4th ESO-ESMO Latin-American Masterclass in Clinical Oncology

18-22 April 2018
Mexico City, Mexico

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A. Cervantes, ES - N. Pavlidis, GR
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Scientific Co-ordinators:
M. Aapro, CH - F. Cardoso, PT

Under the auspices of

CMO - Comité de Medicina Oncológica

SMeO - Sociedad de Médicos de Oncología

Latin-America Programme
Cervical Cancer
• External beam radiation therapy (IMRT/3D)
• Brachytherapy
• Can IMRT replace brachytherapy?
• Surgery or Chemoradiation?
• Optimal chemoradiation
• Role of surgery after chemoradiation
• Postoperative treatment
• Radiation therapy with concurrent chemotherapy followed by brachytherapy is a good alternative to radical surgery with equivalent cure rates (stage IB-IIA, early IIB)
• Radiation with CT is the only standard therapy for advanced stage disease (large IIB, IIIA, IIIB)
• External radiation therapy targets the primary and pelvic lymphnodes
• Brachytherapy provides a booster dose to the central primary disease
• Concurrent chemotherapy is primarily a radiosensitizer
Radiation therapy fields
Radiation therapy fields
3D Conformal RT
IMRT
IMRT pitfalls

- Organ motion between daily fractions
- Tumor shrinkage during treatment course
Interfraction organ motion

Week 1

Week 2

Week 3

Week 4
Interfraction organ motion

Taylor A. et al. Radiotherapy and Oncol 2008
Tumor Shrinkage

2 MRI T2 weighted images of the same patient 4 weeks and 35Gy apart

Huh, SJ et al Radiother. Oncol. 2004
IMRT vs 3D

- Several retrospective studies with encouraging results (tumor control and toxicity)
- Typically lower GI toxicity with IMRT
- RTOG 0418 phase II study; Reported on favorable hematological toxicity if constraints were respected (V40 <37%)

Klopp AH et al. Int J Rad Oncol B P 2013
Isohashi F et al Rad Oncology 2015
IMRT vs 3D

Chronic GI toxicity (>Grade 2)

P=0.023

Isohashi F et al Rad Oncology 2015
IMRT vs 3D

V40: volume of small bowel >40Gy

P<0.001

Isohashi F et al Rad Oncology 2015
IMRT vs 3D

V40: volume of bone marrow >40Gy

Klopp AH et al. Int J Rad Oncol B P 2013
### IMRT vs 3D: RTOG 1203

Postop Cervix or endometrial cancer; 278 patients enrolled

<table>
<thead>
<tr>
<th>STRATIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XRT Dose</strong></td>
</tr>
<tr>
<td>1. 45 Gy</td>
</tr>
<tr>
<td>2. 50.4 Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STRATIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>1. No Chemotherapy</td>
</tr>
<tr>
<td>2. 5 cycles of weekly cisplatin at 40mg/m2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm 1</strong></td>
</tr>
<tr>
<td>IMRT pelvic radiation treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm 2</strong></td>
</tr>
<tr>
<td>4-field pelvic radiation treatment</td>
</tr>
</tbody>
</table>

Yeung AR et al. ASTRO 2016
Brachytherapy

Insertion of an afterloading device inside the uterus-cervix-vagina
Brachytherapy unit
Brachytherapy

- **HDR (High Dose Rate)**
  6 Gy x 5 sessions; 2.5 Wks
- **LDR (Low Dose Rate)**: 30-40 Gy
HDR CT based Brachytherapy
HDR CT based Brachytherapy
Brachytherapy: 3D display

30 Gy in 5 fractions over 2.5 weeks
No chemotherapy during HDR brachytherapy
Brachytherapy vs IMRT

Aydogan B et al. Int J Rad Onc BP 2006
Brachytherapy vs IMRT

- Equivalent isodose conformity to the target volume (i.e. cervical tumor)
- Brachy has a steeper falloff dose
- Brachy has higher tumor integral dose
- Brachy has a lower overall doses to the organs at risk.

