Endometrial Cancer
– An Update

Kathleen Yang, M.D.
Northwest Gynecologic Oncology
Willamette Valley Cancer Institute
Financial Disclosure

I have nothing to disclose.
Endometrial Cancer

• 43,470 new cases in US in 2010.
• Now most common gynecologic cancer in developed countries.
• Death rate rising
• Management complicated by morbid obesity.
• Surgery is mainstay of treatment, but treatments of metastatic disease and recurrent cancer remain inadequate.
What We’ve Seen This Past Year…

• Alarming number of obese pts with occult endometrial cancer at the time of surgery for CAH
• Treatment complicated by history of endometrial ablation
Should patients with CAH be referred to Gyn Onc?
GOG 167

- N=306
- Prospective cohort study
- CAH at office EMB
- Concurrent EMCA at hyst = 42%

Trimble et al, Cancer 2006
Kaiser Permanente Data

- N=824
- CAH on initial sampling
- Concurrent EMCA = 48%!
- Concurrent EMCA after additional preop D&C = 41%
- Rate of unrecognized CA very concerning
- CAH in obese pts warrants consideration of Gyn Onc referral

Suh-Burgmann et al, Obstet & Gynecol 2009
Should obese patients with heavy vaginal bleeding receive EM ablation?
Impact of EM Ablation
• Consider referring pts with CAH to Gyn Onc
• Minimize EM ablation
Endometrial Cancer 2011

- FIGO staging
- Surgical Therapy
  - Minimally invasive surgery
  - Role of lymph node dissection
- Adjuvant Therapy
  - Early stage
  - Advanced stage – resected
- Chemotherapy / Drug Development
New Staging System

• What’s the purpose of a staging system?
• First revision of FIGO staging system since 1989
FIGO Staging

**Old**
- I - uterus only
  - 1A: EM only
  - 1B: <50 myomet invasion
  - 1C: >50% myomet invasion
- II - Cervix
  - IIA: endocx glandular only
  - IIB: cx stroma
- III - local / regional spread
  - IIIA: ut serosa or adnexa or washing
  - IIIB: vagina
  - IIIC: pelvic or paraaortic LN
- IV - mets
  - IVA: bladder or bowel
  - IVB: distant mets

**New**
- I – uterus only
  - IA: myometrial invasion < 50%
  - IB: myometrial invasion ≥ 50%
- II – Cervical stroma
- III – local/regional mets
  - IIIA: ut serosa or adnexa
  - IIIB: vagina / parametrium
  - IIIC: LN+
    - IIIC1: Pelvic LN+
    - IIIC2: Paraaortic LN+
- IV – mets
  - IVA: bladder / bowel mucosa
  - IVB: distant mets
Endometrial Cancer 2011

• FIGO staging
• Surgical Therapy
  - Minimally invasive surgery
  - Role of lymph node dissection
• Adjuvant Therapy
  - Early stage
  - Advanced stage – resected
• Chemotherapy / Drug Development
Minimally Invasive Surgery

Is L/S staging better than traditional open staging?
GOG Lap 2 Trial

- N = 2,616
- LSC : Open -> 2:1 randomization
- 74% successful LSC staging
- 57% BMI > 40
- Longer OR time, shorter hospital stay
- Complications: 14% vs 21%
- Surgical adequacy: 92% vs 96% had pelvic & PA LN identified
- Same OS, improved short-term QoL

Walker JCO 2009
Walker gyn Onc 2010
LACE Trial

- N = 760, 20 centers in Australia, NZ, HK, Scotland.
- Clinical stage I
- L/S staging vs open
- Similar result compared to GOG Lap2 trial
- 4% conversion rate

Kondalsamy-Chennakesavan et al. SGO 2011.
Minimally Invasive Surgery

Is Robotic staging better than L/S staging or open staging?
Robotic

- Advantages: 3-D optics, greater ROM, ergonomics
  - “Easier” L/S LND
  - Obese pts – Seamon (2009) – 109 Robot vs 191 Open, Mean BMI = 40, conversion rate 16%

- 7 Series for EMCA – N=766 (less EBL, shorter stay, similar LN count, conversion rate 7%)
Endometrial Cancer 2011

• FIGO staging
• Surgical Therapy
  - Minimally invasive surgery
  - Role of lymph node dissection
• Adjuvant Therapy
  - Early stage
  - Advanced stage – resected
• Chemotherapy / Drug Development
Is lymphadenectomy necessary in surgery for endometrial cancer?
Is There a Role for Systemic Lymphadenectomy in Clinical Practice?

• Why do we stage?
  - To determine prognosis
  - “Know the enemy” – extent of disease
  - To tailor management
  - To improve survival?

