Recent Advances and current status of radiotherapy for cervix cancer

Richard Pötter MD
Department of Radiation Oncology,
Medical University of Vienna, Austria

ICARO-2, IAEA, Vienna, June, 24, 2017
Outline

• Recent Advances
  Radiochemotherapy
  Image Guided Adaptive Brachytherapy (IGABT)
  ICRU GEC ESTRO Report 89
  Image Guided EBRT (IMRT/IGRT)

• Current Status
  Transition from 2D to 3D IGABT
  3DCRT and IMRT/IGRT (transition)

• Conclusions
Concomitant Radiochemotherapy

• No essential advances in general
  level 1-evidence for stage IIIB RCHT: +6% OS

• Cis-Platinum 40 mg/m2 weekly x 5-6
  plus EBRT 45 Gy in 5 weeks, 1.8 Gy/fract.

• No multi-center level 1-evidence on value of (neo)-adjuvant chemotherapy
  (Outback/Interlace trial results pending)
Primary radiochemotherapy and Image guided adaptive brachytherapy (IGABT)

External beam radiotherapy: 3D EBRT or IMRT/VMAT

- Start
- 45 Gy

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
</table>

Chemotherapy

1. Cycle

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
</table>

5-6 Cycles

Brachytherapy: IGABT

- HDR or PDR
- EQD$_2$ $\geq$60 Gy
- EQD$_2$ $\geq$85 Gy

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
</table>

Cisplatin 40 mg/m$^2$
Recent developments (since 2000):

Brachytherapy: from 2D (to 3) to 4D

- Image guidance (MRI (CT, US))+rep Gynexam
- Adaptive target concept: \( \text{GTV}_{\text{initial}} + \text{GTV}_{\text{residual}} \)
- High radiation dose in HR CTV (>85-90 Gy)
- Reduced dose to organs at risk
  - Bladder, rectum, sigmoid, bowel, vagina
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

Vienna Group, work in progress:
N Nesvacil, M Schmid, C Kirisits

comparison of $CTV_{HR}$ from MRI, TRUS, CT
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/
Example: cervical cancer: total dose 90 Gy EQD2

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

IGABT 45 Gy
Brachytherapy
HR CTV 30 ccm

Modified from ICRU 89, 2016
Example: cervical cancer, FIGO IIIIB (mod. From ICRU report 89, 2016, Fig. 4.3)

**EBRT dose**

- 0 Gy
- 18 Gy
- 36 Gy
- 45 Gy

**Pre-brachytherapy**

- EBRT dose 9 Gy
  - Cisplatin (40 mg/m²) x1
- EBRT dose 27 Gy
  - Cisplatin (40 mg/m²) x3
- EBRT dose 45 Gy
  - Cisplatin (40 mg/m²) x5

**CTV**

- GTV initial and residual
- CTV initial and adaptive

**GTV_{res} total 108 Gy**

**CTV_{HR} total 90 Gy**

**Brachytherapy**
Dose prescription according to risk
large variations in initial/adaptive volumes and doses
(EMBRACE studies (06/2017)) (n=1416 pats.)

<table>
<thead>
<tr>
<th>Volume Type</th>
<th>Volume (cm³)</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial CTV-T_{LR}</td>
<td>230</td>
<td>≈ 50-60</td>
</tr>
<tr>
<td>Initial GTV-T</td>
<td>55</td>
<td>≈ 70-90</td>
</tr>
<tr>
<td>Adaptive CTV-T_{IR}</td>
<td>78</td>
<td>D90 med. 70</td>
</tr>
<tr>
<td>Adaptive CTV-T_{HR}</td>
<td>33</td>
<td>D90 med. 89</td>
</tr>
<tr>
<td>Residual GTV</td>
<td>9</td>
<td>D98 med. 102</td>
</tr>
</tbody>
</table>

EQD2
Dose effect for \( \text{CTV}_{\text{HR}} \), \( \text{GTV}_{\text{res}} \) and \( \text{CTV}_{\text{IR}} \)

