Optimal Multi-modality Therapy For Gynaecological Cancers

Endometrial Cancer

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Endometrial Cancer: Annual Incidence and Mortality

ACS Estimates

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
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</thead>
<tbody>
<tr>
<td>1987</td>
<td>35,000</td>
<td>2,900</td>
</tr>
<tr>
<td>2015</td>
<td>54,870</td>
<td>10,170</td>
</tr>
</tbody>
</table>

American Cancer Society 2015
## Endometrial Cancer: Types

**Table 33-3. Type I and II Endometrial Carcinoma: Distinguishing Features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type I</th>
<th>Type II</th>
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<tbody>
<tr>
<td>Unopposed estrogen</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Pre- and perimenopausal</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Grade</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Minimal</td>
<td>Deep</td>
</tr>
<tr>
<td>Specific subtypes</td>
<td>Endometrioid</td>
<td>Serous, clear cell</td>
</tr>
<tr>
<td>Behavior</td>
<td>Stable</td>
<td>Aggressive</td>
</tr>
</tbody>
</table>

From Kurman, 1994, with permission.

Bokhman. Gyn Onc 15:10 ‘83
A Dualistic Model for Endometrial Tumorigenesis

Background:
- Germline mutations in MLH2, MLH-6
- Epigenetic silencing of MLH1

Polyclonal proliferation
- PTEN silencing
- K-ras and β-catenin mutations
- Microsatellite instability

Type I EEC tumors

Non-Atypical Hyperplasia
- Simple/Complex

Type II NECC tumors

Atrophic Endometrium

Endometrial Intraepithelial Neoplasia (EIN)

Endometrial Intraepithelial Carcinoma (EIC)

RUNX1
- ETV5
- TGFB

p53 mutations
- High Grade Type I

MYOMETRIAL INVASION AND DISSEMINATION

Type I Endometrioid Adenocarcinoma
- (Low Grade)

Type II Serous Adenocarcinoma
- (High Grade)

VASCULAR INVASION AND DISSEMINATION

Loss of ER/PR

her2/neu amplification
- p53 mutations

Aneuploidy
- Loss of heterozygosity
- p53 mutations

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Type 1 Carcinoma (%)</th>
<th>Type 2 Carcinoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN inactivation</td>
<td>50–80</td>
<td>10</td>
</tr>
<tr>
<td>K-ras mutation</td>
<td>15–30</td>
<td>0–5</td>
</tr>
<tr>
<td>β-catenin mutation</td>
<td>20–40</td>
<td>0–3</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>20–40</td>
<td>0–5</td>
</tr>
<tr>
<td>p53 mutation</td>
<td>10–20</td>
<td>80–90</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>10–30</td>
<td>40–80</td>
</tr>
<tr>
<td>p16 inactivation</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>10–20</td>
<td>60–90</td>
</tr>
</tbody>
</table>
Atypical Endometrial Hyperplasia

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Percentage of patients with concurrent carcinoma</th>
<th>Percentage of patients with myoinvasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gusberg and Kaplan, 1963</td>
<td>Retrospective, single-institution case series</td>
<td>18</td>
<td>20.0</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Tavassoli and Kraus, 1978</td>
<td>Retrospective, single-institution case series</td>
<td>48</td>
<td>25.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Kurman and Norris, 1982</td>
<td>Retrospective, referral case series</td>
<td>89</td>
<td>17.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Janicek and Rosenschein, 1994</td>
<td>Retrospective, single-institution case series</td>
<td>44</td>
<td>43.0</td>
<td>39.0</td>
</tr>
<tr>
<td>Dunton et al., 1996</td>
<td>Retrospective, single-institution case series</td>
<td>23</td>
<td>52.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Current study</td>
<td>Prospective, multiinstitutional cohort</td>
<td>289</td>
<td>43.0</td>
<td>13.2</td>
</tr>
</tbody>
</table>
Atypical Endometrial Hyperplasia

GOG 167 - PART A

- Endometrial biopsy, Pipelle Vabra, Novak, or uterine curette

Enrollment

- Confirm Atypical Hyperplasia
- Hysterectomy

Determine joint occurrence of atypia and cancer

SWOG Institutions see Section 5.0 for randomization instructions.

