Linking DVH-parameters to clinical outcome

Alina Sturdza, Richard Pötter, Medical University of Vienna, General Hospital of Vienna, Austria
Outline

• DVH parameters for HR CTV (D90) and OAR (2 ccm)

• Clinical endpoints: local failure, survival, morbidity

• Results: links between DVH parameters and outcome
  CTV D90 and local control
  OAR 2 ccm and morbidity

• Conclusions and limitations
Vienna experience

81 Gy vs. 90 Gy in HR CTV

Pötter R. et al  Radiother Oncol 2007
Vienna 2001-2008: 156 patients

Mean D90: 93 Gy, 91 Gy for tumors >5 cm, 96 Gy 2-5 cm

Pötter & al., Radiother Oncol 100, 2011
CONTINUOUS COMPLETE REMISSION 3 YEARS*
VIENNA 1993-2003: 335 patients

<table>
<thead>
<tr>
<th>TREATMENT PERIOD</th>
<th>CCR 2-5cm (REC.)</th>
<th>CCR &gt;5cm (REC.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2003**</td>
<td>96% (1/34)</td>
<td>90% (3/34)</td>
</tr>
<tr>
<td>1998-2000**</td>
<td>96% (1/33)</td>
<td>71% (9/37)</td>
</tr>
<tr>
<td>1993-1997***</td>
<td>90% (5/65)</td>
<td>67% (27/124)</td>
</tr>
</tbody>
</table>

** Pötter et al. 2007 Radioth Oncol
*** Pötter et al. Cancer Radioth 2000
*Actuarial data (Kaplan Meier)
Linking DVH-parameters to clinical outcome

HR CTV/Tumour

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

D90 for the HR-CTV and probability of local control

D90 HR CTV 90 Gy EQD2
90% probability for local control

D90 HR CTV 70 Gy EQD2
65% probability for local control

Entire population (n=141)

Tumours > 5cm (n=76)
Better local control = improved survival

Aarhus Experience

Leiden Experience

Lindegaard, Acta Oncologica 2013

Rijkmans et al Gyn Oncol 2014
Overall treatment time (OTT)

- Increasing OTT by one week is equivalent to a loss of 5 Gy in CTV_{HR} D90

- Timing of the BT boost?

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Tanderup & al., Radiother Oncol, 2016

Mazeron et al, Radiother Oncol, 2015
Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence

- Mono-institutional cohorts (ongoing, publicat. since 2007)
- Multi-center cohorts with retrospective evaluation
  RetroEMBRACE (2016)
- Prospective Trials
  STIC: comparative 2D vs. 3D (published 2012)
  EMBRACE I: observational, 08/2008 - 12/2015
  EMBRACE II: interventional, start 01/2016
• Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer

• 731 pts

• Eligibility criteria:
  • Diagnosis of cervical cancer and treatment with curative intent by IGABT
  • Reporting according to GEC ESTRO recommendations
EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer

- A prospective observational multi-centre trial
- Initiated enrollment of patients in 2008, >1200 pts accrued
- Finalised 12/2015
### Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>53 (23 – 91) 731</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>2 (0.3 %)</td>
</tr>
<tr>
<td>1B</td>
<td>123 (16.8%)</td>
</tr>
<tr>
<td>2A</td>
<td>42 (5.7 %)</td>
</tr>
<tr>
<td>2B</td>
<td>368 (50.3 %)</td>
</tr>
<tr>
<td>3A</td>
<td>23 (3.1 %)</td>
</tr>
<tr>
<td>3B</td>
<td>145 (19.8 %)</td>
</tr>
<tr>
<td>4A</td>
<td>23 (3.1 %)</td>
</tr>
<tr>
<td>4B</td>
<td>5 (0.7 %)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell Ca</td>
<td>620 (84.8 %)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>71 (9.7 %)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>29 (4 %)</td>
</tr>
<tr>
<td>Others</td>
<td>11 (1.5 %)</td>
</tr>
<tr>
<td>Median tumour width</td>
<td></td>
</tr>
<tr>
<td>Clinically: 50 mm</td>
<td>MRT @ diagnosis: 47 mm</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>296 (40%)</td>
</tr>
<tr>
<td>N-</td>
<td>436 (60%)</td>
</tr>
<tr>
<td>CHT</td>
<td></td>
</tr>
<tr>
<td>Yes: 566 (76.5 %)</td>
<td>No: 165 (22.5 %)</td>
</tr>
<tr>
<td>Median FU</td>
<td>47 months</td>
</tr>
</tbody>
</table>

