Update on the management of gynecologic cancers

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University of Texas, MD Anderson Cancer Center
Disclosures

Investigator initiated study support from Astrazeneca
Learning objectives

• To identify the optimal adjuvant strategy for patients with uterine carcinoma

• To identify the optimal treatment strategy for early and locally advanced cervical carcinoma

• To apply image guided techniques for the management of cervical carcinoma

• To apply 3D contouring in clinical practice for vulvar carcinoma
Management of endometrial cancer
Epidemiology

• Main risk factors:
  • Obesity, nulliparity, tamoxifen,
  • Unopposed estrogen
  • Diabetes, hypertension
  • Lynch syndrome

• Protective factors
  • Breastfeeding, smoking, physical activity

• ~70% diagnosed at early stage
Type of uterine cancer

• **Type I**
  - Favorable prognosis
  - 80% of endometrial carcinomas
  - Endometrioid histology grade 1 or 2
  - Estrogen responsive
  - May be preceded by intraepithelial neoplasm
  - Microsatellite instability (MSI) ~1/3

• **Type II**
  - 10-20% of endometrial carcinomas
  - serous, clear cell, mucinous, grade 3 endometrioid carcinoma
  - Hormone independent
  - More aggressive
  - Rare MSI
  - Frequent tp53, PIK3CA mutations
Histologies

- **POLE:**
  - 6.4% of low grade
  - 17.4% of high grade

- **Hypermutated/MSI unstable**
  - 28.6% low grade
  - 54.3% high grade

- **Copy number low (endometrioid)**
  - 60% low grade endometrioid
  - 8.7% High grade endometrioid
  - 2.3% serous carcinomas
  - 25% mixed histology

- **Copy number high (serous like)**
  - Serous
  - 90% p53 mutations

FIGO Staging

1988

IA  Endometrium only
IB  ≤ 50% Invasion of myometrium
IC  > 50% Invasion of myometrium
IIA Cervix - Endocervical glands
IIB Cervix - Stromal invasion
IIIA Serosa / adnexa / cytology
IIIB Lower vagina
IIIC Pelvic or PA nodes
IVA Bladder or rectum
IVB Distant

2009

IA  Endometrium only
IB  ≤ 50% Invasion of myometrium
IC  > 50% Invasion of myometrium
II  Cervix - Stromal invasion
IIIA Serosa / adnexa /
IIIB Lower vagina
IIIC1 Pelvic nodes
IIIC2 Para-aortic nodes
IVA Bladder or rectum
IVB Distant
Types of hysterectomy

- Subtotal (supracervical)
- Total
- Radical
Lymphatic drainage

- Internal iliac nodes
- External iliac nodes
- Para-aortic nodes
- Sacral nodes
- Superficial inguinal nodes
## GOG-33: Grade and invasion vs. nodal metastases

<table>
<thead>
<tr>
<th>Depth</th>
<th>n</th>
<th>Grade 1 (180)</th>
<th>Grade 2 (288)</th>
<th>Grade 3 (153)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pelvic LN</td>
<td>Pelvic LN</td>
<td>Pelvic LN</td>
</tr>
<tr>
<td>Superficial</td>
<td>281</td>
<td>3 (3%)</td>
<td>7 (5%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Middle</td>
<td>115</td>
<td>0 (0%)</td>
<td>6 (9%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Deep</td>
<td>139</td>
<td>2 (11%)</td>
<td>11 (19%)</td>
<td>22 (34%)</td>
</tr>
</tbody>
</table>
### GOG-33: Relationship of Pelvic and Aortic Nodes

<table>
<thead>
<tr>
<th>Pelvic</th>
<th>Aorta</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Negative</td>
<td>551 (89%)</td>
<td>12 (2%)</td>
<td></td>
<td>563 (91%)</td>
</tr>
<tr>
<td>Positive</td>
<td>36 (6%)</td>
<td>22 (3%)</td>
<td></td>
<td>58 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>587 (95%)</td>
<td>34 (5%)</td>
<td></td>
<td>621 (100%)</td>
</tr>
</tbody>
</table>

- Positive pelvic nodes were associated with a high risk of positive para-aortic nodes (22/58 - 37%)
Surgical Guidelines at Mayo Clinic

• Bilateral pelvic and PA LND
  • PA dissection up to renal vessels
  • Excision of gonadal vessels at insertion (optional)
  • Omit lymphadenectomy if no disease beyond corpus and:
    1. Endometrioid (grade 1 or 2), MI ≤ 50%, PTD ≤ 2 cm, or
    2. Endometrioid and no MI (independent of grade and PTD)

Mariani et al, Gyn Onc 2008
Pelvic and PA nodal distribution

14% (50/349) + pelvic and/or PA nodes (Endometrioid only)

Pelvis and PA: 18/50 (36%)

Pelvis only: 24/50 (48%)

77% PA nodes above the IMA

PA only: 8/50 (16%)

Kumar et al, Gyn Onc 2014
PA nodes: as function of IMA

88% of +PA nodes above IMA
Endometrioid and non-endometrioid

12/34 (35%)
+PA nodes above IMA
ipsilateral PA nodes negative below IMA

18/34 (53%)
+PA nodes above and below IMA

4/34 (12%)
+PA nodes below IMA

Kumar et al, Gyn Onc 2014
Early stage, intermediate risk

Case presentation:

• 65 yo woman s/p TAH/BSO for a IA grade 2 endometrioid adenocarcinoma, no LVSI.

• Treatment options
  • Observation
  • Vaginal brachytherapy
  • EBRT
Surgico-pathologic risk factors

- Depth of myometrial invasion
- Cervical invasion
- Pathologic grade
- Histologic type
  - Higher risk: serous, clear cell, carcinosarcoma
- Tumor size
- Low uterine segment
Adjuvant Radiation Trials

Norwegian
PORTEC-1
GOG 99
PORTEC 2
ASTEC
Swedish
Norwegian (Aalders et al)

Eligibility:
- Clinical stage I
- TAH/BSO w/o LND
- No peritoneal washings

Regimen I
- Pelvic RT 40 Gy
- Midline block after 20 Gy

Regimen II
- No further therapy

Vaginal Brachytherapy 60 Gy (LDR) at surface

*Suspicious LNs could be sampled at surgeon’s discretion
Preoperative CT/MRI enlarged nodes NOT an exclusion criteria
## Norwegian (Aalders et al)

<table>
<thead>
<tr>
<th></th>
<th>No EBRT</th>
<th>+EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 yr Overall Survival</strong></td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Vaginal/Pelvic Recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 1-2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1/2 myometrium</td>
<td>4.0%</td>
<td>2.3%</td>
</tr>
<tr>
<td>&gt;1/2 myometrium</td>
<td>9.8%</td>
<td>9.4%</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1/2 myometrium</td>
<td>5.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>&gt;1/2 myometrium</td>
<td>19.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td><strong>Deaths from Cancer (G3)</strong></td>
<td>27.5%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>
GOG 99

Eligibility:
IB, IC
Occult II
TAH/BSO
Pelvic +/-PA
Nodal sampling
Peritoneal cytology

Pelvic RT
50.4 Gy/1.8 Gy fractions
No vaginal brachy

Randomize

No Adjuvant Therapy

*392 pts

Keys et al, Gyn Onc 2004
PORTEC-1 (Postoperative Radiation Therapy in Endometrial Cancer)

Eligibility:

Stage I:
Grade 1 >1/2 MI
Grade 2 any MI
Grade 3 <1/2 MI

No peritoneal washings

TAH/BSO without LND

Regimen I:
Pelvic RT only
46 Gy/2 Gy fx

Regimen II:
No adjuvant therapy

*Excluded patients with IC G3

Creutzberg, Lancet 2000
Overall Survival

PORTEC-1

GOG-99

Creutzberg, Lancet 2000

Keys et al, Gyn Onc 2004
Pelvic Recurrence

**PORTEC-1**

14% vs. 4%, $p < 0.001$

**GOG-99**

<table>
<thead>
<tr>
<th>Site</th>
<th>NAT</th>
<th>EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Recurrence</td>
<td>18(8.9%)</td>
<td>3(1.6%)</td>
</tr>
<tr>
<td>Vagina</td>
<td>13</td>
<td>2*</td>
</tr>
<tr>
<td>Pelvis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Vagina and pelvic</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
## Patterns of failure: PORTEC and GOG99

<table>
<thead>
<tr>
<th>5 year</th>
<th>EBRT</th>
<th>NAT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional recurrence</td>
<td>4.2%</td>
<td>13.7%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Vaginal recurrence</td>
<td>2.3%</td>
<td>10.2%</td>
<td>~67% of failures in vagina</td>
</tr>
<tr>
<td>Pelvic</td>
<td>2.0%</td>
<td>3.4%</td>
<td>~2/3rds the risk of recurrence in the vagina</td>
</tr>
</tbody>
</table>

### PORTEC

<table>
<thead>
<tr>
<th>Site</th>
<th>NAT</th>
<th>EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Recurrence 18</td>
<td>(8.9%)</td>
<td>3(1.6%)</td>
</tr>
<tr>
<td>Vagina</td>
<td>13</td>
<td>2*</td>
</tr>
<tr>
<td>Pelvis</td>
<td>4</td>
<td>~2</td>
</tr>
<tr>
<td>Vagina and pelvic 1</td>
<td>1</td>
<td>~2/3rds the risk of recurrence in the vagina</td>
</tr>
<tr>
<td>Distant Recurrence 13</td>
<td>(6.4%)</td>
<td>10(5.3%)</td>
</tr>
</tbody>
</table>
PORTEC-2 (Postoperative Radiation Therapy in Endometrial Cancer)

Eligibility:
1) Stage IC G1-2
2) Stage IB G3
3) IIA G1-2 or G3w/<50% myometrial invasion, any age

