>
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<tr>
<td>n=415/600</td>
<td>89</td>
<td>76</td>
<td>64</td>
<td>62</td>
<td>(&gt;90%)</td>
<td>?</td>
</tr>
<tr>
<td>Retro</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>EMBRACE</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n=183/600</td>
<td>89</td>
<td>79</td>
<td>65</td>
<td>65</td>
<td>(&gt;90%)</td>
<td>?</td>
</tr>
</tbody>
</table>

Lindegaard ESTRO 2011
Target Dose prescription for BT (incl. EBT) based on recent clinical experience

High Risk Target Volume D90: Dose 85-90+ Gy

Intermediate Risk Target Volume: Dose ~60-70 Gy

dependent on individual factors
stage, volume, topography, response
dose/volume relation in organs at risk
3D image based treatment planning: four major issues (Gyn GEC ESTRO Rec II)

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3D based dose constraints for OAR

„to be developed based on the past!“

- point dose specification based on radiographs
  - ICRU points
  - other points
- in vivo dosimetry
- reference volume approach (60 Gy (ICRU)) combined with ICRU points
Dose Effect relationship for late rectum side effects based on points (ICRU reference points)

Vienna 93-97

BED $\sim 120-130 \text{ Gy}_3$ "cut-off level" in recent experience

Ioseffective dose in $2\text{Gy/}fr$

$\sim 70-80 \text{ Gy } \alpha\beta_{3,2}\text{Gy/}fr$

32 "events" in 151 patients

Actuarial rate 3y: 24%

no clear dose effect relations bladder, sigmoid, vagina

More evidence: overview in Gerstner et al. R&O 2004
3D-based Dose Volume Parameters for OAR

CLASSICAL MAX DOSE: in 3D no clinical relevant endpoint

FIXED VOLUME: tolerance dose (total dose) - “minimum dose to the most exposed tissue”*

1cc/2cc: teleangiectasia (20 mm x 20 mm x 5 mm)

0.1 cc: 3D “maximum dose”: ulceration (fistula)

0.1 cc: Bladder

0.1 cc: Rectum

0.1 cc: ICRU 38 Ref. Points

*GYN GEC ESTRO Recommendations(II) Radiother Oncol 2006
3D dose volume constraints OAR

$2 \text{ cm}^3 + 0.1 \text{ cm}^3$

(indicating the dose gradient in the most exposed tissue)

- **Rectum:**
  
  $2 \text{ cm}^3 \sim 70-75 \text{ Gy}_{\alpha\beta,3.2\text{Gyfr}}$

- **Sigmoid:** proposal: analogue to rectum, however mobile

- **Bowel:** high dose region, mobile, diff: large/small bowel:
  
  $2 \text{ cm}^3 \sim 65 \text{ Gy}_{\alpha\beta,3.2\text{Gyfr}}$

- **Bladder:** few data available (partly conflicting)
  proposal: analogue to rectum
  however: higher tolerance according to retrospective exp
  
  $2 \text{ cm}^3 \sim 90 \text{ Gy}_{\alpha\beta,3.2\text{Gyfr}}$
N = 35 patients with rectosigmoidoscopy

Dose volume effects for rectal morbidity applying GEC ESTRO recommendations

VRS: Vienna Rectoscopy Score

Clinical late Effects LENT SOMA score

Incidence VRS > 3

0 10 20 30 40 50 60 70 80 90 100

Dose [Gy]

Incidence LENT/SOMA > 2

0 10 20 30 40 50 60 70 80 90 100

D2 ccm

D1 ccm

D0.1 ccm

DICRU

Koom et al. IJROBP 2007

P. Georg et al. Radioth&Oncol 2009

P. Georg et al. IJROBP 2011

Fig. 1. Relationship between $D_{2cc}$ and late side effects in the rectum.
OAR: Published Data (2)


- Kato S, et al. *JRR* 2010
Uncertainties in assessing sigmoid DVH parameters

Assessment of sigmoid topography changes between HDR-brachytherapy fractions

“Is the worst case assumption valid for the sigmoid colon?”

23/44 common observations between observers

- Easy to find or obvious change (score=3-4) in sigmoid topography between fractions in 15/22 (68%) significant movement

- Difficult to find or no change (score=1-2) in remaining little or no movement

Bladder Side Effects

Table 4. Incidence of side effects in the four patient groups for different cutoff doses ($D_{2cc}$) for the bladder

<table>
<thead>
<tr>
<th>Group</th>
<th>$\leq 95$ Gy ($n=87$)</th>
<th>$&gt;95$ Gy ($n=54$)</th>
<th>$\leq 100$ Gy ($n=94$)</th>
<th>$&gt;100$ Gy ($n=47$)</th>
<th>$\leq 105$ Gy ($n=101$)</th>
<th>$&gt;105$ Gy ($n=40$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (G0)</td>
<td>73 (84)</td>
<td>45 (83)</td>
<td>79 (84)</td>
<td>39 (83)</td>
<td>85 (84)</td>
<td>33 (83)</td>
</tr>
<tr>
<td>Group 2 (G1–G4)</td>
<td>14 (16)</td>
<td>9 (17)</td>
<td>15 (16)</td>
<td>8 (17)</td>
<td>16 (16)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Group 3 (G0–G1)</td>
<td>79 (91)</td>
<td>48 (89)</td>
<td>86 (91)</td>
<td>41 (87)</td>
<td>93 (92)</td>
<td>34 (85)</td>
</tr>
<tr>
<td>Group 4 (G2–G4)*</td>
<td>8 (9)</td>
<td>6 (11)*</td>
<td>8 (9)</td>
<td>6 (13)*</td>
<td>8 (8)</td>
<td>6 (15)*</td>
</tr>
</tbody>
</table>

Values are number (percentage)
* indicates the increase in morbidity with increasing the dose cutoff.

