# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Matei D, Filiaci V, Randall ME, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. N Engl J Med 2019;380:2317-26. DOI: 10.1056/NEJMoa1813181

**Supplementary Appendix:**

This appendix has been provided by the authors to give readers additional information about their work.

**Supplement to:** Matei D et al; Combination Platinum Based Chemotherapy And Tumor Volume Directed Irradiation In Optimally Cytoreduced Locally Advanced Endometrial Carcinoma, a NRG/Gynecologic Oncology Group Trial

**Supplementary Appendix**

**Collaborators:**

The following Gynecologic Oncology Group institutions participated in this study: Seoul National University Hospital, Women and Infants Hospital, University of Oklahoma Health Sciences Center, Ohio State University Comprehensive Cancer Center, Washington University School of Medicine, Women's cancer Center of Nevada, University of California Medical Center at Irvine-Orange Campus, Georgia Center for Oncology Research and Education (CORE), Case Western Reserve University, Cancer Trials Support Unit, University of Colorado Cancer Center-Anschutz Cancer Pavilion, University of North Carolina at Chapel Hill, Cancer Research Consortium of West Michigan NCORP, University of Iowa Hospitals and Clinics, Abington Memorial Hospital, University of Kentucky, Cooper Hospital University Medical Center Stony Brook University Medical Center, Yale University, Cancer Research for the Ozarks NCORP, Metro-Minnesota CCOP, University of New Mexico, MD Anderson Cancer Center, Fox Chase Cancer Center, University of Chicago, Walter Reed National Military Medical Center, Rush University Medical Center, State University of New York Downstate Medical Center, Memorial Sloan Kettering Cancer Center, The Hospital of Central Connecticut, Wake Forest University Health Sciences, Cleveland Clinic Foundation, Aurora Women's Pavilion of Aurora West Allis Medical Center, University of Hawaii, Mayo Clinic, Wayne State University/Karmanos Cancer Institute, University of Cincinnati, University of Texas Southwestern Medical Center, Indiana University Hospital/Melvin and Bren Simon Cancer Center, University of Wisconsin Hospitals and Clinics, Kaiser Permanente-Vallejo, Iowa-Wide Oncology Research Coalition NCORP, Duke University Medical Center, University of California at Los Angeles Health System, Fred Hutchinson Cancer Research Center,

University of Pittsburgh Cancer Institute (UPCI), Saint Joseph's Hospital and Medical Center, Carolinas Medical Center/Levine Cancer Institute, Lewis Cancer and Research Pavilion at St. Joseph's/Candler, Kalamazoo CCOP, University of Alabama at Birmingham, University of Mississippi Medical Center, Abramson Cancer Center of The University of Pennsylvania, Penn State Milton S Hershey Medical Center, Gynecologic Oncology of West Michigan PLLC, UCSF-Mount Zion, Froedtert and the Medical College of Wisconsin, Geisinger Medical Center, Saint Vincent Hospital, Wichita CCOP, Sanford NCI Community Oncology Research Program of the North Central Plains, Columbus NCI Community Oncology Research Program, Southeast Cancer Control Consortium CCOP, Sanford NCI Community Oncology Research Program of the North Central Plains, Columbus NCI Community Oncology Research Program, Southeast Cancer Control Consortium CCOP, University of Virginia , University of Texas - Galveston, Baystate Medical Center, Evanston CCOP-NorthShore University Health System, Greenville Health System Cancer Institute/Greenville CCOP, Florida Hospital Cancer Institute CCOP, University of Minnesota Medical Center - Fairview, Henry Ford Hospital, Rutgers Cancer Institute of New Jersey, Thomas Jefferson University Hospital, Huntsman Cancer Institute/University of Utah, Emory University School of Medicine, Johns Hopkins University/Sidney Kimmel Cancer Center, Allegheny General Hospital, Wisconsin NCI Community Oncology Research Program, Central Illinois CCOP, Northern Indiana Cancer Research Consortium, Virginia Mason CCOP, Nevada Cancer Research Foundation CCOP, Sanford Roger Maris Cancer Center, Montana Cancer Consortium-CCOP, University of New Mexico and John H. Stroger Jr. Hospital of Cook County.

