Image guided brachytherapy in cervical cancer – Clinical Aspects

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Outline

• Tumor Response related
  Adaptive Target Concept
• Adapted Application: intracavitary ± interstitial
• Planning Aims and Dose Volume prescription
• Disease Outcome (Clinical evidence)
• Morbidity and Patient reported outcome (Evid)
• Correlations DVH parameters and outcome
Primary radiochemotherapy and Image guided adaptive brachytherapy (IGABT)

External beam radiotherapy: 3D EBRT or IMRT/VMAT

- Start 45 Gy
- Week 1 to Week 5

Chemotherapy

1. Cycle
- Week 1 to Week 5

Brachytherapy: IGABT

- HDR or PDR
- Week 1 to Week 6
- \( EQD_2 \geq 60 \text{ Gy} \)
- \( EQD_2 \geq 85 \text{ Gy} \)
The two step adaptive approach for boosting Residual GTV + High Risk area

Various patterns GTV response

Corresponding patterns adaptive CTVs

ICRU/GEC ESTRO report 89, 2016, Fig 5.3

http://jicru.oxfordjournals.org/
Response ADAPTIVE RADIOTHERAPY in Gyn implies…

two major steps of treatment concomitant external beam radiochemotherapy plus boost through brachytherapy requiring adaptation

... various patterns of GTV response
... tumor response adapted 2nd target volume
... CTV adapted BT application (± needles)
... dose adaptation
The Challenge: Tumour size and topography change during treatment

Before EBT
After 30 Gy EBT
1st Brachy
After 40 Gy EBT
Second Brachy
after 3rd Brachy

The evolution of the concept of residual GTV and HR CTV
Initial tumour extension (3D RT) pattern of response (4D RT) for adaptive MRI based planning

Repetitive MRI:
SE Sequences, T2 weighted
(no functional MRI)
Overview of the adaptive target concept in cervix cancer stage IB, IIB, IIIB

- Initial and residual GTV
- High Risk CTV
- Intermediate Risk CTV
- Low Risk CTV

http://jicru.oxfordjournals.org/
Volumetric tumour regression: FIGO stage IIB cervical cancer, large tumor at diagnosis subgroup from EMBRACE data base, N=183/345

At diagnosis

At brachytherapy

Good response

N=68 (37%)

Mean GTV 45.2 cm³

Mean HR CTV 24.6 cm³

Moderate response

N=98 (54%)

Mean GTV 76.7 cm³

Mean HR CTV 40.1 cm³

Poor response

N=17 (9%)

Mean GTV 62.1 cm³

Mean HR CTV 57.8 cm³

Jastaniyah N, Yoshida K et al; Radiotherapy and Oncology 120, 2016
Multicentre EMBRACE sub-study on interobserver variation

Small tumour
Large tumour, good response
Large tumour, poor response

EMBRACE ftp server

Collected structures data-set

Reference delineations (master)

Res. GTV
HR CTV
IR CTV
OAR

P. Petric, et al.
T. Hellebust et al.
Radioth&Oncol 04/2013
Contouring uncertainties – interobserver variations

Angular dependence of mean inter-delineation Distances

Volumetric conformity Index:
- VCI (HR CTV) = 0.72
- VCI (GTV) = 0.58
Example: cervical cancer IIIB: GTV shrinkage + adaptive CTV<sub>HR</sub>

EBRT dose

- **0 Gy**
  - Initial GTV
  - Volume 75 ccm

- **18 Gy**
  - Cisplatin (40 mg/m²) x2

- **36 Gy**
  - Cisplatin (40 mg/m²) x4

EBRT45 Gy

- Cisplatin (40 mg/m²) x5

EBRT dose

- **9 Gy**
  - Cisplatin (40 mg/m²) x1

- **27 Gy**
  - Cisplatin (40 mg/m²) x3

- **45 Gy**

Pre-brachytherapy
Residual GTV: 8 ccm

Brachytherapy
HR CTV 30 ccm

Cisplatin (40 mg/m²) x1

Cisplatin (40 mg/m²) x2

Cisplatin (40 mg/m²) x3

Cisplatin (40 mg/m²) x4

Cisplatin (40 mg/m²) x5

modified from ICRU 89, 2016
Applicator for up to mid-parametrial residual GTV and residual pathologic tissue

Kirisits et al. IJROBP 2006

Dimopoulos et al. IJROBP 2007
Applicator for up to distal parametrial residual GTV and residual pathologic tissue disease