TAH/BSO without LNS*

Pelvic RT only
46 Gy/2 Gy fx

Randomize

VBT:
HDR: 7 Gy x 3 fractions
LDR: 30 Gy

*Suspicious LNs could be sampled at surgeon’s discretion

Excluded IC, G3

Nout, Lancet 2010

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
## PORTEC-2

<table>
<thead>
<tr>
<th></th>
<th>EBRT</th>
<th>VBT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 yr</td>
<td>5 yr</td>
<td></td>
</tr>
<tr>
<td>Vaginal Recurrence</td>
<td>4</td>
<td>3</td>
<td>0.74</td>
</tr>
<tr>
<td>5 yr %</td>
<td>1.6%</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>Pelvic recurrence</td>
<td>1</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Locoregional</td>
<td>5</td>
<td>10</td>
<td>0.17</td>
</tr>
<tr>
<td>recurrence</td>
<td>2.1%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>13</td>
<td>16</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>5.7%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>First failure type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal recurrence</td>
<td>2</td>
<td>1</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Pelvic recurrence</td>
<td>1</td>
<td>3</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>DFS</td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>78.1%</td>
<td>82.7%</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>79.6%</td>
<td>84.8%</td>
<td></td>
</tr>
</tbody>
</table>

*Median f/u of 45 months
## PORTEC-2: Toxicities

<table>
<thead>
<tr>
<th>N(%)</th>
<th>EBRT 214</th>
<th>VBT 213</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>74(35)</td>
<td>25(12)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>40(19)</td>
<td>1(1)</td>
<td></td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Grade 1</td>
<td>53(25)</td>
<td>41(20)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>4(2)</td>
<td>4(2)</td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal</strong></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Grade 1</td>
<td>11(5)</td>
<td>19(9)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>3(2)</td>
<td>8(4)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>13(6)</td>
<td>2(1)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>7(3)</td>
<td>0(0)</td>
<td></td>
</tr>
</tbody>
</table>
PORTEC 2: Conclusions

• Risk of recurrence is low in this group
  • Criticism: lower risk population than PORTEC-1
• Vaginal Brachytherapy is sufficient for this unstaged population:
  • IB/IC G1-2 >60
  • IIA G1-2 or G3w/<50% myometrial invasion
  • IBG3
• Side effects from VBT are low
## PORTEC-1 v PORTEC-2

<table>
<thead>
<tr>
<th></th>
<th>Observe</th>
<th>vs</th>
<th>EBRT</th>
<th>EBRT</th>
<th>vs</th>
<th>VBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>361</td>
<td></td>
<td>364</td>
<td>214</td>
<td></td>
<td>213</td>
</tr>
<tr>
<td>5 yr Vag RR%</td>
<td>10.2%</td>
<td></td>
<td>2.3%</td>
<td>1.9%</td>
<td></td>
<td>1.5%</td>
</tr>
<tr>
<td>5 yr Pelvic RR%</td>
<td>3.4%</td>
<td></td>
<td>2.0%</td>
<td>0.6%</td>
<td></td>
<td>3.3%</td>
</tr>
</tbody>
</table>

### Site of first relapse

<table>
<thead>
<tr>
<th></th>
<th>Observe</th>
<th>vs</th>
<th>EBRT</th>
<th>EBRT</th>
<th>vs</th>
<th>VBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 yr Overall Survival</td>
<td>85%</td>
<td></td>
<td>81%</td>
<td>79.6%</td>
<td></td>
<td>84.8%</td>
</tr>
<tr>
<td>5 yr DFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths due to Endometrial Ca (5/3 yr)</td>
<td>6%</td>
<td></td>
<td>9%</td>
<td>5.4%</td>
<td></td>
<td>6.5%</td>
</tr>
</tbody>
</table>
**High intermediate risk groupings:**

<table>
<thead>
<tr>
<th>GOG 99</th>
<th>PORTEC</th>
</tr>
</thead>
</table>
| Risk factors:  
  grade 2-3  
  LVSI  
  outer 1/3 MI | Age >60 yo: G1 or G2 ≥50% MI  
  G3 with <50% MI |
| Age ≥ 70 yrs with 1 risk factor  
 Age ≥ 50 yrs with 2 factors  
 Any age with all 3 factors | Any age: IIA G1 or G2  
 G3 with ≤50% MI |
## Intermediate risk endometrial carcinoma: phase III studies

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>Inclusion</th>
<th>Surgery</th>
<th>TX arms</th>
<th>LRR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwegian</td>
<td>540</td>
<td>I</td>
<td>TAH-BSO</td>
<td>VBT vs pelvic RT/VBT</td>
<td>7% vs 2% at 5 years</td>
<td>89% vs 91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>vs 2% at 5 years p&lt;0.01</td>
<td>5 years p=NS</td>
</tr>
<tr>
<td>PORTEC-I</td>
<td>714</td>
<td>IB G2-3 IC G1-2</td>
<td>TAH/BSO</td>
<td>NAT vs pelvic RT</td>
<td>14% vs 4% 5 years</td>
<td>85% vs 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
<td>vs 4% 5 years p&lt;0.001</td>
<td>5 years p=0.31</td>
</tr>
<tr>
<td>GOG 99</td>
<td>392</td>
<td>IB/IC occult II</td>
<td>TAH/BSO</td>
<td>NAT vs pelvic RT</td>
<td>12% vs 3% at 2 years</td>
<td>86% vs 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>vs 3% at 2 years p&lt;0.01</td>
<td>4 years p=0.56</td>
</tr>
<tr>
<td>ASTEC/EN5</td>
<td>905</td>
<td>IA/B G3, IC, II, serous/cc</td>
<td>TAH/BSO</td>
<td>NAT vs pelvic RT</td>
<td>7% vs 4% 5 years</td>
<td>84% vs 84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>vs 4% 5 years p&lt;0.01</td>
<td>5 years p=0.98</td>
</tr>
<tr>
<td>PORTEC-2</td>
<td>547</td>
<td>IB/IC G1-2 &gt;60 yrs IIA G1-2 II A G3 w/ &lt;50% MI</td>
<td>TAH/BSO</td>
<td>pelvic RT vs VBT</td>
<td>5.1% vs 2.1% 5 yrs</td>
<td>79.6% vs 84.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.17</td>
<td>vs 2.1% 5 yrs p=0.17</td>
<td>5 yrs p=0.57</td>
</tr>
<tr>
<td>Swedish</td>
<td>527</td>
<td>I with at least 1 RF: g3, ≥MI, DNA aneuploidy, nuclear g1-2</td>
<td>TAH/BSO</td>
<td>EBRT/VB vs VBT</td>
<td>1.5% vs 5% (p=0.013)</td>
<td>89% vs 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.548</td>
<td>vs 5% (p=0.013) p=0.548</td>
<td>5 years p=0.548</td>
</tr>
</tbody>
</table>
## High risk histologies, early stage: VB/chemo

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N</th>
<th>Inclusion</th>
<th>Survival</th>
<th>Total pelvic recurrence</th>
<th>Vaginal recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uterine serous and clear cell carcinoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFCI</td>
<td>2013</td>
<td>37</td>
<td>Stage I-II USC or CC</td>
<td>2 yo OS 100% 2 yr DFS 89.3%</td>
<td>5.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Mayo</td>
<td>2013</td>
<td>103</td>
<td>Stage I USC or CC</td>
<td>2 yo OS 79%</td>
<td>4.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2012</td>
<td>41</td>
<td>I-II USC</td>
<td>5 yo OS 90%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Carcinosarcoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayo</td>
<td>2015</td>
<td>33</td>
<td>Stage I-II CS</td>
<td>2 yo OS 79%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Penn/Iowa</td>
<td>2016</td>
<td>42</td>
<td>I-II CS</td>
<td>2 yo OS 85%</td>
<td>7.1%</td>
<td></td>
</tr>
</tbody>
</table>
PORTEC 1/2: Integrating Molecular and clinic-pathological factors

**Diagnosed high-intermediate stage I EC**

**Favorable**
- *POLE* mutation

**Unfavorable**
- Substantial LVS1
- >10% L1CAM expression
- p53-mutant expression

**Favorable**
- Microsatellite stable and
- *CTNNB1* exon 3 wild-type

**Intermediate**
- Microsatellite unstable or
- *CTNNB1* exon 3 mutation

---

Recurrence-free survival (%)

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Favorable</th>
<th>Intermediate</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>10</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Stelloo, Clin Cancer Research 2016
## Treatment Guidelines for Intermediate Risk: Staged

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner 1/3</td>
<td>None</td>
<td>None or IVRT*</td>
<td>IVRT</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>+/-IVRT*</td>
<td>IVRT or Pelvic RT*</td>
<td>IVRT or Pelvic RT</td>
</tr>
<tr>
<td>Outer 1/3</td>
<td>+/-IVRT*</td>
<td>IVRT or Pelvic RT*</td>
<td>IVRT or Pelvic RT*</td>
</tr>
</tbody>
</table>

*IVRT if myometrial invasion, LVSI present or age >60
High risk histology: uterine serous, clear cell, carcinosarcoma
## Treatment Guidelines for Intermediate Risk: Unstaged

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner 1/3</td>
<td>None</td>
<td>None or IVRT*</td>
<td>IVRT or Pelvic RT*</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>None or IVRT*</td>
<td>+/-IVRT or Pelvic RT*</td>
<td>IVRT or Pelvic RT*</td>
</tr>
<tr>
<td>Outer 1/3</td>
<td>+/-IVRT or Pelvic RT*</td>
<td>IVRT or Pelvic RT*</td>
<td>Pelvic RT</td>
</tr>
</tbody>
</table>

* Risk factors including age >70, LVSI, tumor size, depth of myometrial invasion
Key take home point:

• Upper vagina main site of LRR in early stage uterine cancer

• Vaginal brachytherapy alone for intermediate risk stage I uterine ca, endometrioid type

• Combined VB and chemo for high risk histologies, early stage
Vaginal brachytherapy

• Dose specification
  • 5 mm vs surface

• Length of vagina
  • Variable
  • 3-5 cm of upper vagina

• Applicators
  • Single channel vs multi-channel

• Treatment planning
  • 3D vs 2D
  • 3D allows for air gap assessment, normal tissue dose
# Vaginal brachytherapy: fractionation

## Monotherapy

<table>
<thead>
<tr>
<th>Dose</th>
<th>Rx point</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Gy x 3</td>
<td>5 mm</td>
</tr>
<tr>
<td>5 Gy x 5</td>
<td>5 mm</td>
</tr>
<tr>
<td>2.5 Gy x 5</td>
<td>5 mm</td>
</tr>
<tr>
<td>6 Gy x 5</td>
<td>Surface#</td>
</tr>
<tr>
<td>4 Gy x 6</td>
<td>Surface$</td>
</tr>
</tbody>
</table>