Georg et al. R&O 2010

Cut-off for bladder morbidity G2–G4 is $D_{2cc} = 100$ Gy

Nevertheless: the dose volume constraint for bladder remains at 90 Gy

Georg et al. IJROBP 2011
Bladder D2cc

76Gy ± 11Gy

EMBRACE experience
Vaginal Dose Points

**EBRT**

![EBRT Image]

**BT**

![BT Image]

**EBRT Physical Total Dose in Gy**

<table>
<thead>
<tr>
<th></th>
<th>mean (±1SD)</th>
<th>median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>45 (±2)</td>
<td>45 (40-50)</td>
</tr>
<tr>
<td>VRL</td>
<td>44 (±2)</td>
<td>44 (40-50)</td>
</tr>
<tr>
<td>Bladder</td>
<td>43 (±2)</td>
<td>43 (33-49)</td>
</tr>
<tr>
<td>Rectum</td>
<td>39 (±9)</td>
<td>42 (3-48)</td>
</tr>
<tr>
<td>VRL</td>
<td>30 (±14)</td>
<td>35 (2-48)</td>
</tr>
<tr>
<td>Bladder</td>
<td>17 (±36)</td>
<td>13 (2-48)</td>
</tr>
<tr>
<td>Rectum</td>
<td>8 (±10)</td>
<td>4 (1-43)</td>
</tr>
</tbody>
</table>

**Total Dose EBRT+BT in EQD2 $G_Y^{eq}$**

<table>
<thead>
<tr>
<th></th>
<th>mean (±1SD)</th>
<th>median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3'</td>
<td>309/120 (±161/34)</td>
<td>268/115 (61-815)</td>
</tr>
<tr>
<td>6'</td>
<td>72/62 (±12/7)</td>
<td>72/62 (47-109)</td>
</tr>
<tr>
<td>9'</td>
<td>250/109 (±118/31)</td>
<td>226/101 (55-611)</td>
</tr>
<tr>
<td>12'</td>
<td>89/73 (±22/16)</td>
<td>85/70 (51-146)</td>
</tr>
<tr>
<td>VRL</td>
<td>61 (±15)</td>
<td>56 (44-97)</td>
</tr>
<tr>
<td>VRL</td>
<td>53 (±12)</td>
<td>50 (32-60)</td>
</tr>
<tr>
<td>VRL</td>
<td>46 (±16)</td>
<td>45 (5-94)</td>
</tr>
<tr>
<td>VRL</td>
<td>33 (±15)</td>
<td>37 (3-68)</td>
</tr>
<tr>
<td>VRL</td>
<td>18 (±14)</td>
<td>12 (2-54)</td>
</tr>
<tr>
<td>VRL</td>
<td>8 (±10)</td>
<td>4 (1-46)</td>
</tr>
</tbody>
</table>

Westerveld, Pötter et al. 2013
Vaginal Dose Points: PIBS, PIBS+2, PIBS-2

Westerveld, Pötter et al. 2013
Dose Effects: vaginal morbidity multi-centre data, prospective (EMBRACE)

Vaginal morbidity (shortening /stenosis) and dose in 446 patients (EMBRACE, Doctor reported outcome) (Kirchheiner et al, ESTRO Geneva 2013, unpublished data)

Such dose effect correlations also possible for Patient reported outcome (?) see Bergmark et al. 1999, 2002, recent endometrium work
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Parameters, Planning Aims and dose constraints for 3D image based dosimetric evaluation cervix BT

GTV/HR CTV

- TRAK
- Point A Dose (from 2D): reciprocal to CTV volume
- Planning Aim (based on traditional evidence)
  e.g. HR CTV 4x7 Gy plus 45 Gy EBRT: 85 Gy
- Prescribed Dose: D 90, e.g. >87 Gy (recent evidence)
- D98, D50: under evaluation, values not yet established

- V 100 (Volume receiving $\geq 100\%$ of PD)
- V 150/200 (150%/200% of PD)
Constraints for 3D image based dosimetric evaluation cervix BT

Organs at Risk

- Doses for absolute volumes: 2 cc, (0.1 cc)
  - Rectum 70-75 Gy, Sigmoid 70-75 (few data),
  - Bladder <90 Gy, adjac. bowel <65 Gy (few data)
- Reference Point Doses
  - Vagina: <65 Gy rectovaginal pt, PIBS <30 Gy