Management of GYN Malignancies

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Duke Cancer Center
ASTRO Refresher 2015
Disclosures

• None
Learning Objectives

• Review the diagnosis, workup, and management of:
  – Cervical Cancers
  – Uterine Cancers
  – Vulvar Cancers
Cervical Cancer
WE ARE NOW OFFERING

HPV

TO ALL OUR FEMALE AND MALE PATIENTS

AGE 11 YEARS AND OLDER
Cervical Cancer

• 3rd most common malignancy in the World
• 2nd most common malignancy in women
• The Leading cause of cancer deaths in women for the developing world
• In the US however...
  – 12th most common malignancy in women
  – Underserved populations disproportionately affected
> 6 million lives saved by the Pap Test


“Diagnosis of Uterine Cancer by the Vaginal Smear” Published

*Per 100,000, age adjusted to the 2000 US standard population. *Rates are uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Pap Test

• Start screening within 3 years of onset of sexual activity, or at age 21
• Annual testing till age 30
• If no history of abnormal paps, risk factors, reduce screening to Q2-3 years.
• Stop at 65-70 years
• 5-7% of all pap tests are abnormal
  – Majority are ASCUS
Pap-test Interpretation

ASCUS or LSIL -> reflex HPV -> If HPV + then Colposcopy, If – Repeat in 1 year
HSIL -> Colposcopy
Cannot diagnose cancer on Pap test alone
CIN

• CIN 1 – low grade dysplasia confined to the basal 1/3 of epithelium
  – HPV negative: repeat cytology at 12 months
  – HPV positive: Colposcopy

• CIN 2-3 – 2/3 or greater of the epithelial thickness
  – Cold Knife Cone or LEEP

• CIS – full thickness involvement.
  – Cold Knife Cone or LEEP
Epidemiology

• 12,900 women expected to be diagnosed in 2015
  – 4,100 deaths due to disease
• Median Age at diagnosis 48 years

<table>
<thead>
<tr>
<th>Incidence Rates by Race</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>8.1 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>7.9 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>10.1 per 100,000 women</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>7.5 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>7.7 per 100,000 women</td>
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<tr>
<td>Hispanic</td>
<td>12.0 per 100,000 women</td>
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</table>

<table>
<thead>
<tr>
<th>Death Rates by Race</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>2.4 per 100,000 women</td>
</tr>
<tr>
<td>White</td>
<td>2.2 per 100,000 women</td>
</tr>
<tr>
<td>Black</td>
<td>4.4 per 100,000 women</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>2.1 per 100,000 women</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>3.4 per 100,000 women</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.1 per 100,000 women</td>
</tr>
</tbody>
</table>

Cancer Statistics, ACS 2015
Risk Factors: Cervical Cancer

- Early onset sexual activity
- Multiple sexual partners
- Hx of STDs
- Multiple pregnancy
- Immune suppression (s/p transplant, HIV)
- Tobacco
HPV

• The human papilloma virus is a double stranded DNA virus
• The most common oncogenic strains are 16, 18, 31, 33 and 45.
• 16 and 18 account for 70% of US cases, with slightly less prevalence worldwide.
HPV: oncogenesis

• E6 binds to p53, inhibiting apoptosis and encouraging immortality
• E7 binds to Rb, thus activating the cell cycle and promoting uncontrolled proliferation

Yim & Park, Cancer Res Treat 2005
HPV: prevalence

- ~50% of women will be exposed to HPV within 4 years of the onset of sexual activity
- 2 year clearance rate of HPV is 90% with only 5% developing any cytological abnormality

Schiffman et al, Lancet 2007
Vaccine

- Cervarix: HPV 16, 18
- Gardasil: HPV 6, 11, 16, 18
  - Most common in US
- Gardasil 9 just approved (6, 11, 16, 18, 31, 33, 45, 52, 58)

- All approved by FDA
- All are a series of 3 injections over 6 months
- Neither prevent or speed clearance of an existing HPV infection
Quadrivalent Vaccine Efficacy

Time until the Development of High-Grade Cervical Disease Associated with HPV-16, HPV-18

Time until the Development of High-Grade Cervical Disease Associated with any HPV

The Future II study Group. NEJM 2007;356:1915
### Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2010

For those who fall behind or start late, see the schedule below and the catch-up schedule.

<table>
<thead>
<tr>
<th>Vaccine ▼</th>
<th>Age ▼</th>
<th>7–10 years</th>
<th>11–12 years</th>
<th>13–18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus, Diphtheria, Pertussis¹</td>
<td>Tdap</td>
<td>Tdap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Papillomavirus²</td>
<td>see footnote 2</td>
<td>HPV (3 doses)</td>
<td>HPV series</td>
<td></td>
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<tr>
<td>Meningococcal³</td>
<td>MCV</td>
<td>MCV</td>
<td>MCV</td>
<td></td>
</tr>
<tr>
<td>Influenza⁴</td>
<td>Influenza (Yearly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal⁵</td>
<td>PPSV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A⁶</td>
<td>HepA Series</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B⁷</td>
<td>Hep B Series</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated Poliovirus⁸</td>
<td>IPV Series</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, Mumps, Rubella⁹</td>
<td>MMR Series</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella¹⁰</td>
<td>Varicella Series</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Range of recommended ages for all children except certain high-risk groups

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups
HPV vaccination rates ~32%

FIGO (2009)

- **Stage I** – confined to the Uterus
  - IA1: 3mm or less stromal invasion, 7mm or less horizontal spread
  - IA2: >3mm to 5mm invasion, 7mm or less horizontal spread
  - IB1: 4.0 cm or less
  - IB2: >4cm
- **Stage II** – local extension
  - IIA1: involves upper 2/3 of vagina, 4cm or less
  - IIA2: involves upper 2/3 of vagina, >4cm in size
  - IIB: parametrial involvement
- **Stage III** – regional extension
  - IIIA: involves lower 1/3 of vagina
  - IIIB: extends to pelvic side wall or hydronephrosis seen on imaging
- **Stage IVA**: invades bladder, rectum, or extends beyond true pelvis
- **Stage IVB**: distant mets
AJCC

• T stage Mirrors FIGO, however adds N category
• N1 = regional nodes (AJCC IIIB)
• M1 = distant mets, and paraaortic nodes (AJCC IVB)
Imaging

• The only imaging allowed to affect FIGO stage is IVP (CT can be used to look for hydro)
• MRI is the most accurate for determining local extent (~90% accurate for parametrial/vaginal involvement)
• PET is the most accurate for nodal staging (sensitivity ~85%, specificity ~95%)
<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Stage Distribution (%)</th>
<th>5-year Relative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized (confined to primary site)</td>
<td>49</td>
<td>91.2</td>
</tr>
<tr>
<td>Regional (spread to regional lymphnodes)</td>
<td>35</td>
<td>57.8</td>
</tr>
<tr>
<td>Distant (cancer has metastasized)</td>
<td>11</td>
<td>17.0</td>
</tr>
<tr>
<td>Unknown (unstaged)</td>
<td>5</td>
<td>58.1</td>
</tr>
</tbody>
</table>
Histology

- >90% squamous cell
- 7 - 10% adenocarcinoma
- 1 - 2 % clear cell, small cell
Para-Aortic Dissection usually only extends to the IMA
# Risk of Pelvic LN

Risk of nodes with <4mm invasion (stage IA1) is <5%, therefore nodal dissection or elective RT is not necessary

<table>
<thead>
<tr>
<th>Size</th>
<th>Stage Ib</th>
<th>Stage Ila</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 cm</td>
<td>18%</td>
<td>27%</td>
</tr>
<tr>
<td>2 - 3 cm</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>4 - 5 cm</td>
<td>35%</td>
<td>43%</td>
</tr>
<tr>
<td>&gt;6 cm</td>
<td>50%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Lymph Node Distributions

- Stage IB - IIA Cervix

Lymph Node Distribution

- Locally Advanced Cervix

Locating the Obturator Nodes

Find Obturator Groove (containing obturator nerve and vessels)
Locating the Obturator Nodes

Follow vessels superiorly until they enter the pelvis.
## Para-aortic Lymph Node Involvement