*Sturdza & al., Radiother Oncol, 2016*
RetroEMBRACE: Local, Pelvic, Distant Control, Cancer Specific Survival, Overall Survival

Pattern of Relapse

Sturdza & al., Radiother Oncol, 2016
Local control and FIGO stage (RetroEMBRACE)

Loc failure (Retro 3-5y):
- IB: 2%
- IIB: 7-9%
- IIIB: 21-25%
- IVA: 24%

RetroEMBRACE 3y:
- IB: 98%*
- IIB: 93%
- IIIB: 79%

*2 events in IB2

Loc failure (Vienna 3y):
- IB: 0%
- IIB: 4%
- IIIB: 14%
- IVA: 24%

Loc failure (Vienna 3y):
- IB: 100%
- IIB: 96%
- IIIB: 86%

Sturdza et al. 2016
Heterogeneity of dose prescription: HRCTV D90 (EMBRACE)
Heterogeneity of dose prescription: Bladder D2cc (EMBRACE)

Mean Values
Local outcome for adaptive CTV_{HR} volume and dose per stage (RetroEMBRACE)

- **Stage I**
- **Stage II**
- **Stage III+IV**
Local outcome for adaptive CTV$_{HR}$ volume and dose (EMBRACE)

Predicted local control based on RetroEMBRACE outcome

769 pts EMBRACE

- 96% predicted local control
- 92% predicted local control
- 95% predicted local control
- 90% predicted local control
- 82% predicted local control
- 92% predicted local control
Actuarial local control for adaptive CTV$_{HR}$ volume and dose

CTV$_{HR}$ volume

CTV$_{HR}$ dose

Tanderup et al, Radiation Oncol, 2016
Effect of dose, volume and time:

Dose: 10Gy → ~ 5% LC
Time: 7 days ~ 5Gy
Volume: 10cm³ ~ 5Gy

- Cox regression
- Dose and volume continuous co-variates
- Significance:
  - p=0.07 for CTV_{HR} D90
  - p=0.01 for CTV_{HR} volume
- Hazard ratios:
  - 0.962 for CTV_{HR} D90 (per Gy)
  - 1.018 for CTV_{HR} volume (per cm³)

Local control at 3 years

Tanderup et al, Radiation Oncol, 2016
Actuarial local outcome for residual GTV
Dose volume response (res GTV D 100)

163pts: >85Gy
104pts: <85Gy

Local control and res GTV dose (D100)
## LOCAL CONTROL - CLINICAL DATA/AIMS

**DOSE at POINT A vs. as D90 IN IMAGE GUIDED ADAPTIVE BT**

<table>
<thead>
<tr>
<th>EARLY DISEASE</th>
<th>DOSE Pt A / D90 HR</th>
<th>BEST STANDARDS*</th>
<th>AIM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 Gy / 85-95+</td>
<td>90-95%</td>
<td>~100%</td>
</tr>
</tbody>
</table>

**Expected Improvement through Image Guided Adaptative BT**
- Local control by 5-40%; overall survival by ~10%

| IIIB<5cm      | 80 Gy / 85-90 Gy   | 70-85%          | 95-100% |
|               |                    |                 |        |
| IIIB/IIIB>5cm | 85 Gy / 90+ Gy     | 50-65%          | 85-90%  |

* Including a gain through chemoradiation of 5-10%
Pelvic control and FIGO stage

Pattern of Relapse 5 years

RetroEMBRACE 3y: overall 87%
Vienna (2011) 3y: overall 91%

RetroEMBRACE Outcome Sturdza et al. 2016
296/731 N+ at diagnosis

63/731

Pattern of Nodal Relapse

Nodal boost through IMRT/VMAT may result in improved nodal control
Systemic (distant) recurrence analysis
(EMBRACE data, 133 events in 753 patients)