The contributions of the Buffalo Statistical and Data Monitoring Center, and especially of Betty Stonebreaker, Helen Huang and Dr. Heather Lankes are acknowledged.

**Patient Eligibility**

Eligible Patients

- All patients with Surgical Stage III or IVA endometrial carcinoma per FIGO 2009 staging criteria, including clear cell and serous papillary and undifferentiated carcinomas.

  Surgical Stage III disease includes those patients with positive adnexa, parametrial involvement, tumor invading the serosa, positive pelvic and/or para-aortic nodes, or vaginal involvement.

  Surgical Stage IVA includes patients with bladder or bowel mucosal involvement, but no spread outside the pelvis.

- Patients with FIGO 2009 surgical Stage I or II endometrial clear cell or serous carcinoma and with positive peritoneal cytology.

- Surgery must have included a hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymph node sampling and para-aortic lymph node sampling are optional.

- Patients with a GOG Performance Status of 0, 1, or 2.

- Patients with adequate organ function, reflected by the following parameters:

  WBC ≥ 3000/mcl
  Absolute neutrophil count (ANC) ≥ 1500/mcl
  Platelet count ≥ 100,000/mcl
  SGOT, SGPT, and alkaline phosphatase ≤ 2.5 X upper limit of normal (ULN)
  Bilirubin ≤ 1.5 X ULN
  Creatinine ≤ institutional ULN

- Patients who have met the pre-entry requirements specified in Section 7.0; testing values/results must meet eligibility criteria specified in Section 3.1.

- Patients who have signed an approved informed consent and authorization permitting release of personal health information.

- Patients must be 18 years of age or older.

- Entry into the study is limited to no more than 8 weeks from the date of surgery.

Ineligible Patients

- Patients with carcinosarcoma.

- Patients with recurrent endometrial cancer.
- Patients with residual tumor after surgery (any single site) exceeding 2 cm in maximum dimension.
- Patients who have had pelvic or abdominal radiation therapy.
- Patients with positive pelvic washings as the only extra-uterine disease are NOT eligible if the histology is other than clear cell or papillary serous carcinoma.
- Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of active malignancy within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
- Patients with a history of serious co-morbid illness or uncontrolled illnesses that would preclude protocol therapy.
- Patients with an estimated survival of less than three months.
- Patients with FIGO 2009 Stage IVB endometrial cancer.
- Patients with parenchymal liver metastases.
- Patients who have received prior chemotherapy for endometrial cancer.
- Patients with a history of myocardial infarction, unstable angina, or uncontrolled arrhythmia within 3 months from enrollment.

SCHEMA

Enroll patients with either FIGO 2009 surgical Stage III or IVA endometrial carcinoma or patients with FIGO 2009 Stage I or II serous (UPSC) or clear cell endometrial carcinoma and positive cytology. **(01/03/2011)**