<table>
<thead>
<tr>
<th></th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagasse (GOG, 1980)</td>
<td>6% 8/143</td>
<td>18% 4/22</td>
<td>33% 19/58</td>
<td>0% 0/3</td>
<td>31% 19/61</td>
<td>25% 1/4</td>
</tr>
<tr>
<td>Nelson (1977)</td>
<td>—</td>
<td>—</td>
<td>16% 5/31</td>
<td>—</td>
<td>46% 13/28</td>
<td>—</td>
</tr>
<tr>
<td>Piver (1981)</td>
<td>—</td>
<td>—</td>
<td>13% 6/46</td>
<td>—</td>
<td>37% 18/49</td>
<td>57% 4/7</td>
</tr>
<tr>
<td>Wharton (1977)</td>
<td>0% 0/21 (0)</td>
<td>0% 0/10</td>
<td>21% 10/47</td>
<td>—</td>
<td>33% 14/42</td>
<td>—</td>
</tr>
</tbody>
</table>

Risk of PA Nodes also increases with ~5% per pelvic node involved, though with 4+ nodes the risk is >40%

Sakuragi et al, *Cancer*, 1999
## Treatment Overview

<table>
<thead>
<tr>
<th>FIGO</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| IA1  | Cervical conization or extrafascial hysterectomy  
|      | *Consider vaginal radical trachelectomy for fertility sparing*  |
| IA2  | Modified radical hysterectomy & PLND |
| IB1  | MRH & PLND only in well selected Pts  
|      | otherwise CTRT + Brachy |
| IB2  | MRH & PLND only in well selected Pts  
|      | otherwise CTRT + Brachy |
| IIA1 | Definitive chemoradiation  
|      | (EBRT + weekly cisplatin  
|      | → brachytherapy boost)  |
| IIA2 |  |
| IIB  |  |
| IIIA |  |
| IIIB |  |
| IVA  |  |
| IVB  | Chemotherapy +/- palliative radiotherapy |
Modified Radical Hysterectomy

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Randomized Data: Early Stage Disease

Surgery vs RT
Milan trial: Radical surgery vs. XRT

n = 337 FIGO Ib-IIa cervical cancer

Years: 1986-1991

Radical hysterectomy + PLND (PA LN sampling if suspicious)
- 50.4 Gy adjuvant XRT if ≥ pT2a, cut-through, +LN, <3 mm uninvolved cervical stroma

Definitive radiation
- WPRT (median dose 47 Gy)
  - 45 Gy to PA nodes if +LN
  - 5-10 Gy boost to +LN
- LDR brachy (median cumulative point A dose 76 Gy)

54% in Surgery arm received RT

Primary outcome: 5-yr OS and complication rate
Median f/u: 87 months

No difference in OS or DFS

G2-3 toxicity worse with RH (28% vs 12%, SS)
Edema 9% if RH + PORT

Take Home – Outcomes the same but toxicity worse with RH in bulkier early stage disease

Landoni et al, Lancet 1997
Randomized Data: Early Stage Disease Post-hysterectomy

RT vs NFT
RT vs CTRT
GOG 92: Postop XRT for Stage IB, intermediate risk

n = 277
FIGO IB cervical cancer s/p rad hys & PLND with risk factors (see inset)

Exclusion criteria:
• +LN

Primary outcome: Recurrence risk/recurrence-free interval
Secondary outcomes: OS
Median f/u: 5 years for surviving patients

Intermediate Risk

<table>
<thead>
<tr>
<th>CLS</th>
<th>Stromal invasion</th>
<th>Tumor size</th>
</tr>
</thead>
<tbody>
<tr>
<td>+CLS</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>+CLS</td>
<td>Middle 1/3</td>
<td>≥ 2 cm</td>
</tr>
<tr>
<td>-CLS</td>
<td>Deep or middle 1/3</td>
<td>≥ 4 cm</td>
</tr>
<tr>
<td>+CLS</td>
<td>Superficial 1/3</td>
<td>≥ 5 cm</td>
</tr>
</tbody>
</table>

No further tx

WPRT (46 Gy/23 fx or 50.8 Gy/28 fx)

Years: 1988-1995

Sedlis et al, Gyn Onc 1999
Rotman, et al. IJROBP 2006 May 1;65(1):169-76
Fig. 2. Progression-free survival by treatment group: 30 RT patients and 49 OBS patients recurred or died. RT significantly increased progression-free survival ($p = 0.009$). OBS = observation; RT = irradiation.
Fig. 3. Survival by treatment group \((p = 0.074)\): 27 RT patients and 40 OBS patients died. Beyond 6 years, only 4 disease-related deaths (2 RT, 2 OBS) occurred, and, hence, the convergence of the curves is the result of other causes. OBS = observation; RT = irradiation.
GOG 109, SWOG 8797, RTOG 9112: Postop RT vs. RT+CDDP/5-FU for high-risk

n = 243
FIGO IA₂ – IIA high-risk cervical cancer s/p hys & PLND
• +LN &/or
• +margin &/or
• +parametria

Years: 1991-1996

Primary outcomes: PFS, OS
Secondary outcomes: Toxicity
Median f/u: 3.5 years

WPRT
• 49.3 Gy/29 fractions (EBRT)
• 45 Gy to PA field (1.5 Gy/fx) if high common iliac LN+

WPRT + CDDP/5-FU (4 cycles)
• Bolus CDDP (70 mg/m²) & 5-FU (4000 mg/m² in 4 days) Q3 weeks
• Cycles 1 & 2 with XRT

Peters et al, JCO 2000
Improved PFS with XRT+CDDP/5-FU

PFS: 80% with chemoXRT vs. 63% with XRT
Adjusted HR 2.01 ($p = 0.003$)

Peters et al, JCO 2000
Improved OS with XRT+CDDP/5-FU

OS: 81% with chemoXRT vs. 71% with XRT
Adjusted HR 1.96 ($p = 0.007$)

Peters et al, JCO 2000
Adjuvant RT conclusions

• Women with large tumors, deep invasion, and/or LVSI should be considered for adjuvant RT.

• Women with positive margins, nodes or parametrium should be offered radiation with chemo.
Ongoing trials

• Intermediate risk
  – GOG 263: RT vs CTRT

• High risk
  – RTOG 0724: CTRT +/- adjuvant chemotherapy (4 cycles carbo/paclitaxel)

• TIME-C/RTOG 1203
  – 3D vs IMRT for postoperative cervix/uterine
Advanced Disease

Definitive CTRT and Brachytherapy
RTOG 90-01: WPRT/Chemo vs. Pelvic/PA XRT

- **n = 389**
  - FIGO IIB-IVA cervical cancer or IB-IIA cervical cancer if tumor > 5 cm or +LN

- **Years:** 1990-1997

- **Exclusion criteria:**
  - Pos. PA LN
  - Disease outside pelvis
  - Prior tx for cervical ca

**Randomize**

- **45 Gy to pelvis and para-aortic LN (EFRT) → LDR brachy**
- **Cumulative point A dose ≥ 85 Gy**

- **45 Gy to pelvis with concurrent CDDP/5-FU → LDR brachy**
  - 3 cycles chemo (Q3 weeks)
    - 75 mg/m² cisplatin
    - 4000 mg/m² 5-FU over 4 days

**Primary outcome:** OS

**Secondary outcomes:** DFS, LR, PA node recurrence, distant metastases

**Median f/u:** 43 months (NEJM 1999); 79 months for surviving patients (JCO 2004)

Toxicity

• Acute toxicity worse with CTRT
  – 11% G4-5 toxicity with CTRT vs 1% RT
  – Difference was largely due to Heme toxicity

• Late toxicity no different
  – 14% in both arms
Improved DFS with ChemoXRT

LR recurrence: 19% with chemoXRT vs. 35% with XRT
Distant mets: 14% with chemoXRT vs. 33% with XRT

Morris et al, NEJM 1999
Improved OS with ChemoXRT

Morris et al, NEJM 1999

Survival (%) vs Months

Radiotherapy and chemotherapy: 73%
Radiotherapy alone: 58%
P = 0.004
CTRT other trials

