ARROCase: Locally Advanced Endometrial Cancer

Charles Vu, MD (PGY-3)
Faculty Advisor: Peter Y. Chen, MD, FACR
Beaumont Health (Royal Oak, MI)
November 2016
Case

- 62yo female with a 3yr history of vaginal discharge and bleeding
- April 2015: CT abdomen/pelvis: heterogeneous appearing uterus with fundal calcification and a central uterine hypodensity
- May 2015: Endometrial biopsy showed Grade 1 endometrioid adenocarcinoma
Case (continued)

• Late May 2015: total robotic hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy

• Pathology
  – Grade 1 endometrioid adenocarcinoma, measuring 8.5 cm in greatest dimension.
  – Near-complete involvement of the myometrium (21.8 mm/22 mm).
  – Tumor involved the lower uterine segment and the stroma of the endocervix, but not the parametrial tissues, ovaries, or fallopian tubes.
  – 3/18 right pelvic nodes and 1/10 left pelvic nodes were positive for disease, without extranodal extension. One right common iliac node was negative.
  – Peritoneal washings were positive for metastatic adenocarcinoma.
Case Summary

• 62y.o. female with stage IIIIC1, grade 1 endometrial carcinoma status post total robotic hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy

• What are the patient’s options for adjuvant treatment?
Background

- Incidence: USA: 50,000 cases with 8,000 deaths in 2013, 65-75% early-stage (Most common gynecologic malignancy)
- Risk Factors (unopposed estrogen): Age, Nulliparity, Early menarche, Late menopause, Obesity, PCOS, Tamoxifen use, Hormone replacement therapy
- Clinical presentation: typically vaginal bleeding, but may be incidental finding on Pap smear, imaging, or hysterectomy
Workup (per NCCN)

- H&P
- CBC
- Endometrial biopsy
- Chest imaging (CXR or CT)
- Optional: LFTs, chemistry, genetic counseling
- If suspected/gross cervical involvement: consider cervical biopsy or MRI
- If suspected extrauterine disease: Consider CT/MRI/PET, as clinically indicated

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>FIGO Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>IA</td>
<td>Tumor confined to uterus, limited to endometrium or &lt;50% of myometrium</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Tumor confined to uterus, &gt;50% of myometrium</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Invades connective tissue of cervix</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Involves serosa and/or adnexa by direct extension</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Vaginal or parametrial involvement</td>
</tr>
<tr>
<td>N1</td>
<td>IIIIC1</td>
<td>Regional LN metastasis to pelvic nodes</td>
</tr>
<tr>
<td>N2</td>
<td>IIIIC2</td>
<td>Regional LN metastasis to para-aortic nodes</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

**Notes:**
- Peritoneal washings are not included in staging
- Endocervical glandular involvement alone is Stage I, not II
Treatment Options

• Radiotherapy alone (EBRT +/- brachytherapy)
• Chemotherapy alone
• Chemoradiation: sequential, concurrent, or sandwich (EBRT +/- brachytherapy)
GOG 122

• Purpose: Can chemotherapy replace WAI in locally advanced pts?
• Patients
  – 422 Stage III/IV pts
  – WAI 30Gy/20 fractions + 15Gy boost
  – AP chemo (doxorubicin 60mg/m² + cisplatin 50mg/m² x 7 + cisplatin x 1)
• Results
  – 5yr DFS: 50% vs. 38% favoring chemotherapy (P < .01)
  – 5yr OS: 55% vs. 42% favoring chemotherapy (P < .01)
• Conclusion: AP chemotherapy superior to WAI in Stage III-IV pts
• Criticism: Stage adjustment required to achieve results, which should not be necessary in a RCT

Randall et al. JCO 2006 Jan 1;24(1):36-44.
Purpose: Is the addition of chemotherapy sequentially to RT beneficial?

Patients

- NSGO/EORTC (383 pts): Mostly Stage I, many different chemo regimens, RT > 44Gy, RT then CT, VBT optional
- Mango-ILIADE (157 pts): Mostly IIB-IIIC, AP chemo, pelvic RT + PA field if N+ to 45Gy, VBT only for cervical stromal involvement

Results

- In combined analysis of trials, addition of chemotherapy was associated with improved PFS (p = 0.009) and CSS (p = 0.01)
- Addition of chemotherapy trended toward improved OS (p = 0.07)

Conclusion: Sequential adjuvant chemoradiation associated with improved outcomes in high-risk endometrial pts

Hogberg et al. Eur J Ca 2010 Sep;46(13):2422-31
RTOG 9708 (Phase II)

