The Management of Endometrial Cancer

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University of North Carolina
Disclosure

• I have no conflicts of interest to disclose.
Learning Objectives

• Describe the epidemiology, clinical presentation, natural history, staging, and pathologic classification

• Review the major / randomized clinical trials which guide the management strategies and treatment techniques for early and advanced stage endometrial cancer
### 2008 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Men</th>
<th>Women</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>31%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

- **Men**: 294,120
- **Women**: 271,530

*ONS=Other nervous system.
Source: American Cancer Society, 2008.
# 2008 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men 745,180</th>
<th>Women 692,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

- **26%** Breast  
- **14%** Lung & bronchus  
- **10%** Colon & rectum  
- **6%** Uterine corpus  
- **4%** Non-Hodgkin lymphoma  
- **4%** Thyroid  
- **4%** Melanoma of skin  
- **3%** Ovary  
- **3%** Kidney & renal pelvis  
- **3%** Leukemia  
- **23%** All Other Sites  

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.  
Source: American Cancer Society, 2008.
Cancer Death Rates* Among Women, US, 1930-2004

Rate Per 100,000

*Age-adjusted to the 2000 US standard population.
Endometrial Cancer Review

- 4th most common malignancy in women
- 85 - 90% early stage
- Staging system clinical --> surgical
- Low risk, early stage: minimize morbidity
- High risk, advanced stage: improve locoregional control and overall survival
Epidemiology

- 44,000 new cases, 7,500 deaths
- Overall incidence 21/100,000
- 75% postmenopausal
- Fewer than 5% under age of 40
- Peak incidence 50 - 70 years
- Type I - typically endometrioid, low-grade tumors, estrogen related
- Type II - papillary serous or clear cell, high grade tumors, not estrogen related
Etiology - Type I

• Most risk factors associated with estrogen exposure
• Unopposed estrogens lead to endometrial hyperplasia
• 20 - 30 % with atypical hyperplasia progress to carcinoma
## Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Increased Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (20 - 30 lbs)</td>
<td>3.0</td>
</tr>
<tr>
<td>Obesity &gt; 50 lbs</td>
<td>10.0</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>none vs. 1 child</td>
<td>2.0</td>
</tr>
<tr>
<td>none vs 5 children</td>
<td>5.0</td>
</tr>
<tr>
<td>Late menopause (&gt;52 yo)</td>
<td>2.4</td>
</tr>
<tr>
<td>Factor</td>
<td>Increased Risk Ratio</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.5</td>
</tr>
<tr>
<td>Unopposed estrogen rx</td>
<td>6.0</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2.2</td>
</tr>
<tr>
<td>Sequential OC</td>
<td>7.0</td>
</tr>
<tr>
<td>Combination OC</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Tamoxifen

- NSABP P-1 randomized 13,388 women between tamoxifen vs. placebo
- RR 4.01 (1.7 – 10.9) in women ≥ 50 yo
- Distribution of stage and grade not different, all cases in Tam group stage 1
- Placebo 5.4/1000
- Tam 13.0/1000

Familial and genetic factors

• Lynch syndrome II (HNPCC)
  – Lifetime cumulative risk 40 – 60%
  – Median age 15 - 20 years younger

• Polycystic ovary syndrome (Stein-Leventhal syndrome)
  – PCOS in ~30% of women < 40 yo with endometrial ca
  – Similar risk factors: obesity, anovulation, hyperinsulinemia

## Pathogenesis

<table>
<thead>
<tr>
<th></th>
<th>Dependent (Type I)</th>
<th>Independent (Type II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Gr 1/2 Endometriod</td>
<td>Uterine Serous Carcinoma</td>
</tr>
<tr>
<td>Median age</td>
<td>60’s</td>
<td>70’s</td>
</tr>
<tr>
<td>Stage I</td>
<td>85%</td>
<td>10-15%</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Important</td>
<td>Less important</td>
</tr>
<tr>
<td>Risk factors</td>
<td>as above</td>
<td>not necessarily</td>
</tr>
</tbody>
</table>
Diagnosis / Workup