• GOG 165 (Lanciano, JCO 2005) – weekly CDDP (40mg/m2) vs CI 5FU
  – Stopped early due to worse outcome in 5FU
• GOG 120 (Rose, JCO 2007) – weekly CDDP (40) vs CDDP + 5FU vs Hydroxyurea
  – CDDP arms superior for OS, 5FU only added to toxicity
• GOG 85 (Whitney, JCO 1999) – Hydroxyurea vs CDDP + 5FU x 2 cycles
  – CDDP + 5FU superior for OS & PFS, less toxicity
• NCIC (Pearcey, JCO 2002) – weekly CDDP (40mg/m2)
  – negative trial
HR for survival

RT + CDDP

Eifel, JCO 2004
CTRT conclusion

• CDDP 40mg/m² is the most tolerable regimen for concurrent treatment
• 5FU has no direct evidence that it improves outcomes, and does add toxicity
• Hydroxyurea is inferior to CDDP based regimens
Argentinian Trial

**Background**

- **n = 515**
- FIGO IIB-IVA cervical cancer
- Exclusion criteria:
  - +FNA of PA node
  - Prior XRT or chemo
- Years: 2002-2004

**Randomization**

- 2 variables: drug (cis vs. gem/cis) and chemo timing (concurrent + “out back” vs. concurrent)

**Treatment arms**

- WPRT + weekly gemcitabine/cisplatin → brachy → 2 cycles gem/cis
- WPRT + weekly cisplatin → brachy

**Outcomes**

- Primary outcome: 3-year PFS
- Secondary outcomes: OS, time to progressive disease, local failure rate, tumor response rate, toxicity
- Median f/u: 47 months

**References**

Duenas-Gonzalez et al, *JCO* 2011
Improved PFS & OS with concurrent + adjuvant gemcitabine/cisplatin

- More toxicity in Gem/CDDP arm (p < 0.001) but infrequent grade 3 or 4 toxicities

OUTBACK trial

• Ongoing phase III trial
  – RT (45-50.4Gy) + CDDP (40mg/m² weekly) + Brachy
  – Same + 4 cycles adjuvant Carbo-Taxol
  – Accrual ongoing internationally, endorsed by RTOG and GOG (now NRG)
  – Expected to be complete in 2016
Other Factors

• Treatment time matters:
  – Prolongation of entire course beyond 8 weeks decreases local control up to 1.2%/day
  – Still relevant in with concurrent chemotherapy

• Pretreatment Hb levels <12 have poorer local control and survival
  – Large MDA series shows no association of Hb with local control, after controlling for known confounders
  – transfusion did not improve results
New directions in CTRT

• Triapine (phase III under development at NRG)
  – Ribonucleotide Reductase inhibitor limits DNA synthesis
  – Initial Phase I/II compare very favorably with historical results (Kunos, Gyn Onc 2014)
  – Phase III looking to open 2016

• Bevacizumab
  – Improved survival in advanced disease (Tewar, NEJM 2014)
  – RTOG 0417 (Schefter, IJROBP 2014) shows combination tolerable
  – DFS and OS rates similar to RTOG 9001 rates
Tirapine Data – Majority of women with node positive or stage III disease.

External Beam Technique
The Whole Pelvis Field
GOG Targets of Whole Pelvic RT

• Targets: All suspected disease with minimum 1-2cm margin.
  – Upper ½ of vagina
  – Paracervical region
  – Parametrial region
  – Utero-sacral tissue
  – External iliac nodes
  – Hypogastric nodes
  – Obturator nodes
GOG AP/PA fields
Whole Pelvis

• Cephalad L4-5 interspace
• Caudal mid portion of obturator foramina or 2cm on lowest portion of suspected disease
  – I usually cover a little lower (bottom of foramina)
  – But don’t flash introitius if you don’t have to!
• Lateral borders 1-2 cm on true pelvis
• Small crescent of femoral head usually included to cover obturator/hypogastric nodes
Obturator Nodes
GOG Lateral Fields
Whole Pelvis

• Superior and inferior borders the same
• Posterior: include sacrum to at least S3 to cover uterosacral ligaments, presaral nodes
• Anterior: To the pubic symphysis, superiorly to cover the common iliac nodes, usually 2cm from the anterior aspect of L5.
To ensure coverage of the Presacrals if contouring not performed
The Para-Aortic Field
Para-aortic Fields

• Patients with pelvic nodes or para-aortic nodes on CT or PET
• Superior border is extended to L1-2
• Laterally the tips of Lumbar transverse processes included, ~5cm wide
• Anteriorly 2cm from anterior aspect of vertebral body
• Posteriorly include at least ½ of vertebral body, shielding cord to minimum of 0.5cm
• Kidneys must be identified and kept within tolerance
Para-Aortic Field
PA nodal distribution
PA nodal distribution

- The majority of nodes are in the L paraaortic region
- 2\textsuperscript{nd} most common in the Aorto-Caval Region
- Few noted to the right of the IVC
- Special care must be taken to include the space lateral to the Aorta on the L side
Rational PA CTV
Sidewall Boosts

- May be added to improve lateral coverage IIIB & IIIB disease
  - 1.8-2 Gy x 2-4 fractions
  - Increases toxicity to sigmoid/rectum/bowel
- Consider omitting if good response to CTRT
- Use of interstitial needles in brachy may also reduce need
Sidewall Boost

~5cm
IMRT

• RTOG 0418 studied IMRT for postoperative cervix and endometrial
  – 2 year DFS 87%, OS 95% (ASTRO 2011) for cervix
• TIME-C trial of 3D vs IMRT for postoperative cervix and endometrial currently accruing
• IMRT for intact disease is controversial
  – most reasonable when PA nodal treatment needed
• Care should be taken to keep good coverage on primary
Change in tumor size during treatment

Displacement of Cervix during treatment

(b)

<table>
<thead>
<tr>
<th>Direction</th>
<th>Mean Maximal Displacement (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>3.2</td>
</tr>
<tr>
<td>Inferior</td>
<td>1.8</td>
</tr>
<tr>
<td>Anterior</td>
<td>1.5</td>
</tr>
<tr>
<td>Posterior</td>
<td>2.0</td>
</tr>
<tr>
<td>Right</td>
<td>0.5</td>
</tr>
<tr>
<td>Left</td>
<td>1.3</td>
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</table>

Pelvic CTV for early stage
RTOG 0418
Nodal CTV

• Internal Iliac nodes (hypogastric, obturator)
• External Iliac nodes
  – To top of the femoral heads
• Common Iliac nodes to L4-5
• Presacral Nodes to the level of S3
  – 1-2 cm of tissue anterior to S1,2, and 3 added to cover presacral nodes and the uterosacral ligaments
• Identify Vessels and operative clips
• Margin is 7mm on vessels/clips
  – Caution applying these globally – especially in the area lateral to the Aorta
Intracavitary Brachytherapy
Cervical Cancer

• A solution to the problem of giving high dose to a highly mobile tumor in close proximity to bladder and rectum

• 3D conformal, IMRT and SBRT boosts are severely limited by intrafraction and interfraction movement

• Film based treatment has resulted local control rates of ∼80%, with grade 3-4 late toxicity of ∼15% (RTOG 9001)
Declining Utilization
Declining Survival

Gill, et al. IJROBP 2014 Dec 1;90(5):1083-90
LDR planning
LDR planning

50-60cGY/hr. For 40Gy (85Gy with 45Gy WPRT) = 72-80hours
Brachytherapy Doses

LDR

• Total doses should be summed with Prior External Beam
• Point A doses should be 75-90 Gy
• Point B doses should be 55-60 Gy
  – May boost sidewall with external beam for IIB disease to an additional 5-15 Gy
• Bladder point should be limited to 75Gy
• Rectal points should be limited to 70Gy
Image Guided Brachytherapy

• Current HDR applicators allow for utilization of CT and MRI to visualize the target

• HDR applicators also allow for customization of dose not possible with LDR technique
CT-Based Planning (OAR)

• Weeks & Montana, developed CT compatible T&O set in 1997 at Duke
  – Systematic underestimation of max bladder and rectal doses with Film based plans
• MD Anderson series from 2005
  – rectal point a reasonable surrogate for rectal max
  – bladder point resulted in systematic underestimation of bladder max

CT-Based Planning: Limitations

- CT is not to be ideal at determining extent of disease
- Preoperative CT studies show:
  - 50-65% accurate for extent within cervix
  - 75-80% accurate for determining extension outside of cervix

