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

(WP 30 Gy + CS 20 Gy + ICBT > 24 Gy/4Fr to HR-CTV D90)

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
Results – DVH values / ICRU ref. points (Vienna)
EBRT Dose to 50% of rectum: 43 Gy; total dose $D_{30cc} 50$ Gy

Bladder
- $D_{2cc}$: 95 ($\pm$22) Gy$_{\alpha\beta3}$
- $D_{0.1cc}$: 162 ($\pm$75) Gy$_{\alpha\beta3}$
- ICRU point dose: 72 ($\pm$15) Gy$_{\alpha\beta3}$

Rectum
- $D_{2cc}$: 65 ($\pm$12) Gy$_{\alpha\beta3}$
- $D_{0.1cc}$: 86 ($\pm$27) Gy$_{\alpha\beta3}$
- ICRU point: 67 ($\pm$13) Gy$_{\alpha\beta3}$

Sigmoid
- $D_{2cc}$: 62 ($\pm$12) Gy$_{\alpha\beta3}$
- $D_{0.1cc}$: 78 ($\pm$12) Gy$_{\alpha\beta3}$

EQD2: Biologically weighted to 2 Gy/fraction, $\alpha/\beta=3$ Gy
145 patients with individual MRI treatment plans. Georg et al. 2011 IJROBP
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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)

\[ \text{total: } \sim 85-90\text{Gy} + \frac{\alpha}{\beta} 10,2\text{Gyfr} \]

variation (1s): +/- 20%


**Kirisits et al. IJROBP 2005, de Brabandere et al. R&O 2007; Lindegaard et al. IJROBP 2008
DOSE EFFECT RELATIONSHIP POINT A

<table>
<thead>
<tr>
<th>Stage</th>
<th>Dose pt A</th>
<th>Pelvic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB and IIA (&lt;2 cm)</td>
<td>70-80 Gy</td>
<td>&lt;10%</td>
</tr>
<tr>
<td></td>
<td>up to 85-90 Gy</td>
<td>25-37%</td>
</tr>
<tr>
<td>Stage IB and IIA (&gt;2 cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIB</td>
<td>70 Gy</td>
<td>50%</td>
</tr>
<tr>
<td>nonbulky</td>
<td>&gt;80 Gy</td>
<td>20%</td>
</tr>
<tr>
<td>bulky</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)

$D_{90}$ for the HR-CTV and probability of local control

Dimopoulos et al., R&O 2010
Dimopoulos et al. IJROBP 2008
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}

HR-CTV D90 need more than 60 Gy\textsubscript{EQD2}
(WP 30 Gy + ICBT 5.8 Gy x 4 to HR-CTV)

P = 0.001

2011 JASTRO Kato
Correlation between HR-CTV D90 and local control: Gunma University

Group 1 tumor size < 4cm (n=13)
Group 2 tumor size ≥ 4cm で D90 ≥ 58 GyEQD2 (n=13)
Group 3: tumor size ≥ 4cm で D90 < 58 GyEQD2 (n=16)

p=0.0470

p=0.0884

(DJSGO 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>
<td>73</td>
<td>70</td>
<td>61</td>
<td>58</td>
<td>79% (74)</td>
<td>1% (14)</td>
</tr>
<tr>
<td>Def EBRT+BT n=201</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EMBRACE 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 EMBRACE n=183/600</td>
<td>89</td>
<td>79</td>
<td>65</td>
<td>65</td>
<td>(&gt;90%)</td>
<td>?</td>
</tr>
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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
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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 ~120-130 Gy3 „cut-off level“ in recent experience

Ioseffective dose in 2Gy/fr ~ 70-80 Gy $\alpha\beta_{3,2}$ Gy/fr

no clear dose effect relations bladder, sigmoid, vagina

32 „events“ in 151 patients
Actuarial rate 3y: 24%

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)

*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

Incidence LENT/SOMA > 2

Dose [Gy] 30 40 50 60 70 80 90 100 110 120 130 140

Probability of score ≥ 2 (%)

ICRU_{RP} (p = 0.03)

D_{\alpha\times\alpha} (p = 0.05)

D_{1cc} (p = 0.02)

D_{2cc} (p = 0.02)

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

Nevertheless: 
the dose volume constraint for bladder remains at 90 Gy
Bladder D2cc

76Gy ± 11Gy

EMBRACE experience
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 ≥ 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