# MDA  
$BWH

## Post EBRT

<table>
<thead>
<tr>
<th>Dose</th>
<th>Rx point</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Gy x 3</td>
<td>Surface*</td>
</tr>
<tr>
<td>6 Gy x 2</td>
<td>Surface*</td>
</tr>
<tr>
<td>5 Gy x 2</td>
<td>Surface#</td>
</tr>
</tbody>
</table>

* RTOG 0921 and 0418  
# MDA
Vaginal brachy: fractionation

Eligibility:
Stage IA-IB
Grade 1-2

Regimen I:
5 Gy x 5 fractions
Over 8 days

Regimen II:
2.5 Gy x 5 fractions
Over 8 days

*IR-192, HDR, Dose Rx: 5 mm

Sorbe, IJROBP 2005
Vaginal brachy: fractionation

5 Gy per fx

2.5 Gy x fx

Sorbe, IJROBP 2005
High intermediate risk
Case presentation:

61 yo woman with no significant PMH with grade I endometrioid adenocarcinoma on biopsy. TAH/BSO/pelvic LND
- Endometrioid adenocarcinoma, FIGO grade 3, invasive to 1.7 cm to 1.9 cm of myometrium with LVSI
- Pelvic LN: 0/6 left, 0/9 right
- Ibgrade 3
Treatment options

• Vaginal brachytherapy

• VB + chemotherapy

• EBRT

• EBRT with chemotherapy (concurrent or adjuvant)
ASTRO Endometrial Cancer Guidelines

The role of postoperative radiation therapy for endometrial cancer: Executive Summary of an American Society for Radiation Oncology evidence-based guideline

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15Department of Radiation Oncology, University of California San Diego, San Diego, California

Klopp et al, PRO 2014

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
Key question #3A: Which women with early stage endometrial cancer should receive postop EBRT?

- Grade 3 with ≥ 50% myometrial invasion or cervical stromal invasion (Grade: strong recommendation, high quality evidence)

- Grade 1 or 2 with ≥ 50% myometrial invasion may also benefit if other risk factors such as age >60 years and/or LVSI (Grade: strong recommendation, high quality evidence)
PORTEC-1 (ICG3) Probability of Death

Creutzberg C L et al. JCO 2004;22:1234-1241
Risk of relapse is high: what about chemotherapy?
JGOG 2033

Eligibility:

Stage IC-IIIC with >50% Myometrial invasion

TAH/BSO + Pelvic/PA LNS

Regimen I: Pelvic RT only
45-50 Gy/2 Gy fx

Regimen II: CAP chemo
Adriamycin, Cylcophosphamide
Cisplatin x 3 cycles

*stage II-III <50%MI excluded

Susumu et al, Gyn Onc 2008
LIR: Age<70 G1/2 endometrioid adenocarcinoma

HIR:
1) Stage IC > age 70 or grade 3
2) Stage II or IIIA (+cytology), >50%MI
NSGO9501/EORTC55991 and MaNGO

Eligibility:
NSGO/EORTC
Surgical Stage I-II
IIIA+cytology
IIIC (+pelvic LN only)
(optional LND)

MaNGO
IIB, IIIA(only excluded), IIIC
(included PA nodes)

Serous/clear cell/anaplastic
Ineligible

1996-2007

Primary Endpoint: PFS

Regimen I:
Pelvic RT only
≥44 Gy
Optional VBT (39%)

RT→CT or CT→RT
VBT (44%)

NSGO/EORTC CT: initially AP
Later AP, TcP, TAP, TEcP

MaNGO CT: AP

Hogberg et al, Eur J Cancer 2010

ASTRO Annual Refresher Course  •  Fort Lauderdale Marriott Harbor Beach Resort & Spa  •  March 2-4, 2018  #REFRESHER18
NSGO9501/EORTC55991 and MaNGO Pooled PFS

- Probability
  - RT+CT: ---
  - RT: -

- Number at risk:
  - RT: 267, 231, 198, 165, 138, 104
  - RT+CT: 267, 242, 214, 195, 159, 113

- Years: 0, 1, 2, 3, 4, 5

- HR: 0.63 (95% CI: 0.44 - 0.89, p=0.009)

Hogberg et al, Eur J Cancer, 2010
# NSGO9501/EORTC55991 and MaNGO Pooled PFS

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>n</th>
<th>RT-CT better</th>
<th>RT-better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled data</td>
<td>0.63</td>
<td>0.44-0.89</td>
<td>534</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSGO</td>
<td>0.70</td>
<td>0.43-1.15</td>
<td>317</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td>0.44</td>
<td>0.17-1.15</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MaNGO</td>
<td>0.61</td>
<td>0.33-1.12</td>
<td>156</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original NSGO/EORTC protocol</td>
<td>0.65</td>
<td>0.39-1.10</td>
<td>233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSGO/EORTC Amendment 1</td>
<td>0.56</td>
<td>0.26-1.21</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSGO/EORTC Amendment 2</td>
<td>0.72</td>
<td>0.28-1.85</td>
<td>61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hogberg et al, Eur J Cancer, 2010
### High intermediate risk groupings:

<table>
<thead>
<tr>
<th>GOG 99</th>
<th>PORTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors:</strong></td>
<td><strong>Age &gt;60 yo:</strong> G1 or G2 ≥50% MI</td>
</tr>
<tr>
<td>grade 2-3</td>
<td>G3 with &lt;50% MI</td>
</tr>
<tr>
<td>LVSI</td>
<td>Any age: IIA G1 or G2</td>
</tr>
<tr>
<td>outer 1/3 MI</td>
<td>G3 with ≤50% MI</td>
</tr>
<tr>
<td><strong>Age ≥ 70 yrs with 1 risk factor</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age ≥ 50 yrs with 2 factors</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Any age with all 3 factors</strong></td>
<td></td>
</tr>
</tbody>
</table>
GOG249

Eligibility:

Stage I endometrioid type
Age ≥ 18 with 3 RF
Age ≥ 50 with 2 RF
Age ≥ 70 with 1 RF

Stage II
Stage I-II serous and clear cell

*high-intermediate risk uterine risk factors (endometrioid):
G2-3, outer ½ depth of MI, LVSI
89% lymphadenectomy

Pelvic RT only
46 Gy/2 Gy fx

VBT
Carboplatin/paclitaxel

M. Randall, ASTRO 2017 presentation
GOG249

Relapse free survival

Overall Survival

Randall et al ASTRO 2017 presentation
Toxicities: GOG249

• Acute toxicity ≥grade 3
  • EBRT 11% vs VB/C 64%

• Late toxicities ≥grade 3
  • EBRT 13% vs VB/C 12%
Summary and Key Points

• Consider pelvic radiotherapy for HIR staged based on GOG99 risk factors and multiple risk factors in unstaged (LVSI, high grade, deep myometrial invasion, large tumor size)

• No evidence that addition of chemotherapy improves survival in this subset
Treatment technique
3DCRT

L4/L5
Common iliac bifurcation

Outer obturator foramen

Mid-pubis or 4 cm below vaginal apex

Tip of pubis

S3/S4

Courtesy Ann Klopp
Eligibility

Women with endometrial or cervical cancer requiring post-op pelvic RT or chemoRT

Stratification Factors

XRT Dose: 45 Gy, 50.4 Gy

Chemo: No chemo, 5 cycles of weekly cisplatin at 40mg/m²

Disease Site: Endometrial, Cervix

TIME-C Schema

Courtesy Ann Klopp
Treatment planning

IMRT planning
- Nodal CTV
  - RTOG atlas
- Vaginal
  - ITV w bladder full and empty
- 7mm PTV expansion
- OARs: Bone marrow, bowel, bladder, rectum

Standard RT
**EPIC Bowel Score**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 3 of RT</th>
<th>Week 5 of RT</th>
<th>4-6 weeks post-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>128</td>
<td>113</td>
<td>111</td>
<td>102</td>
</tr>
<tr>
<td>4 Field</td>
<td>148</td>
<td>132</td>
<td>130</td>
<td>125</td>
</tr>
</tbody>
</table>

*p-value = 0.048*
IMRT contouring

http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx
Nodal contouring
Nodal contouring

Obturator foramen
Contouring of Vaginal ITV

- Empty rectum
  - Vaginal ITV extends anteriorly into bladder by at least 2 cm
- Distended rectum
  - Vaginal ITV extends posteriorly to within 1.5 cm of posterior rectal wall

Eifel and Klopp, Gynecologic Radiation Oncology 2017, LWW
Advanced Endometrial Cancer
Case presentation

52 yo woman with IIIC1 endometrioid adenocarcinoma of the uterus s/p TLH, BSO and bilateral SLN mapping

• Pathology:
  • 4.1 cm FIGO grade 2 EAC
  • 7/19 mm invasion
  • +LVSI
  • SLN (1/2)
    • positive right external iliac SLN
    • negative left obturator SLN
## Randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Stage</th>
<th>Treatment</th>
<th>LR</th>
<th>Distant recurrence</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 122*</td>
<td>422</td>
<td>III/IVA</td>
<td>WAI vs AP</td>
<td>WAI 13%</td>
<td>38%</td>
<td>WAP 38% AP 32% WAI 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WAP 38%</td>
<td>WAP 38%</td>
<td></td>
<td>AP 53% HR0.68 (95% CI=0.52-0.89)</td>
</tr>
<tr>
<td>GOG 184</td>
<td></td>
<td>III/IVA</td>
<td>EBRT→AP vs EBRT→TAP</td>
<td>10%</td>
<td>30%</td>
<td>AP 56% TAP 59%</td>
</tr>
<tr>
<td>JGOG2033</td>
<td>385</td>
<td>IC-IIIC</td>
<td>WPRT vs CAPx3</td>
<td>WPRT 6.7%</td>
<td>13.5%</td>
<td>WPRT 85.3% CAP 81.8%</td>
</tr>
<tr>
<td>Milan</td>
<td>345</td>
<td>ICg3 IIa-bG3 with ≥MI</td>
<td>EBRT vs CAP x 5</td>
<td>EBRT 12%</td>
<td>26%</td>
<td>EBRT 69% CAP 66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td></td>
<td>CAP 15%</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