Subak et al. OB GYN 1995;86(1):43-50
T2 weighted MRI as a Imaging Standard

• MRI superior in same preoperative studies compared to CT
  – 75-90% accurate for extent within cervix
  – 85-95% accurate for extension beyond cervix

• Viswanathan compared CT contours to MRI
  – Found systematic overestimation of cervix with CT
    • 20% median deviation between CT and MRI
    • CT overestimates in the lateral dimension

GEC-ESTRO recommendations for MRI contouring

- GTV: all MRI visible tumor at time of brachytherapy
- HRCTV: GTV + cervix + “grey zones” of indeterminate signal (usually in parametrium)
- IRCTV: HRCTV + 10mm margin, restricted to 5mm anterior and posterior + initial extent of disease
- Normal tissue including bladder, rectum, sigmoid

Potter et al. Rad Onc. 2006 Jan;78(1):67-77
Red – GTV, Orange – HRCTV, Yellow - IRCTV
Clinical Results: Vienna Group

• 141 women with IB-IVA cervical cancer treated with 45-50.4 Gy, concurrent cisplatin
• First 3 years, dose to HRCTV/IRCTV recorded but not used for optimization
• Last 3 years, dose optimized to cover HRCTV/IRCTV

Clinical Results: Vienna

• HRCTV D90
  – <86Gy resulted in local control of 80%
  – >86Gy resulted in local control of 96%

• HRCTV D100
  – <66Gy resulted in local control of 83%
  – >66Gy resulted in local control of 93%

• IRCTV dose was not significantly associated with clinical outcome
Toxicity: Vienna

- Same group demonstrated association with late toxicity
- Rectum Grade 2-4 late toxicity:
  - D2cc 67GY = 5%
  - D2cc 78Gy = 10%
  - D2cc 90Gy = 20%
- Bladder Grade 2-4 late toxicity
  - D2cc 70Gy = 5%
  - D2cc 101Gy = 10%
  - D2cc 134Gy = 20%
- No small bowel or sigmoid association noted

Georg, et al. IJROBP. 2012 Feb 1;82(2):653-7
<table>
<thead>
<tr>
<th>Volume</th>
<th>2D point analogue</th>
<th>3D dosimetric measures</th>
<th>Dosimetric Goal/Limit</th>
<th>Endpoint</th>
<th>Level of Evidence for Goal/Limit</th>
</tr>
</thead>
</table>
| HRCTV (tumor + cervix + parametrial extent at time of implant) | Point A (2 cm superior to ovoids, 2 cm lateral to tandem) | D90 D100 | D90 > 85-90 Gy  
D100 > 65 Gy | Pelvic Control >90% | Strong |
| IRCTV (HRCTV + margin, + initial extent of disease) | Closest analogue is Point B (3 cm lateral to point A) for IIB disease | D90 | D90 > 60-75 Gy | Pelvic Control (no firm data) | Weak |
| Bladder                                         | Bladder point (most dependent point of foley balloon) | D2cc | D2cc < 90 Gy | G2-4 late toxicity < 5-10% | Strong |
| Rectum                                          | Rectal point (5 mm posterior to vaginal packing) | D2cc | D2cc < 75 Gy | G2-4 late toxicity < 5-10% | Strong |
| Sigmoid                                         | None              | D2cc | D2cc < 75 Gy | No firm data | Weak |
| Small Bowel                                      | None              | D2cc | D2cc < 65 Gy | No firm data | Weak |
Applicator Selection

• T&R will cover most small tumors
  – Posterior and anteriorly based tumors may benefit from loading the anterior and posterior ring
• T&O: lateral coverage for larger cervical disease
• T&O/R with interstitial: parametrial disease
• Tandem Cylinder/Miami: thin vaginal disease
• Syed template + Tandem: thick vaginal disease
IGBT conclusions

• MRI is superior to CT and film based delineation of tumor
• Doses to MRI based volumes are associated with clinically relevant outcomes
• Doses to the contoured Bladder and Rectum are associated with late toxicity
• IGBT as a technique is associated with decreased toxicity with the same or improved control
Detail of *Sky Above Clouds IV*. Georgia O’Keeffe, 1965. Art Institute of Chicago
Uterine Cancer
Epidemiology

- Most Common Gynecologic Cancer
- 4\textsuperscript{th} most common malignancy in Women
- 54,870 new cases
- 7\% of Cancer in Women
- 7\textsuperscript{th} most common cause of cancer death
- 10,170 Deaths
- 4\% of Cancer Deaths in Women

American Cancer Society 2015
Risks: Unopposed Estrogen

- Obesity (RR 3, increases to 10 if >50lbs overweight)
- Nulliparity (RR 2-3)
- Menopause after 52yrs (RR 2)
- Diabetes (RR 3)
- Unopposed estrogen replacement (RR 5)
- ALSO: Older age, Caucasian, North American/European, High Socioeconomic status
Lynch Syndrome (HNPCC)

- Microsatellite Instability (MSI)
  - Defects in MSH2 (60%) and MLH1 (30%)
- Confers an 80% lifetime risk of CRC
- 50% lifetime risk of Endometrial Cancer
- Median age 45yrs for both
- Tumors can be screened for MSI prior to formal genetic testing (not routinely performed)
- Accounts for only 2% of Uterine cancers
- No evidence that prognosis is different for HNPCC related cancers
Tamoxifen

- Relative Risk is 7.5
- Absolute Annual Risk is ~1 in 1,000
- Aromatase Inhibitors conversely protect against Endometrial cancer
Presentation and Work Up

• All Postmenopausal Bleeding requires an Endometrial Biopsy (10% will have cancer)
  – Biopsy false negative in ~3% of cases

• Endovaginal US often obtained
  – Postmenopausal Endometrial stripe <4mm unlikely to be malignant
Histology

• Type I cancers:
  – Low Grade
  – Endometrioid
  – Estrogen related
  – Early Stage
  – Common (85%)

• Type II cancers: the inverse of the above (Serous, Clear Cell)
Type I: Endometrioid
Type II: Serous Adenocarcinoma
FIGO staging 1988-2008

- IA – limited to endometrium
- IB – <1/2 myometrial invasion
- IC – >1/2 myometrial invasion
- IIA – endocervical involvement
- IIB – cervical stromal invasion
- IIIA – involves serosa, adnexae or washings positive
- IIIB – vaginal involvement
- IIIC – nodal metastases
- IVA – bladder or bowel invasion
- IVB – distant mets
FIGO staging 2009

- IA – <1/2 myometrial invasion
- IB – >1/2 myometrial invasion
- II – invades cervical stroma
- IIIA – invades serosa or adenexae
- IIIB – vaginal or parametrial involvement
- IIIC1 – positive pelvic nodes
- IIIC2 – positive paraaortic nodes
- IVA – invasion of bladder or bowel
- IVB – distant mets
### Table 5. Grade, Depth of Invasion and Pelvic Node Metastasis

<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>Grade</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(N = 180)</td>
<td>(N = 288)</td>
</tr>
<tr>
<td>Endometrium only</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>(N = 86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inner (N = 281)</td>
<td>3 (3%)</td>
<td>7 (5%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Middle (N = 115)</td>
<td>0 (0%)</td>
<td>6 (9%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Deep (N = 139)</td>
<td>2 (11%)</td>
<td>11 (19%)</td>
<td>22 (34%)</td>
</tr>
</tbody>
</table>

Creasman, Cancer 1987; 60(8 Suppl):2035-41
Incidence of PA Nodes

**TABLE 6. Grade, Depth of Invasion, and Aortic Node Metastasis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>G1 (N = 180)</th>
<th>G2 (N = 288)</th>
<th>G3 (N = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrium only</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Inner (N = 281)</td>
<td>1 (1%)</td>
<td>5 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Middle (N = 115)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Deep (N = 139)</td>
<td>1 (6%)</td>
<td>8 (14%)</td>
<td>15 (23%)</td>
</tr>
</tbody>
</table>

If Pelvic Node +, PA nodes + in 22/58 = 38%
If Pelvic Node -, PA nodes + in 12/563 = 2%

Creasman, Cancer 1987
509 women with stage I-IIA uterine cancer

For G3 OS improved if >11 nodes submitted (HR 0.25, p<0.001)
MRC ASTEC (LND trial)