- AEH dx not confirmed in 61%
- Ca found in 40% (31% > IA GI)
  - 37% in confirmed AEH
  - 67% with no agreement
    - Zaino et al. Cancer 106:804 ‘06
    - Trimble et al. Cancer 106:812 ‘06
LNG-IUS for Endometrial Hyperplasia

Multicentre randomised trial, N=170

Responses were obtained for all the women in the LNG-IUS group (53/53, 95% CI 0.93–1.0) and for 96% of the women in the continuous oral group (46/48, 95% CI 0.86–0.99).

Only 69% of the women in the cyclic oral group were responders (36/52, 95% CI 0.55–0.81).
  – Orbo et al. BJOG 121:477 ‘14
Endometrial Cancer Histopathologic correlation

- 22% (144/621) of patients had metastatic disease
- 11% (70/621) had LN metastases (pelvic &/or PAN)
- Fewer than 10% of metastatic nodes were palpably enlarged
- Depth of myometrial invasion increased with tumor grade (dedifferentiation)
- Risk of lymph node metastasis increased with
  - Depth of myometrial invasion
  - tumor grade (i.e. tumor dedifferentiation)

- Creasman, Ca 60(8S)2035 ‘87
## Risk of Pelvic Node Metastasis

<table>
<thead>
<tr>
<th>Invasion</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium only</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Inner 1/3</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>0%</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Outer 1/3</td>
<td>11%</td>
<td>19%</td>
<td>34%</td>
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</table>

*Creasman WT, et al. Cancer 1987;60:2035-2041*
# Endometrial Cancer: Nodal Involvement

<table>
<thead>
<tr>
<th>Situation</th>
<th>% Positive Nodes</th>
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<tbody>
<tr>
<td>G1, no myometrial invasion, no extrauterine disease.</td>
<td>&lt;1%</td>
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</tbody>
</table>
| G2 or G3, inner 1/3 invasion, no extrauterine disease | 5-9% Pelvic  
               |                       | 4% Aortic             |
| G3, outer muscle, and/or extrauterine disease   | 20-60% Pelvic  
               |                       | 10-30% Aortic          |
# Endometrial Cancer

**FIGO 2009**

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>IA</td>
<td>No invasion or &lt;=1/2 myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>&gt;1/2 myometrial invasion</td>
</tr>
<tr>
<td>II</td>
<td>Extension to cervical stroma</td>
</tr>
<tr>
<td>IIIA</td>
<td>Extension to uterine serosa and/or adnexae</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension to vagina and/or parametrium and/or pelvic peritoneum</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Metastasis to pelvic nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Metastasis to para-aortic nodes with/without pelvic node metastasis</td>
</tr>
<tr>
<td>IVA</td>
<td>Extension to bladder and/or rectal mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant mets including intraabdominal and/or inguinal nodes</td>
</tr>
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</table>
Phase III Randomized Clinical Trial of Laparoscopic Pelvic and Para Aortic Node Sampling with Vaginal Hysterectomy and BSO Versus Open Laparotomy with Pelvic and Para Aortic Node Sampling and Abdominal Hysterectomy and BSO in Endometrial Adenocarcinoma and Uterine Sarcoma, Clinical Stage I, IIA, Grade I, II, III

Endometrial adenocarcinoma or uterine sarcoma
- Clinical stage I, IIA
- Grade I, II, III

GOG LAP-2

Laparoscopy
LAVH/BSO + pelvic and para-aortic lymphadenectomy

Open Laparotomy
TAH/BSO + pelvic and para-aortic lymphadenectomy
Laparoscopic (n=1696) vs laparotomy (n=920)
- Laparoscopy: 74% completed
- Lymphadenectomy 92% vs 96%, p<0.0001
- Operative minutes 204 vs 130, p<0.001
- Post op complications >G2: 14% vs 21%, p<0.0001
- Hospital days 3 vs 4, p<0.001
- “Laparoscopic surgical staging is feasible and safe”
LAP-2 Recurrence & Survival