*included 25% serous and clear cell, stage IV, and residual tumor up to 2 cm
GOG 122

Eligibility:
Stage III or IV
No single site of residual tumor > 2 cm
Any histology

* Nodal sampling optional
+ PA nodes → required scalene biopsy and chest CT

WAI (AP/PA)
30 Gy/20 fx
15 Gy pelvic boost

Doxorubicin 60 mg/m2
Cisplatin 50 mg/m2
Q3 weeks x 7 cycles → cisplatin x 1

Randall et al, JCO 2006
GOG 122

PFS

Overall survival

Randall et al, JCO 2006
# GOG 122: Patterns of failure

<table>
<thead>
<tr>
<th></th>
<th>WAI</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>13% (27/202)</td>
<td>18% (34/194)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>16% (33/202)</td>
<td>14% (27/194)</td>
</tr>
<tr>
<td>Extra-abdominal/Liver</td>
<td>22% (45/202)</td>
<td>18% (34/194)</td>
</tr>
<tr>
<td>Distant (exclude liver)</td>
<td>19%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Randall et al, JCO 2006
GOG258

Eligibility:
Surgical stage III or IVA EC
Stage I/II cc/serous + cytology

Regimen 1:
Cis 50 mg/m2 IV x2
and EBRT 45 Gy +/-VB +/- boost
→ Carbo AUC5/paclitaxel 175 mg/m2 X 4

Regimen 2:
Carbo AUC6/paclitaxel 175 mg/m2 X 6

Ineligible:
Residual tumor after surgery >2 cm
Carcinosarcoma
Recurrent EC

Matei et al, ASCO 2017
GOG258

RFS

Proportion Alive, Recurrence-Free

Events Total HR 90% CI
C-RT 132 370 0.90 (.74, 1.10)
CT 139 366

Overall Survival

Events Total
C-RT 86 370
CT 79 366

Matei et al, ASCO 2017
GOG 258: Cumulative incidence of recurrence

**Vaginal recurrence**
- Incidence at 5 years: 3% (C-RT) vs. 7% (CT)

**Pelvic and PA recurrence**
- Incidence at 5 years: 10% (C-RT) vs. 19% (CT)

---

Matei et al, ASCO 2017
GOG 258: Cumulative incidence of recurrence

Distant recurrence

Cumulative Proportion

Months from Study Activation

Distant recurrence incidence at 5 years

C-RT: 27%
CT: 21%

Matei et al, ASCO 2017
GOG 258: Summary

• No difference in OS or RFS with CRT vs Chemo

• Higher local relapse with chemo 26% vs 13%
  • Boost was allowed by at discretion of MD

• 25% in CRT did not receive full chemo
PORTEC-3 (Postoperative Radiation Therapy in Endometrial Cancer)

Eligibility:
Stage IAg3 with LVSI
Stage IBg3
Stage II or III
Stage I-III USC/CC(>25%)

*No residual macroscopic tumor after surgery

De Boer et al, Lancet Oncology 2018
# Treatment characteristics

<table>
<thead>
<tr>
<th></th>
<th>RT alone (N=330)</th>
<th>CTRT (N=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of surgery (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAH or TLH/BSO</td>
<td>41.8%</td>
<td>42.4%</td>
</tr>
<tr>
<td>TH/BSO plus LND</td>
<td>58.2%</td>
<td>57.6%</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>grade 1</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>grade 2</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>grade 3</td>
<td>27%</td>
<td>29%</td>
</tr>
<tr>
<td>Serous</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Clear cell</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Chemo completion (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 cisplatin</td>
<td>-</td>
<td>93%</td>
</tr>
<tr>
<td>4 carboplatin/paclitaxel</td>
<td>-</td>
<td>80%-72%</td>
</tr>
</tbody>
</table>

De Boer et al, Lancet Oncology 2018
5 yr survival (OS and FFS)

A

Overall survival (%)

Number at risk

Radiotherapy
330
(0)

Radiotherapy
319
(1)

Radiotherapy
299
(1)

Radiotherapy
266
(11)

Radiotherapy
202
(60)

Radiotherapy
135
(123)

Chemoradiotherapy
330
(0)

Chemoradiotherapy
316
(0)

Chemoradiotherapy
295
(1)

Chemoradiotherapy
261
(18)

Chemoradiotherapy
208
(71)

Chemoradiotherapy
143
(130)

B

Failure-free survival (%)

Number at risk

Radiotherapy
330
(0)

Radiotherapy
286
(1)

Radiotherapy
257
(1)

Radiotherapy
223
(10)

Radiotherapy
178
(50)

Radiotherapy
119
(105)

Chemoradiotherapy
330
(0)

Chemoradiotherapy
304
(0)

Chemoradiotherapy
275
(1)

Chemoradiotherapy
244
(16)

Chemoradiotherapy
192
(63)

Chemoradiotherapy
126
(120)

5 yr OS 81.8% v 76.7% CRT vs RT

5 yr FFS 75.5% v 68.6% CRT vs RT

de Boer, Lancet Oncology 2018
### Recurrence patterns

<table>
<thead>
<tr>
<th></th>
<th>CTRT</th>
<th></th>
<th>RT</th>
<th></th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Vaginal</td>
<td>1</td>
<td>0.30%</td>
<td>1</td>
<td>0.3%</td>
<td>0.99</td>
<td>0.999</td>
</tr>
<tr>
<td>recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Pelvic</td>
<td>3</td>
<td>0.95%</td>
<td>5</td>
<td>1.5%</td>
<td>0.60</td>
<td>0.478</td>
</tr>
<tr>
<td>recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>79</td>
<td>23.1%</td>
<td>97</td>
<td>29.7%</td>
<td>0.77</td>
<td>0.077</td>
</tr>
<tr>
<td>(total)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any pelvic</td>
<td>16</td>
<td>4.9%</td>
<td>31</td>
<td>9.2%</td>
<td>0.51</td>
<td>0.026</td>
</tr>
<tr>
<td>recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

De Boer, Lancet Oncology 2018
Stage III (OS and FFS)

**Overall survival in stage III (%)**

- **chemoRT**
- **RT alone**

**Time since randomisation (years)**

<table>
<thead>
<tr>
<th>Number at risk (number censored)</th>
<th>Radiotherapy</th>
<th>Chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>143 (0)</td>
<td>152 (0)</td>
</tr>
<tr>
<td></td>
<td>137 (1)</td>
<td>145 (0)</td>
</tr>
<tr>
<td></td>
<td>123 (1)</td>
<td>133 (1)</td>
</tr>
<tr>
<td></td>
<td>106 (4)</td>
<td>115 (8)</td>
</tr>
<tr>
<td></td>
<td>81 (23)</td>
<td>98 (26)</td>
</tr>
<tr>
<td></td>
<td>49 (53)</td>
<td>69 (52)</td>
</tr>
</tbody>
</table>

- $P_{\text{log-rank}}=0.13$, HR 0.71 (95% CI 0.45–1.11)

**Failure-free survival in stage III (%)**

- **chemoRT**
- **RT alone**

**Time since randomisation (years)**

<table>
<thead>
<tr>
<th>Number at risk (number censored)</th>
<th>Radiotherapy</th>
<th>Chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>143 (0)</td>
<td>152 (0)</td>
</tr>
<tr>
<td></td>
<td>116 (1)</td>
<td>139 (0)</td>
</tr>
<tr>
<td></td>
<td>95 (1)</td>
<td>122 (0)</td>
</tr>
<tr>
<td></td>
<td>82 (5)</td>
<td>106 (8)</td>
</tr>
<tr>
<td></td>
<td>67 (18)</td>
<td>88 (23)</td>
</tr>
<tr>
<td></td>
<td>40 (44)</td>
<td>57 (50)</td>
</tr>
</tbody>
</table>

- $P_{\text{log-rank}}=0.031$, HR 0.66 (95% CI 0.45–0.97)

De Boer, Lancet Oncology 2018
QOL

De Boer et al, Lancet 2016

Presented By Stephanie de Boer at 2017 ASCO Annual Meeting

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
PORTEC-3: summary

• 5 yr FFS better with CRT vs RT
  • Stage III HR 0.66, absolute 11% improvement in FFS
  • no difference in stage I-II

• Serous carcinoma
  • Lower FFS and OS than other subtypes
  • 5 yr FFS 58% v 48% CRT vs RT, p=0.11

• Higher incidence of AEs and decreased QOL with CRT
Role of ChemoRT in stage IIIC

Secord et al, Gyn Onc 2013
Summary and Key Points

• Lack of survival benefit to combined CRT vs RT vs chemo alone in randomized studies

• Combined modality therapy in patients with locally advanced endometrial cancer

• Greatest benefit in FFS with CRT in stage III
  • CRT in stage IIIC
  • Other stage III dependent on uterine risk factors and/or risk of LRR

• Limited rationale for CRT in high risk stage I/II endometrioid
  • Trend towards improvement with CRT in serous histology
Case presentation

52 yo woman with IIIC1 endometrioid adenocarcinoma of the uterus s/p TLH, BSO and bilateral SLN mapping

- Pathology:
  - 4.1 cm FIGO grade 2 EAC
  - 7/19 mm invasion
  - +LVSI
  - SLN (1/2)
    - positive right external iliac SLN
    - negative left obturator SLN
## Risk of PA nodal involvement w/+PLN

<table>
<thead>
<tr>
<th>Grade</th>
<th>MI≤50%</th>
<th>MI≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1%</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>0%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Kumar et al Gyn Onc 2014
PA nodes: as function of IMA

88% of +PA nodes above IMA
Endometrioid and non-endometrioid

12/34 (35%)
+PA nodes above IMA
ipsilateral PA nodes negative below IMA

18/34 (53%)
+PA nodes above and below IMA

4/34 (12%)
+PA nodes below IMA

Kumar et al Gyn Onc 2014
Sentinel lymph node: Approach to PA LN?