Georg D. et al Int J Rad Onc BP 2008
Brachytherapy is essential

SEER study; 7359 pts; 63% BCT and 37% No BCT

Han K et al. Int J Rad Onc BP 2013
Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

Kari Tanderup, PhD,*,† Patricia J. Eifel, MD,‡ Catheryn M. Yashar, MD,§ Richard Pötter, MD,‖ and Perry W. Grigsby, MD*
Outline

- External beam radiation therapy (IMRT/3D)
- Brachytherapy
- Can IMRT replace brachytherapy?
- Surgery or Chemoradiation?
- Optimal chemoradiation
- Role of surgery after chemoradiation
- Postoperative treatment
Radical Sx vs Definitive Radiation

343 pts; Stage IB, IIA; Radical Hx (± RT) vs Definitive RT

Londoni F et al. The Lancet 1997
Radical Hysterectomy

GOG 141

Eddy G. et al Gyn Oncol 2007
CTRT Metaanalysis/GOG 141

J Clin Oncol 2008/Gyn Oncol 2007
General Facts about chemotherapy

- Chemotherapy is typically single agent cisplatin
- Delivered weekly during external RT
- **NO** CT during brachytherapy
- Drugs other than Cisplatin failed to show superiority
- Adjuvant CT is gaining momentum particularly for high risk patients
CTRT vs RT: Metaanalysis

13 trials

CTRT Metaanalysis J Clin Oncol 2008
Cisplatin vs. Cis-Gemcitabine

Wang CC et al. Gyn Oncology 2015

P=0.71
Cisplatin vs. Paclitaxel

Geara F et al. Radiat Oncol 2010
Cisplatin vs. Cis-Tirapazamine

Cisplatin vs. IFN-Retinoic Acid

Chittaranjan National Cancer Institute; India

P=0.08

Cisplatin

Cis-IFN-RA

Grade 3-4 acute toxicities increase with CTRT

2-10 fold increase in leucopenia \( p<0.001 \)
3-10 fold increase in thrombocytopenia \( p=0.005 \)
2 fold increase in GI toxicity \( p<0.001 \)

Late complications were not sufficiently studied with CTRT; but the data is not in favor of a major increase of these late effects

Kirwan JM, et al. Radiother Oncol. 2003
CTRT metaanalysis, J Clin Onc 2008
## Late complications: RT data

[@10 yrs; ≥ Grade III]

<table>
<thead>
<tr>
<th>Complication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RT complication</td>
<td>12.3%</td>
</tr>
<tr>
<td>Rectal</td>
<td>3.4%</td>
</tr>
<tr>
<td>Fistula</td>
<td>1.7%</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>2.3%</td>
</tr>
<tr>
<td>Urinary tract excluding US</td>
<td>3.9%</td>
</tr>
<tr>
<td>Ureteral stricture</td>
<td>0%</td>
</tr>
</tbody>
</table>

Late complications: RT data

Is there a need for adjuvant RT?

15 trials

CTRT $\rightarrow$ CT
CTRT
RT

CTRT Metaanalysis J Clin Oncol 2008
Adjuvant Multinational study

CTRT-CT

CT = Cis-Gem

CTRT

CT = Cis alone

P = 0.023

Gr 3-4 toxicity: 86.5% vs 46.5%

Adjuvant Thai study

1988-1994; 926 pts; Randomized

CT = MMC-5FU

CTRT->CT
CTRT
RT
RT->CT

RTOG 1174 Study (outback trial)

Gynecologic Cancer InterGroup (GCIG)
Australia New Zealand Gynecological Oncology Group (ANZGOG)
Australia & New Zealand, USA, Saudi Arabia, and Canada

Arm 1: standard cisplatin-based chemo-radiation
Arm 2: Same followed by 4 cycles of carboplatin and paclitaxel CT

Opened: 2011
Target: 780 patients

Linda R. Mileshkin et al. ASCO 2014
Outline

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- Optimal chemoradiation
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- Postoperative treatment
CTRT-Brachy Vs CTRT-Radical Hx