TREATMENT RANDOMIZATION

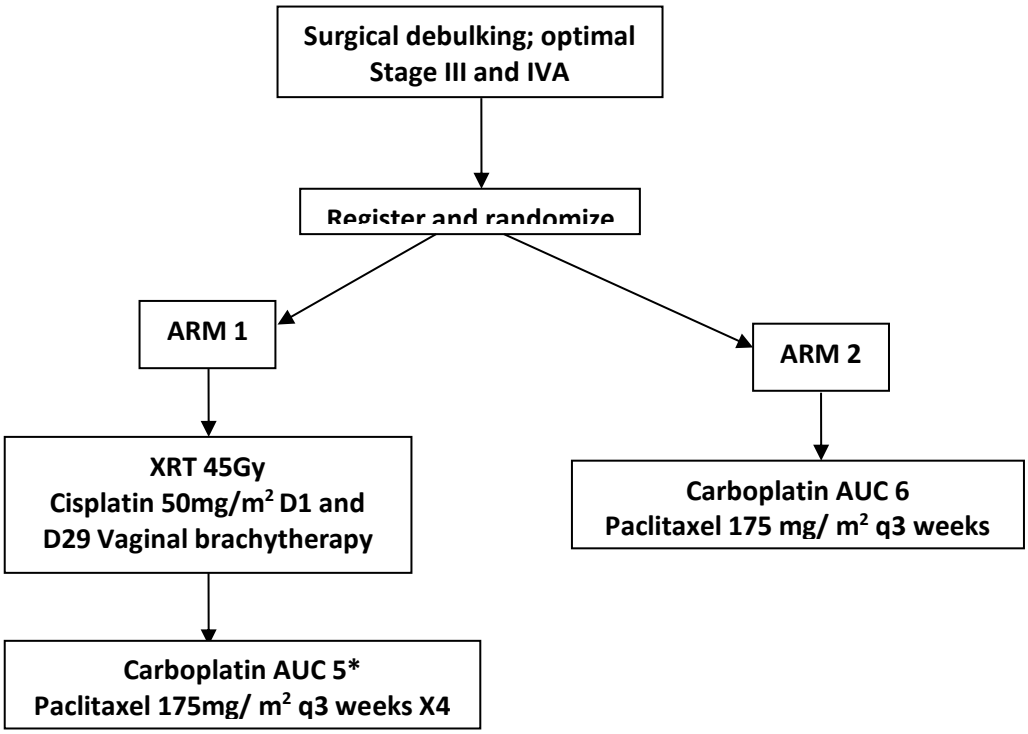
**REGIMEN I:**

Cisplatin 50 mg/m$^2$ IV Days 1 and 29
plus Volume-directed radiation therapy
followed by Carboplatin AUC 5* plus Paclitaxel 175 mg/m$^2$ q 21 days for 4 cycles with G-CSF support

or

**REGIMEN II:** Carboplatin AUC 6 plus Paclitaxel 175 mg/m$^2$ 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




Translational Research

- Archival formalin-fixed, paraffin-embedded primary or metastatic tumor tissue
- Whole blood

Quality of Life Assessment

- At baseline (within 14 days prior to starting protocol therapy)
- 6 weeks from start of protocol treatment (1 week post-completion of RT for Regimen I or three weeks post completion of 2 cycles of chemotherapy for Regimen II)
- 18 weeks from start of protocol treatment (three weeks after completion of protocol therapy)
- 70 weeks from start of protocol treatment (1 year from completion of protocol therapy)

CARCINOMA OF THE ENDOMETRIUM
FIGO CLASSIFICATION
2009

| | |
|---|---|
| Stage I* | Tumor confined to the corpus uteri. |
| IA* | No or less than half myometrial invasion |
| IB* | Invasion equal to or more than half of the myometrium |
| Stage II* | Tumor invades cervical stroma, but does not extend beyond the uterus** |
| Stage III* | Local and/or regional spread of the tumor |
| IIIA* | Tumor invades the serosa of the corpus uteri and/or adnexae[#] |
| IIIB* | Vaginal and/or parametrial involvement[#] |
| IIIC* | Metastases to pelvic and/or para-aortic lymph nodes[#] |
| IIIC1* | Positive pelvic nodes |
| IIIC2* | Positive para-aortic lymph nodes with or without positive pelvic lymph nodes |
| Stage IV* | Tumor invades bladder and/or bowel mucosa, and/or distant metastases |
| IVA* | Tumor invasion of bladder and/or bowel mucosa |
| IVB | Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes |

*Either G1, G2, or G3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[#]Positive cytology has to be reported separately without changing the stage.

**Gynecologic Oncology Group Performance Status Scale**

0 – fully active.

1 – restricted in physically strenuous activities, but ambulatory.