• Postmenopausal bleeding
  – overall 15% of patients have endometrial ca

• Workup:
  – H+P, pap, endometrial bx.
  – Bloodwork: CBC, OP7, consider Ca-125
  – CXR, EKG
  – Ultrasound normal endometrial stripe 4 - 5 mm, mean thickness 20 mm for endometrial ca
  – MRI best for myometrial invasion and cervical involvement, but no additional info if surgery planned
  – CT abd/pelvis typically not necessary unless suspicion of extra-pelvic disease
Staging - FIGO 1971 Clinical

Stage 0  Carcinoma in situ
Stage IA  Confined to uterus <= 8 cm sound
         IB  “  > 8 cm sound
Stage II  Involves cervix
Stage III Extends outside corpus, but not true pelvis
Stage IV Bladder, rectum, or outside pelvis
GOG 33 - Creasman

621 patients, surgical pathologic features
1977 – 1983
Clinical stage I patients
Peritoneal cytology
TAH/BSO selective pelvic and PA nodal lymphadenectomy.
## Grade and Depth of Invasion
### GOG 33 (Creasman)

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>24%</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Superficial 1/3</td>
<td>53%</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>12%</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>Deep 1/3</td>
<td>10%</td>
<td>20%</td>
<td>42%</td>
</tr>
</tbody>
</table>
Risk of LN in Uterine Confined Disease:

Low Risk: No invasion or Grade I with invasion

Medium Risk: All other

High Risk: Grade 3 or outer third invasion

<table>
<thead>
<tr>
<th></th>
<th>Pelvic LN</th>
<th>PALN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk:</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Medium Risk:</td>
<td>5-10%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>High Risk:</td>
<td>&gt;10%</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

Creasman Cancer 60: 2035-41, 1987
Surgical Staging (FIGO 1988)

- Laparotomy/Laparoscopy+/-robot
- Sampling of peritoneal fluid
- Visual/palpation exam of pelvic LN, para-aortic LN and abdominal/pelvic organs
- Biopsy any suspicious areas
- TAH/BSO
- Radical hysterectomy is considered if gross cervical invasion
- Lymphadenectomy (at least 11 nodes)
FIGO 1988 Staging

- IA confined to endometrium
- IB inner half invasion
- IC outer half invasion
- IIA cervical mucosal involvement
- IIB cervical stromal involvement
- IIIA uterine serosa, adenxa, or positive cytology
- IIIB vaginal mets
- IIIC pelvic or PA nodes
- IV A bowel/bladder
- IVB distant
FIGO 2009 Staging

Stage IA None or < half myometrial invasion
   IB Equal to or > half of myometrium
Stage II Tumor invades cervical stroma
Stage III Local and/or regional spread of the tumor
   IIIA Tumor invades serosa and/or adnexa
   IIIB Vaginal and/or parametrial involvement
   IIIC1 Positive pelvic nodes
   IIIC2 Positive paraaortic lymph nodes
IVA Tumor invasion of bladder and/or bowel
IVB Distant mets, intra-abd and/or inguinal LN

Int J Gyn and Ob 105 (2009)103-104
Changes in 2009 staging

• Endocervical glandular involvement only considered stage I (previously IIA)
• New IA = old IA + IB / IC moved to IB
• Stage II not subdivided
• Stage III does not include peritoneal cytology
• Stage III subdivides pelvic vs PA nodes
• No longer includes uterine sarcoma (keep in mind when reading literature)
Peritoneal cytology

- Positive peritoneal cytology as only risk factor of little prognostic significance
  - Compared patients with no extrauterine spread of tumor +/- positive cytology
  - No difference in overall or disease free survival
- Mariani et al: (Gynecol Oncol 86: 38-44, 2002)
  - Patients with no LVSI, no cervical involvement and only risk factor peritoneal washings had 0% recurrence
- Adjuvant therapy as the remainder of their risk factors would dictate
  - Depth of invasion, grade, etc.
Stage IIIB Disease

