Basics of Cervix Cancer Brachytherapy

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Incidence Cervix: 445,000
Cervix Cancer Demographics

- 87% of cervix cancer occurs in less developed regions of the world
- 18 fold difference in mortality rate for cervix cancer depending on region of the world
Incidence and Mortality in More and Less Developed Regions for Women

Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012

Jacques Ferlay¹, Isabelle Soerjomataram¹, Rajesh Dikshit², Sultan Eser³, Colin Mathers⁴, Marise Rebelo⁵, Donald Maxwell Parkin⁶, David Forman⁷ and Freddie Bray⁸

Int J Cancer 2015
FIGURE 3. Estimated Percentage of Patients Able to Access Radiotherapy, 2013.
Trends in Brachytherapy in the US

Han et al IJROBP 2013

- SEER study
- 7359 patients
- 1988-2009
- 37% EBRT alone
- Brachytherapy use↑OS
  HR 0.66 (95% CI 0.6-.74)
Is type of boost important in cervix cancer?

- NCDB analysis
- 2004-2011
- 7654 patients
- SBRT/IMRT survival decrement was > than omission of chemo (p<0.01)

Gill et al, IJROBP 2014
Why does Brachytherapy work?

In a study of 125 patients from Washington University, probit analysis estimated the mean dose required for ≥90% local control to be 260 Gy (P<.001).

*Dyk et al IJROBP, 90:794-801, 2014*
Successful Tx of advanced cervix cancer requires combination of external beam and brachytherapy

High dose rate vs low dose rate intracavity brachytherapy for carcinoma of the uterine cervix cancer: Systematic review and meta-analysis


- 18,937 patients
- 15 articles
  - 3 randomized trials
  - 12 retrospective studies
- No difference in survival, pelvic recurrence, rectal and bladder complications
- Liu et al Cochrane Meta-analysis: same conclusion
# Importance of Overall Treatment Time

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMH</td>
<td>1992</td>
<td>830</td>
<td>LC</td>
</tr>
<tr>
<td>Inst. Gustave Roussy</td>
<td>1993</td>
<td>386</td>
<td>LC OS</td>
</tr>
<tr>
<td>Patterns of Care</td>
<td>1993</td>
<td>837</td>
<td>LC OS</td>
</tr>
<tr>
<td>Washington Univ.</td>
<td>1995</td>
<td>1224</td>
<td>LC CSS</td>
</tr>
<tr>
<td>Univ. of Wisconsin</td>
<td>2013</td>
<td>206</td>
<td>DFS not sig.</td>
</tr>
</tbody>
</table>

![Graph showing probability of pelvic control (%) against treatment time (days)]

~1% loss of local control per day
1. Historic Good Results
2. Imaging Renaissance

<table>
<thead>
<tr>
<th>Stage</th>
<th>% 5 yr cure (RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>79</td>
</tr>
<tr>
<td>II</td>
<td>41</td>
</tr>
<tr>
<td>III</td>
<td>27</td>
</tr>
</tbody>
</table>

Regaud, Paris: 1922-26, n=329
Anesthesia

• General
  – Laryngeal Mask Airway
  – Intubation
• Regional
  – Spinal
  – Epidural
• Monitored Anesthesia Care (MAC)
  – Procedural sedation
• Local
  – Pudendal block
• Oral medicines (Smit sleeve in place)
  – Narcotics
  – Benzodiazepines

Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand
Posttraumatic Stress Disorder After High-Dose-Rate Brachytherapy for Cervical Cancer With 2 Fractions in 1 Application Under Spinal/Epidural Anesthesia: Incidence and Risk Factors


- N=50
- Validated questionnaires
- Acute Stress in 30%
- PTSD in 41%
- Helpful Experiences
  - Treatment team
  - Psychological support
  - Positive attitude
- Stressful Factors
  - Pain
  - Organizational problems
  - Immobility
Applicator Choice

- Tandem and Ovoids
  - Fletcher
  - Henschke
  - Rotterdam
- Tandem and Ring
- Vaginal Mold
- Combination applicators
  - Utrecht
  - Vienna
- Tandem and Cylinder
  - Miami
- Interstitial
  - Template based
  - Free hand

- Angle of tandem
- Diameter of upper vagina
INTRAOP US

• CT-based study showed a perforation rate of 14% (experienced investigators)
  – Still occurred 8% when physician was confident of correct placement
  – Physician concern, age > 60, and tumor size were predictors of perforation

• US should be used to avoid perforation
  – If perforation: consider antibiotics

• US can be used for treatment planning and IGBT

Barnes et al IJGC 17(4):821-6, 2007
Importance of Vaginal Packing

• Essential aspect of good technique

• For MRI packing
  – Ultrasound gel (best contrast)
  – Conjugated estrogen cream + ultrasound gel
  – Gadolinium

• For Xray or CT packing
  – Radiopaque wire impregnated gauze
  – Contrast soaked gauze

Does Implant Technique Effect Survival?