2 – ambulatory, capable of self-care; unable to work; up 50% of waking hour

3 – limited self-care; confined to bed or chair 50% of waking hours

4 – completely disabled; no self-care

## Radiation Therapy

Patients randomized to Regimen I will receive concomitant chemo-radiation therapy followed by systemic chemotherapy. Radiation Therapy will be given to the pelvis or pelvis and para-aortic fields (extended field RT), as described below. Given that nodal staging is optional for this study, it is the intention of the study that some flexibility be given to the treating physicians regarding the extent of the radiation therapy fields (See below.) Adequate hematological parameters as evidenced by WBC≥3000/mcl, ANC≥1500/mcl, platelet count ≥ 100000/mcl are required prior to initiating chemo-radiotherapy.

Treatment will be randomized after enrollment to either chemo-radiation therapy followed by systemic chemotherapy or to chemotherapy alone.

Chemotherapy will be administered concomitantly with the radiation therapy. Cisplatin (50 mg/m2) will be given on Days 1 and 29 of the course of external beam radiation therapy.

Physical Factors: All treatment will be delivered by megavoltage equipment ranging from 6 MV to a maximum of 25 MV photons. Cobalt-60 equipment will not be acceptable for treatment on this protocol. Tomotherapy is allowed.

Localization and Simulation Methods: Localization images taken on the conventional or CT-simulator will be necessary in all cases.

Treatment Plan and Dose Specification: Patients may be treated with either conventional radiation therapy approaches or with IMRT. (See Sections 4.62, 4.64 and 5.1 for credentialing requirements.) For patients treated with a conventional 4 field approach, it is highly recommended that each patient swallow a dilute solution of an appropriate contrast material at least 30 minutes before simulation so that the small bowel can be identified on the simulator films. The use of individualized custom blocking is required.

Before ANY patient is enrolled on this study, each treating radiation oncologist must complete on-line a Knowledge Assessment Questionnaire found on the RPC website (http://rpc.mdanderson.org). For patients treated with IMRT, the treatment plan for the first patient to be treated by each radiation oncologist on this protocol must be digitally submitted to the ITC where it will be processed in preparation for rapid review. A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by the Radiological Physics Center (RPC) and suggestions regarding protocol compliance will be forwarded to the participating institution's radiation oncologist. Instructions for electronically submitting the patient case can be found on the Advanced Technology Consortium (ATC) web site, http://act.wustl.edu. The treatment plans for the subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed.

Daily Tumor Dose, Total Dose, and Overall Treatment Time: A daily tumor dose of 180 cGy per day will be given to a total dose of 4500 cGy (180 cGy *x* 25 treatments) in approximately five weeks. Treatment will be given 5 days a week, from Monday through Friday

Dose Distribution (Site): Dose to the CTV should not vary by more than +/- 5% from the prescribed dosage for 3D conformal plans. The use of tissue wedges and/or compensating filters may be necessary to accomplish this goal. Isodose distributions shall be obtained and submitted for review.

As a general rule, only pelvic radiation therapy will be given, unless there is imaging, intra-operative, histologic, or other evidence of para-aortic node involvement. However, the treating radiation oncologist may reasonably elect to treat with extended-field radiation therapy in the setting of positive pelvic nodes in the absence of adequate surgical staging data indicating the para-aortic lymph nodes are negative. Similarly, the treating radiation oncologist might elect not to treat the para-aortic field (only in the absence of proven metastatic disease in this region) to improve the patient's acute tolerance to RT. In general these treatment decisions will not be deemed protocol violations, given sufficient information regarding the decision-making process.

If there is tumor extension into the vagina, the external beam fields will be modified to include the disease volume with at least a 2 cm margin. For involvement of the distal 1/3 of the vagina, inguino-femoral nodes should also be covered in the external beam RT ports. If the patient's tumor extends into the cervix, or invades deeply and extends into the lower uterine segment, or if there is lymph-vascular space invasion by tumor, or if the tumor has extended into the vagina, such a patient will receive intravaginal boost brachytherapy (HDR or LDR) at the discretion of the radiation oncologist. Patients with residual gross disease in the vagina following surgery are eligible as long as the maximum dimension is no greater than 2 cm by physical exam and imaging studies, if indicated.