Fortin et al. ASTRO 2015
Provisional comparison
DVH parameters & local control
based on multi-centre experience

<table>
<thead>
<tr>
<th>Study</th>
<th>HR CTV</th>
<th>Bladder</th>
<th>Rectum</th>
<th>Sigmoid</th>
<th>2y Local Control</th>
<th>2y G3-G4 BL+GI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D90 (Gy)</td>
<td>D2cc (Gy)</td>
<td>D2cc (Gy)</td>
<td>D2cc (Gy)</td>
<td></td>
<td></td>
</tr>
<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</td>
<td>n=201</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMBRACE</td>
<td>89</td>
<td>76</td>
<td>64</td>
<td>62</td>
<td>&gt;90%</td>
<td>?</td>
</tr>
<tr>
<td>n=850</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retro</td>
<td>89</td>
<td>79</td>
<td>65</td>
<td>65</td>
<td>&gt;91%</td>
<td>~10%</td>
</tr>
<tr>
<td>EMBRACE</td>
<td>n=698</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Interpretation of RetroEMBRACE results (IGABT compared to large population based cohorts 2D BT)

<table>
<thead>
<tr>
<th>Pelvic failure (crude)</th>
<th>Concomitant chemo</th>
<th>IB</th>
<th>IIB</th>
<th>IIIB</th>
<th>Total</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>retroEMBRACE (n=731)</td>
<td>77%</td>
<td>4%</td>
<td>11%</td>
<td>25%</td>
<td>13%</td>
<td>Δ 8-9%</td>
</tr>
<tr>
<td>Perez 1998</td>
<td>0%</td>
<td>12%</td>
<td>21%</td>
<td>41%</td>
<td>23%</td>
<td>Δ 10-13%</td>
</tr>
<tr>
<td>Barillot 1997</td>
<td>0%</td>
<td>13%</td>
<td>24%</td>
<td>49%</td>
<td>13%</td>
<td>Δ 16-24%</td>
</tr>
<tr>
<td>Improvement</td>
<td></td>
<td>Δ8-9%</td>
<td>Δ10-13%</td>
<td>Δ16-24%</td>
<td>Δ10%</td>
<td></td>
</tr>
</tbody>
</table>

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of pts</td>
<td>394</td>
<td>471</td>
<td>3246</td>
<td>2571</td>
</tr>
<tr>
<td>5y OS</td>
<td>67%</td>
<td>55%</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>Improvement</td>
<td>Reference</td>
<td>Δ12%</td>
<td>Δ12%</td>
<td>Δ13%</td>
</tr>
</tbody>
</table>
## BENEFIT FROM CONCOMITANT RADIOCHEMOTHERAPY