- Postoperative imaging
- Re-operation to address PA LN (controversial)

- Extended field RT
  - Positive PA nodes on imaging
  - Proximal iliac lymph node metastases
  - High grade, deeply invasive
  - Multiple positive SLNs
Management of Cervical Cancer
Global Statistics

• 2nd most common cancer in the developing world
• ~500,000 new cases worldwide
• AIDS defining in the setting of HIV
• ~10,500 new cases per year in US
Transient HPV infection

>90% Clearance

Progression/regression

CIN 1

CIN 2

CIN 3

Invasive Cervical Cancer

Cofactors for Persistence:
Smoking
Increasing age
HPV type
Mutagens
Immunosuppression
Inflammation
Hormones
Genetic Factors

Kahn J, NEJM 2009; 361:271-278
HPV

- **High Risk Types:**
  - 16 and 18 (responsible for 70% of cervical cancers)
  - 31 and 45 (responsible for 10%)
  - Others: 33, 35, 39, 51, 52, 56, 58, 59, 68, 73, and 82

- **Low risk types:**
  - 6 and 11 (genital warts)
HPV Vaccine

- **Gardasil (Merck): HPV 6, 11, 16, 18**
  - 6, 11 cause 90% of genital warts
  - 16, 18 cause 70-80% of cervical cancers, and 20-25% H&N cancers, as well as vaginal, penile, anal

- **Cervarix (GSK): HPV 16, 18**
  - Approved 2009

- **Timing:**
  - FDA approved for women age 9-26
  - Extended to boys 9-26 in 9/09
  - Seeking approval for women aged 27-45
  - Given in 3 injections at 0, 2, and 6 months

- 32% of women eligible have received all 3 doses
Histologic Subtypes

- Squamous cell carcinoma (85%)
- Adenocarcinoma (10%)
- Clear cell carcinoma (associated with in utero DES exposure) 1%
- Other (rare)
  - Sarcoma
  - Lymphoma
  - Neuroendocrine carcinoma
Prognostic Factors

• Treatment related:
  • Overall treatment time
  • Use of brachytherapy
  • Chemotherapy

• Patient related
  • Hgb status
  • Smoking

• Tumor related
  • Posthysterectomy (LVSI, size, stromal invasion)
  • Nodal status
Staging and Workup
FIGO Staging 2009

IIA1 ≤4 cm

IIA2 >4 cm
FIGO Clinical Staging

- Pelvic exam-under anesthesia
- Cystoscopy
- Proctoscopy
- Chest Xray
- Intravenous Pyelogram
- Skeletal Survey
FIGO Clinical Staging-Not allowed

• CT

• MRI

• PET/CT

• Exploratory Surgery
Patterns of Spread
## Risk of Lymph Node Metastases

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pelvic LN</th>
<th>PA LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>IA2</td>
<td>6-7%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>IB</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>IIB</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>III</td>
<td>45%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Determining Extent of Primary Tumor

• Pelvic examination
  • Staging Accuracy: 47%
    • Bipat et al, Gyn Onc 2003

• MRI vs CT
  • Staging Accuracy: 86%
  • MR is superior to CT for detecting uterine body involvement/PM invasion (ACRIN 6651/GOG 183)
    • JCO 2006
  • MR superior in detecting vaginal extension
Determining of Primary disease: MR
Determining Extent of LN/Distant Metastases: Role of FDG-PET/CT
CT vs PET for PA node detection

CT+, PET+    CT-, PET-

CT-, PET+

p < 0.0001

Grigsby et al JCO 2001
DSS by FDG PET/CT Nodal Status

Kidd et al, JCO 2010

Recurrence-Free Survival (probability)

Time (months)

None
Pelvic
Para-aortic
Supraclavicular

$P < .001$
DSS by FDG PET/CT Nodal Status

Stage II

Stage III

Kidd et al, JCO 2010
Treatment

• Surgery

• Radiation Therapy

• Chemotherapy
Surgical Management: Early stage IA

• LEEP (Loop electrosurgical excision procedure)
• Conization
• Cryotherapy
• Radical trachelectomy
  • 3-6% recurrence rate when limited to <2 cm (-nodes, -LVSI)
• Radical hysterectomy: IA2
Surgery

• Radical Hysterectomy:
  ▪ Class II hysterectomy generally sufficient
  ▪ Lymphadenectomy:

Partial mobilization of the ureters.

<table>
<thead>
<tr>
<th>Uterosacral ligaments ligated midway b/t uterus and sacrum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial mobilization of the ureters</td>
</tr>
<tr>
<td>Medial half of cardinal ligament excised</td>
</tr>
<tr>
<td>Upper third of vagina excised</td>
</tr>
<tr>
<td>Uterine vessels ligated medial to ureters.</td>
</tr>
</tbody>
</table>

- Stage IA2 or small IB1:
  - low risk of node + (2 - 8%)
  - pelvic LN resection only (no
    - Exception: pelvic + paraaortic LN resection if PET/CT data that they may be positive.)
Treatment for Stage IB

• Radical hysterectomy and pelvic +/- PA LND

• Radiotherapy
  • EBRT and brachytherapy: 85-90 Gy to point A

HRCTV
Primary radiotherapy vs Radical Hysterectomy

469 Pts 1986-1991
Stages IB-IIA

Radical surgery
Class III rad hyst

RT 40-53 Gy
1.8-2 Gy
ICI x1
Pt A dose 70-90 Gy

Stage pT2b/+LN/+SM

Adj XRT
50.4 Gy to pelvis
PA to 45 Gy if PA nodes +

Landoni et al, Lancet 1997
Primary radiotherapy vs Radical Hysterectomy
Landoni et al, Lancet 1997

• Median follow-up 87 months
• No difference in survival/LC
• Adjuvant RT
  • 64% of patients overall
  • IB1 54%, IB2 88%
  • Higher rates of urologic complications with combined surgery/adjuvant RT
Role of Adjuvant Radiotherapy
Role of adjuvant radiotherapy

• Who needs adjuvant pelvic RT?
  • GOG92

• Who needs adjuvant pelvic chemo/RT?
  • GOG109
GOG 92: LN Negative
Role of adjuvant post-operative radiotherapy

277 Pts Stage IB
1988-1995
Rad Hyst & LND
>1/3 stromal invasion/LVSI/LTD*

RT 46-50.4 Gy pelvis
23-28 fx 1.8-2.0 Gy
(No brachy)

No Further Therapy

*S pts with LN not eligible
# GOG 92 Eligibility Criteria

<table>
<thead>
<tr>
<th>CLS</th>
<th>Stromal Invasion</th>
<th>Tumor Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>Positive</td>
<td>Middle 1/3</td>
<td>≥2 cm</td>
</tr>
<tr>
<td>Positive</td>
<td>Superficial 1/3</td>
<td>≥5 cm</td>
</tr>
<tr>
<td>Negative</td>
<td>Deep or middle 1/3</td>
<td>≥4 cm</td>
</tr>
</tbody>
</table>

Need 2 of 3 factors: Positive CLS, Middle 1/3, ≥ 4 cm

Sedlis et al, Gyn Onc 1999
## GOG 92: Sites of Failure

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy</th>
<th>No Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>13%</td>
<td>19%</td>
</tr>
<tr>
<td>Distant</td>
<td>2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Sedlis et al, Gyn Onc 1999
GOG 92: Update

- Median f/u: 10 years
- PFS: 46% reduction in HR
- Overall survival:
  - 30% improvement (p=0.074)
- Grade 3/4 toxicity:
  - 6.6% (RT) vs 2.1% (obs)
- Adenocarcinoma and adenosquamous recurrence rate:
  - 8.8% (RT) vs 44% (obs), p=0.019

Rotman et al, IJROPB 2006
Chemoradiation after Hysterectomy
GOG 109
Role of Chemo/RT in high risk pts in post-operative setting

243 Pts Stage IA2, IB, IIA
1991-1996
Rad Hyst & LND

RT only
49.3 Gy / 29 fx

RT + CT
CDDP 70 mg/m²
5-FU 4,000 mg/m²
Days 1, 22, 43, 66

Peters et al, JCO 2000
Eligibility Criteria

- Positive Pelvic Lymph Nodes
- Positive Parametrial Involvement
- Positive Surgical Margins
GOG 109/SWOG 8797

- 4 year PFS
  - 80% CT+RT vs. 63% RT alone

- 4 year OS:
  - 81% CT+RT vs. 71% RT alone
Role of concurrent chemotherapy in addition to radiotherapy intermediate risk cervical cancer

Radical hysterectomy
Risk factors:
Deep stromal invasion, LVSI, G3

Pelvic RT only
Pelvic RT Weekly cis
RTOG/GOG0724
Role of outback chemotherapy

Radhys
Risk factors:
Positive nodes, PM

Weekly cis + RT

Pelvic RT
Weekly cis →
Carbo/taxol x 4
Treatment of Locally Advanced Cervical Cancer
Cervical Cancer
Definitive Chemoradiation

Relative Risk Estimate of Survival from Five Chemoradiation Clinical Trials

Eifel et al, JCO 2004
## Concurrent weekly CDDP/RT

<table>
<thead>
<tr>
<th></th>
<th>GOG 120</th>
<th>NCIC</th>
<th>GOG 123</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td>IIB-IVA</td>
<td>IA – IIA, &gt; 5cm IIB</td>
<td>IB2</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>WPRT/B/H</td>
<td>WPRT/B</td>
<td>WPRT/B + SH</td>
</tr>
<tr>
<td></td>
<td>WPRT/B/cis/5FU/HU</td>
<td>WPRT/B + wkly cis</td>
<td>WPRT/B/wkly cis + SH</td>
</tr>
<tr>
<td></td>
<td>WPRT/B/wkly cis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>47%</td>
<td>62%</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>65% (3 year)</td>
<td>58% (5 year), p = NS</td>
<td>83% (3 year)</td>
</tr>
<tr>
<td><strong>LR</strong></td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>↓toxicity with cis or HU alone</td>
<td>Non-surgical staging of nodes</td>
<td>↑pCR with chemo (52 vs 41%)</td>
</tr>
</tbody>
</table>
## Concurrent CDDP/5FU and RT

<table>
<thead>
<tr>
<th></th>
<th>RTOG 90-01 Morris, 1999</th>
<th>SWOG 8797 Peters, 2000</th>
<th>GOG 85 Whitney, 1999</th>
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<tbody>
<tr>
<td><strong>Stage</strong></td>
<td>IIB – IVA</td>
<td>IA2-IIA (posthys)</td>
<td>IIB-IVA</td>
</tr>
<tr>
<td></td>
<td>IB-IIA &gt; 5cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LN +</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>EFRT/B</td>
<td>WPRT</td>
<td>WPRT/B /HU</td>
</tr>
<tr>
<td></td>
<td>WPRT/B + cis5FU</td>
<td>WPRT + cis/5FU x 4</td>
<td>WPRT/B/cis/5FU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cycles</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>41%</td>
<td>81% (4 year)</td>
<td>55% (3 year)</td>
</tr>
<tr>
<td></td>
<td>67% (8 year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LR</strong></td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>NS ↑ PAN failures in CRT arm</td>
<td>Postop (+LN, +PM, +margins)</td>
<td>Late complications 16% (equivalent)</td>
</tr>
</tbody>
</table>
Chemo-radiotherapy Meta-analysis

- 15 randomized trials of CT+RT vs RT
  - 11 Platinum based
  - 3 Nonplatinum

- 3452 pts

- CT+RT vs RT
  - 8% absolute improvement in DFS (50% to 58%)
  - Also for locoregional DFS and distant metastases free survival
  - Overall survival benefit of 6% (60% to 66%) for CT+RT vs RT

- CT+RT vs RT alone
  - Two trials
  - 19% absolute OS improvement (60% to 79%)

---

Vale et al JCO 2008
Should we be giving outback chemo?