2004-2009; 211 pts (IB2-IIB); CTRT; then randomized

CT = Cis-Gem

CTRT-BCT – SX vs CTRT-BCT

2003-06; IB2-II; CTRT-BCT; CR (PE-MRI) randomized

Disease Free survival

Morice P. et al. Oncologist 2012
Postoperative RT and CTRT

- Positive nodes
- Positive Parametria
- Positive margins

If all negative, look for the Sedlis criteria (GOG 92)

<table>
<thead>
<tr>
<th>LVS1</th>
<th>Stromal Invasion</th>
<th>Tumor Size (cm) (Determined by clinical palpation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>+</td>
<td>Middle 1/3</td>
<td>( \geq 2 )</td>
</tr>
<tr>
<td>+</td>
<td>Superficial 1/3</td>
<td>( \geq 5 )</td>
</tr>
<tr>
<td>-</td>
<td>Middle or Deep 1/3</td>
<td>( \geq 4 )</td>
</tr>
</tbody>
</table>
Postoperative CTRT

GOG 109; 278 patients

Overall survival

Take home messages

• Chemoradiation for advanced carcinoma of the cervix is a well established standard of care
• Single agent Cisplatin remains the best concurrent chemotherapy at present
• The role of adjuvant chemotherapy is not fully established. A phase III trial is in progress
• Brachytherapy is essential for an optimal local disease control and survival
• Hysterectomy is not better than BCT AND is not needed after CTRT+ brachytherapy; BUT may be helpful when brachy is not available
Endometrium
General facts and principles

- Surgery is the mainstay of treatment
- RT is an adjuvant therapy
- RT Reduces Vaginal recurrences
- RT Reduces Pelvic recurrences
- CT is effective in advanced disease
- Recurrences increase with stage, pathology, and LN involvement
Risk stratification

Low risk
- Stage IA, G 1-2

Intermediate risk
- Stage IA G3, IB G1-2

High intermediate risk
- IB G3; Age>70; LVSI; Low uterine segment

High risk
- Advanced stage; aggressive pathology
## Pattern of failure (stage I)

<table>
<thead>
<tr>
<th></th>
<th>Vagina</th>
<th>Pelvis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>High intermediate risk</strong></td>
<td>20%</td>
<td>6%</td>
</tr>
</tbody>
</table>

PORTEC 1; Creutzberg C. et al: Lancet 2000; IJROBP 2011  
## Randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Exp</th>
<th>Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aadlers S/BT</td>
<td>RT vs NAT</td>
<td>1980</td>
<td></td>
</tr>
<tr>
<td>Portec 1 S</td>
<td>RT vs NAT</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>GOG 99 S</td>
<td>RT vs NAT</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Astec/EN5 S (BT)</td>
<td>RT vs NAT</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Portec 2 S</td>
<td>RT vs BT</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Swedish 1 (LR) S</td>
<td>BT vs NAT</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Swedish 2 S/RT</td>
<td>BT vs NAT</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Metaanalysis</td>
<td>Combined</td>
<td>Combined</td>
<td>2012</td>
</tr>
</tbody>
</table>
### Results (EBRT vs no EBRT)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No</th>
<th>Yes</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>15.1</td>
<td>14.9</td>
<td>0.99 (0.82 to 1.20)</td>
</tr>
<tr>
<td>DSS</td>
<td>7.8</td>
<td>7.5</td>
<td>0.96 (0.72 to 1.28)</td>
</tr>
<tr>
<td>LRF</td>
<td>7.5</td>
<td>2.7</td>
<td>0.36 (0.25 to 0.52)</td>
</tr>
<tr>
<td>Acute Toxicity</td>
<td>0.4</td>
<td>19</td>
<td>4.68 (1.35 to 16.2)</td>
</tr>
<tr>
<td>Late Toxicity</td>
<td>1.4</td>
<td>3.6</td>
<td>2.58 (1.61 to 4.11)</td>
</tr>
</tbody>
</table>