3-year recurrence rate of 11% with laparoscopy and 10% with laparotomy

5-year OS was 90% in both

Walker, et al. JCO 30:695 ‘12

Fig 2. Cumulative incidence of recurrence by randomly assigned treatment group. (*) Deaths prior to recurrence.
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.
Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

Pierluigi Benedetti Panici, Stefano Basile, Francesco Maneschi, Andrea Alberto Lissoni, Mauro Signorelli, Giovanni Scambia, Roberto Angioli, Saverio Tateo, Giorgia Mangili, Dionysios Katsaros, Gaetano Garozzo, Elio Campagnutta, Nicoletta Donadello, Stefano Greggi, Mauro Melpignano, Francesco Raspagliesi, Nicola Ragni, Gennaro Cormio, Roberto Grassi, Massimo Franchi, Diana Giannarelli, Roldano Fossati, Valter Torri, Mariangela Amoroso, Clara Crocè, Costantino Mangioni

Background
Pelvic lymph nodes are the most common site of extraperitoneal tumor spread in early-stage endometrial cancer, but the clinical impact of lymphadenectomy has not been addressed in randomized studies. We conducted a randomized clinical trial to determine whether the addition of pelvic systematic lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy improves overall and disease-free survival.

Methods
From October 1, 1996, through March 31, 2006, 514 eligible patients with preoperative International Federation of Gynecology and Obstetrics stage I endometrial carcinoma were randomly assigned to undergo pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250). Patients’ clinical data, pathological tumor characteristics, and operative and early postoperative data were recorded at discharge from hospital. Late postoperative complications, adjuvant therapy, and follow-up data were collected 6 months after surgery. Survival was analyzed by use of the log-rank test and a Cox multivariable regression analysis. All statistical tests were two-sided.

Results
The median number of lymph nodes removed was 30 (interquartile range = 22–42) in the pelvic systematic lymphadenectomy arm and 0 (interquartile range = 0–0) in the no-lymphadenectomy arm (P < .001). Both early and late postoperative complications occurred statistically significantly more frequently in patients who had received pelvic systematic lymphadenectomy (81 patients in the lymphadenectomy arm and 34 patients in the no-lymphadenectomy arm, P = .001). Pelvic systematic lymphadenectomy improved surgical staging as statistically significantly more patients with lymph node metastases were found in the lymphadenectomy arm than in the no-lymphadenectomy arm (13.3% vs 3.2%, difference = 10.1%, 95% confidence interval [CI] = 5.3% to 14.9%, P < .001). At a median follow-up of 49 months, 78 events (ie, recurrence or death) had been observed and 53 patients had died. The unadjusted risks for first event and death were similar between the two arms (hazard ratio [HR] for first event = 1.10, 95% CI = 0.70 to 1.71, P = .68, and HR for death = 1.20, 95% CI = 0.70 to 2.07, P = .50). The 5-year disease-free and overall survival rates in an intention-to-treat analysis were similar between arms (81.0% and 85.9% in the lymphadenectomy arm and 81.7% and 90.0% in the no-lymphadenectomy arm, respectively).

Conclusion
Although systematic pelvic lymphadenectomy statistically significantly improved surgical staging, it did not improve disease-free or overall survival.

J Natl Cancer Inst 2008;100:1707–1716
Nodal Metastasis Risk in Endometrioid Endometrial Cancer

• N = 971 endometrioid from LAP-2
• Tumor < 2cm, < 50% invasion, G1-2 identified 40% at low risk (0.8%) of node mets
• High risk 6.3 X risk of node mets
  – (95% CI 1.67–23.8, P=.007)
• “Low-risk …criteria may be used to help guide treatment planning”
  • Ob Gyn 119:286 ‘12
Robotics for surgical staging of endometrial cancer