Corn et al. Gyn Onc 53:294300,1994

FIG. 1. Asymmetric implant. Note that the distance between the tandem and right colpostat is greater than the distance between the tandem and left colpostat.

FIG. 2. Displacement of left colpostat. Note that the inferior tip of the caudal tandem source is separated from the left colpostat source.

FIG. 3. Idealized brachytherapy implant for patients with carcinoma of the uterine cervix.

Ideal

Displaced

Asymmetric
Local Control Impacts Survival

- > 85Gy, Multivariate Analysis p=0.01
- Technical adequacy of implant important determinant of local control

<table>
<thead>
<tr>
<th></th>
<th>Acceptable implant</th>
<th>Unacceptable implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr Local Control</td>
<td>68%</td>
<td>35%</td>
</tr>
<tr>
<td>5 yr Overall Survival</td>
<td>61%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Corn et al. Gyn Onc 53:294300,1994
Use standard reference points (ICRU 38)

Fig. 3.2. Determination of the reference points for bladder and rectum (see text).
2D to 3D to 4D: Image Guided Brachytherapy

- Reduction in dose to OARs
- Dose escalation (improved tumor control)
- MR, CT and US can be used for IGBT
- Continue to use standard reference points
- Document HRCTV, D90, D2cc for bladder, rectum, and sigmoid
- Iterative Brachy
Brachytherapy Dose

• Standard regimens
  – 5-6 Gy x 5
  – 7 Gy x 4
  – 8 Gy x 3
  – 9 Gy x 2

• 2 LDR implants preferable to 1

• Guiding principle: mitigating late toxicity
# OAR Targets

<table>
<thead>
<tr>
<th>Volume</th>
<th>ABS</th>
<th>EMBRACE</th>
<th>Geortg et al ED10</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2cc bladder</td>
<td>≤90 Gy</td>
<td>&lt;90 Gy</td>
<td>101 Gy</td>
</tr>
<tr>
<td>D2cc rectum</td>
<td>≤75 Gy</td>
<td>&lt;70-75 Gy</td>
<td>78 Gy</td>
</tr>
<tr>
<td>D2cc Sigmoid</td>
<td>≤75 Gy</td>
<td>≤75 Gy</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

Doses in EQD2. Modified from Harkendrider et al. IJROBP, 2015. ED10 = dose corresponding to 10% rate of toxicity.

- ICRU rectal point/D2cc correspond
  - Limit to 70-75 Gy EQD2
- ICRU bladder point/D2cc do not correspond
  - 75 Gy for ICRU point dose
  - 90 Gy for D2cc dose

Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand
CT (red) vs. MR (blue) for IGBT

For all 3 cases, the mean tumor volume was smaller on MR than on CT (P<.001)

Viswanthan et al, IJROBP 2014

MR at the time of brachytherapy may be of greatest benefit in patients with large tumors with parametrial extension that have a partial or complete response to external beam.
Issues with MRI

• Superior soft tissue resolution
• HRCTV smaller than on CT
• Greater conformality will lead to decrease dose to OARs
  – More critical for large lesions
• First fraction or every fraction
  – Beware of significant tumor response
  – $T_{1/2}$ for tumor response 20-21 days (CT, MR, clinical exam)
Indications for Interstitial Implant for Cervix Cancer

- Stage IIIA
- Large cancer not amenable to intracavitary approaches
- Recurrence after hysterectomy/radiation therapy
- Cervical stump cancer
  - Post supracervical hyst.
- Tandem should always be used (if possible)
- Subvolumes can easily be defined
Treatment planning

• Develop a standard
  – Team approach: Physician, Physicist, Nurse
• Plan each implant
• D90, V100, V150, V200, point A
  – Inverse Planning: watch the hot spots
• Combination applicators (Intracavitary + Interstitial)
  – Start with intracavitary positions, add ~10-15% of activity from the needle dwell positions
• Iterative approach
Conclusions

• The goal of treatment is cure with minimal side effects in most women
  – Stages I-IVa

• Brachytherapy works

• Incorporate advanced imaging

• Thanks for your attention!
Definitive CRT: Trial Example

- 45 Gy/25 fractions
- 37.5 Gy/15 fractions
- 7 Gy x 4 Brachy
- 9 Gy x 2 Brachy
- EBRT + SURGERY