• Rare presentation (<1% of endometrial cancers)
• Surgical treatment varies by presentation:
  – Can include radical hysterectomy
  – Upfront hysterectomy may be avoided due to morbidity if large amounts of vagina involved
  – Instead may be treated with EBRT and brachytherapy
  – Post brachytherapy, some patients may receive consolidative hysterectomy
IIIC Disease

• 11% of patients with clinical stage I/II cancer have positive pelvic LN on sampling and 5% have positive PALN
• 30% patients with pelvic LN have para-aortic LNs involved
Prognostic Factors

Stage (most important)
Grade
Special histology
Nodal status
LVI (also predicts for nodal involvement)
Age
Positive peritoneal cytology (?)
Histology

- Adenocarcinomas 75 - 80%
- Uterine papillary serous 10%
- Clear cell carcinoma 4%
- Rare: squamous cell, transitional cell, undifferentiated
- Sarcoma: endometrial stromal sarcoma / mixed mullerian tumor / leiomyosarcoma / carcinosarcoma
Uterine Papillary Serous Carcinoma

Clinical importance recognized in the early 1980’s
Morphologically identical to high grade serous carcinoma of the ovary
Deep myometrial invasion, LVSI, and a marked tendency to disseminate IP
50% of patients with recurrent endometrial ca have this subtype
Mean age 7 – 10 years older
Clear Cell

Rare subtype associated with UPSC (in about 50%)
Pure clear cell has better prognosis
Experienced path review
Randomized Trials – Early Stage

- Norwegian / Aalders
- Piver Obs vs Cylinder vs Preop Uterine Brachy
- Pelvic XRT vs No additional therapy
  - PORTEC-1
  - GOG 99
  - ASTEC/EN5
- PORTEC-2 pelvic vs vag brachytherapy
  - QOL endpoints
Randomized trials Stage I

Norway trial - Aalders
1968-72 386 pts had surgery and intravaginal brachytherapy (no LN dissection)
Randomized to no further rx or pelvic XRT
Subgroup analysis showed OS benefit for IC high grade, improved LC with XRT
50% gr I with <50% invasion
Piver trial

Randomized 189 CS I patients:
- TAH
- TAH + cylinder
- preop uterine brachy + TAH

DFS and OS not different

Vaginal recurrence 12%, 0%, 5% respectively
PORTEC 1

Post Operative Radiation Therapy in Endometrial Carcinoma (Netherlands)

715 patients with IC Gr1 or IB/C Gr2 or IBGr3: whole pelvis vs no further rx

TAH/BSO without node sampling

Local recurrence 4% XRT VS 14% observation, no diff OS

Complications 6% control, 25% irradiated (most grade I)
715 patients randomised
(10 were not eligible)

354 allocated postoperative radiotherapy
(4 ineligible)

339 received radiotherapy
(7 discontinued radiotherapy)
15 did not receive radiotherapy
8 minor violations

354 were followed

361 allocated no further treatment
(6 ineligible)

355 received no further treatment
6 received radiotherapy
2 minor violations
1 lost to follow-up

360 were followed
PORTEC 1 – Local recurrence

No difference OS
Toxicity - Mostly GI in the XRT group (25%)
  No difference AP/PA vs 3 or 4 field
  Mostly grade 1 (68%)
Control group – 73% vaginal cuff recurrence as first site, most events within 18 months
GOG 99

392 eligible pts with “intermediate risk” assigned to whole pelvis (5040 cGy) vs observation

Surgically staged patients

High intermediate subgroup (post hoc):
  - Grade 2/3, LVSI, outer 1/3 invasion
  - Age >50 with two risk factors
  - Age >70 with one risk factor

Outcomes by arm / risk group

Patterns of failure in observation group
GOG 99 demographics

Total 392 patients:

- IB 58%
- IC 32%
- IIA 9%

Grade 1/2 82%
Grade 3 18%
Median f/u 56 months
GOG 99 Local recurrence

High risk surgery only

Cumulative Incidence

Risk:Rx Group	Censored	Recur	Death* Total
Low:Surgery	110	11	11	132
Low:Surgery+XRT	114	5	9	128
High:Surgery	43	20	7	70
High:Surgery+XRT	44	8	10	62
* deaths prior to recurrence