Radiation Therapy Volumes and Technique

Pelvic field: 3D Conformal
Portal and Treatment Volume Definition:
The boundaries are as follows:
AP/PA Fields: Cephalad Border:
A transverse line drawn within 2 cm of the L5-S1 interspace, or higher if necessary to include known areas of lymph node involvement by tumor.

AP/PA Fields: Caudal Border:

The mid-portion of the obturator foramen or a minimum of 4 cm margin on the vaginal cuff, preferably defined by marker seed placement or by placement of a vaginal swab at the time of simulation.

Lateral Borders:
≥1 cm beyond the lateral margin of the true pelvis at its widest points. Alternatively, use of a CT scan to outline the target vessels with a border of at least 1 cm is acceptable.

Lateral Pelvic Fields:
The cephalad and caudal borders are same as above.

Anterior Border:
A horizontal line drawn anterior to the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodal regions or, in the absence or radiographic documentation, the line should pass at least 1.5 cm anterior to the L5 vertebral body. Individualized custom blocks can be used to achieve this goal.

Posterior Border:
A cephalo-caudal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm.

Pelvic Radiation Therapy: IMRT
In addition to the rapid review requirements for all radiation oncologists treating on this protocol (see Section 4.55), please note that all institutions that are considering the use of IMRT MUST be credentialed by the Radiological Physics Center (RPC) at M.D. Anderson Cancer Center before entering any patient on this study. (See Section 5.1). A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by the Radiological Physics Center (RPC) and suggestions regarding protocol compliance will be forwarded to the participating institution – radiation oncologist. Instructions for electronically submitting the patient case can be found on the Advanced Technology Consortium (ATC) web site, http://atc.wustl.edu. Institutions that have been previously credentialed for IMRT by RTOG or GOG via the head and neck phantom or the pelvic phantom can determine what additional requirements must be completed by filling out the "Credentialing Status Inquiry" form on the RPC website. The RPC will issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center.

Institutions that have not been credentialed by GOG or RTOG must apply for IMRT credentialing. See Section 5.1 for credentialing requirements.

Portal and Treatment Volume Definition:
Patient Immobilization: Prior to simulation, it is recommended that radiopaque marker seeds be inserted into the vaginal apex to help to identify the area by CT scan. Patients are to be immobilized in the supine position in an immobilization device such as Vac-lok or alpha-cradle, with fixation of the upper body, trunk, and proximal thighs. Patients are to be treated in the immobilization device. CT scan thickness should be 3 mm or smaller through the region that contains the PTV, extending from at least L3-4 level to below the perineum.

Simulation: CT simulation is required to define clinical target volume (CTV) and planning target volume (PTV). The CT scan should be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast are highly recommended for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation, as well as small bowel contouring, respectively.

Contouring the Target volumes: Please refer to the ***RTOG Gynecological Atlas for volume specification. The atlas may be accessed on the RTOG website at:*** http://www.rtog.org/gynatlas/main.html

The Clinical Target Volume (CTV) is defined as the vaginal apex with margins as given in Section 4.6, in addition to pelvic nodal regions lying within the field borders given in Section 4.61.m If gas/stool distends the rectum, the CTV is to be expanded to include the anterior half of the rectum to account for evacuation of the rectum

The nodal portion of the CTV should include the internal (hypogastric and obturator), and external iliac lymph node regions. The CTV should be delineated using the contrast-enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 6 mm axial margin around the vessels). Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 6 mm margin around the vessels). Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) may be added to the CTV for adequate coverage of pre-sacral nodes, although this is optional and at the discretion of the treating radiation oncologist. In addition, the most antero-lateral margin of the external iliac nodes that lie just proximal to the inguinal canal should be excluded from the CTV (nodal CTV should stop at the femoral head). Proximally, the CTV should end 7 mm from the L5-S1 interspace to account for the PTV. The CTV should include the inguino-femoral nodes if the distal one-third of the vagina is involved with tumor.