The Vienna II Applicator

additional divergent template guided needles

Berger et al. ABS 2010
Example: cervical cancer, FIGO IIIB (mod. From ICRU report 89, 2016, Fig. 4.3)

EBRT dose
- 0 Gy
- 18 Gy: Cisplatin (40 mg/m²) x2
- 36 Gy: Cisplatin (40 mg/m²) x4
- 45 Gy: Cisplatin (40 mg/m²) x5

EBRT dose
- 9 Gy: Cisplatin (40 mg/m²) x1
- 27 Gy: Cisplatin (40 mg/m²) x3
- 45 Gy

GTV initial and residual
- GTVres total 108 Gy

Pre-brachytherapy

Brachytherapy
- CTVHR total 90 Gy

EBRT dose
- 45 Gy + 45 Gy

Imaging technology development integrating US, CT and MRI for $CTV_{HR}$ contouring

TRUS: target delineation, applicator reconstruction

TRUS/CT registration via applicator + target transfer to CT

Comparison of $CTV_{HR}$ from MRI, TRUS, CT

Vienna Group, work in progress: N Nesvacil, M Schmid, C Kirisits
Dose prescription according to risk
large variations in initial/adaptive volumes and doses
(EMBRACE studies (06/2017))

Initial $\text{CTV-T}_{LR}$ $\phi$ 230 cm$^3$
Initial $\text{GTV-T}$ $\phi$ 55 cm$^3$
Adaptive $\text{CTV-T}_{IR}$ $\phi$ 78 cm$^3$
Adaptive $\text{CTV-T}_{HR}$ $\phi$ 33 cm$^3$
Residual GTV $\phi$ 9 cm$^3$

LR CTV 50 – 60 Gy
HR CTV $\bar{d}$ 89 Gy
IR CTV $\bar{d}$ 70 Gy
$\bar{d}$ 102 Gy
Dose prescription protocol in cervix cancer
EMBRACE II (2016-2020)
prospective validation of DVH parameters for adaptive BT

<table>
<thead>
<tr>
<th></th>
<th>D90 CTV\textsubscript{HR} EQD2\textsubscript{10}</th>
<th>D98 CTV\textsubscript{HR} EQD2\textsubscript{10}</th>
<th>D98 GTV EQD2\textsubscript{10}</th>
<th>D98 CTV\textsubscript{IR} EQD2\textsubscript{10}</th>
<th>Point A EQD2\textsubscript{10}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Aims</td>
<td>&gt; 90 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>

Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive Brachytherapy in locally advanced Cervical cancer
Dose effect for CTV_{HR}, GTV_{res} and CTV_{IR}

Tanderup et al RO, Radiother and Oncol, vol 120, 2016
Dose prescription protocol in cervix cancer
EMBRACE II (2016-2020): OAR dose volume constraints
prospective validation of DVH parameters for adaptive BT

<table>
<thead>
<tr>
<th></th>
<th>Bladder (D_{2\text{cm}^3}) EQD(_2)</th>
<th>Rectum (D_{2\text{cm}^3}) EQD(_2)</th>
<th>Recto-vaginal point EQD(_2)</th>
<th>Sigmoid/Bowel (D_{2\text{cm}^3}) EQD(_2)</th>
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</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>
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<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>
Uncertainties in cervix cancer brachytherapy: overview (budget)

Table 1 Uncertainty budget (SD) for intracavitary brachytherapy

<table>
<thead>
<tr>
<th>Source</th>
<th>Target (HR CTV D90)</th>
<th>OARs (D₂cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source strength</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Dose and DVH calculation</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dwell position uncertainty</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>and source positioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVH addition across fractions</td>
<td>NA</td>
<td>1%* - ?%</td>
</tr>
<tr>
<td>(previously called “worst case</td>
<td></td>
<td></td>
</tr>
<tr>
<td>assumption”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contouring (inter-observer)</td>
<td>9%</td>
<td>5-11%</td>
</tr>
<tr>
<td>Intra- and inter-fraction (intra-</td>
<td>11%</td>
<td>20-25%</td>
</tr>
<tr>
<td>application) uncertainties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12%</td>
<td>21-26%</td>
</tr>
</tbody>
</table>

(Tanderup, Nesvacil, Pötter, Kirisits, Radioth&Oncol 04/2013)
Expected interfraction variations

Target
will remain fixed relative to applicator which is stabilized through gauze packing