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

<table>
<thead>
<tr>
<th>Planning Aims</th>
<th>D90 CTV$<em>{HR}$ EQD2$</em>{10}$</th>
<th>D98 CTV$<em>{HR}$ EQD2$</em>{10}$</th>
<th>D98 GTV EQD2$_{10}$</th>
<th>D98 CTV$<em>{LR}$ EQD2$</em>{10}$</th>
<th>Point A EQD2$_{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90 Gy &lt; 95 Gy</td>
<td>&gt; 75 Gy &gt;95 Gy</td>
<td>&gt; 60 Gy</td>
<td>&gt; 65 Gy</td>
<td></td>
<td></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>
Dose prescription according to risk: different volumes receive different doses
(EMBRACE studies (06/2017))

Volumes
From 230 cm³
78 cm³
55 cm³
33 cm³
9 cm³

LR CTV 50 – 60 Gy

\[ d = 89 \text{ Gy} \]
\[ d = 70 \text{ Gy} \]
\[ d = 102 \text{ Gy} \]
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 $D_{2\text{cm}^3}$ EQD2₃</th>
<th>Rectum $D_{2\text{cm}^3}$ EQD2₃</th>
<th>Recto-vaginal point EQD2₃</th>
<th>Sigmoid/ Bowel $D_{2\text{cm}^3}$ EQD2₃</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>
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
Advances in EBRT: IMRT and IGRT

Significant reduction of V43 Gy by 500-1000 ccm achievable (EMBRACE)

Elective field is big and can rise up high

Homogeneous dose to future brachy region

Lymph node boosting (integrated)

Seppenwoolde et al. 2017
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
## Monoinstitutional patient cohorts

<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>96%</td>
<td>96%</td>
<td>81%</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>97%</td>
<td>97%</td>
<td>68%</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</td>
<td>68</td>
<td>5.6%</td>
</tr>
<tr>
<td>Tata Mumbai India [17]</td>
<td>2011</td>
<td>24</td>
<td>HDR</td>
<td>MRI</td>
<td>24</td>
<td>NR</td>
<td>Yes</td>
<td>70.9 +/- 10.6</td>
<td>87.5 (2-y)</td>
<td>74</td>
<td>4.1%</td>
</tr>
<tr>
<td>STIC France [12]</td>
<td>2012</td>
<td>117</td>
<td>PDR</td>
<td>CT 81.8% MRI 18.1%</td>
<td>24.3</td>
<td>NR</td>
<td>Yes</td>
<td>73.1 +/- 11.3</td>
<td>78.5</td>
<td>74</td>
<td>2.6%</td>
</tr>
<tr>
<td>Utrecht University The Netherlands [19]</td>
<td>2013</td>
<td>46</td>
<td>HDR (10.9%)PDR (84.8%)</td>
<td>CT 81.8% MRI 18.1%</td>
<td>41</td>
<td>30.4%</td>
<td>Yes</td>
<td>84 +/- 9</td>
<td>93</td>
<td>65</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% CT 2%</td>
<td>36</td>
<td>43%</td>
<td>Yes</td>
<td>91</td>
<td>91%</td>
<td>79%</td>
<td>7%</td>
</tr>
<tr>
<td>Chiang Mai University Thailand [24]</td>
<td>2013</td>
<td>17</td>
<td>HDR</td>
<td>CT</td>
<td>19</td>
<td>0%</td>
<td>Yes</td>
<td>88.3 (+/- 3.8)</td>
<td>100</td>
<td>94.1</td>
<td>11.8%</td>
</tr>
<tr>
<td>Pittsburg medical center USA [24]</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%</td>
<td>0.9%</td>
</tr>
<tr>
<td>University of Leiden The Netherlands [21]</td>
<td>2014</td>
<td>83</td>
<td>HDR</td>
<td>MRI 86.7% CT 13.3%</td>
<td>42.3</td>
<td>20%</td>
<td>Yes</td>
<td>80.8</td>
<td>93%</td>
<td>86%</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</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>HDR</td>
<td>US</td>
<td>49.2</td>
<td>0%</td>
<td>No</td>
<td>80.1 +/- 5.5</td>
<td>87.5%</td>
<td>65%</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%</td>
<td>75%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Gustave Roussy Villejuif France</td>
<td>2015</td>
<td>225</td>
<td>PDR</td>
<td>MRI 89.3% CT 10.7%</td>
<td>38.8</td>
<td>2.2%</td>
<td>Yes</td>
<td>80.4 +/- 10.3</td>
<td>86.4%</td>
<td>76.1%</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.
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