• Who do we stage?
  - Selective
  - All
  - None
### Frequency of Nodal Metastasis

- **For all comers = 9%**
- **Enrichment**
  - UPSC, CC
  - GOG 33: DOI/Grade

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>LN+</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 33</td>
<td>621</td>
<td>9%</td>
</tr>
<tr>
<td>ASTEC (+LND)</td>
<td>686</td>
<td>9%</td>
</tr>
<tr>
<td>CONSORT (+LND)</td>
<td>264</td>
<td>13%</td>
</tr>
<tr>
<td>Lap 2</td>
<td>2510</td>
<td>9%</td>
</tr>
<tr>
<td>(-) LND ASTEC</td>
<td>685</td>
<td>1%</td>
</tr>
<tr>
<td>(-) LND CONSORT</td>
<td>250</td>
<td>3%</td>
</tr>
</tbody>
</table>
Surgical Staging

- LND Proponents
  - GOG 33
  - SEPAL Trial
- LND Detractors
  - ASTEC Trial
  - CONSORT (Italian Trial)
GOG 33

- 621 clinical stage I
- all get TAH/BSO/PPALND/washing
- 22% has mets outside of uterus
- <10% pts w/ LN mets have bulky LNs -> palpation for bulky LNs not reliable

GOG 33

prognostic factors for extrauterine spread = grade, DOI

<table>
<thead>
<tr>
<th></th>
<th>PLN</th>
<th>PALN</th>
</tr>
</thead>
<tbody>
<tr>
<td>low risk (1A gr1)</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>mod risk (gr 2/3, up to mid 1/3)</td>
<td>5-10%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>high risk (outer 1/3 and gr3)</td>
<td>&gt;10%</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>(but 1A gr3 and 1C gr1 are gray zones)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# SEPAL Trial

<table>
<thead>
<tr>
<th>Number of deaths/number of patients in group</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic lymphadenectomy</td>
<td>Pelvic and para-aortic lymphadenectomy</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0.45 (0.17-1.19)</td>
<td>0.11</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.43 (0.23-0.82)</td>
<td>0.0106</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.68 (0.26-1.73)</td>
<td>0.43</td>
</tr>
<tr>
<td>High risk</td>
<td>0.50 (0.31-0.81)</td>
<td>0.0051</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.53 (0.28-0.99)</td>
<td>0.0448</td>
</tr>
<tr>
<td>Total</td>
<td>0.53 (0.38-0.76)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

- Pelvic and para-aortic lymphadenectomy better
- Pelvic lymphadenectomy better
Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study

The writing committee on behalf of the ASTEC study group*

Summary
Background Hysterectomy and bilateral salpingo-oophorectomy (BSO) is the standard surgery for stage I endometrial cancer. Systematic pelvic lymphadenectomy has been used to establish whether there is extra-uterine disease and as a therapeutic procedure; however, randomised trials need to be done to assess therapeutic efficacy. The ASTEC surgical trial investigated whether pelvic lymphadenectomy could improve survival of women with endometrial cancer.

Methods From 85 centres in four countries, 1408 women with histologically proven endometrial carcinoma thought preoperatively to be confined to the corpus were randomly allocated by a minimisation method to standard surgery (hysterectomy and BSO, peritoneal washings, and palpation of para-aortic nodes; n=704) or standard surgery plus lymphadenectomy (n=704). The primary outcome measure was overall survival. To control for postsurgical treatment, women with early-stage disease at intermediate or high risk of recurrence were randomised (independent of lymph-node status) into the ASTEC radiotherapy trial. Analysis was by intention to treat. This study is registered, number ISRCTN 16571884.
ASTEC Trial

- N=1400, clinical stage I or II
- LND vs no LND
- 2nd randomization: pelvic RT vs obs
- Primary outcome: survival
ASTEC Trial
ASTEC Trial

Are the results real?
Is less more?
ASTEC Trial - limitations

• Power calculation
• Removal of bulky LN allowed in control arm.
• LN+ pts also underwent 2nd randomization using uterus-only pathology to stratify risks.
• Brachytherapy allowed and not adjusted – 51% of “no LND” arm
CONSORT (Italian) Trial

\[ \chi^2 = 0.17; P = 0.68 \]