- Da Vinci surgical Robotic system was FDA approved in gynecology in April 2005
- Studies have compared robotics to traditional laparotomy and laparoscopy for endometrial cancer staging
  - Improved visualization (3-D imaging), wrist-like instrument rotation, tremor ablation and motion scaling
  - Lower EBL, lower conversion rates, can accommodate higher BMI pts, shorter operative time, significantly shorter learning curve, lower complication rates

(Boggess 2008; Bell 2008; Lowe 2009; Hoekstra 2009; Seamon, 2009; Holloway 2009; Cardenas-Goicoechea, 2010)
Molecular Staging

- Biologic Specimen Collection
  - Tumor tissue
  - Normal tissue
  - Serum samples
  - Urine samples

- Data Collection
  - Demographics
  - Reproductive history
  - Contraceptive and hormone use
  - Medical history
  - Family cancer history
  - Surgical and pathologic staging
  - Recurrence and survival

GOG 210

Review and Banking
Centrally reviewed and banked

- Study Content
  An investigator's study concept

- Concept review and approval

- Data Analysis
  - Biomarker data
  - Tissue genomic microarrays
  - Proteomics

- 9/22/2003
- 6096/3500
- Closed 12/2011
## GOG-210 Associated Studies

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<thead>
<tr>
<th>ID</th>
<th>PI</th>
<th>Type</th>
<th>Grant</th>
<th>Status</th>
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<td>2006-1</td>
<td>Cohn</td>
<td>Copy number alterations and metastasis</td>
<td>DOD grants P30 CA016056</td>
<td>Genes Chrom Ca 2010;49:791-802</td>
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<tr>
<td>8014</td>
<td>Boren</td>
<td>microRNAs associated with metastasis</td>
<td>CTSA UL1 RR024982</td>
<td>Testing</td>
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<tr>
<td>8015</td>
<td>Gunter</td>
<td>Hormone and IGF-axis and recurrence</td>
<td>R01 CA133010</td>
<td>Specimen Dist / Testing</td>
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<tr>
<td>8016</td>
<td>Maxwell</td>
<td>Genomic/proteomic profile and recurrence</td>
<td>DOD grants</td>
<td>Testing</td>
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<tr>
<td>8017</td>
<td>Zighelboim</td>
<td>ATR mutations and recurrence/progression</td>
<td>R21 pending</td>
<td>Specimen Dist / Testing</td>
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<tr>
<td>8020</td>
<td>Goodfellow</td>
<td>Endometrial SPORE: FGFR2 mutations, methylation profiling, DNA repair defects, ERK signaling, SNPs</td>
<td>P50 CA134254 R21 CA133295 GOG YI Award</td>
<td>Specimen Dist / Testing / Analysis / Manuscript Development</td>
</tr>
<tr>
<td>8022</td>
<td>Rocconi</td>
<td>Racial admixture and recurrence/progression</td>
<td>GOG YI Award</td>
<td>Specimen Distr</td>
</tr>
</tbody>
</table>
Radiation Therapy
GOG #99: Surgery +/- Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

* Except papillary serous and clear cell carcinomas.

**Regimen I**
- No additional treatment

**Regimen II**
- 5040 cGY total pelvic radiotherapy must begin no later than 8 weeks after surgery.
GOG #99

- 6/87 – 7/95
- 392 eligible
- Most Ib, G1/2, adeno
- 6% vs 14% G3/4 tox
- More heme, GI, GU, skin tox p<.0001
- 44 recurrences
- >50% deaths not CA

  - Keys et al. Gyn Onc 92:744 ‘04
GOG #99

- High intermediate risk:
  - G2/3, LVSI, >2/3 invasion
  - >50 yrs + 2
  - >70 yrs + 1

- Keys et al. Gyn Onc 92:744 ‘04

RH = 0.42 (90% CI: 0.21, 0.83)

RH = 0.73 (90% CI: 0.43, 1.26)
GOG #99

• Conclusion: “strong evidence for … RT in … high intermediate risk. … not recommended for … lower risk”

• Take home:
  – RT will cut recurrence from 27% to 13%, death from 26% to 12% in HIR
  – But, increase toxicity 6% to 14%
  – Thus, 100 patients will be treated to benefit 14