RETRO EMBRACE

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

RetroEMBRACE (n=731),

Local failure

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>3y Local Control</th>
<th>5y Local Control</th>
<th>Events</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1B</td>
<td>98%</td>
<td>98%</td>
<td>2</td>
<td>123</td>
</tr>
<tr>
<td>2A</td>
<td>97%</td>
<td>94%</td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td>2B</td>
<td>93%</td>
<td>91%</td>
<td>28</td>
<td>368</td>
</tr>
<tr>
<td>3A</td>
<td>71%</td>
<td>71%</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>3B</td>
<td>79%</td>
<td>75%</td>
<td>28</td>
<td>145</td>
</tr>
<tr>
<td>4A</td>
<td>76%</td>
<td>76%</td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

*2 events in IB2

Vienna (2011)

Local failure

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>3y Local Control</th>
<th>Events</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>2/6 (n)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total: 5%

Sturdza et al. R&O 2016

Pötter et al. R&O 2011
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

Fokdal et al RO, Radiotherapy and Oncology 2016
Fortin et al, World Conference Brachytherapy 2016
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)
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
Rectal dose volume effects

\[ \geq \text{G2 rectal morbidity (bleeding)} \]

(EMBRACE cohort, \( n = 960 \))

\[ \geq \text{G2 rectal morbidity} \]

(Vienna cohort, \( n = 145 \))

\[ 60 \text{Gy} \]

\[ 75 \text{Gy} \]

\[ <2\% \]

\[ 12\% \]

\[ \geq 65 \text{Gy}: 15-25\% \]

\[ <65 \text{Gy}: 5-10\% \]

Mazeron et al., RO 2016

P. Georg et al., IJROBP 2011

Fig. 1. Relationship between \( D_{2cc} \) and late side effects in the rectum.
Status Radiotherapy in LACC (062017)

- Radiochemotherapy with concomitant cis-Platin
- CCRT as 3D CRT or IMRT (favourably as IGRT)
  Para-aortic RT (risk adapted) (IMRT), SIB (IMRT)
- Transition from 2D to 3D adaptive Brachytherapy (IGABT)
  preferably based on MRI (US, CT), rep. gyn exam
  adaptive target concept, adapted application: IC/IS
  high radiation doses to CTV_{HR} >85-90 Gy EQD2
  moderate doses to adjacent OARs
- Patterns of events and understanding dose/volume effects
- Adjuvant treatment no standard at present
Ongoing Activities
Education & Training

Hands-on workshops (Vienna, Aarhus…>25)
International hands-on workshops (~10)
ESTRO School (international programmes):
  – ESTRO School technology transfer grants (since 2008)
  – web based contouring workshops (3 so far)
  – AROI ESTRO Teaching and Training Programme (2017-2019)
Cambridge CCMO: web based e-learning program cervix cancer (EMBRACE II)

IAEA programmes

Linking research and education

Umesh Mahantshetty, AROI
C. Verfaillie
ESTRO School •
I. Aalders, BT acad.

E. Fidarova et al.

J. Swamidas, AROI

LT Tan, Cambridge
Outlook

• More evidence from EMBRACE studies (I and II)
  volume and dose modelling
  multi-parametric prescription protocols
• Spread of image guided BT and EBRT
  using different workflows/technologies CT, US, MRI
• Prognostic and predictive parameters
  More patient and treatment selection
• Development of efficient adjuvant therapy
  in risk groups