515 Pts Stage IIB-IVA
KPS ≥ 70

EBRT 50.4 Gy/1.8 Gy fx
Brachy 30-35 Gy in 96 hours
Cisplatin weekly 40 mg/m²

EBRT+brachy
Cis 40 mg/m² and gem125 mg/m² weekly
Outback: Cis 50 mg/m² and gem 1000 mg/m²
Q21 day cycles x 2
Should we be giving outback chemo?

• Use of cisplatin plus gemcitabine resulted in
  • Improvement in PFS vs cis alone
    • 3 year PFS 74% versus 65%
  • An improvement in overall survival
  • Toxicities
    • More serious (grade ¾) toxicities (87% vs 43%)
    • More hospitalizations (30% vs 11%)

Duenas-Gonzalez A et al, JCO 2011
IB2, II, IIIB or IVA cervical cancer
ANZGOG 0902
GOG0724
RTOG1174

45-50.4 Gy/1.8 Gy
Cisplatin 40 mg/m2 weekly x 5
brachytherapy

Concurrent chemoradiation →
Adjuvant carbo AUC 5
paclitaxel 155 mg/m2 x 4
NRG: Phase II Concurrent ChemoRT +/- Triapine

**IB2, II, IIIB-IVA cervical cancer**

- 45-50.4 Gy/1.8 Gy (IMRT or 3D)
- Cis 40 mg/m2 weekly x 5 brachytherapy

- 45-50.4 Gy/1.8 Gy (IMRT or 3D)
- Cisplatin 40 mg/m2 weekly x 5 Brachytherapy
- Triapine IV 3x/week
Treatment of Locally advanced IB2- IVA cervical cancer

• EBRT 45 Gy (1.8 Gy fx)
  • 3D CRT, AP/PA, 4 fields
  • Boost to parametrial or sidewall disease

• Brachytherapy 80-90 Gy

• Concurrent chemotherapy
  • (weekly CDDP 40 mg/m2)
Radiation Therapy
RT Fields
FDG PET/CT and MR simulation
FDG PET/CT Simulation
MR Simulation
Use of IMRT for Intact Cervix: Controversies

• Contouring

• Organ Motion

• Simulation/Setup/IGRT
CLINICAL INVESTIGATION

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOThERAPY FOR THE DEFINITIVE TREATMENT OF CERVIX CANCER


• http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx
IMRT for Intact Cervix Cancer

Lim et al, IJROBP 2011
How much margin is needed?
## Interfraction Cervical Motion

<table>
<thead>
<tr>
<th>Study</th>
<th># of Pts</th>
<th>Modality</th>
<th>Imaging frequency</th>
<th>Method</th>
<th>Average movement (mm)</th>
<th>Maximal movement (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Statistic used</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AP/PA</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sup/Inf</td>
<td></td>
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<td>R/L</td>
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<td>AP/PA</td>
<td>Sup/Inf</td>
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<td></td>
<td></td>
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<td></td>
<td>L/R</td>
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<tr>
<td>Kaatee</td>
<td>10</td>
<td>EPID and seeds</td>
<td>Daily</td>
<td>Seed</td>
<td>Mean of means</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.3</td>
<td>NR</td>
</tr>
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<td></td>
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<td>Systematic motion</td>
<td></td>
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<td>3.5</td>
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<td>Random motion</td>
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<td>3.9</td>
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<td>2.2</td>
<td></td>
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<tr>
<td>Haripotenpornkul</td>
<td>10</td>
<td>KV and seeds</td>
<td>Daily</td>
<td>Seed</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>4.2 (3.5)</td>
<td>4.1 (3.2)</td>
</tr>
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<td></td>
<td></td>
<td>1.9 (1.9)</td>
<td></td>
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<tr>
<td>Latifi</td>
<td>15</td>
<td>MVCT and seeds</td>
<td>Daily</td>
<td>Seed</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>7.6 (3.4)</td>
<td>0.7-25 mm</td>
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<tr>
<td>Mens</td>
<td>12</td>
<td>Kk portal, CBCT, seeds</td>
<td>Daily portal, biweekly CBCT</td>
<td>Seed Random</td>
<td>Systematic motion</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>7.9</td>
<td>6.9</td>
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<td>6.6</td>
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<td>6.2</td>
<td>4.9</td>
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<td></td>
<td></td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>17</td>
<td>Portal films</td>
<td>Weekly</td>
<td>Ring motion</td>
<td>Median</td>
<td></td>
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<td></td>
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<td></td>
<td>16</td>
<td>8</td>
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<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Chan</td>
<td>20</td>
<td>MRI</td>
<td>Weekly</td>
<td>Cervical motion</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>2.4</td>
<td>1.5</td>
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<td>NR</td>
<td>NR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Beadle</td>
<td>16</td>
<td>CT</td>
<td>Weekly</td>
<td>Center of mass Perimeter</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ant 17</td>
<td>Sup 23 Inf 13</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Post 18</td>
<td>L 9 R 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ant 29 Post 63</td>
<td>Sup 35 Inf 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L 18</td>
<td>R 18</td>
</tr>
</tbody>
</table>

Adapted from Jadon et al, Clin Onc 2014.
## Interfraction Uterine Motion

<table>
<thead>
<tr>
<th>Study</th>
<th># of Pts</th>
<th>Modality</th>
<th>Imaging frequency</th>
<th>Method</th>
<th>Average movement (mm)</th>
<th>Maximal movement (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Statistic used</td>
<td>AP/PA</td>
<td>Sup/Inf</td>
</tr>
<tr>
<td>Taylor</td>
<td>33</td>
<td>MRI</td>
<td>2 Days</td>
<td>Superior/ anterior fundus</td>
<td>Median</td>
<td>5</td>
</tr>
<tr>
<td>Wang</td>
<td>8</td>
<td>4DCT</td>
<td>Biweekly</td>
<td>Superior fundus</td>
<td>Mean (SD)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Chan</td>
<td>20</td>
<td>MRI</td>
<td>Weekly</td>
<td>Uterine fundus</td>
<td>Mean</td>
<td>-4.8</td>
</tr>
<tr>
<td>Collen</td>
<td>10</td>
<td>MVCT</td>
<td>Daily</td>
<td>Boundary shifts</td>
<td>Mean (SD)</td>
<td>3.3 (11.9)</td>
</tr>
<tr>
<td>Lee</td>
<td>13</td>
<td>CT (using SBDS)</td>
<td>Weekly</td>
<td>Distance from iso</td>
<td>Mean</td>
<td>Ant -1.1</td>
</tr>
</tbody>
</table>

**Max motion 32-45 mm (S/I) 20-48 mm (A/P)**
45 yo with IB2 cervical carcinoma

Initial CT sim  Fx 1 CBCT
Initial CT sim  Fx 4 CBCT
IMRT Considerations for Intact Cervix Cancer

• Simulation: bladder full and bladder empty
• MRI pretreatment or at the time of simulation
• Use all available imaging for contouring ITV
• Margins:
  • CTV→ PTV margins for primary CTV: 1.5-2 cm
  • CTV→ PTV margins for nodal CTV: 7 mm
• Daily soft tissue IGRT
Uses for IMRT

• PA nodes

• Inguinal nodes

• Boost
  • Nodal boost
  • Sidewall boost
Contouring PA Nodes

Takiar et al, IJROBP 2013
Contouring Inguinal nodes: How much margin is necessary?

- Margin on nearest femoral vessel required to encompass ≥90% of the positive nodes:
  - anteromedial ≥35 mm
  - anterior ≥23 mm
  - anterolateral ≥25 mm
  - medial ≥22 mm
  - posterior ≥9 mm
  - lateral ≥32 mm

Kim et al, PRO 2012
Key points:

• Concurrent chemo/RT remains standard of care for locally advanced cervical cancer

• IMRT may be appropriate in select situations (groin or PA+) with careful accounting of cervix/uterine motion
Brachytherapy
Brachytherapy utilization for cervical cancer
Overall survival by brachy utilization
Implant quality matters RTOG 0116 and 0128

- Mean f/u: 24.5 months
- Reviewed brachytherapy records
- Higher LR with unacceptable geometry
  - Displacement of ovoids relative to os HR 2.67
  - Unacceptable symmetry of ovoids and tandem HR 2.50
  - Inappropriate packing placement HR 2.06
Sequencing

Cis

EBRT

<table>
<thead>
<tr>
<th>EBRT</th>
<th>Brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 Gy (or 50.4 Gy)</td>
<td>EQD2: ~40-45 Gy</td>
</tr>
</tbody>
</table>

EBRT: 45 or 50.4 Gy (45 Gy as effective)
45 Gy Pelvis EQD2

<table>
<thead>
<tr>
<th>Fx #</th>
<th>Dose</th>
<th>EQD2 Tumor</th>
<th>EQD2 Normal tissue (90% PD)</th>
<th>EQD2 Normal tissue (70% of PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>7 Gy</td>
<td>83.9 Gy</td>
<td>90.1 Gy</td>
<td>74.2 Gy</td>
</tr>
<tr>
<td>5</td>
<td>6 Gy</td>
<td>84.3 Gy</td>
<td>88.6 Gy</td>
<td>73.4 Gy</td>
</tr>
<tr>
<td>6</td>
<td>5 Gy</td>
<td>81.8 Gy</td>
<td>83.7 Gy</td>
<td>70.5 Gy</td>
</tr>
<tr>
<td>5</td>
<td>5.5 Gy</td>
<td>79.8 Gy</td>
<td>82.6 Gy</td>
<td>69.6 Gy</td>
</tr>
</tbody>
</table>
Classical & Revised Manchester System
Normal Tissue Dose Points