Months on Study
GOG 99

No overall survival difference
Half of deaths in both arms due to intercurrent causes
insufficient power for overall survival endpoint
<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Surgery + XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NED</td>
<td>171 (84%)</td>
<td>177 (93.2%)</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>V+P</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gr 3/4 comp</td>
<td>6%</td>
<td>15%</td>
</tr>
</tbody>
</table>
ASTEC and EN.5

• EN5 started July 1996, ASTEC July 1998
• Determine benefit of EBRT in women with early stage, intermediate risk following surgery
• EN5 modified in 1998 to allow combined analysis with ASTEC
• Lymphadenectomy not required (30% did have nodal dissection)

Lancet vol 373, Jan 2009
# ASTEC/EN5 Patient Distribution

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Papillary serous/ CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>8 (1%)*</td>
<td>15 (2%)**</td>
</tr>
<tr>
<td>IB</td>
<td>1 (&lt;1%)</td>
<td>5 (1%)</td>
<td>99 (11%)*</td>
<td>48 (5%)**</td>
</tr>
<tr>
<td>IC</td>
<td>213 (24%)*</td>
<td>337 (37%)*</td>
<td>100 (11%)**</td>
<td>27 (3%)**</td>
</tr>
<tr>
<td>IIA</td>
<td>9 (1%)*</td>
<td>19 (2%)*</td>
<td>6 (1%)**</td>
<td>3 (&lt;1%) **</td>
</tr>
<tr>
<td>IIB</td>
<td>2 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

*Intermediate subgroup  **High risk subgroup  N=905 total
ASTEC/EN5 Treatment

• Radiation started 6 – 8 weeks postop
• 40 – 46 Gy in 20 – 25 fx
• Brachytherapy allowed per centre’s policy
  – HDR 4 Gy at 0.5 cm over 3 – 7 days
  – LDR 170 cGy/h 13.5 Gy at 0.5 cm
• Lymphadenectomy not required (35%)
  – 50% had 1 – 5 nodes
  – 36% had 5 – 10 nodes
  – 23% had 11 – 15 nodes
Results: ASTEC/EN5

- Median follow up 58 months, no difference in overall survival, 5 yr OS 84%
- Local recurrence 5 yr cumulative incidence
  - 6.1% observation
  - 3.2% external beam radiation
- Update of meta-analysis
  PORTEC/GOG99/ASTEC/EN5 – rules out absolute benefit of more than a 3% increase in overall survival for whole pelvis external beam radiation
PORTEC-2

Non-inferiority trial at 19 Dutch centers

427 patients stage I or IIA, high intermediate risk, assigned to pelvic EBRT (46 Gy / 23 fx) or VBT (7 Gy x 3 fractions or 30 Gy LDR)

No routine lymphadenectomy, but clinically suspicious node removed
## PORTEC-2 characteristics

<table>
<thead>
<tr>
<th></th>
<th>EBRT (n=214)</th>
<th>VBT (n=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGO IB</td>
<td>19 (8.9%)</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>IC</td>
<td>172 (80.4%)</td>
<td>171 (80.3%)</td>
</tr>
<tr>
<td>IIA</td>
<td>23 (10.7%)</td>
<td>26 (12.2%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>99 (46.3%)</td>
<td>103 (48.4%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>97 (45.3%)</td>
<td>94 (44.1%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>18 (8.4%)</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>LVSI +</td>
<td>25 (11.7%)</td>
<td>21 (9.9%)</td>
</tr>
<tr>
<td>LVSI -</td>
<td>189 (88.3%)</td>
<td>191 (90.1%)</td>
</tr>
</tbody>
</table>

Median f/u 45 months
## PORTEC-2 Results

### Primary endpoint vaginal recurrence

<table>
<thead>
<tr>
<th></th>
<th>EBRT (est 5-year)</th>
<th>VBT (est 5-year)</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal recurrence</td>
<td>4/183 (1.9%)</td>
<td>2/183 (1.5%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pelvic recurrence</td>
<td>1/183 (0.6%)</td>
<td>6/183 (3.3%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>10/183 (5.0%)</td>
<td>11/183 (6.4%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Overall survival</td>
<td>19/183 (82.1%)</td>
<td>22/183 (86.2%)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
PORTEC-2 Toxicity / QOL