Rectum:
may slightly change in configuration and gas filling

Bladder:
use of bladder filling protocols, changes possible

Sigmoid:
may change considerably in location and configuration

Recent developments (since 2000): Brachytherapy: from 2D (to 3) to 4D

- Image guidance (MRI (CT, US))+rep Gynexam
- Adaptive target concept: $GTV_{\text{initial}} + GTV_{\text{residual}}$
- High radiation dose in HR CTV (>85-90 Gy)
- Reduced dose to organs at risk
  - Bladder, rectum, sigmoid, bowel, vagina
To provide common concepts and terms (level 1-3) for cervix cancer brachytherapy for:

- volumes, in particular initial/residual GTV
- initial/adaptive CTV and OAR (2D/3D/4D)
- radiobiological variations (equi-effective dose)
- dose volume parameters (3D/4D)
- the process from planning aims to prescription

International Commission for Radiation Units: ICRU (since 1920)

European Brachytherapy Group: GEC ESTRO
Significant reduction of V43 Gy by 500-1000 ccm achievable (EMBRACE)
Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence

• Mono-institutional cohorts (ongoing, >14 publicat. since 2007)
• Multi-center cohorts with retrospective evaluation
  RetroEMBRACE (n=731, first publications in 2016)
• Prospective Trials
  STIC: comparative 2D vs. 3D (n=200; published 2012)
  EMBRACE I: observational, 08/2008 - 12/2015 (n=1416)
  EMBRACE II: interventional, start 04/2016
Cervical Cancer FIGO IIIB