The PTV should provide a 7 mm-1 cm margin in all directions around the CTV.

The definitions of volumes will be in accordance with the 1993 ICRU report #50. Prescribing, recording and reporting photon beam therapy and 1999 ICRU report #62. Critical normal surrounding structures:

Bladder will be contoured in each slice in which it appears.

Rectum will be contoured in each slice in which it appears. As a general guideline, the radiation oncologist can consider the maximum caudal extent of the rectum to lie 1.5-2.0 cm from the bottom of the ischial tuberosities. Superiorly, judgment will be required to establish where the rectum ends and the sigmoid colon begins. The transition to the sigmoid colon is marked by increased curvature and tortuosity in its path.

Small bowel will be contoured in each slice in which it appears, including at least 2 cm above the PTV. The small bowel will be contoured in its entirety within these parameters, including adipose and mesentery.

Femoral heads will be contoured in all the slices in which they appear.

Constraints: Participants are strongly encouraged to respect the following limits, whether 3-D conformal or IMRT approaches are used.

Small bowel: <30% to receive ≥ 40Gy, Dmax ≤46 Gy
Rectum: < 80% to receive ≥ 40Gy, Dmax ≤55 Gy
Bladder: < 50% to receive ≥ 45Gy, Dmax ≤60 Gy
Femoral heads: < 50% to receive ≥ 40Gy, Dmax ≤50 Gy.
Unspecified tissue (tissue contained within the skin or any other normal structure not delineated above and outside the PTV, not included within any other structure): No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

Extended Field Radiation Therapy: 3D Conformal

Portal and Treatment Volume: The boundaries are as follows:

AP/PA Fields: Cephalad Border:

A transverse line drawn within 2 cm of the T11-T12 interspace.

AP/PA Fields: Caudal Border:

The mid-portion of the obturator foramen or a minimum of 4 cm margin on the vaginal cuff, preferably defined by marker seed placement or by placement of a vaginal swab at the time of simulation.

Lateral Borders:
In the pelvis >1 cm beyond the lateral margin of the true pelvis at its widest points. Alternatively, use of a CT scan to outline the target vessels with a border of at least 1 cm is acceptable. Moving superiorly, the width of the field will taper to the lateral aspects of the spinal transverse processes at L4 and superior to L4. The approximate field width for the para-aortic portion of the field should be 8 cm, although some variation is expected.

Lateral Pelvic Fields:

The cephalad and caudal borders are same as above.

Anterior Border:

A horizontal line drawn anterior to the symphysis pubis. When extended in the cephalad direction, this line should pass at least 1 cm anterior to known nodal regions or, in the absence or radiographic documentation, the line should pass at least 1.5 cm anterior to the L5 vertebral body. Individualized custom blocks can be used to achieve this goal. Moving superiorly, the anterior border of the para-aortic field should remain a minimum of 1.5-2 cm anterior to the anterior border of the vertebral body. Again, some variation is expected, particularly in patients who have positive PA nodes or in patients who kidneys are located more anteriorly than normal. The overall width of the PA field should be at least 5 cm.

Posterior Border:

A cephalo-caudal line passing through the third sacral vertebra. Every effort should be made to include the upper vaginal stump with a margin of at least 3 cm. Moving superiorly, the posterior border of the PA field should extend back approximately 50% of the width of each vertebral body.

Suggested technique: Different techniques have been used to deliver extended field radiation therapy. The suggested technique for this study is to treat the pelvic and para-aortic fields in continuity, as opposed to splitting fields, or treating the para-aortic portion with AP-PA fields only. Treating in continuity, it is suggested that the AP-PA fields be weighted 70:30 in relation to the lateral fields, in terms of isocenter dose. This technique strikes an appropriate balance, in most cases, between small bowel dose and kidney dose. Other techniques or beam weightings are potentially permissible, if appropriate dose distributions to PTV and organs at risk (OAR's) are obtained. Should there be questions, the treating radiation oncologist is encouraged to contact the Radiation Oncology Co-Chair.