• Randomized trial examining the utility of LND
• 1408 women with presumed stage I disease randomized to
  – TAH, BSO, peritoneal cytology, palpation of the PA nodes (LND allowed if suspicious nodes noted)
  – Same + LND in all
• LND performed in 5% of no LND arm

Incidence of + nodes

- Low Risk (IA, G1-2): 6/255 (2%)
- High - Intermediate Risk (IB or G3): 21/244 (9%)
ASTEC LND trial

HR=1.35 (95% CI 1.06–1.73); p=0.017

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>6</th>
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</thead>
<tbody>
<tr>
<td>Standard</td>
<td>704</td>
<td>591</td>
<td>469</td>
<td>304</td>
<td>204</td>
<td>115</td>
<td>31</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>704</td>
<td>597</td>
<td>462</td>
<td>303</td>
<td>200</td>
<td>107</td>
<td>37</td>
</tr>
</tbody>
</table>
ASTEC LND trial

A Overall survival

HR=1.16 (95% CI 0.87–1.54); p=0.31

Proportion alive

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>88</td>
<td>704</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>103</td>
<td>704</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>704</td>
<td>704</td>
</tr>
</tbody>
</table>

Years from randomisation

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>704</td>
<td>614</td>
<td>488</td>
<td>317</td>
<td>214</td>
<td>119</td>
<td>33</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>704</td>
<td>620</td>
<td>489</td>
<td>327</td>
<td>211</td>
<td>116</td>
<td>69</td>
</tr>
</tbody>
</table>
LND toxicity

• Moderate to severe complications
  – No LND 12%
  – LND 17%
LND conclusions

• LND cannot be routinely recommended
• LND upstages ~10% of women with pathologic risk factors (IB or G3 disease)
Adjuvant Radiotherapy:
Early Stage
PORTEC 1 (WPRT vs nothing)

• Endometrial adenocarcinoma s/p TAH/BSO
  – G1 and IB (FIGO 2009)
  – G2
  – G3 and IA (FIGO 2009)

• 715 Randomized to no further treatment (NFT) v WPRT (46 Gy)
  – 5y LRR: NFT 14% vs WPRT 4% (p<0.001)
  – 5y OS: NFT 85% vs WPRT 81% (NS)

Creutzberg et al. Lancet 2000;355:1404
PORTEC 1

- Vaginal Recurrence most common at 75% (30/40 in the NFT arm)
- 2y OS after vaginal recurrence 79%  
  - better with NFT, though more NFT patients recurred
- Note PORTEC excluded IBG3
PORTEC 1 update

- 10y LRR: RT 5% vs 14% NFT (p<0.0001)
- 10y OS: RT 66% vs 73% NFT (p=0.09)
- 10y DSS: RT 11% vs 9% NFT (p=0.47)
- Upon Excluding G1 with superficial invasion:
  - 10 y LRR: RT 5% vs 17% NFT (p<0.0001)

Sholten et al. IJROBP 2005;63:834
GOG 99 (WPRT vs NFT)

• Intermediate risk patients
  – Stage IA&B and occult II (FIGO 2009) s/p TAH/BSO with LND

• 448 Pts Randomized to NFT or WPRT (50.4 Gy)
  – LR (2) NFT 12% vs WPRT 3% (p=0.007)
  – OS (4) NFT 86% vs WPRT 92% (p=0.56)

Keys et al. Gyn Onc 2004;92:744
GOG 99

• Subgroup Analysis: High Intermediate Risk (HIR)
  – 3 risk factors
    • LVSI
    • G2-3
    • Deep 1/3 invasion
  – Stratified by Age
    • Need 3/3 factors if <50
    • Need 2/3 factors if 50-70
    • Need any factor if >70
  – 2 year recurrence rate 26% (NFT) vs 6% (WPRT)
PORTEC 2 (VBT vs WPRT)

• 427 patients with one of the following
  – >60yo with IBG1-2 or IAG3 disease (FIGO 2009)
  – *No IBG3 disease allowed on trial*

• Randomized to
  – 46Gy in 23fx WPRT
  – VBT (7Gy x 3 to 5mm, ½ length)
    • Also allowed 30Gy LDR and 28Gy MDR

• Primary endpoint was vaginal recurrence

Lancet 2010; 375: 816–23
PORTEC 2: Results

Vaginal Recurrence

Pelvic Recurrence

3% difference
PORTEC 2: Toxicity

D

Limited Daily Activities as a Result of BS (99% CI)

Time of Assessment (months)

EBRT

VBT

P time < .001
P random assignment < .001
P time x random assignment = .48
PORTEC 2 conclusions

• VBT and WPRT prevent most vaginal recurrences
• WPRT improved pelvic control by ~3%, though no survival benefit
• WPRT more toxic
• Therefore VBT treatment of choice for most intermediate risk women
Swedish Low Risk Trial (VBT vs NFT)

• 645 women with IA (2009), G1-2 randomized to:
  – 3-8Gy x 3-6 fractions (5 mm depth)
  – No Further Treatment (NFT)
• Vaginal recurrences 1.2% with VBT, 3.1% with NFT (p=0.114)
• G1-2 toxicity 2.8% with VBT, 0.6% with NFT
• Conclusions: Safe to omit VBT if Low Risk

Swedish Trial Intermediate Risk Trial (VBT +/- WPRT)

- 527 patients with stage I endometrioid adenocarinoma with at least one factor: G3, IB, or DNA aneuploidy

- Randomized to:
  - WPRT (46Gy) + VBT
  - VBT alone

- VBT doses: 3.0Gy x 6, 5.9Gy x 3 or 20Gy x 1 (LDR) to 5mm, 2/3 vagina

Sorbe, et al. IJROBP. 2012 Mar 1;82(3):1249-55
Swedish Trial (VBT +/- WPRT)

Red line = Vaginal irradiation alone (N = 223)
Blue line = External + vaginal irradiation (N = 224)

15 pelvic recurrences in VBT alone arm, 1 in WPRT + VBT arm
5 y LRF 1.5% with WPRT+VBT, 5% with VBT alone

Log rank test = 2.443; P = 0.015

3% difference
Swedish Trial (VBT +/- WPRT)

Blue line = external + vaginal irradiation (N = 264)
Red line = vaginal irradiation (N = 263)

Log-rank test = 0.600; P = 0.548
Swedish Trial (VBT +/- WPRT)

Table 6. Late side effects vs. type of treatment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A</td>
<td>9.8%</td>
<td>2.9%</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td>2.3%</td>
<td>0.4%</td>
<td>0.0%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A</td>
<td>26.9%</td>
<td>6.4%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td>20.2%</td>
<td>2.7%</td>
<td>0.8%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>VAGINA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A</td>
<td>12.7%</td>
<td>0.7%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td>4.1%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Arm A = VBT + WPRT, Arm B = VBT alone
GOG 249

- 601 women with HIR uterine cancer, stage II, or pap serous/clear cell stage I-II, randomized to:
  - WPRT alone
  - VBT followed by Carbo Taxol x 3
GOG 249 results

No Difference in 2 yr Relapse Free Survival (WPRT 82% vs 84% VBT/CT) or Overall Survival (WPRT 93% vs 92% VBT/CT)
GOG 249 Results

- No differences were seen for all subgroups
  - The HR for Serous/Clear cell did tend towards favoring VBT/CT, but crossed 1.0

<table>
<thead>
<tr>
<th>Site of Recurrence</th>
<th>WPRT</th>
<th>VBT + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>5 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Pelvic</td>
<td>2 (1%)</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Para-aortic</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Distant</td>
<td>32 (11%)</td>
<td>24 (8%)</td>
</tr>
</tbody>
</table>
Ongoing Trials

• PORTEC 3 – High risk Early (and later) stage cancers (>= IBG3):
  – Randomizing to WPRT +/- Chemotheary
• TIME-C – randomized trial of IMRT vs 3D
• PORTEC 4 – Intermediate Risk:
  – NFT
  – VBT (5Gy x 3 to 0.5cm depth)
  – VBT (7Gy x 3 to 0.5cm depth)
Adjuvant Recommendations

• Stage IA G1 - Observe
• Stage IA G2-3, IB G1-2, – Offer VBT
  – 7Gy x 3 to 0.5cm depth
  – 5Gy x 5 to 0.5cm depth
  – 6Gy x 5 to surface
• Stage IBG3 – Strongly Consider VBT or WPRT particularly if nodes not adequately dissected.
• Stage II – WPRT + VBT +/- chemo (45Gy + 4Gy x 3 to 0.5cm depth)
Advanced Stage (stage III/IV)
GOG 122 (Chemo vs RT)

• 388 pts. Stage III-IV, all histologies.
• Required TAH/BSO, surgical staging, <2cm residual tumor.
• Randomized to:
  – WAI (30 Gy, 20 fx, AP/PA plus boost to pelvic +/- para-aortic LN 15 Gy in 8 fx)
  – CT (doxorubicin + cisplatin q3w x 8 cycles).
• Recurrence:
  – WAI 54% vs CT 50% p<0.01)
• 5y OS:
  – WAI 42% vs CT 55% (p<0.01)
• More acute toxicity with chemo:
  – 4% tx related deaths CT, 2% WAI.