• Keys et al. Gyn Onc 92:744 ‘04
Adjuvant Radiotherapy for Stage I Endometrial Cancer: Cochrane Database of Systematic Reviews

- Gynaecological Cancer Group
- “in patients without any of the high risk factors … greater risk of endometrial carcinoma-related deaths”
  – Kong, et al. DOI: 10.1002/14651858.CD003916.pub2 ‘07

Figure 4. Subgroup analysis of patients without high-risk features, i.e. patients with either stage 1a/b or grade 1/2. (A) Death from all causes. (B) Endometrial carcinoma-related death.
Radiation +/- Chemo
Phase III Trial of Pelvic Radiation Therapy Versus Vaginal Cuff Brachytherapy Followed by Paclitaxel/Carboplatin Chemotherapy in Patients with High Risk, Early Stage Endometrial Carcinoma

**Eligible:**
- Stage I-IIA endometrial carcinoma, with high-intermediate risk factors
- Stage IIB (occult) endometrial carcinoma (any histology), with or without risk factors
- Stage I-IIB (occult) serous or clear cell endometrial carcinoma, with or without other risk features

**GOG 0249**

**Regimen I:**
- Pelvic Radiation Therapy (4500/25 fractions-5040 cGy/28 fractions) over 5-6 weeks
- Optional Vaginal Cuff Boost ONLY for Stage II patients and Stage I patients with papillary serous and clear cell carcinomas

**Regimen II:**
- Vaginal Cuff Brachytherapy + 3 cycles of chemotherapy* consisting of:
  - Paclitaxel 175 mg/m2 (3hr) + Carboplatin AUC 6 q 21 days

*To start within 3 weeks of initiating brachytherapy
GOG 249: Recurrence-Free Survival

- Over 600 pts enrolled
- Median F/U 24 mo
- 87 events
- Pelvic Failures
  - 2 in RT arm (0.6%)
  - 19 in VCB/Chemo arm (6.3%)
- Death from disease
  - 12 in RT arm
  - 18 in VCB/C arm
  - McMeekin et al. Gyn Onc 134:438 “14
Chemo vs. Radiation

PLATINOL-AQ
(CIS platin injection)

Vs.

Radiation treatment image
GOG 122

- Endometrial carcinoma
- Surgical stage III/IV with (distant metastasis excluded)
- Hysterectomy and BSO
With either:
- Para-aortic nodes negative.
  or
- Unknown para-aortic node status.
  or
- Positive para-aortic nodes with biopsy negative scalene nodes, and negative chest CT scan.

Randomize

Regimen I
Whole Abdomen Radiation Therapy

Regimen II
Doxorubicin
60 mg/m²
Cisplatin
50 mg/m²

* Maximum total dose is 420 mg/m².
Fig 2. Survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.
GOG #122: Phase III Whole-Abdominal Irradiation vs. Doxorubicin + Cisplatin in Optimal Advanced Endometrial Carcinoma

- WAI 3000 cGy (150 cGy X 20) vs. DOX 60 → CDDP 50 mg/m2 iv q 3 wks X 8
- 5/92 - 2/00, n=422
- Adverse effects were much more common with AP
- 24 months (p<0.01):
  - disease-free (WAI: 46%, AP: 59%)
  - Alive (WAI: 59%, AP: 70%)
- “AP … improves PFS and S”
Radiation + Chemo
GOG #184: Tumor Volume-Directed Pelvic +/- Para-Aortic Irradiation Followed by Cisplatin and Doxorubicin +/- Paclitaxel for Advanced Endometrial Carcinoma
Endometrial Carcinoma

Advanced Minimal Residual

- GOG 184
  - 80% completed 6 cycles
  - More heme, neuro, myalgia in TAP, p<.01
  - 36 mo. RFS: 62% vs 64%
    - 50% reduction in death in gross residual disease for TAP
  - “addition of paclitaxel ... not associated with a significant improvement in RFS”

Gynecol Oncol 112:543, 2009
Chemo +/- Radiation
Endometrial: Stage III/IV

- Endorsed by RTOG
- 813/804 accrued

Enroll patients with either FIGO 2009 surgical stage III or IVA endometrial carcinoma (<2 cm residual disease) or patients with FIGO 2009 Stage I or II serous (UPSC) or clear cell endometrial carcinoma and positive cytology.