- GI toxicity (EORTC-RTOG small/large intestine) Grade 1 and 2 increased significantly at completion of EBRT vs VBT (53.8% EBRT vs 12.6% VBT)

- This difference decreased with further follow up and lost statistical significance after 24 months

- QOL outcomes at 2 years reported separately, VBT provided better QOL and should be the preferred treatment
### SEER analysis: 56,360 Stage I

<table>
<thead>
<tr>
<th>Group</th>
<th>Lymph Node Dissection (41.6%)</th>
<th>Radiation (17.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 70.4%</td>
<td>93.7 LND vs 92.7 no LND, p&lt;0.001</td>
<td>91.6 RT vs 92.9 no RT, p = 0.23</td>
</tr>
<tr>
<td>Intermed 26.2%</td>
<td>82.1 LND vs 76.5 no LND, p&lt;0.001</td>
<td>80.6 RT vs 74.9 no RT, p&lt;0.001 No diff RT modality</td>
</tr>
<tr>
<td>High 3.4%</td>
<td>68.8% LND vs 54.1 no LND, p&lt;0.001</td>
<td>66.9 RT vs 57.2 no RT, p&lt;0.001 If no LND, VB alone inferior to WPRT (0.01)</td>
</tr>
</tbody>
</table>

## Adjuvant Therapy for High Risk and Advanced-Stage

### Radiation vs. chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Treatment Arms</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 122 Randall et al.</td>
<td>396 Stage III (72%) and IV residual &lt; 2 cm</td>
<td>WART vs APx8</td>
<td>Chemotherapy improved OS with trend for greater pelvic failure</td>
</tr>
<tr>
<td>Japanese GOG Susumu et al.</td>
<td>385 stage I – III with &gt;50% inv. IB 60%</td>
<td>Pelvic RT vs CAP x 3</td>
<td>No difference in pelvic recur. or Overall Survival</td>
</tr>
<tr>
<td>Italian Maggi et al.</td>
<td>345 stage III (65%) or IB/II gr3</td>
<td>Pelvic RT vs CAP x 5</td>
<td>No difference in pelvic recur. or Overall Survival</td>
</tr>
</tbody>
</table>
GOG 122: Background

• Basically a randomization between GOG 107 (AC chemo) and GOG 94 (WAI)
• Primary endpoint: progression free survival
• 422 patients with stage III-IVA disease randomized
GOG 122: Therapy

• Whole Abdomen RT
  – 30 Gy @ 1.5 Gy/fraction
  – Pelvic boost: 15 Gy/8 fractions
  – Total dose = 45 Gy
  – PALN included in boost if positive or not sampled

• Chemotherapy
  – Doxorubicin/cisplatin Q 3 weeks for 8 cycles
GOG 122 Chemo = Greater Toxicity

More patients failed to complete treatment in chemo arm due to toxicity or patient refusal

More treatment related deaths in chemo arm

Table 4. Reason for Treatment Discontinuation

<table>
<thead>
<tr>
<th>Reason</th>
<th>WAI Regimen (n = 202)</th>
<th></th>
<th>AP Regimen (n = 194)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Completed treatment</td>
<td>170</td>
<td>84.2</td>
<td>123</td>
<td>63.4</td>
</tr>
<tr>
<td>Progression</td>
<td>9</td>
<td>4.5</td>
<td>18</td>
<td>9.3</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>8</td>
<td>4.0</td>
<td>14</td>
<td>7.2</td>
</tr>
<tr>
<td>Toxicity</td>
<td>6</td>
<td>3.0</td>
<td>33</td>
<td>17.0</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0.5</td>
<td>4</td>
<td>2.1</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>4.0</td>
<td>2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin.