Extended Field Radiation Therapy: IMRT

In addition to the rapid review requirements for all radiation oncologists treating on this protocol (see Section 4.55), please note that all institutions that are considering the use of IMRT MUST be credentialed by the Radiological Physics Center (RPC) at M.D. Anderson Cancer Center before entering any patient on this study.

Please note that ALL institutions, when IMRT is to be used, must submit and successfully complete a plan for the first patient to be treated by each radiation oncologist treating on this protocol. A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by the Radiological Physics Center (RPC) and suggestions regarding protocol compliance will be forwarded to the participating institution – radiation oncologist. Instructions for electronically submitting the patient case can be found on the Advanced Technology Consortium (ATC) web site, http://atc.wustl.edu. The treatment plans for the subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed.

Portal and Treatment Volume Definition:

Patient Immobilization:

Prior to simulation, it is recommended that radiopaque marker seeds are inserted into the vaginal apex to help to identify the area by CT scan. Patients are to be immobilized in the supine position in an immobilization device such as Vac-lok or alpha-cradle, with fixation of the upper body, trunk, and proximal thighs. Patients are to be treated in the immobilization device. CT scan thickness should be 3 mm or smaller through the region that contains the PTV, extending from at least L3-4 level to below the perineum.

Simulation:
CT simulation is required to define clinical target volume (CTV) and planning target volume (PTV). The CT scan should be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast are highly recommended for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation, as well as small bowel contouring, respectively.

Contouring the Target volumes: Contouring in the pelvis is identical to that described in Sections 4.61- 4.63.

The Clinical Target Volume (CTV) is defined as the vaginal apex with margins as given in Section 4.6 in addition to pelvic and para-aortic nodal regions lying within the field borders given in Sections 4.61- 4.63.

The nodal portion of the CTV should include the internal (hypogastric and obturator), external iliac lymph node, and para-aortic regions. The CTV should be delineated using the contrast-enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 6 mm axial margin around the vessels). Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 6 mm margin around the vessels).
Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) may be added to the CTV for adequate coverage of presacral nodes, although this is optional and at the discretion of the treating radiation oncologist. In addition, the most antero-lateral margin of the external iliac nodes that lie just proximal to the inguinal canal should be excluded from the CTV (nodal CTV should stop at the femoral head. Proximally, the CTV should end 7 mm from the T11-T12 interspace to account for the PTV.

The PTV should provide a 7 mm-1 cm margin in all directions around the CTV.

The definitions of volumes will be in accordance with the 1993 ICRU report #50. Prescribing, recording and reporting photon beam therapy and 1999 ICRU report #62.

Critical normal surrounding structures:

Bladder will be contoured in each slice in which it appears.

Rectum will be contoured in each slice in which it appears. As a general guideline, the radiation oncologist can consider the maximum caudal extent of the rectum to lie 1.5-2.0 cm from the bottom of the ischial tuberosities. Superiorly, judgment will be required to establish where the rectum ends and the sigmoid colon begins. The transition to the sigmoid colon is marked by increased curvature and tortuosity in its path.

Small bowel will be contoured in each slice in which it appears, including at least 2 cm above the PTV. The small bowel will be contoured in its entirety within these parameters, including adipose and mesentery.

Femoral heads will be contoured in all the slices in which they appear.

Constraints: Participants are strongly encouraged to respect the following limits, whether 3-D conformal or IMRT approaches are used.

Small bowel: <30% to receive ≥ 40Gy, Dmax ≤46 Gy

Rectum: < 60% to receive ≥ 40Gy, Dmax ≤55 Gy

Bladder: < 50% to receive ≥ 45Gy, Dmax ≤60 Gy

Femoral heads: < 50% to receive ≥ 40Gy, Dmax ≤50 Gy.