GOG 258

Regimen I
- Cisplatin 50 mg/m² IV Days 1 and 29
- Plus Volume-directed radiation therapy
- Followed by Carboplatin AUC 5* plus Paclitaxel 175 mg/m² q 21 days for 4 cycles with G-CSF support

Regimen II
- Carboplatin AUC 6 plus Paclitaxel 175 mg/m² q 21 days for 6 cycles

* first dose of Carboplatin will be at AUC of 5, in subsequent cycles the dose will be escalated to AUC 6, as described in Section 6.2
Endometrial Cancer: Recurrence

- 80% of recurrences happen first 3 years
- Most will be symptomatic
- 50% vaginal recurrences cured
- Rare to cure distant recurrences
Radiation +/- Chemo
Pelvic Recurrence

- 2/25/2008
- Endorsed by RTOG
- 90/154 accrued, 5% CCOP

**GOG 238**

**Regimen I**
Whole Pelvis Radiation
4500 cGy in 25 fractions to the whole pelvis
(180 cGy/fraction)
Interstitial or Intracavitary Brachytherapy or external beam boost

**Regimen II**
Whole Pelvis Radiation
4500 cGy in 25 fractions to the whole pelvis
(180 cGy/fraction)
Weekly Cisplatin
40 mg/m²/wk
Interstitial or Intracavitary Brachytherapy or external beam boost

Institution IMRT Credentialing is required when IMRT is to be used before registering any patient on this trial. A Knowledge Assessment for this study must be completed by the treating radiation oncologist before registering patients on this trial.

For patients with tumors involving the distal vagina and clinically negative groins, the bilateral inguino-femoral lymph node regions should be treated to 4500 cGy.

3-D conformal or IMRT boost is allowed for patients who are not candidates for brachytherapy.
Chemo vs. Chemo

PLATINOL-AQ
(CIS platin injection)

100 mg in 100 mL

1 mg per mL Aqueous

BRISTOL LABORATORIES
ONCOLOGY PRODUCTS
Randomized Study of Doxorubicin Plus Cisplatin Versus Doxorubicin Plus Cisplatin Plus 3-Hour Paclitaxel With G-CSF Support in Patients With Primary Stage III & IV or Recurrent Endometrial Carcinoma

GOG 177

Regimen I
- Doxorubicin
  - 60 mg/m2 IV day 1 q 21 days x 7
- Cisplatin
  - 50 mg/m2 IV day 1 q 21 days x 7
- G-CSF
  - As specified in protocol section 6.0

Regimen II
- Doxorubicin
  - 45 mg/m2 IV day 1 q 21 days x 7
- Cisplatin
  - 50 mg/m2 day 1 q 21 days x 7
- Paclitaxel
  - 160 mg/m2 day 2 over 3 hrs q 21 days x 7
- G-CSF
  - 5 mcg/kg days 3-12, q 21 days x 7

*Patients with prior radiotherapy or who are over the age of 65 will have initial Doxorubicin dose reduced to 45 mg/m2.
Phase III Trial of Doxorubicin Plus Cisplatin With or Without Paclitaxel Plus Filgrastim in Advanced Endometrial Carcinoma: GOG Protocol 177

Randomized Phase III Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF Versus Carboplatin/Paclitaxel in Patients with Stage III and IV or Recurrent Endometrial Cancer

GOG 209

Regimen I
- Doxorubicin 45 mg/m² IV day 1
- Cisplatin 50 mg/m² day 1
- Paclitaxel 3 hr 160 mg/m² day 2
- GCSF* Repeated every 21 days for 7 cycles