Randall JCO 2006 24(1):36
Chemotherapy vs RT
JGOG High Risk Trial

• IC-IIIIC endometrial cancer (61% were IC)
• 385 Randomized to CAP vs 45-50GY WPRT
• 95% had pelvic nodal evaluations
• G3/4 toxicity 1.6% WPRT vs 4.7% CAP

JGOG: CAP vs WPRT

EBRT reduced LRF
Chemo reduced DM

? More benefit to chemo in >70 IB or G3, or stage II with Deep invasion
Chemotherapy vs RT
Maggi High Risk Trial

• ICG3, IIG3 with deep invasion, and stage III
• 345 randomized to
  – Chemo (CDDP, Dox, Cyclo) x 5 cycles
  – EBRT 45-50Gy
• ~25% IB G3 (FIGO 2009)
• RT G3 GI toxicity 16%, GU toxicity 5%
• Chemo >= G3 heme toxicity 35%

Maggi Trial

Overall Survival

EBRT reduced LRF
Chemo reduced DM

χ² (log-rank): 0.0836 (P=0.7724)

Patients at risk
Radio: 166, 151, 129, 109, 100, 88, 77, 68, 51, 42, 27
Chemio: 174, 156, 141, 119, 105, 91, 79, 65, 54, 39, 30

Years from randomisation

EORTC/MaNGO trials
Hogberg Analysis

• Two phase III trials with similar design analysed together
• 534 women with stage I-III randomized to
  – RT alone
  – RT with Chemotherapy (chemo varied)
• DFS was improved with RT + CT (HR 0.63, p=0.009)
• Trend in improved OS (HR 0.69, p=0.07)

Hogberg et al. Eur J Cancer 2010 Sep;46(13):2422-31
**Hogberg: EORTC/MaNGO**

**Figure 2.**
Progression-free survival in the pooled NSGO-EC-9501/EORTC-5591 and MaNGO studies.
(CI: Confidence interval, HR: Hazard ratio, RT: radiotherapy, RT-CT: sequential radiotherapy and chemotherapy).
Summary Chemo vs RT Trials

• JGOG and Maggi trials have not demonstrated superiority of chemotherapy or RT in advanced disease

• Combined Hogberg analysis of 2 Phase III trials demonstrated an improvement in PFS with CT after RT

• Retrospective Series from Duke (Secord, 2007) suggested sandwich CT -> RT -> CT superior, however never tested in phase III

• RTOG 9708 also looked at concurrent treatment in Phase II
  • WPRT/EFRT + VBT + CDDP (50mg/m2 x 2)
  • 4 cycles adjuvant CDDP + paciltaxel

Ongoing Trials

• PORTEC 3 (includes IBG3 – IVA):
  – WPRT vs
  – WPRT with concurrent CDDP x 2 (50mg/m²) followed by 4 cycles of carboplatinum - paclitaxel

• GOG 258 (stage III or IVA)
  – carboplatinum – paclitaxel x 6 vs
  – WPRT/EFRT with concurrent CDDP x 2 (50mg/m²) followed by 4 cycles of carboplatinum - paclitaxel
  – Accrual complete – expect results in late 2016
What to do off protocol

• For most patients with stage III disease there are two options:
  – RTOG 9708 regimen
    • WPRT/EFRT + VBT + CDDP (50mg/m2 x 2)
    • 4 cycles adjuvant CDDP + taxol
  – Sequential Chemotherapy (Carbo/Taxol) and RT (sandwich or otherwise)
Bleu II. Joan Miró, 1961. Musée National d'Art Moderne
Vulvar Cancer
Vulvar Cancer

• 5,150 new cases estimated for 2015, with 1,080 deaths

• Two groups:
  – Young smokers, HPV positive, perhaps VIN
  – Older patients with lichen sclerosus/vulvar dysplasia
Carcinogenesis: HPV

• HPV can be isolated in 40% of invasive lesions
  – 16
  – 18
  – 33
• Risk for HPV related disease follows patterns from other HPV related disease from the anogenital region
  – Genital warts, smoking, multiple sexual partners, immune suppression
• Reports are mixed, however HPV associated disease may be associated with improved prognosis
Carcinogenesis: VIN

• 1/3 of vulvar cancers have a association with VIN
• <5% of women with VIN will develop invasive disease
• This is in stark contrast to the much stronger relationship between CIN and cervical cancer
Carcinogenesis: Lichen Sclerosus

- Associated in 30-60%
- No direct transformation has been documented histopathologically
- Women with lichen sclerosus have an ~5% risk of developing invasive disease
## Histopathologic Patterns of Squamous Carcinoma (85% of lesions)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Keratinizing Squamous Carcinomas</th>
<th>Basaloid Squamous Carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Age</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td>Related Disease</td>
<td>LS and other vulvar dystrophy</td>
<td>HPV infection, other anogenital lesions, VIN, multifocality</td>
</tr>
<tr>
<td>p16</td>
<td>often -</td>
<td>often +</td>
</tr>
<tr>
<td>p53</td>
<td>either + or -</td>
<td>often -</td>
</tr>
</tbody>
</table>
Other Histologies

• Melanoma (10%)
  – Behave similar to melanoma of other mucosal sites

• Adenocarinomas (5%)
  – May present as a mass below the epidermis
  – May present in more advanced stages with LN positivity
FIGO 2009

- IA: $\leq 2\text{cm}$ primary, $\leq 1\text{mm}$ invasion
- IB: $>2\text{cm}$ primary and/or $>1\text{mm}$ invasion
- II: lower urethra, vagina, anus
- IIIA: 1-2 nodes $<5\text{mm}$ each or 1 node $>5\text{mm}$
- IIIB: 2 nodes $>5\text{mm}$ each, or 3+ nodes
- IIIC: + LN with ECE
- IVA: fixed/ulcerated nodes
- IVB: pelvic nodes or distant mets
Radiation Considerations

• After Surgery
  – Control of the Primary
  – Control of the Pelvic, Inguinal Nodes

• Locally advanced
  – Preoperative CTRT
  – Definitive CTRT
Wide Local Excision

Need for RT to the Vulvectomy Bed
GOG 36

• 5-year OS (1988 stage)
  – 98% stage I
  – 85% stage II
  – 74% stage III
  – 31% stage IV

• Local Control after radical vulvectomy:
  – if tumor size >4cms and/or LVI, LR 20.7% (30/184)
  – if neither factor LR 9.2% (37/404).

Homesley HD, Gynecol Oncol. 1993 Jun;49(3):279-83
Control of Primary

• Faul (U. Pitt) retrospective
• 62 pts with close (<8mm) or positive margins
  – 31 observed
  – 31 received RT (vulva, bilateral groins, and lower pelvis, mean dose 56 Gy)
• Mean f/u 3 yrs
• Local Recurrences:
  – Positive margins: in 69% obs vs 33% RT (SS)
  – Close margins: 31% obs vs 5% RT (SS)

Faul CM et al. IJROBP. 1997;38(2):381-9
Heaps Factors

• Local Recurrence
  – margin >= 8mm 0%
  – Margin < 8mm 48%

• Other factors predicting LR
  – Depth of invasion >9mm
  – Thickness >10mm
  – Infiltrative growth pattern (“spray” pattern)
  – LVI
  – Increased Keratin
  – >10 mitoses/10 HPF
Central Block?