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomisation Arms</th>
<th>Stage</th>
<th>Locoregional Recurrence</th>
<th>3 Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keys et al</td>
<td>RT + Cisplatin + HE</td>
<td>Bulky IB</td>
<td>9%</td>
<td>83%</td>
</tr>
<tr>
<td>N Engl J Med. 1999</td>
<td>RT + HE</td>
<td></td>
<td>21%</td>
<td>74% (p=0.008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 0.51 (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Whitney et al</td>
<td>RT + Cis/5-FU</td>
<td>IIB, III, IVA</td>
<td>24.9%</td>
<td>67%</td>
</tr>
<tr>
<td>J Clin Oncol. 1999</td>
<td>RT + HU</td>
<td></td>
<td>30.4%</td>
<td>57% (p=0.018)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 0.79 (90% CI)</td>
<td></td>
</tr>
<tr>
<td>Rose et al</td>
<td>RT + Cisplatin</td>
<td>IIB, III, IVA</td>
<td>Not reported</td>
<td>65%</td>
</tr>
<tr>
<td>N Engl J Med. 1999</td>
<td>RT + Cis/5-FU+HU</td>
<td></td>
<td></td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>RT + HU</td>
<td></td>
<td></td>
<td>47% (p=0.004)</td>
</tr>
<tr>
<td>Morris et al</td>
<td>RT + Cis/5-FU</td>
<td>IB-IVA</td>
<td>19%</td>
<td>75%</td>
</tr>
<tr>
<td>N Engl J Med. 1999</td>
<td>RT (pelvis + paraaortal)</td>
<td>(~70% IB-IIB in each group)</td>
<td>35%</td>
<td>63% (p=0.004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 0.47 (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Peters et al</td>
<td>HE + RT + Cis/5-FU</td>
<td>IA2, IIB, IIA</td>
<td>5.5%</td>
<td>81%</td>
</tr>
<tr>
<td>J Clin Oncol. 2000</td>
<td>HE + RT</td>
<td></td>
<td>17%</td>
<td>71% (p=0.007)</td>
</tr>
<tr>
<td>Pearcey et al</td>
<td>RT+Cisplatin</td>
<td>IB-IVA</td>
<td>Not reported</td>
<td>69%</td>
</tr>
<tr>
<td>J Clin Oncol. 2002</td>
<td>RT</td>
<td></td>
<td></td>
<td>66% (p=0.42)</td>
</tr>
</tbody>
</table>
Overall Survival locally advanced cervical cancer: the impact of brachytherapy

Total 25% increase in Overall Survival from „no brachy“ (Han) to „4D brachy“ (RetroEMBRACE)

Han et al Int J Radiation Oncol Biol Phys 2013;87:111-119
Sturdza et al. Improved local control and survival in LACC through image guided adaptive brachytherapy, submitted
Planning aims and Dose prescription (I)  
CTV-T EMBRACE II protocol (EBRT+BT) (1/2016)

<table>
<thead>
<tr>
<th>Planning Aims</th>
<th>D90 $\text{CTV}_{\text{HR}}$ EQD2₁₀</th>
<th>D98 $\text{CTV}_{\text{HR}}$ EQD2₁₀</th>
<th>D98 GTV EQD2₁₀</th>
<th>D98 $\text{CTV}_{\text{IR}}$ EQD2₁₀</th>
<th>D Point A EQD2₁₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Aims</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>
</tr>
<tr>
<td>Limits for Prescribed Dose</td>
<td>&gt; 85 Gy</td>
<td>-</td>
<td>&gt;90 Gy</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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”*

*GYN GEC ESTRO Recommendations(II)
Radiother Oncol 2006

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

0.1 cc: 3D “maximum dose“:
ulceration (fistula)
Bladder D2cc (EMBRACE)

- EMBRACE CTCAE
- All endpoints except ureter stenosis G≥2

![Graph showing bladder morbidity](image)

- ≥80 Gy: 30-40%
- <80 Gy: 15-30%

QOL (EORTC)

- ≥18 months follow up

Fokdal et al 2015
Linking DVH-parameters to outcome
Bladder - evaluation

for 34 patients with D 2 ccm > 90 Gy

<table>
<thead>
<tr>
<th>Bladder wall(bw)</th>
<th>Position</th>
<th>P = 0.006</th>
<th>Low</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>bw</td>
<td>bw</td>
<td></td>
</tr>
<tr>
<td>With Side effect</td>
<td>10</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Side effect</td>
<td>6</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arie et al./Berger et al., Vienna 2008/10

Weak overall dose volume effect for all patients, e.g. 2 ccm
(Georg et al. 2010, in press)

<table>
<thead>
<tr>
<th>Bladder</th>
<th>D2cc</th>
<th>≤100 Gy</th>
<th>&gt;100 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1-G4</td>
<td>13% (12/94)</td>
<td>17% (8/47)</td>
<td></td>
</tr>
</tbody>
</table>
$D_{2cc} = 81 \text{ Gy EQD}_2$