Kong A et al. Cochrane 2012
Results (EBRT vs no EBRT)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No</th>
<th>Yes</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS (all)</td>
<td>7.8</td>
<td>7.5</td>
<td>HR 0.96 (0.72 to 1.28)</td>
</tr>
<tr>
<td>DSS (LR)</td>
<td>2.3</td>
<td>6.1</td>
<td>2.64 (1.05 to 6.66)</td>
</tr>
<tr>
<td>DSS (IR)</td>
<td>6.7</td>
<td>6.9</td>
<td>1.03 (0.70 to 1.51)</td>
</tr>
<tr>
<td>DSS (HR)</td>
<td>21.4</td>
<td>17.9</td>
<td>0.84 (0.51 to 1.40)</td>
</tr>
</tbody>
</table>
Survival (EBRT vs no EBRT)

RT vs nothing

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total (EBRT)</th>
<th>Total (No EBRT)</th>
<th>Total Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 99</td>
<td>-0.15</td>
<td>0.25</td>
<td>190</td>
<td>202</td>
<td>15.0%</td>
<td>0.86 [0.53, 1.40]</td>
</tr>
<tr>
<td>PORTEC-1</td>
<td>0.2</td>
<td>0.2</td>
<td>354</td>
<td>360</td>
<td>23.5%</td>
<td>1.22 [0.83, 1.81]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>544</td>
<td>562</td>
<td>38.5%</td>
<td>1.06 [0.76, 1.48]</td>
</tr>
</tbody>
</table>

RT vs nothing or BT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total (EBRT)</th>
<th>Total (No EBRT)</th>
<th>Total Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTEC/EN.5 (1)</td>
<td>0.05</td>
<td>0.175</td>
<td>452</td>
<td>453</td>
<td>30.7%</td>
<td>1.05 [0.75, 1.48]</td>
</tr>
<tr>
<td>Sorbe 2011 (2)</td>
<td>-0.14</td>
<td>0.23</td>
<td>264</td>
<td>263</td>
<td>17.8%</td>
<td>0.87 [0.55, 1.36]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>716</td>
<td>716</td>
<td>48.4%</td>
<td>0.98 [0.75, 1.29]</td>
</tr>
</tbody>
</table>

RT vs BT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Total (EBRT)</th>
<th>Total (VBT)</th>
<th>Total Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORTEC-2 (3)</td>
<td>-0.16</td>
<td>0.268</td>
<td>214</td>
<td>213</td>
<td>13.1%</td>
<td>0.85 [0.50, 1.44]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>214</td>
<td>213</td>
<td>13.1%</td>
<td>0.85 [0.50, 1.44]</td>
</tr>
</tbody>
</table>

Kong A et al. Cochrane 2012
What is then the benefit from adjuvant RT?

- RT Reduces **Vaginal** recurrences
- RT Reduces **Pelvic** recurrences
- Biggest effect in **high intermediate** risk patients
High Intermediate Risk patients

**PORTEC 2 study**

427 patients with IB G3; IB G2 ≥60; IIA
TAHBSO: Randomized: Pelvic RT vs BT

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>BT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vag relapse</td>
<td>1.6</td>
<td>1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Pelvic rec</td>
<td>0.5</td>
<td>1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Both</td>
<td>2.1</td>
<td>5.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Acute GI (1-2)</td>
<td>54</td>
<td>12.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Late GI (3)</td>
<td>1.3</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Nout RA. et al: Lancet 2010
Take home messages

- **Surgery is the mainstay** of the treatment of endometrial cancer
- **Pelvic RT** and/or vaginal cuff brachytherapy provide better pelvic disease control but without impact on survival
After adequate radical surgery for stage I endometrial cancer:

- **Low risk** disease needs no additional treatment
- **Intermediate risk** disease (LIR and HIR) can be treated by vaginal brachytherapy alone
- **High risk disease** (pap serous, clear cell, stage II) may benefit from both EBRT and vaginal BT

**Take home messages**