High Risk CTV = HRCTV

IGABT = Image Guided Adaptative Brachytherapy

25 Months Follow up
<table>
<thead>
<tr>
<th>Type</th>
<th>Year</th>
<th>N</th>
<th>Dose rate</th>
<th>Image modality</th>
<th>Median follow-up (month)</th>
<th>Interstitial</th>
<th>GEC-ESTRO recommendations applied</th>
<th>D90 HR-CTV (Gy +/- SD)</th>
<th>% CL (year)</th>
<th>% OS (year)</th>
<th>Severe morbidity rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addenbrooke's hospital UK [23]</td>
<td>2009</td>
<td>28</td>
<td>HDR</td>
<td>CT</td>
<td>23</td>
<td>0%</td>
<td>No</td>
<td>-</td>
<td>96% (3-y)</td>
<td>81% (3-y)</td>
<td>11%</td>
</tr>
<tr>
<td>National center Korea [14]</td>
<td>2010</td>
<td>97</td>
<td>HDR</td>
<td>CT</td>
<td>41</td>
<td>0%</td>
<td>No</td>
<td>-</td>
<td>97% (3-y)</td>
<td>68% (3-y)</td>
<td>2.0%</td>
</tr>
<tr>
<td>Vienna University Austria [20]</td>
<td>2011</td>
<td>156</td>
<td>HDR</td>
<td>MRI</td>
<td>42</td>
<td>44%</td>
<td>Yes</td>
<td>93 +/- 13</td>
<td>95% (3-y)</td>
<td>68% (3-y)</td>
<td>5.6%</td>
</tr>
<tr>
<td>Tata Mumbai India [17]</td>
<td>2011</td>
<td>24</td>
<td>MRI</td>
<td>MRI 81.8%</td>
<td>24</td>
<td>NR</td>
<td>Yes</td>
<td>70.9 +/- 10.6</td>
<td>87.5 (2-y)</td>
<td>96% (2-y)</td>
<td>4.1%</td>
</tr>
<tr>
<td>STIC France [12]</td>
<td>2012</td>
<td>117</td>
<td>PDR</td>
<td>MRI 18.1%</td>
<td>24.3</td>
<td>NR</td>
<td>Yes</td>
<td>73.1 +/- 11.3</td>
<td>77.5 (2-y)</td>
<td>74% (2-y)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Utrecht University The Netherlands [19]</td>
<td>2013</td>
<td>46</td>
<td>HDR (10.9%)</td>
<td>MRI 98%</td>
<td>41</td>
<td>30.4%</td>
<td>Yes</td>
<td>84 +/- 9</td>
<td>93% (3-y)</td>
<td>65% (3-y)</td>
<td>9.5%</td>
</tr>
<tr>
<td>Aarhus University Denmark [16]</td>
<td>2013</td>
<td>140</td>
<td>PDR</td>
<td>MRI 98%</td>
<td>36</td>
<td>43%</td>
<td>Yes</td>
<td>91</td>
<td>91% (3-y)</td>
<td>79% (3-y)</td>
<td>7%</td>
</tr>
<tr>
<td>Chiang Mai University Thailand [24]</td>
<td>2013</td>
<td>17</td>
<td>HDR</td>
<td>CT 2%</td>
<td>19</td>
<td>0%</td>
<td>Yes</td>
<td>88.3 +/- 3.8</td>
<td>100% (3-y)</td>
<td>94% (3-y)</td>
<td>11.8%</td>
</tr>
<tr>
<td>Pittsburg medical center USA [13]</td>
<td>2014</td>
<td>128</td>
<td>HDR</td>
<td>MRI</td>
<td>24.4</td>
<td>0%</td>
<td>Yes</td>
<td>82.7</td>
<td>91.6 (2-y)</td>
<td>87.7% (2-y)</td>
<td>0.9%</td>
</tr>
<tr>
<td>University of Leiden The Netherlands [21]</td>
<td>2014</td>
<td>83</td>
<td>MRI</td>
<td>MRI 86.7%</td>
<td>42.3</td>
<td>20%</td>
<td>Yes</td>
<td>80.8</td>
<td>93% (3-y)</td>
<td>86% (3-y)</td>
<td>8.4%</td>
</tr>
<tr>
<td>Medical college Wisconsin USA [15]</td>
<td>2014</td>
<td>18</td>
<td>HDR</td>
<td>MRI 13.3%</td>
<td>20</td>
<td>NR</td>
<td>Yes</td>
<td>88</td>
<td>100% (2-y)</td>
<td>93% (2-y)</td>
<td>11.1%</td>
</tr>
<tr>
<td>University of Melbourne Australia [18]</td>
<td>2014</td>
<td>292</td>
<td>US</td>
<td>MRI</td>
<td>49.2</td>
<td>0%</td>
<td>No</td>
<td>80.1 +/- 5.5</td>
<td>87.5% (3-y)</td>
<td>65% (5-y)</td>
<td>6.0%</td>
</tr>
<tr>
<td>University of California, San Diego, USA [22]</td>
<td>2015</td>
<td>76</td>
<td>HDR</td>
<td>CT</td>
<td>17</td>
<td>5.3%</td>
<td>Yes</td>
<td>86.3 +/- 8.1</td>
<td>94.2% (2-y)</td>
<td>75% (2-y)</td>
<td>2.2%</td>
</tr>
<tr>
<td>Gustave Roussy villejuif France (this study)</td>
<td>2015</td>
<td>225</td>
<td>PDR</td>
<td>MRI 89.3%</td>
<td>38.8</td>
<td>2.2%</td>
<td>Yes</td>
<td>80.4 +/- 10.3</td>
<td>86.4% (3-y)</td>
<td>76.1% (3-y)</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

N: number of patients, HDR: high dose rate, PDR: pulsed-dose rate, NR: not reported, US: ultrasound.

> 1,300 patients from 14 centres

Castelnau-Marchand et al. Gyn Onc 2015
Local, pelvic and distant control, cancer specific and overall survival

Vienna (2011) 3y:
- Loc failure 5%
- Pelv failure 9%
- Syst failure 18%

Vienna: mean D90 HR CTV 92 Gy

RETRO EMBRACE
- 731 patients
- 12 institutions
- Loc fail 9-11%
- Pelv fail 13-16%
- Syst fail 23-27%

Mean D90 HR CTV 84 Gy

Sturdza et al. R&O 2016
Clinical Results for adaptive RT/BT
Local control and FIGO stage

RetroEMBRACE (n=731)

Local failure
RetroEMBRACE

- 3y
- Total: 9%
- IB 2%*
- IIB 7%
- IIIIB 21%
- IVA 24%

*2 events in IB2

Vienna (n=158)

Local failure
Vienna (2011)

- 3y
- Total: 5%
- IB 0%
- IIB 4%
- IIIIB 14%
- IVA 2/6 (n)

Sturdza et al. R&O 2016

Pötter et al. R&O 2011
Improved local control with IC/IS in large tumours (retroEMBRACE)

Large tumours (≥30 cm³ CTV_{HR})  Small tumours (<30 cm³ CTV_{HR})

Survival Functions

Advanced adaptive brachytherapy: 17 events
Limited adaptive brachytherapy: 24 events
P-value= 0.02