ENDPOINT: RFS
## Hypofraction: BED and EQD2

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dose per fraction</th>
<th>Alpha/Beta</th>
<th>BED</th>
<th>EQD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>1.8</td>
<td>3</td>
<td>72.0</td>
<td>43.2</td>
</tr>
<tr>
<td>44</td>
<td>2.0</td>
<td>3</td>
<td>73.2</td>
<td>44.0</td>
</tr>
<tr>
<td>37.5</td>
<td>2.5</td>
<td>3</td>
<td>68.8</td>
<td>41.3</td>
</tr>
<tr>
<td>30</td>
<td>3.0</td>
<td>3</td>
<td>60.0</td>
<td>36.0</td>
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<thead>
<tr>
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<tbody>
<tr>
<td>45</td>
<td>1.8</td>
<td>10</td>
<td>53.1</td>
<td>44.3</td>
</tr>
<tr>
<td>44</td>
<td>2.0</td>
<td>10</td>
<td>52.8</td>
<td>44.0</td>
</tr>
<tr>
<td>37.5</td>
<td>2.5</td>
<td>10</td>
<td>46.9</td>
<td>39.1</td>
</tr>
<tr>
<td>30</td>
<td>3.0</td>
<td>10</td>
<td>39.0</td>
<td>32.5</td>
</tr>
</tbody>
</table>

### Brachy

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<thead>
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<th>Dose</th>
<th>Dose per fraction</th>
<th>Alpha/Beta</th>
<th>BED</th>
<th>EQD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>6.0</td>
<td>3</td>
<td>90.0</td>
<td>54.0</td>
</tr>
<tr>
<td>28</td>
<td>7.0</td>
<td>3</td>
<td>93.3</td>
<td>56.0</td>
</tr>
<tr>
<td>24</td>
<td>8.0</td>
<td>3</td>
<td>88.0</td>
<td>52.8</td>
</tr>
<tr>
<td>18</td>
<td>9.0</td>
<td>3</td>
<td>72.0</td>
<td>43.2</td>
</tr>
</tbody>
</table>

45/1.8 + 30/6 = 97.2 EQD2  vs  37.5/2.5 + 24/8 = 94.1 EQD2 for alpha/beta 3
30 fractions vs 18 fractions
Outcomes: Non-inferiority to External Beam & Brachy for 2-year survival; Equivalence for Toxicity/QoL
Analysis: Stratify on Stage and Node Involvement
Data: Standardized; Tissues (Genetics; HPV type); Blood (Nutritional Status)
Sites: Brazil and Mexico; Minimum requirement---CT image of Abdomen and Pelvis and Chest x-ray
In close or positive margins, what is the role for a brachytherapy boost after hysterectomy?

- 230 patients negative margins
  - LR 10% to 0% with RT
- 46 patients close margins (< 1 cm)
  - LR 17% to 0% with RT
- 8 patients with positive margins
  - LR 50% to 25% with RT
- Significant factors on univariate for RFS
  - Depth of invasion
  - Margin status and margin width
  - Tumor Size
  - LVSI

Viswanathan et al IJROBP 2006

Table 5. Retrospective studies assessing patients with positive/close margins treated with RT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>RT</th>
<th>Relapse rate (%)</th>
<th>Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estape et al. (33)</td>
<td>51</td>
<td>EB + VB</td>
<td>12.5</td>
<td>Close (≤ 5 mm) paravaginal</td>
</tr>
<tr>
<td>Hong et al. (34)</td>
<td>29</td>
<td>EB + VB*</td>
<td>25</td>
<td>Close (&lt; 3 mm) and positive†</td>
</tr>
<tr>
<td>Kim et al. (35)</td>
<td>11</td>
<td>VB ± EB</td>
<td>55</td>
<td>Close (&lt; 1 cm) and positive†</td>
</tr>
<tr>
<td>Russell et al. (29)</td>
<td>16</td>
<td>EB</td>
<td>36</td>
<td>Close (not defined)</td>
</tr>
<tr>
<td>Hogan et al. (30)</td>
<td>6</td>
<td>EB</td>
<td>33</td>
<td>Positive</td>
</tr>
<tr>
<td>Snijders-Keilholz et al. (32)</td>
<td>17</td>
<td>EB + VB</td>
<td>6</td>
<td>Positive</td>
</tr>
<tr>
<td>Snijders-Keilholz et al. (32)</td>
<td>6</td>
<td>EB + VB</td>
<td>Not given</td>
<td>Close (&lt; 5 mm)</td>
</tr>
</tbody>
</table>