- Bladder
  - ICRU Bladder pt<75 Gy
  - D2cc <90 Gy

- Rectum
  - ICRU Rectal pt<70 Gy
  - D2cc: 70-75 Gy

- Vagina:
  - Upper: 120-140 Gy
  - Lower: 90 Gy
MR Brachytherapy Guidelines

- **GTV**
  - Macroscopic tumor at brachytherapy
  - High signal intensity mass(es) (FSE, T2) in cervix/corpus, parametria, vagina, bladder and rectum

- **High Risk-CTV**
  - Includes gtv, whole cervix, and presumed extracervical tumor extension.
  - Grey zones in parametria, uterine corpus, vagina, or rectum, and bladder

- **Intermediate Risk-CTV**
  - Encompasses HRCTV with margins added according to tumor size and regression; minima margins of 5-15 mm
  - Extensive disease: w/ good remission HR-CTV and initial tumor extension

GEC-ESTRO Guidelines, Radiother Oncol 2005
MRI for Image Guided Brachytherapy

GEC-ESTRO Guidelines, Radiother Oncol 2005
**Results of image guided brachytherapy**

<table>
<thead>
<tr>
<th>Location</th>
<th># yr</th>
<th>Local control</th>
<th>Overall Survival</th>
<th>Late toxicity (Grade 3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIC</td>
<td>2</td>
<td>78.5-100%</td>
<td>74-96%</td>
<td>2.6-8.9%</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>2</td>
<td>90%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Vienna</td>
<td>3</td>
<td>91%</td>
<td>94%</td>
<td>0%</td>
</tr>
<tr>
<td>Addenbrooke</td>
<td>3</td>
<td>96%</td>
<td>82%</td>
<td>11% crude (14% actuarial)</td>
</tr>
<tr>
<td>Korea</td>
<td>3</td>
<td>97%</td>
<td>NR</td>
<td>2%</td>
</tr>
<tr>
<td>Paris</td>
<td>4</td>
<td>91%</td>
<td>94%</td>
<td>0%</td>
</tr>
<tr>
<td>Australia</td>
<td>5</td>
<td>87-88%</td>
<td>60%</td>
<td>0.6-4.6%</td>
</tr>
<tr>
<td>Leuven</td>
<td>5</td>
<td>96%</td>
<td>65%</td>
<td>6%</td>
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</tbody>
</table>
## Chemo-radiotherapy Meta-analysis

<table>
<thead>
<tr>
<th>Events</th>
<th>CT/RT</th>
<th>RT</th>
<th>Hazard ratio (fixed)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-IIA</td>
<td>78/338</td>
<td>131/347</td>
<td>0.62</td>
<td>10%</td>
</tr>
<tr>
<td>IIIB</td>
<td>260/948</td>
<td>379/996</td>
<td>0.61</td>
<td>7%</td>
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<tr>
<td>IIIA-IVA</td>
<td>401/924</td>
<td>472/914</td>
<td>0.81</td>
<td>3%</td>
</tr>
</tbody>
</table>

Vale et al, JCO 2008

CRT better RT better
RETROEMBRACE

Tanderup et al, Radiother Oncol 2016
RETROEMBRACE

HRCTV $\geq 30$ cm$^3$  

HRCTV $< 30$ cm$^3$

Lokdal et al
Dose levels per EMBRACE

- HRCTV: >85 Gy
- IRCTV: >60 Gy
- GTV
- Subclinical disease
Initial presentation

Confined to anatomic borders

Complete response

Brachytherapy

Cervix=HRCTV

Initial disease=IRCTV

Confined to anatomic borders
Initial presentation

HRCTV = cervix plus residual disease

IRCTV > initial tumor extent

Poor partial response
## Sequencing

<table>
<thead>
<tr>
<th>MRI</th>
<th>Cis</th>
<th>EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EBRT: 45 Gy (or 50.4 Gy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brachytherapy EQD2: ~40-45 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nodal boost</td>
</tr>
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</table>

EBRT: 45 or 50.4 Gy (45 Gy as effective)
Gyn GEC ESTRO: OAR planning goals

<table>
<thead>
<tr>
<th></th>
<th>Bladder D2cc EQD2</th>
<th>Rectum D2cc EQD2</th>
<th>Sigmoid D2cc EQD2</th>
<th>RV point EQD2</th>
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</thead>
<tbody>
<tr>
<td><strong>Planning goal</strong></td>
<td>&lt;80 Gy</td>
<td>&lt;65 Gy</td>
<td>&lt;70 Gy</td>
<td>&lt;65 GY</td>
</tr>
<tr>
<td><strong>Upper limit</strong></td>
<td>&lt;90 Gy</td>
<td>&lt;75 Gy</td>
<td>&lt;75 Gy</td>
<td>&lt;75 Gy</td>
</tr>
</tbody>
</table>
# Gyn GEC ESTRO: Planning target goals

<table>
<thead>
<tr>
<th>Planning goals</th>
<th>D90 HRCTV EQD2</th>
<th>D98 HRCTV EQD2</th>
<th>D98 GTV EQD2</th>
<th>D98 IRCTV EQD2</th>
<th>Point A EQD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limit</td>
<td>&gt; 85 Gy</td>
<td>-</td>
<td>&gt;90 Gy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Planning goals</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>
</tbody>
</table>
Key take home points

• Image guided brachytherapy results in improved local control and decreased normal tissue toxicities

• Advanced image guided brachytherapy may allow further dose escalation and improved local control
Advances in Vulvar Cancer
Epidemiology

- 4\textsuperscript{th} most common gyn malignancy
  - \(\sim\)3500 cases per year
- Bimodal age distribution
- Risk factors: HPV+, smoking, VIN, Paget’s disease, lichen sclerosis
- Histology:
  - Squamous cell carcinoma 85%
  - Adenocarcinoma
  - Melanoma
  - basaloid
Vulvar Cancer: Anatomy

2/3rds of cases on labia
Workup

• H&P

• Pap smear, EUA, biopsy of primary

• MRI/CT +/- PET/CT

• Lymph node evaluation

• Cystoscopy/sigmoidoscopy
# Vulvar Cancer Staging

<table>
<thead>
<tr>
<th>AJCC</th>
<th>FIGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1a</td>
<td>Confined to vulva/perineum, size ≤2cm, stromal invasion ≤1mm, N0</td>
</tr>
<tr>
<td>T1b</td>
<td>Confined to vulva/perineum, size &gt;2cm or any size with stromal invasion &gt;1mm, N0</td>
</tr>
<tr>
<td>T2</td>
<td>Any size with adjacent spread to lower 1/3 urethra, vagina, or anus</td>
</tr>
<tr>
<td>T3</td>
<td>Invades upper 2/3 urethral mucosa, upper 2/3 vagina, bladder mucosa, rectal mucosa, or is fixed to bone</td>
</tr>
<tr>
<td>N1a</td>
<td>1-2 Lymph Node Metastases each &lt; 5 mm</td>
</tr>
<tr>
<td>N1b</td>
<td>Single Lymph Node Metastasis measuring &gt; 5 mm</td>
</tr>
<tr>
<td>N2a</td>
<td>3 or more Lymph Node Metastases, Each &lt; 5 mm</td>
</tr>
<tr>
<td>N2b</td>
<td>2 or more Lymph Node Metastases ≥ 5 mm</td>
</tr>
<tr>
<td>N2c</td>
<td>Lymph Node Metastases with ECE</td>
</tr>
<tr>
<td>N3</td>
<td>Fixed or Ulcerated Regional Nodes</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis (including pelvic lymph node metastasis)</td>
</tr>
</tbody>
</table>
LN drainage from vulva

Lymphatics:

1\textsuperscript{st} echelon:
- Superficial inguinofemoral

2\textsuperscript{nd} echelon:
- Deep inguinofemoral
- Femoral

3\textsuperscript{rd} echelon:
- External iliac/pelvic nodes

*Clitoral lesions may drain directly to iliac

Courtesy A. Jhingran
## Incidence of LN mets

<table>
<thead>
<tr>
<th>Depth of Invasion (P &lt; 0.0001)</th>
<th>Groin Nodes (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 mm</td>
<td>2.6%</td>
</tr>
<tr>
<td>2 mm</td>
<td>8.9%</td>
</tr>
<tr>
<td>3 mm</td>
<td>18.6%</td>
</tr>
<tr>
<td>4 mm</td>
<td>30.9%</td>
</tr>
<tr>
<td>5 mm</td>
<td>33.3%</td>
</tr>
<tr>
<td>&gt; 5 mm</td>
<td>47.9%</td>
</tr>
</tbody>
</table>

Vulvar Cancer: Treatment

- Surgery
  - WLE, hemi-vulvectomy, vulvectomy
  - SLND or LND

- Radiotherapy
  - Adjuvant, primary management

- Chemotherapy
Risk factors for recurrence

• Large tumor size
• Multifocal disease
• Lichen sclerosis
• Tumor free surgical margin
• Deep stromal invasion
Margin status

Freedom from vulvar relapse
By margin status

- Negative margins
- Close margins
- Positive margins

By Radiation Dose

- Dose >56 Gy
- Dose <56 Gy

Viswanathan et al, Gyn Onc 2013
Management of groins
GOG88: Management of groins (RT vs surgery)

**Eligibility:**
cN0, T1-3 s/p vulvectomy

- N=58
- Pelvic RT only
  - 50 Gy/2 Gy fx
  - Prescribed to 3 cm from skin
- Bilateral inguinofemoral LND

*No CT planning

Stehman FB et al., IJROBP. 1992
GOG88: Management of groins (RT vs surgery)

- Closed early due to increased failure and ↓survival at 2 years in RT arm
- 20% in surgery arm had +LN