Advanced adaptive brachytherapy: 4 events
Limited adaptive brachytherapy: 10 events
P-value= 0.50

Numbers at risk
118 103 76 60 54
38
169 149 122 103 87 63
124 121 104 82 59 40

~10%

Fokdal et al RO, in press
Fortin et al, WCB 2016
Clinical evidence: Overall local outcome

EMBRACE cohort (n=1230)

• 24 incomplete remissions (IR) (98% complete remission rate) (72 incomplete remissions (IR) at 3 months, 48 resolved at 6-9 months)

• 56 local recurrences (LR) (at median 25 months FUP)
  • Median time to local recurrence: 11.5 months (86% of local recurrences occurred within 24 months)

• 80 local failures (IR+LR) (6.5%)
  • 42 (52%) synchronous nodal or distant failures

M. Schmid ESTRO 2017
Anatomical location of local failures (n=1230)

108 locations in 63 patients with local failure
(data available in 63/80 patients (79%), multiple locations possible)

Cervix and uterus: 80% (n=50)
Proximal parametria: 13% (n=8)
Distal parametria / pelvic wall: 29% (n=18)
Vagina: 29% (n=18)
Urinary bladder: 19% (n=12)
Rectum: 3% (n=2)
Local failures in regard to boost brachytherapy target volumes

Inside HRCTV: 51% (n=27 (+16))
Inside IRCTV: 17% (n=9)
Inside HR & IRCTV: 30% (n=16)
Not related: 2% (n=1)

Failure pattern provides prospective clinical validation of adaptive target concept
For locally advanced cervix cancer applying BT boost (one major aim of the EMBRACE study)
Overall Survival locally advanced cervical cancer: the impact of brachytherapy

Total 25% increase in Overall Survival with „4D brachy“ (RetroEMBRACE) compared to „no brachy“ (Han et al)

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
Results on morbidity, PRO, QoL
DVH based predictive dose factors

- **Rectum** proctitis, bleeding (G1-2), fistula rare
- **Bowel** diarrhea, flatulence (G1-2), anal incontinence (low), stenosis and fistula rare
- **Bladder** frequency/urgency, incontinence (G1-2), cystitis, bleeding, fistula, ureter strict. (low)
- **Vagina (G≤2)** stenosis/shorten, dryness, bleeding, mucos.

**PRO shows significantly more burden from G2 symptoms for patients**

- Descriptive and analytical evaluations

Work in progress, much to learn in near future (EMBRACE)
## Max. incidence bladder morbidity

1176 patients with CTC-assessment

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Incontinence</th>
<th>Spasm</th>
<th>Bladder stenosis</th>
<th>Ureter Stenose(^{\text{a}})</th>
<th>Cystitis</th>
<th>Bleeding</th>
<th>Fistula(^{\text{a}}) (N=1093)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>470 (40.0%)</td>
<td>784 (66.7%)</td>
<td>1081 (91.9%)</td>
<td>1166 (99.1%)</td>
<td>1125 (95.7%)</td>
<td>958 (81.5%)</td>
<td>1098 (93.4%)</td>
<td>1083 (99.1%)</td>
</tr>
<tr>
<td>G1</td>
<td>470 (40.0%)</td>
<td>267 (22.7%)</td>
<td>75 (6.4%)</td>
<td>7 (0.6%)</td>
<td>15 (1.3%)</td>
<td>132 (11.2%)</td>
<td>55 (4.7%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>G2</td>
<td>123 (10.4%)</td>
<td>106 (9.0%)</td>
<td>19 (1.6%)</td>
<td>3 (0.3%)</td>
<td>12 (1.0%)</td>
<td>75 (6.4%)</td>
<td>19 (1.6%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>G3</td>
<td>14 (1.2%)</td>
<td>14 (1.2%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>17 (1.4%)</td>
<td>10 (0.9%)</td>
<td>4 (0.3%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>G4</td>
<td>5 (0.4%)</td>
<td>0 (0.1%)</td>
<td>0 (0%)</td>
<td>2 (0.2%)</td>
<td>1 (0.1%)</td>
<td>0 (0%)</td>
<td>3 (0.3%)</td>
<td></td>
</tr>
</tbody>
</table>

* Total of 17 fistulas were diagnosed. 7 patients had tumor involvement of the bladder at time of diagnosis and were excluded

\(^{\text{a}}\) 5 patients were censored due to ureter stricture G3 that persisted from baseline