Regimen II
- Carboplatin AUC 6 IV day 1
- Paclitaxel 3 hr 175 mg/m² day 1
  Repeated every 21 days for 7 cycles

Randomize

- Stage III, IV or recurrent endometrial carcinoma
- Measurable disease
- No prior cytotoxic chemotherapy
- ER/PR assessed on primary tumor (required)
- ER/PR assessed on metastatic tumor (optional)

Filgrastim (G-CSF, Neupogen) 5 mcg/kg days 3-12 or Pegfilgrastin (G-CSF) 6 mg day 3.
Median OS (months) 40.3 vs 36.5 HR=1.05

Adjusted 90% upper confidence limit for the death hazard ratio (HR) of TC relative to TAP was 1.16 and excludes the inferiority region bounded at 1.2

Miller, et al.  Gyn Onc 125:771 ’12
Biologic therapies in endometrial cancer evaluated by the Gynecologic Oncology Group.

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>ORR (%)</th>
<th>PFS at 6 months (%)</th>
<th>Progression-free survival (median, months)</th>
<th>Overall survival (median, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide⁴</td>
<td>34</td>
<td>12.5</td>
<td>8.3</td>
<td>1.7</td>
<td>6.3</td>
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<tr>
<td>Gefitinib¹²</td>
<td>26</td>
<td>3.8</td>
<td>15.4</td>
<td>1.8</td>
<td>7.1</td>
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<tr>
<td>Lapatinib¹³</td>
<td>30</td>
<td>3.3</td>
<td>10</td>
<td>1.8</td>
<td>7.3</td>
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<tr>
<td>Bevacizumab⁵</td>
<td>52</td>
<td>13.5</td>
<td>40.4</td>
<td>4.2</td>
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<td>Aflibercept⁶</td>
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<td>6.8</td>
<td>40.9ᵃ</td>
<td>2.9</td>
<td>14.6</td>
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<tr>
<td>Brivanib⁸</td>
<td>43</td>
<td>18.6</td>
<td>30.2</td>
<td>3.3</td>
<td>10.7</td>
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<tr>
<td>Nintedanib</td>
<td>32</td>
<td>9.4</td>
<td>21.9</td>
<td>3.3ᵇ</td>
<td>10.1ᶜ</td>
</tr>
</tbody>
</table>

ᵃ The proportion of patients EFS at 6 months in this study was 23%, which was significantly less than 40.9%. Patients who went off of study therapy for toxicity were often scanned for progression less frequently, which probably produced an artificially high frequency of patients PFS at 6 months. The longer median OS may have resulted in part from selection bias.

ᵇ The 90% CI for median PFS is 1.9–3.84 months.

ᶜ The 90% CI for median OS is 6.0–14.0 months.
A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study

David Bender a,*, Michael W. Sill b, Heather A. Lankes b, Henry D. Reyes a, Christopher J. Darus c, James E. Delmore d, Jacob Rotmensch e, Heidi J. Gray f, Robert S. Mannel g, Jeanne M. Schilder h, Mark I. Hunter i, Carolyn K. McCourt j,†, Megan I. Samuelson a, Kimberly K. Leslie a

- N = 53
- ORR 12%
- PFS: median 3.6 mo, 29% 6 mo
- OS: 12.5 mo

Cediranib is an active multi-tyrosine kinase inhibitor in uterine cancer.
Cediranib for recurrent uterine cancer had a 33% six-month progression free survival.
Cediranib is a safe and well-tolerated oral treatment for recurrent uterine cancer.
**Endometrial: Stage IV or Measurable**

- 9/14/2009, 1/9/2012
- 349/330, 8% CCOP

**GOG 86-P**

- **Arm I**
  - Paclitaxel 175 mg/m² IV over 3 hours day 1
  - Carboplatin AUC=6 IV day 1
  - Bevacizumab 15 mg/kg IV day 1 (starting with cycle 2 for those patients who are entering post surgery)
  - Every 21 days x 6 cycles
  - Maintenance regimen – Bevacizumab 15 mg/kg IV every 21 days