$D_{1cc} = 90 \text{ Gy EQD}_2$

$D_{0.1cc} = 108 \text{ Gy EQD}_2$

Georg et al. IJROBP 2011
Rectum $D_{2cm^3}$

R Mazeron, IGR Paris
$\geq$G2 rectal bleeding

Georg et al 2011, 141 pts
$\geq$G2 (mainly rectal bleeding)

![Graph showing the relationship between $D_{2cc}$ and late side effects in the rectum.](image)

Fig. 1. Relationship between $D_{2cc}$ and late side effects in the rectum.
**Vaginal dose assessment and reporting**

**UNCERTAINTIES IN ASSESSMENT OF THE VAGINAL DOSE FOR INTRACAVITARY BRACHYTHERAPY OF CERVICAL CANCER USING A TANDEM-RING APPLICATOR**


**DVH parameters have HIGH uncertainty for representative vaginal dose estimation**

They are influenced by the resolution of sectional imaging, contouring accuracy and applicator reconstruction

Berger et al, IJROBP 2007
Vaginal morbidity and radiation doses

ICRU/GEC ESTRO Report  88  under publication   Fig. 6.1/Fig. 8.11

(Westerveld et al. Vienna 2013)
DVH Parameters and Reference Points, variations in application

ICRU/GEC ESTRO report 88
Fig. 6.4, Fig. 8.8
Vaginal stenosis (EMBRACE)
ICRU recto-vaginal point (630 pts)

Cox-regression, 2 year actuarial risk of ≥G2 stenosis
- Significant impact of EBRT dose (45Gy versus 50Gy)
- Significant impact of BT ICRU recto-vaginal dose

Prevalence vaginal stenosis

Kirchheiner K et al. Manifestation pattern of early-late vaginal morbidity. IJROBP 2014 May 1;89(1):88-95

Kirchheiner et al, 2016, Radiation Oncol
Sigmoid D2cc, preliminary data (EMBRACE)

- No dose effect established – so far

Diarrhea

<table>
<thead>
<tr>
<th>Sigmoid D2cc</th>
<th>&lt;58Gy</th>
<th>58-63Gy</th>
<th>63-68Gy</th>
<th>&gt;68Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>not at all</td>
<td>55%</td>
<td>55%</td>
<td>58%</td>
<td>61%</td>
</tr>
<tr>
<td>a little</td>
<td>35%</td>
<td>35%</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>quite a bit</td>
<td>17%</td>
<td>18%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>very much</td>
<td>9%</td>
<td>13%</td>
<td>14%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Maximum from 12 months on diarrhea
Bowel D2cc, preliminary data (EMBRACE)

- No dose effect established – so far

Bowel control

Diarrhea

maximum from 12 months on difficulties in bowel control
- not at all
- a little
- quite a bit
- very much

maximum from 12 months on diarrhea
- not at all
- a little
- quite a bit
- very much

Prozenten

Bowel D2cc

<57Gy 57-64Gy 64-70Gy >70Gy

<57Gy 57-64Gy 64-70Gy >70Gy
Dose Volume Effect for sigmoid for 2 ccm (?)

In addition: No clear correlation in endoscopy study (2007)

Topographical interfractional changes

Sigma
N=141

Mean VS
Common observation

Sturdza et al. Boston 2008
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?”

Results

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

Sturdza et al. Boston 2008
# Planning aims and Dose prescription (II) OAR

EMBRACE II protocol (EBRT+BT) (1/2016)

<table>
<thead>
<tr>
<th></th>
<th>Bladder $D_{2\text{cm}^3}$ EQD2$_3$</th>
<th>Rectum $D_{2\text{cm}^3}$ EQD2$_3$</th>
<th>Recto-vaginal point EQD2$_3$</th>
<th>Sigmoid/Bowel $D_{2\text{cm}^3}$ EQD2$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Aims</td>
<td>&lt; 80 Gy</td>
<td>&lt; 65 Gy</td>
<td>&lt; 65 Gy</td>
<td>&lt; 70 Gy*</td>
</tr>
<tr>
<td>Limits for Prescribed Dose</td>
<td>&lt; 90 Gy</td>
<td>&lt; 75 Gy</td>
<td>&lt; 75 Gy</td>
<td>&lt; 75 Gy*</td>
</tr>
</tbody>
</table>