Table 5. Factors Contributing to Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>WAI Regimen (n = 126)</th>
<th></th>
<th>AP Regimen (n = 96)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Treatment</td>
<td>4</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>100</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment and disease</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>15</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not related to protocol treatment or endometrial cancer.
Progression free survival @ 60 mo

Improved with chemotherapy
(50% vs. 38%), P = .007
Overall Survival Better with AP

(55% vs. 42%), P=.004
GOG 122 Patterns of Failure

<table>
<thead>
<tr>
<th>Site</th>
<th>WART (%)</th>
<th>AP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Distant</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>All failures</td>
<td>54%</td>
<td>50%</td>
</tr>
</tbody>
</table>

• Pelvic failure rate higher if no radiation given
• Patterns of failure only recorded for **first** site of failure – may underestimate true rates of recurrence
### Patterns of Failure: Chemo Alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>Median FU (mo)</th>
<th>All failures</th>
<th>Pelvic</th>
<th>Extra pelvic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoki (1988-1998)</td>
<td>30</td>
<td>71</td>
<td>13</td>
<td>54% (all)</td>
<td>100% (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(43.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faught (1985-1993)</td>
<td>20</td>
<td>58</td>
<td>5</td>
<td>80% (first only)</td>
<td>20% (first only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mundt (1992-1998)</td>
<td>43</td>
<td>27 mo</td>
<td>29</td>
<td>39.5% (all)</td>
<td>55.5% (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(67.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When all sites of failure recorded, pelvic failure is a significant problem after chemotherapy alone.
## Adjuvant Therapy for High Risk and Advanced-Stage Sequential Radiation and Chemotherapy

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Arms</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOG 184</strong> Homesley et al.</td>
<td>552 patients, stage III (88%) and stage IV</td>
<td>Volume directed pelvic +/- PA XRT and CD vs CDP chemo</td>
</tr>
<tr>
<td><strong>Nordic and Iliad</strong> Hogberg et al.</td>
<td>534 patients Stage I – III, no residual, high risk</td>
<td>XRT +/- sequential chemo (few regimens)</td>
</tr>
</tbody>
</table>
GOG 184

No gross residual

CDP + gross residual

CD + gross residual

Proportion Surviving Recurrence - Free

Months from Randomization

Rx/GRD
CD/No GRD
CDP/No GRD
CDP/GRD
CD/GRD

185 80 245
188 87 350
4 21 25
12 20 32
PFS pooled NSGO/EORTC + MaNGO
“Sandwich Approach”

- Alternative approach
- Patients receive first 3 cycles of chemo, then receive their RT, then complete chemo
- Phase II / multi-institutional data
Sandwich Therapy

• Lupe et al. (Western Ontario)
  – Prospective, Stage III (63%) and IV
  – Carbo + paclitaxel x 4, then RT (45-50.4 to pelvis), then chemo to complete 6 cycles
  – Median f/u 30 mo, 49% recurred (median 17 mo)
  – Only 3 local recurrences

• Secord et al. (multicenter)
  – Retrospective analysis of sandwich vs RC vs CR
  – Sequential CRC associated with improved survival
Radiation Field Considerations

Superior:
L5/S1 if pelvis
T11/12 if treating PALN

Inferior:
Mid obturator foramen

Lateral:
1.5-2 cm pelvic brim

Anterior:
Pubic symphysis

Posterior:
Post to S3

Additional resources:
RTOG atlas for postop IMRT whole pelvis
ABS guidelines for vaginal cuff brachytherapy
## Ongoing Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>PORTEC - 3</td>
<td>670 Stages I–III with high-risk factors; serous/clear cell</td>
<td>Pelvic RT vs RT-CT (2× C during RT and 4× TC)</td>
</tr>
<tr>
<td>GOG 249</td>
<td>562 Stages I–II with high-risk factors or serous/clear cell</td>
<td>Pelvic RT vs VBT and CT (3× TC)</td>
</tr>
<tr>
<td>GOG 258</td>
<td>804 Stages III/IV</td>
<td>RT-CT (2× C during RT and 4× TC) vs CT (6× TC)</td>
</tr>
</tbody>
</table>

Unresolved questions: Concurrent and sequential?  
What sequence?  
How many cycles of chemotherapy?  
What is the optimal chemo regimen?