• Purpose: Can concurrent chemo/RT be given in locally advanced pts?
• Patients
  – 46 pts, Stage IC – III endometrial adenocarcinoma
  – 45Gy/25 pelvic RT + VBT (20Gy/1 LDR or 18/3 HDR)
  – Cisplatin 50mg/m^2 during RT
  – Adjuvant Cisplatin (50mg^m2) / Paclitaxel (175mg/m2)
• Results:
  – 4yr OS: 85%, 4yr DFS: 81%
  – Stage III pts: 4yr OS 77%, 4yr DFS: 72%
  – Maximum Overall Late Toxicity from Chemo-RT: G1 14%, G2 41%, G3 16%, G4 5%
• Conclusion: Concurrent CRT is a feasible regimen
# Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pts</th>
<th>Randomization</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 122 (Randall)</td>
<td>III-IV</td>
<td>Chemo (Adr/Cis) vs. whole abdomen RT</td>
<td>Chemo has improved outcomes compared to whole abdomen radiation</td>
</tr>
<tr>
<td>NSGO / EORTC</td>
<td>I-IIIC</td>
<td>Sequential CRT vs. RT alone</td>
<td>Sequential CRT improves PFS and trends towards improved OS</td>
</tr>
<tr>
<td>RTOG 9708</td>
<td>IC-III</td>
<td>Phase II concurrent CRT (Cis-RT with VBT + Cis/Taxol)</td>
<td>Excellent PFS and OS with reasonable toxicity using concurrent chemoradiation</td>
</tr>
</tbody>
</table>
Patient received sandwich chemoradiation
Three cycles of carboplatin / paclitaxel, then
External beam RT (45Gy in 25Fx IMRT), then
HDR vaginal cuff brachytherapy (5Gy x 3), then
Three more cycles of carboplatin/paclitaxel
CT Simulation

• Typically supine (but can be done prone)
• Immobilization with cradle if supine, belly board if prone
• Full bladder (can also additionally do empty bladder in patients receiving IMRT)
• <=3mm slice thickness
• IV contrast can be used to assist in vessel delineation
• Radio-opaque vaginal marker can be used

Adapted from IMRT Handbook edited by NY Lee et al.
Contouring: Consensus Guidelines

<table>
<thead>
<tr>
<th>Target</th>
<th>Consensus Guideline Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common iliac LN</td>
<td>7mm below L4-L5 interspace to common iliac bifurcation</td>
</tr>
<tr>
<td>External iliac LN</td>
<td>Common iliac bifurcation to superior aspect of femoral head</td>
</tr>
<tr>
<td>Internal iliac LN</td>
<td>Common iliac bifurcation to paravaginal tissues at level of vaginal cuff</td>
</tr>
<tr>
<td>Upper vagina</td>
<td>Vaginal cuff and 3cm inferior to vaginal cuff</td>
</tr>
<tr>
<td>Parametrial/Paravaginal Tissue</td>
<td>Vaginal cuff to medial internal obturator muscle / ischial ramus</td>
</tr>
<tr>
<td>Presacral LN</td>
<td>Anterior to S1/S2</td>
</tr>
</tbody>
</table>
Treatment Plan: Axial

[Image of axial treatment plan]
Treatment Plan: Sagittal
Treatment Plan: Coronal
# IMRT Dose Constraints (per RTOG 1203/TIME-C)

<table>
<thead>
<tr>
<th>Normal Structure</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Deviation Unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel</td>
<td>V40 &lt; 30%</td>
<td>V40 = 30-70%</td>
<td>V40 &gt; 70%</td>
</tr>
<tr>
<td>Rectum</td>
<td>V40 &lt; 80%</td>
<td>V40 = 80-99%</td>
<td>V40 = 100%</td>
</tr>
<tr>
<td>Bladder</td>
<td>V45 &lt; 35%</td>
<td>V45 = 35-70%</td>
<td>V45 &gt; 70%</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>D90% &lt; 10Gy</td>
<td>D90% = 10-25Gy</td>
<td>D90% &gt; 25Gy</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>V40 &lt; 37%</td>
<td>V40 = 37-60%</td>
<td>V40 &gt; 60%</td>
</tr>
</tbody>
</table>
Vaginal Cuff Brachytherapy

- 500cGy x 3 HDR brachytherapy in this patient
- 600cGy x 3 HDR or 2000cGy LDR in RTOG 9708
Surveillance and Follow-up (NCCN)

- Physical exam q3-6m x 2-3y, then q6-12m
- CA-125 is optional
- Imaging only as clinically indicated
References