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Fokdal ESTRO 2017
All bladder morbidity
All single CTCae endpoints grouped together

Kaplan-Meier estimates

<table>
<thead>
<tr>
<th>Follow up time in months</th>
<th>Probability of morbidity</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0,0</td>
</tr>
<tr>
<td>12</td>
<td>0,0</td>
</tr>
<tr>
<td>24</td>
<td>0,0</td>
</tr>
<tr>
<td>36</td>
<td>0,0</td>
</tr>
<tr>
<td>48</td>
<td>0,0</td>
</tr>
<tr>
<td>60</td>
<td>0,0</td>
</tr>
</tbody>
</table>

77.3% (720 patients)
32.1% (251 patients)
4.7% (39 patients)

Prevalence rates at follow up

All bladder morbidity (p<0.001)

<table>
<thead>
<tr>
<th>Months</th>
<th>BL</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>1176</td>
<td>1148</td>
<td>1025</td>
<td>911</td>
<td>880</td>
<td>769</td>
<td>667</td>
<td>527</td>
<td>458</td>
<td>327</td>
<td>189</td>
</tr>
</tbody>
</table>

- Grade 1
- Grade 2
- Grade 3
- Grade 4

Fokdal ESTRO 2017
Conclusions

- **Low actuarial 5-year grade 3-4 morbidity**
  - All bladder symptoms 4.7%
    - Frequency/incontinence 1.9%/2.1%
    - Fistula 0.7%
    - Bleeding 0.6%
    - Ureteral stricture 3.4%

- **Maximal prevalence rates of mild and moderate physician assessed morbidity**
  - Urinary frequency G1/G2: 25.6%/4.8%
  - Incontinence G1/G2: 19.4%/5.8%
  - Cystitis G1/G2: 8.4%/4.0%

- **The burden of morbidity is weighted different by physicians and patients**

- **PRO is necessary for the evaluation of morbidity in future studies**
# Overview Rectum (CTCAE)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Proctitis</th>
<th>Bleeding</th>
<th>Stenosis</th>
<th>Fistula</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Grade 0</td>
<td>782</td>
<td>81.5</td>
<td>805</td>
<td>83.8</td>
<td>949</td>
</tr>
<tr>
<td>Grade 1</td>
<td>135</td>
<td>14.1</td>
<td>114</td>
<td>12.0</td>
<td>5</td>
</tr>
<tr>
<td>Grade 2</td>
<td>39</td>
<td>4.1</td>
<td>31</td>
<td>3.2</td>
<td>6</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4</td>
<td>0.4</td>
<td>10</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median Follow-up:** 25.4 months

**Times to onset From 1st fraction**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4</td>
<td>16.8 +/- 12.7</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td>17.5 +/- 9.5</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>15.8 +/- 5.3</td>
</tr>
</tbody>
</table>

Mazeron et al. 2016
Prevalence and actuarial cumulative incidence: rectal morbidity

EMBRACE, Mazeron et al. green journal 2016
Rectal dose volume effects

≥G2 rectal morbidity (EMBRACE cohort, n=960)

<65Gy: 5-10%

≥65Gy: 15-25%

≥G2 rectal morbidity (bleeding) (Vienna cohort, n=145)

60Gy: <2% 75Gy: 12%

P. Georg et al., IJROBP 2011

Mazeron et al., RO 2016
Dose effect relation
Vaginal stenosis and ICRU recto-vaginal point
(ICRU 89)

N=630 multi-centre, prospective EMBRACE patients

Kirchheiner et al. Radiotherapy and Oncology 2016
Status IGABT in LACC (062017)

• Transition from 2D to 3D adaptive Brachytherapy (IGABT) preferably based on MRI (US, CT), rep. gyn exam adaptative target concept, adapted application: IC/IS high radiation doses to $CTV_{HR} > 85-90$ Gy EQD2 also for $GTV_{res} (>90-95$ Gy) and $CTV_{IR}$ (65-70 Gy) moderate doses to adjacent OARs volumes and points (see EMBRACE data)

• Patterns of events and understanding dose/volume effects local disease control and morbidity
Outlook

• More evidence from EMBRACE studies (I and II)
  volume and dose modelling
  multi-parametric prescription protocols (CTVs/OARs)
• Spread of image guided BT and EBRT
  using different workflows/technologies CT, US, MRI
• Prognostic and predictive parameters (incl. translational)
  More patient and treatment selection