- Dusenberry Series (U. Minn)
- 27 pts with positive nodes treated with post-op RT
- Midline was blocked in 26/27
- Median dose 45 Gy
- Recurrences in 63% at a median of 9 months from surgery
- 3/4 recurrence were under midline block
- *This is in contrast however to the results in GOG 37 and GOG 88 where vulvar recurrences of 4-9% were seen without RT to the vulva*

Dusenbery. IJROBP. 1994; 29(5):989-98
Treating the Perineum

Conclusions

• For low grade tumors with wide margins, no LVI, sparing the primary is reasonable
• For close margins, or multiple risk factors, treat the primary
• For negative margins 45-50GY reasonable
• For close margins 50-55Gy reasonable +/- CDDP
• For gross residual disease 60-65Gy as tolerated + weekly CDDP
Inguinal & Pelvic Control

Radiotherapy Post WLE/Dissection to nodal basins
## Risk of Nodal Inguinal Nodes by depth of Invasion

<table>
<thead>
<tr>
<th>Depth (mm)</th>
<th>n</th>
<th># of nodes</th>
<th>incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>120</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1.1-2</td>
<td>121</td>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td>2.1-3</td>
<td>97</td>
<td>8</td>
<td>8%</td>
</tr>
<tr>
<td>3.1-4</td>
<td>50</td>
<td>11</td>
<td>22%</td>
</tr>
<tr>
<td>4.1-5</td>
<td>40</td>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>&gt;5</td>
<td>32</td>
<td>12</td>
<td>38%</td>
</tr>
</tbody>
</table>

20% of cN0 pts are pN+
if +inguinal nodes, 30% have +pelvic nodes

Adapted from Gunderson 2007
Nodal Dissection

• Nodal dissections standard for all with >1mm invasion
• Unilateral OK with a small, well lateralized lesion (>1cm from midline)
• Bilateral for others
Sentinel LN Bx

- GROINSS-V study
  - 276 Small Tumors (<4cm) selected
  - Dye + Radiotracer, Surgeons needed 10 cases experience to participate
  - If SNBx negative, no further treatment
  - 3% local recurrence at 2 years in the untreated nodal basin
  - If lesion was unifocal, 2.3% recurrence.
  - 3 years DSS for unifocal, negative SNB: 97%
GROINSS-V II (GOG 270)

- Single arm trial
- SNBx for all
- If negative: Observe
- If positive:
  - <2mm, no ECE then 50Gy RT to ipsilateral groin and ipsilateral low pelvis
  - >2mm or ECE then complete dissection, then 56Gy RT to ipsilateral groin and pelvis

- 2mm cut-off was determined at interim analysis:
  - 9/45 failures with >2mm and 50Gy
  - 1/46 failures with <2mm and 50Gy
  - Inadequate volumes?
  - 80% done
GOG 37 (RT vs LND)

• Resectable vulvar SCC
• s/p radical vulvectomy & bil superficial and deep inguinal dissection found to have + inguinal LNs
• 114 pts randomized to:
  – Pelvic node dissection - PLND (15/53 patients had + pelvic LNs)
  – RT (45-50 Gy to inguinal nodes and pelvic nodes BUT NOT vulvar region)
• 50% of patients were cN0 (PE not sensitive for groin node mets)
• Groin recurrence PLND 13/55 vs RT 3/59 (p=0.02)
• OS (2) PLND 54% vs RT 68% (p=0.03)

Homesley et al. OB Gyn 1986;68:733
Figure 1. Survival related to type of treatment.
Figure 3. Survival related to number of positive groin nodes and treatment.
What about 1 node positive?

- Consider treatment if <10-12 nodes submitted (<5-6 nodes on the positive side)
- Alternatively, one could easily justify treatment in all with 1 node positive as this was a unplanned subgroup
Inguinal Nodes: GOG 88

• Resectable vulvar SCC; Excluded T1 lesions unless LVI or >5mm invasion; s/p radical vulvectomy

• 58 pts randomized to
  – Bilateral groin dissection, RT if positive
  – Bilateral groin irradiation

• 50 Gy/ 25fx, with 50% of dose given with 12-13 MeV electrons; Rx'd to 3 cm

• 5/25 patients had + nodes in Arm A

Stehman et al. IJROBP 1992;24:389
GOG 88 fields

Fig. 1. Radiation treatment fields.
GOG 88: PFS

Dissection

Radiation

p = 0.033
GOG 88: OS

Dissection

p = 0.035

RT

<table>
<thead>
<tr>
<th>Rx</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
<th>P = 0.035</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groin Dissection</td>
<td>22</td>
<td>3</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Groin Rt</td>
<td>17</td>
<td>10</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>
## Patterns of Failure

### Table 4. Recurrences and deaths

<table>
<thead>
<tr>
<th>Recurrences/deaths</th>
<th>Groin dissection</th>
<th>Groin radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvar</td>
<td>1 (4.0)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Groin</td>
<td>0 (0.0)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Distant</td>
<td>1 (4.0)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>None</td>
<td>23 (92.0)</td>
<td>19 (70.4)</td>
</tr>
<tr>
<td><strong>Deaths:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>1 (4.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Intercurrent</td>
<td>1 (4.0)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Disease</td>
<td>1 (4.0)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Alive</td>
<td>22 (88.0)</td>
<td>17 (63.0)</td>
</tr>
</tbody>
</table>
Is 3cm enough?

• University of Washington Anatomic Study
• Examined CT scan of 50 patients undergoing treatment for Gynecologic Cancer
### GOG 88: the 5 groin failures

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>QI</th>
<th>EstD (cm)*</th>
<th>Ph dose</th>
<th>E dose</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>5.2</td>
<td>2345↑</td>
<td>&lt; 960**</td>
<td>&lt; 3305</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>7.3</td>
<td>2014↑</td>
<td>&lt; 252**</td>
<td>&lt; 2266</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>4.9</td>
<td>4679↑</td>
<td>None</td>
<td>4679</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>6.0</td>
<td>4284‡</td>
<td>None</td>
<td>4284</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>8.7</td>
<td>1868§</td>
<td>&lt; 240**</td>
<td>&lt; 2108</td>
</tr>
</tbody>
</table>
Location of Inguinal Nodes

• The distance of vessels to nodes is much greater than in the pelvis
• A study by Beriwal found margins needed to be 2.2-2.9cm from the vessels to cover 90% of the nodes involved (much greater than the 7mm used in the pelvis)
• Anatomic boundaries are more appropriate

Kim et al, Practical Radiation Oncology (2012) 2, 274-278
laterally – medial border of the iliopsoas

medially - lateral border of adductor longus or medial end of pectineus

posteriorly - iliopsoas muscle laterally and anterior aspect of the pectineus muscle medially

anteriortly - at least along the anterior edge of sartorius muscle.
Inguinal/Pelvic Conclusions

• Nodal evaluation needed if >1mm
• May consider sentinel node biopsy with small, unifocal, disease
  – If negative, observe
  – If positive, complete dissection vs RT in well selected patients
• After nodal dissection
  – One positive nodes of 5+ submitted: +/- RT
  – 2+ nodes: RT to inguinal and pelvic basins
• Pay special attention to inguinal CTV contours
## Unresectable Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>RT</th>
<th>Surgery</th>
<th>f/u (yr)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montana 2000</td>
<td>46</td>
<td>N2/3</td>
<td>FU + CDDP</td>
<td>47.6 BID, partly</td>
<td>83%</td>
<td>6.5</td>
<td>crude NED 26% nodal control 36/37 vulvar control 29/38</td>
</tr>
<tr>
<td>Moore 1998</td>
<td>71</td>
<td>T3/4</td>
<td>FU + CDDP</td>
<td>47.6 BID, partly</td>
<td>90%</td>
<td>4</td>
<td>crude NED 67%</td>
</tr>
<tr>
<td>Landoni 1996</td>
<td>54</td>
<td>T2-4, N+, X</td>
<td>FU + MMC</td>
<td>54 QD</td>
<td>72%</td>
<td>2</td>
<td>crude NED 49% 2y OS 36%</td>
</tr>
</tbody>
</table>
Preop RT

• GOG 101
  – With preop CTRT (47Gy), cCR was seen in ~50%, and pCR in these patients was 70%.
  – Overall pCR rate of ~35%

• Other preop series (Beriwal, 2008)
  – 45Gy IMRT with CDDP/5FU
  – pCR rate 64%
GOG 205