* for the sigmoid/bowel structures these dose constraints are valid in case of non-mobile bowel loops resulting in the situation that the most exposed volume is located at a similar part of the organ.
Conclusion (I)

- **Dose effect demonstrated for:**
  - Residual GTV D100, adaptive CTV_{HR} D90, and CTV_{IR} D90
  - Bladder D $2\text{cm}^3$
  - Rectum D $2\text{cm}^3$
  - Vagina (recto-vaginal point)

- **Dose effect not demonstrated for**
  - Sigmoid and bowel

**Perspective:** prospective dose prescription protocol taking into account multiple parameters:
- Target dose, volume and overall treatment time
- OARs
CONCLUSIONS AND LIMITATIONS (IGABT)

Linking DVH parameters to clinical outcome

- D90 HR CTV, GTV 100 and local control: strong link
- 2/0.1 ccm for rectal morbidity: strong link
- 2 ccm for bladder morbidity: link
  improvement by location assessment? (bladder point)
- 2 ccm for sigmoid/ bowel morbidity: weak link
  improvement by movement assessment?
- *Any DVH parameter for vaginal morbidity: no link so far*
- ICRU rectovaginal Point: strong link

Limitations: prospective study data only upcoming multicenter study: RetroEMBRACE/EMBRACE
**Local control – advanced treatment adaptation including interstitial brachytherapy (RetroEMBRACE)**

<table>
<thead>
<tr>
<th>Width in MRI at diagnosis</th>
<th>Local control at 5 year (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limited adaptation</td>
<td>Advanced adaptation</td>
</tr>
<tr>
<td>Tumor &lt;5cm</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>Tumor ≥5cm</td>
<td>77%</td>
<td>86%</td>
</tr>
</tbody>
</table>

The use of advanced adaptation including interstitial BT improves local control in large tumors

Fokdal et al. and Fortin et 2016
In big tumors (>5cm), **262 patients**, there is a trend for better local control in advanced adaption group, difference in actuarial 3y LC 6%, in 5y 9%
Conclusion (II)

- Dose and volume adaptation for tumor related parameters achievable:
  
  combined intracavitary/interstitial techniques
  
  in large tumors (adaptive CTV_{HR} >30 ccm)

- Dose and volume adaptation in case of unfavourable topography of CTV_{HR} and/or GTV_{res} in relation to OARs achievable:
  
  combined intracavitary/interstitial techniques
  
  in tumors of any size with very close OARs

- Perspective: systematic use of advanced intracavitary/interstitial techniques in cervix cancer BT
# EMBRACE II Planning AIMS and Limits for Prescription

<table>
<thead>
<tr>
<th>OTT &lt; 50 Days</th>
<th>D90 CTV&lt;sub&gt;HR&lt;/sub&gt; EQD&lt;sub&gt;210&lt;/sub&gt;</th>
</tr>
</thead>
</table>
| **Planning Aims** | > 90 Gy  
< 95 Gy |
| **Limits for Prescribed Dose** | > 85 Gy |

<table>
<thead>
<tr>
<th>OAR</th>
<th>Bladder D&lt;sub&gt;2cm³&lt;/sub&gt; EQD&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Planning Aims</strong></td>
<td>&lt; 80 Gy</td>
</tr>
<tr>
<td><strong>Limits for Prescribed Dose</strong></td>
<td>&lt; 90 Gy</td>
</tr>
</tbody>
</table>

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![Graph showing dose distribution and escalation](image)
EMBRACE II
Start 1/2016

MRI guided adaptive brachytherapy (IGABT)

Residual Gross Tumor D98 >>95Gy
High Risk Target D90 >90Gy
Intermediate Risk Target > 60Gy

Sigmoid D2cc= 61Gy (< 70Gy)
Rectum D2cc= 64Gy (< 65Gy)
Bladder D2cc= 76Gy (< 80Gy)

Residual GTV-T, Adaptive HR CTV-T, IR CTV-T