<table>
<thead>
<tr>
<th></th>
<th>Groin Dissection</th>
<th>Groin XRT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groin Recurrence</td>
<td>0/25 (0%)</td>
<td>5/27 (18.5%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>22/25 (88%)</td>
<td>17/27 (63%)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Concluding statement: RT cannot control groin disease

Stehman FB et al., IJROBP. 1992
GOG 88

- Inguinal RT prescribed to 3 cm
- No CT planning
- 3/5 patients w/inguinal recurrence underdosed by 30%

Koh et al, IJROBP 1993
**Sentinel Lymph Node Biopsy: GROINSS-V**

<table>
<thead>
<tr>
<th></th>
<th>SLNB</th>
<th>Complete LND</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Breakdown</td>
<td>11.7%</td>
<td>34.0%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>1.9%</td>
<td>25.2%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>4.5%</td>
<td>21.3%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Van der Zee et al, JCO 2008 (GROINSS V)
Sentinel node biopsy: GROINSS-V

- **T1/2 >1mm DOI <4 cm cN0**
- **SLNB**
  - SLNB-: No further dissection
  - SLNB+: Inguinal femoral LND

Van der Zee et al, JCO 2008 (GROINSS V)
## Sentinel node biopsy: GROINSS-V

<table>
<thead>
<tr>
<th>Size</th>
<th>Non-SN metastases (% per groin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITC</td>
<td>4.2%</td>
</tr>
<tr>
<td>≤1 mm</td>
<td>10%</td>
</tr>
<tr>
<td>&gt;1-2 mm</td>
<td>11.1%</td>
</tr>
<tr>
<td>&gt;2-5 mm</td>
<td>13.3%</td>
</tr>
<tr>
<td>&gt;5-10 mm</td>
<td>38.5%</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>62.5%</td>
</tr>
<tr>
<td>Total</td>
<td>19.0%</td>
</tr>
</tbody>
</table>

Oonk et al, Lancet Oncology 2010
Key Points: Management of the Groins

• +SLN → further groin treatment irrespective of size of LN metastases

• Radiotherapy management of groins:
  • +SLN → RT if no further dissection
  • Could consider omission if <5 mm lymph node and fully dissected groin (>9 nodes, medial femoral nodes)
  • Imaging and FNA/biopsy of suspicious nodes
GOG37: Groin positive

Eligibility:
cStage I-IV
s/p vulvectomy
+ groin LND (ipsi/bi)

*No CT planning

Ipsilateral pelvic node dissection

Pelvic and groin RT
40-50 Gy/2 Gy fx
(groin/obturator/iliac)
Midline block to central vulva

Stehman FB et al., IJROBP. 1992

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
GOG 37: Surgery vs RT

• Groin failures reduced with XRT from 23.6% (n=13) in the surgery arm to 5.1% (n=3) in the XRT arm (p=0.02)

• Pelvic failure rate 6.8% (n=4) in XRT arm and 1.8% (n=1) in surgery arm (NS). Pelvic nodes (+) in 28.3% of dissected patients

• No OS benefit in patients with 1 node positive

<table>
<thead>
<tr>
<th></th>
<th>2yr OS Pelvic XRT</th>
<th>2 yr OS Surgery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical N2-3 Groin Nodes</td>
<td>59%</td>
<td>31%</td>
<td>0.01</td>
</tr>
<tr>
<td>≥ 2 Inguinal nodes Positive</td>
<td>63%</td>
<td>37%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Management of Vulvar SCC

Resectable?

Yes

Surgery per stage

Stage 1A

WLE only

Post-op radiation as indicated

Stage > 1A

WLE+ Inguinal LN dissection

No

RT +/- chemo

Definitive

Preop ChemoRT

RT

Preop

Chemo

RT
Management of Vulvar SCC:

• Adjuvant indications:
  • + or close margins
  • Inguinal/pelvic nodes
    • Clinically + groin nodes, >1 groin LN+ (if complete nodal staging), nodal ECE

• Preop/Definitive
  • Unresectable
  • High complete response rate with CRT
Radiotherapy management of vulvar cancers
Preoperative RT: Phase II study of RT and weekly cis

- T3/T4
- Treatment:

  - EBRT 57.6 Gy/1.8 Gy
  - Weekly cis 40 mg/m2
  - 4-6 weeks

- Results
  - 58 evaluable pts
  - 37 (63.8%) cCR
  - 29 (50%) pathological CR

Moore et al Gyn Onc 2012
Definitive RT

- MDACC 1992-2014
- 33 pts with grossly positive groin nodes (imaging or clinically)
- 48% with pelvic node metastases
- Median RT dose to nodes 66 Gy (60-70 Gy)
## Adjuvant RT: Primary

<table>
<thead>
<tr>
<th>Margin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 mm</td>
<td>45-50 Gy</td>
</tr>
<tr>
<td>&gt;1-2 mm, but &lt;5 mm</td>
<td>50 Gy</td>
</tr>
<tr>
<td>&lt;1 to 2 mm</td>
<td>56 Gy</td>
</tr>
<tr>
<td>Positive</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>

56 Gy
### Adjuvant RT: Nodes

<table>
<thead>
<tr>
<th>Node</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic, no ECE, -RAD</td>
<td>45-50 Gy</td>
</tr>
<tr>
<td>Grossly enlarged nodes, no ECE, -RAD</td>
<td>50-56 Gy</td>
</tr>
<tr>
<td>ECE</td>
<td>60-66 Gy</td>
</tr>
<tr>
<td>Gross residual disease, +RAD</td>
<td>60-70 Gy</td>
</tr>
</tbody>
</table>
## Primary Treatment

<table>
<thead>
<tr>
<th>Site</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>60-68 Gy</td>
</tr>
<tr>
<td><strong>Nodes</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>56-60 Gy</td>
</tr>
<tr>
<td>1-2 cm</td>
<td>60-66 Gy</td>
</tr>
<tr>
<td>Nodes &gt;2 cm</td>
<td>64-70 Gy</td>
</tr>
<tr>
<td>Massive or fixed nodes</td>
<td>65-70 Gy</td>
</tr>
</tbody>
</table>
Treatment technique

• At simulation:
  • Mark scars, tumor,
  • Frog-legged, avoid overlapping regions of skin
  • Bolus

• Fractionation
  • 1.8-2 Gy/day
  • Mild hypofractionation 2-2.5 Gy

• Infection control
  • Early skin reaction: infectious

• Use of TLDs to check skin dose
Traditional photon/electron technique

- **Advantages:**
  - Broad coverage of targets
  - Provides some protection of femoral heads

- **Downsides:**
  - Electrons insufficient in obese cases
  - ↑ diarrhea contaminating raw vulvar surfaces
  - Unnecessary tx of large areas of skin
  - High heterogeneity

---

**18 MV photons**

**6 MV photons**

---

12 MeV e- 12 MeV e-

---

Courtesy Eifel/Jhingran
Traditional photon/electron technique

• Advantages:
  • Broad coverage of targets
  • Provides some protection of femoral heads

• Downsides:
  • Electrons insufficient in obese cases
  • \( \uparrow \) diarrhea contaminating raw vulvar surfaces
  • Unnecessary tx of large areas of skin

Eifel and Klopp, Gyn Rad Onc, LWW 2017
IMRT for vulvar cancer

• Advantages
  • Sparing of central bowel, femoral heads
  • Concurrent boost
  • Protection of skin outside PTV
  • Reduced acute and late toxicities
  • Better for obese patients

• Disadvantages
  • Steep learning curve
  • Controversies about target delineation
Contouring Inguinal nodes: How much margin is necessary?

• Margin on nearest femoral vessel required to encompass ≥90% of the positive nodes:
  • anteromedial ≥35 mm
  • anterior ≥23 mm
  • anterolateral ≥25 mm
  • medial ≥22 mm
  • posterior ≥9 mm
  • lateral ≥32 mm

Kim et al., PRO 2012
Contouring of inguinal nodes
Contouring of inguinal nodes

- Nodes usually anterior and medial to femoral and saphenous veins
- May lie along branch vessels
Contouring of the vulva

- Fiducials/wire to define tumor
- EUA if vagina involved
- Minimize high dose to Mons

51 yo woman with T3N1 vulvar squamous cell carcinoma, 6 cm with lower vaginal involvement
Contouring of the vulva

51 yo woman with T3N1 vulvar squamous cell carcinoma, 6 cm with lower vaginal involvement
Consensus Recommendations for Radiation Therapy Contouring and Treatment of Vulvar Carcinoma

David K. Gaffney, MD, PhD,* Bronwyn King, MBBS,† Akila N. Viswanathan, MD, MPH,‡ Maroie Barkati, MD,§ Sushil Beriwal, MD,¶ Patricia Eifel, MD,‖ Beth Erickson, MD,# Anthony Fyles, MD,** Jennifer Goulart, MD,†† Matthew Harkenrider, MD,‡‡ Anuja Jhingran, MD,¶ Ann Klopp, MD, PhD,¶ Wui-Jin Koh, MD,§§ Karen Lim, MBBS,¶¶ Ivy Petersen, MD,¶¶ Lorraine Portelance, MD,## William Small, Jr, MD,### Alexandra Stewart, DM, MRCP, FRCR,### Ericka Wiebe, MD,#### Aaron Wolfson, MD,## Catheryn Yashar, MD,##### and Walter Bosch, DSc####

Clinical Investigation
Consensus contouring guidelines: Vulvar carcinoma

Locally advanced vulvar carcinoma

• Primary:
  • CTV=entire vulva
  • If GTV extends beyond vulva, add 1 cm margin

• Invasion of vagina
  • Gross disease + 3 cm
  • Entire vagina if uncertainty regarding extent or if LVSI

• Anus, anal canal, bladder or rectum invasion
  • Gross disease + 2 cm

• Periurethral
  • Gross disease + 2 cm of urethra

• Periclitoral
  • Gross disease + 2 cm

Gaffney et al, IJROBP 2016
Consensus contouring guidelines: Vulvar carcinoma

Locally advanced vulvar carcinoma

Postoperative vulvar carcinoma
CTV= entire operative bed (+2 cm if +margin)
Key take home points:

• Treatment of vulvar carcinoma requires multidisciplinary management and individualization

• IMRT can reduce acute/late toxicities and should be carefully used
Thank you for your attention!

Email: LLLin@mdanderson.org