• T3 or T4 tumors
• $180\text{cGy} \times 32 = 5760\text{cGy}$, + weekly CDDP (40mg/m²) with planned surgical resection of primary tumor
• 69% completed treatment as planned
• 64% had a complete clinical response
• Of these 78% achieved a pathCR (by biopsy or surgical resection)
• Overall pCR of 50%

GOG 205 compared to 101

<table>
<thead>
<tr>
<th></th>
<th>GOG 101</th>
<th>GOG 205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable</td>
<td>71</td>
<td>58</td>
</tr>
<tr>
<td>CCR</td>
<td>34 (48%)</td>
<td>37 (64%)</td>
</tr>
<tr>
<td>PCR</td>
<td>22 (31%)</td>
<td>29 (50%)</td>
</tr>
<tr>
<td>PCR/CCR</td>
<td>22/34 (65%)</td>
<td>29/37 (78%)</td>
</tr>
</tbody>
</table>
GOG 205

Proportion Surviving vs Months on Study

Response
- Incomplete
- Complete Clinical
- Pathologic

<table>
<thead>
<tr>
<th>Response</th>
<th>Alive</th>
<th>Dead</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete</td>
<td>9</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Complete</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Pathologic</td>
<td>21</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>
## Chemoradiation for Advanced Vulvar Cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of patients</th>
<th>Chemotherapy</th>
<th>Radiation Therapy dose (Gy)</th>
<th># Post-Tx surgery</th>
<th>Median &amp; range of FU (months)</th>
<th>Clinical Complete Response (%)</th>
<th>Clinical Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore, 2011</td>
<td>58</td>
<td>P</td>
<td>57.6</td>
<td>34</td>
<td>NS</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>Mak, 2011</td>
<td>16 28</td>
<td>P</td>
<td>50 55</td>
<td>4 6</td>
<td>32 32</td>
<td>60 58</td>
<td>62 (2 yr DFS) 56 (2 yr DFS)</td>
</tr>
<tr>
<td>Mak, 2011</td>
<td></td>
<td>F + P/M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tans, 2011</td>
<td>28</td>
<td>F + M</td>
<td>60</td>
<td>NS</td>
<td>42</td>
<td>72</td>
<td>71 (4 yr PFS)</td>
</tr>
<tr>
<td>Beriwal, 2008</td>
<td>18</td>
<td>F + P</td>
<td>44.6-46.4</td>
<td>14</td>
<td>22 (2-60)</td>
<td>72</td>
<td>75 (2 yr DSS)</td>
</tr>
<tr>
<td>Gerszten, 2005</td>
<td>18</td>
<td>F + P</td>
<td>44.6</td>
<td>14</td>
<td>27</td>
<td>72</td>
<td>83 (crude NED)</td>
</tr>
<tr>
<td>Montana, 2000</td>
<td>46</td>
<td>F + P</td>
<td>47.6</td>
<td>38</td>
<td>78 (56-89)</td>
<td>NS</td>
<td>54 (crude NED)</td>
</tr>
<tr>
<td>Moore, 1998</td>
<td>71</td>
<td>F + P</td>
<td>47.6</td>
<td>64</td>
<td>45</td>
<td>48</td>
<td>63 (crude NED)</td>
</tr>
<tr>
<td>Landoni, 1996</td>
<td>58*</td>
<td>F + M</td>
<td>54</td>
<td>42</td>
<td>(4-48)</td>
<td>27*</td>
<td>49* (crude NED)</td>
</tr>
<tr>
<td>Lupi, 1996</td>
<td>24</td>
<td>F + M</td>
<td>54</td>
<td>22</td>
<td>34 (22-73)</td>
<td>42</td>
<td>55 (5 yr OS)</td>
</tr>
<tr>
<td>Wahlen, 1995</td>
<td>19</td>
<td>F + M</td>
<td>45-50</td>
<td>6</td>
<td>(3-67)</td>
<td>53</td>
<td>89 (5yr DSS)</td>
</tr>
<tr>
<td>Sebag-Montefiore, 1994</td>
<td>37</td>
<td>F + M</td>
<td>45</td>
<td>14</td>
<td>NS</td>
<td>47</td>
<td>37 (2 yr OS)</td>
</tr>
<tr>
<td>Koh, 1993</td>
<td>17</td>
<td>F + P/M</td>
<td>54</td>
<td>10</td>
<td>(1-75)</td>
<td>53</td>
<td>49 (5 yr DSS)</td>
</tr>
<tr>
<td>Russell, 1992</td>
<td>18</td>
<td>F + P</td>
<td>46.8-72</td>
<td>1</td>
<td>24 (2-52)</td>
<td>89</td>
<td>75 (crude NED)</td>
</tr>
</tbody>
</table>
Preop Conclusions

• Daily RT to 45 to 57Gy with weekly CDDP reasonable

• 5FU seems to add toxicity without proven benefit (Mak, 2011)

Mak, et al. Gynecol Oncol. 2011 Jan;120(1):101-7
Definitive RT

- 65Gy to gross disease with concurrent weekly CDDP
- 2yr OS 70%, DFS 60%, LRR 30%, DM 10%
IMRT for Vulvar Cancer

• Reports are limited
• Largest series from Pittsburgh (Beriwal) shows reasonable results with LR in 2/18
• Atlas in development

Beriwal, el al. IJROBP 2013 Apr 1;85(5):1269-74
The Future: GOG 279

• Phase II trial of Gem + CDDP + RT
  – 64Gy to gross disease, 45-50Gy to elective volume
  – Gem 50mg/m2, CDDP 40mg/m2 weekly
• If nodes resectable – stop at 50Gy and resect
• If complete clinical response – confirmation biopsy performed, and no surgery
• If no complete clinical response – surgery
• IMRT is allowed on trial
Biopsy Proven Vulvar Cancer

Clinically Assesss +/- CT, +/- PET

Localized, Resectable
Radical Wide Excision With Tailored Adjuvant Therapy

Locally Advanced
Multimodality Therapy

Distant Metastasis
Palliative Chemotherapy, Radiotherapy, & Supportive Care

Radical Wide Excision

<1mm invasion, negative margins, negative risk factors*
Observe

>1mm invasion or clinically node positive
Nodal Evaluation: Sentinel vs Full Dissection
Unilateral vs Bilateral

Node Negative
Observe or Radiotherapy

1 node positive
Observe or Radiotherapy

2+ nodes positive
Radiotherapy +/- Chemotherapy

Positive/Close Margins, positive risk factors*
Re-excise (for margins) or Radiotherapy +/- Chemotherapy

Multimodality Therapy

Preoperative Chemoradiotherapy (45-57Gy with CDDP)
Surgery

Definitive Chemoradiotherapy (60-65Gy with CDDP)

* Risk Factors for Local Recurrence: margins < 8mm, >10mm thickness, infiltrative pattern, LVI, high mitotic activity, increased keratin
Atlas Update

• Vulvar atlas completed, manuscript under preparation
• Intact cervix EBRT atlas under construction
• Postop Cervix/Uterine atlas under revision
• Image guided brachytherapy atlas published (Viswanathan, IJROBP 2014)
Vaginal Cancer

• No randomized data
• Tumors which abut the cervix or vulva are re-classified even if the disease is center vaginally
• Excision only considered for earliest disease
• All others Radiation therapy with CDDP reasonable
• Brachytherapy boost depends on response and extent of disease
Ovarian Cancer

• Ovarian cancer is actually quite radioresponsive
• Unfortunately, most ovarian tumors have early access to the peritoneal cavity
• For tumors confined to a nodal pattern of spread or recurrence, RT is quite reasonable
Key Points

• Cervix
  – IB1 and lower stages adequately treated with surgery and risk based use of adjuvant RT+/- CT
  – Concurrent CTRT for all others
  – Brachytherapy is standard of care!

• Uterus
  – Early stage adjuvant recommendations should be risk stratified
    • no RT for low risk
    • Consider VBT vs WPRT for intermediate and high risk
  – Advanced stage should be treated with multi-modality treatment

• Vulva
  – Early stage disease adequately treated with surgery alone
  – If nodes positive or risk of local recurrence high, radiation should be offered
  – Special Care should be taken when designing fields/PTVs
  – For advanced disease, multimodality treatment preferred
Thanks for your Attention!

junzo.chino@duke.edu