- **Arm II**
  - Paclitaxel 175 mg/m² IV over 3 hours day 1
  - Carboplatin AUC=5 IV day 1
  - Temsirolimus 25 mg IV days 1 and 8 (starting with cycle 2 for those patients who are entering post surgery)
  - Every 21 days x 6 cycles
  - Maintenance regimen – Temsirolimus 25 mg IV weekly days 1, 8, and 15 (one cycle = 21 days)

- **Arm III**
  - Ixabepilone 30 mg/m² IV over 1 hour day 1
  - Carboplatin AUC=6 IV day 1
  - Bevacizumab 15 mg/kg IV day 1 (starting with cycle 2 for those patients who are entering post surgery)
  - Every 21 days x 6 cycles
  - Maintenance regimen – Bevacizumab 15 mg/kg IV every 21 days

**Eligibility:**
- Stage III or IVA endometrial cancer with measurable disease
- Stage IVB endometrial cancer (whether there is measurable disease or not)
- Recurrent endometrial cancer (whether there is measurable disease or not)
- No prior chemotherapy

**Randomize**

- Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy.

*Patients who have had prior external beam pelvic or extended field pelvic/para-aortic radiation therapy must receive treatment at a reduced dose. Patients who enter and are treated within less than or equal to 12 weeks of surgery, must start bevacizumab or temsirolimus with cycle 2.*
Endometrial focus

GOG86P: OS

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median Point Estimate</th>
<th>p-value</th>
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<tbody>
<tr>
<td>1</td>
<td>34.0 (p&lt;0.039)</td>
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<tr>
<td>2</td>
<td>25.0</td>
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<tr>
<td>3</td>
<td>25.2</td>
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<tr>
<td>Reference</td>
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<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 PC + bevacizumab</td>
<td>58</td>
<td>116</td>
</tr>
<tr>
<td>Arm 2 PC + temsirolimus</td>
<td>68</td>
<td>115</td>
</tr>
<tr>
<td>Arm 3 IC + bevacizumab</td>
<td>72</td>
<td>118</td>
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<tr>
<td>Reference PC</td>
<td>287</td>
<td>462</td>
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</table>

Proportion Alive vs Months on Study
A Randomized Phase II/III Study of Paclitaxel/Carboplatin/Metformin (NSC#91485) Versus Paclitaxel/Carboplatin/Placebo as Initial Therapy for Measurable Stage III or IVA, Stage IVB, or Recurrent Endometrial Cancer

ELIGIBILITY

Stage III or IVA endometrial cancer with measurable disease
Stage IVB endometrial cancer (whether there is measurable disease or not)
Recurrent endometrial cancer (whether there is measurable disease or not)
AND
NO PRIOR CHEMOTHERAPY

Opened 3/17/2014
184/540
GOG #119: Phase II Alternating Tamoxifen plus Medroxyprogesterone for Advanced, Recurrent, or Metastatic Endometrial Cancer

- TMX 20 mg po bid + MPA 200 mg po qd X 1 wk qow
- 6/91-2/96, n=60
- CR 10% + PR 23% = 33% (95% CI: 21-46%)
- PFS = 3 mo., OS = 13 mo.
- “active treatment ”

- Whitney et al. Gyn Onc 92:4 ‘04
A Randomized Phase II Trial of Everolimus and Letrozole or Hormonal Therapy (Tamoxifen/Medroxyprogesterone Acetate) in Women with Advanced, Persistent, or Recurrent Endometrial Carcinoma

**GOG 3007**

**Arm 1**
- Everolimus
  - 10 mg daily
- Letrozole
  - 2.5 mg PO daily
- One cycle = 28 days

**Arm 2**
- Tamoxifen
  - 20 mg PO bid days 1-28
- Medroxyprogesterone Acetate
  - 200mg PO (days 8-14 and 22-28)
- One cycle = 28 days

Until progression of disease or adverse effects prohibit further therapy.

Advanced (stage III or IV) persistent or recurrent measurable endometrial carcinoma which is not likely to be curable by surgery or radiotherapy.

Opened 2/19/2015