% disease-free survival

\begin{tabular}{ccccccc}
months & & & & & & \\
0 & 6 & 12 & 18 & 24 & 30 & 36 & 42 & 48 & 54 & 60 \\
Lymphad. 264 & 225 & 196 & 159 & 131 & 89 \\
No lymph 250 & 218 & 184 & 150 & 114 & 85 \\
\end{tabular}

events total

42 264
36 250

Panici et al. JNCI 2008
CONSORT (Italian) Trial

• N = 514, clinical stage I, with myometrial invasion, <75yo.
• LND vs no LND
• Removal of bulky LN allowed in control arm.
• Power calculation: short of trial design
• Positive LN: 13% vs 3% (p<0.001)
• Post-op adjuvant Tx: 16% vs 25% (p<0.03)
• Brachytherapy allowed and not controlled.
So, what’s the conclusion?
How does this change clinical practice?
• These trials creates more questions than they can potentially answer
• Intra-op stratification is a complicated process
• Should the focusing efforts on whether or not a LND is “therapeutic” when LND clearly has prognostic significance?
• Role of accurately triage adjuvant therapy
Endometrial Cancer 2011

• FIGO staging

• Surgical Therapy
  - Minimally invasive surgery
  - Role of lymph node dissection

• Adjuvant Therapy
  - Early stage
  - Advanced stage – resected

• Chemotherapy / Drug Development
Adjuvant Tx for Early Stage Update

- Bottom-line: reduces local recurrence but does not improve survival
- Who needs adjuvant treatment? (Selection, selection, selection…)
- “Bang for the buck” model – treat “High-intermediate risk group” with EBRT
  - GOG 99 (DOI, grade, LVSI, age)
  - PORTEC Trial (DOI, grade, age)
- Is EBRT the best XRT?
Adjuvant Tx for Early Stage Update

• PORTEC 2 Trial: EBRT vs “Puff to the Cuff”
• ASTEC/NCIC Trial: Obs vs EBRT, VCB at discretion

Nout, JCO 2009
ASTEC Study Group, Lancet 2009
PORTEC 2

Is EBRT better than vaginal brachy?
**PORTEC 2**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Vaginal</th>
<th>Pelvic</th>
<th>Distant</th>
<th>3yr PFS/OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>214</td>
<td>1.6%</td>
<td>0.5%</td>
<td>5.7%</td>
<td>89% / 91%</td>
</tr>
<tr>
<td>VCB</td>
<td>213</td>
<td>1.8%</td>
<td>1.5%</td>
<td>8.3%</td>
<td>89% / 90%</td>
</tr>
</tbody>
</table>

- H-IR pts: >60yo + 1C/Gr1-2, IB/Gr3, any age + IIA/Gr1-2, IBGr3
- EBRT: 46 Gy in 23 fx
- VCB: 21 Gy HDR in 3 fx or 30 Gy LDR
- Better QoL with VCB

*Nout, Lancet 2010*
Endometrial Cancer 2011

- FIGO staging
- Surgical Therapy
  - Minimally invasive surgery
  - Role of lymph node dissection
- Adjuvant Therapy
  - Early stage
  - Advanced stage – resected
- Chemotherapy / Drug Development
Individualized Care in EMCA

- GOG 210 – molecular staging / translational research
- Targeted Therapies
  - mTOR inhibitors
  - Bevacizumab
  - PI3K / AKT inhibitors
mTOR Inhibitors

• Ridaforolimus (Oral mTOR inhibitor)
  - phase II
  - recurrent EMCA
  - PFS: 19 wks vs 8wks (progestin)

Oza et al. IGCS 2010.
mTOR Inhibitors

- Temsirolimus + Avastin (GOG 229G, ph2, RR 26%)
- Temsirolimus + C/T (GOG)
- Temsirolimus + Tamoxifen (GOG)
- Temsirollimus + C/T vs C/T/avastin (GOG 86p)
mTOR Inhibitors

- Novetis (USON, phase 2 trial)
Bevacizumab

- GOG 229E
- Phase II trial
- 40% has PFS > 6 months

Aghajanian et al. JCO 2011.
## Where are we today?

<table>
<thead>
<tr>
<th>Trials</th>
<th>Population</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 249</td>
<td>H-IR, stage I/II, UPSC/CC I/II</td>
<td>WP vs VCB + C/Tx3</td>
</tr>
<tr>
<td>GOG 258</td>
<td>III/IV, optimal</td>
<td>C/Tx6 vs WP +/- EF XRT + cddp x2 -&gt; C/Tx4</td>
</tr>
<tr>
<td>PORTEC 3</td>
<td>IBgr3+LVSI, ICgr3, III, IB-III UPSC/CC</td>
<td>WP vs WP + cddpx2 -&gt; C/Tx4</td>
</tr>
<tr>
<td>RTOG 0921</td>
<td>IC-IIA gr3, IIB gr2/3, III-IVA</td>
<td>IMRT + cddp + bev -&gt; C/Tx4</td>
</tr>
<tr>
<td>GOG 238</td>
<td>Locally recurrent dz</td>
<td>WP +/- weekly cddp</td>
</tr>
</tbody>
</table>
Thank You!