Kidney volume (combined right and left): <40% to receive ≥15 Gy

Spinal cord: <10% to receive ≥40 Gy, Dmax ≤45 Gy **(06/07/2010)**
Unspecified tissue (tissue contained within the skin or any other normal structure not delineated above and outside the PTV, not included within any other structure): No more than 1% or 1 ml (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

Boosts to Gross Disease

As reflected in the eligibility and ineligibility criteria, otherwise eligible patients with up to 2 cm of residual disease (single site) are eligible. For these patients, it is permissible to deliver a radiotherapy boost to these areas provided that they are clearly definable by standard imaging modalities, allowing the radiation boost to be accurately targeted.

Dose
A further 10-15 Gy in 5-8 fractions can be delivered at the discretion of the radiation oncologist. The boost dose can be delivered to the initial volume of gross disease as identified on the initial imaging studies. Should the initial

chemo-radiation treatment result be a partial or complete response of the identifiable gross disease, the boost dose should be limited to 10 Gy.

Margin and Definition of Volume

The original gross disease with a 1.0-1.5 cm margin should be targeted.

Technique

Either 3-D conformal or IMRT techniques can be used. However, as noted in Section 4.62, it is NOT acceptable to treat initially with 3-D conformal treatment and then switch to IMRT for the boost.

The actual treatment technique is expected to vary considerably due to the location of the targeted area, surrounding radiosensitive structures, and dose distribution of the initial treatment.

Treatment Plan, Dose Specification, and Distribution

The volume irradiated with the whole pelvic fields will include the CTV and PTV as defined above.

The whole pelvis will receive a total dose of 4500 cGy in 25 fractions at 180 cGy/fx. For patients treated with IMRT, the prescription dose is the isodose that encompasses at least 97% of the PTV. No more than 20% of any PTV should receive >110% of the prescribed dose. No more than 1% of the PTV should receive <93% of the prescribed dose. No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV will receive >110% of the dose prescribed to the PTV. However, with respect to this last constraint, it is recognized that there may be patients in which, due to obesity or other factors, this constraint may not be obtainable if other constraints, e.g. rectum, are met. In these cases it is recommended that the OAR constraints be favored to the extent possible that is consistent with good radiotherapy practice.

Documentation requirements

For 3-D conformal treatments, digital reconstructed radiographs (DRR) of the treatment fields with the three-dimensional reconstruction of the CTV are to be obtained and submitted for evaluation.

For 3-D conformal plans, localization or block-check images of virtually simulated fields are to be obtained in the simulator and/or treatment machine for all the treatment fields independently, whether cerrobend blocks or multi-leaf collimators are used.

For 3-D conformal plans, all plans must be submitted electronically to the Image-Guided Therapy Center (ITC) (http://atc.wustl.edu).

For IMRT plans, all plans must be submitted electronically to the ITC (http://atc.wustl.edu) for review, in addition to what is required from RPC in Section 10.2.

For IMRT plans, Dose-Volume Histograms (DVHs) are to be obtained for each one of the target volumes defined above, as well as the critical surrounding structures, and need to be submitted for evaluation. For detailed description of radiation pelvic fields, please see Section 4.62.

Therapy Interruptions: If interruption of two weeks or less occurs, radiation should be completed to the prescribed total dose. Therapy interruptions of more than two weeks will be considered a major or minor deviation from the protocol, depending on clinical circumstances, and resumption of therapy will be at the discretion of the radiation oncologist. Follow-up must continue regardless of radiation treatment received.

Expected Toxicity: Toxicity will vary depending upon tolerance of individual patient, daily dose, total dose, overall treatment time, associated illness, etc. The following toxicity criteria may be used:

Gastrointestinal: Nausea and vomiting is unusual, but may be seen after pelvic radiation. Antiemetics may be used during treatment or may be given prophylactically the night prior to treatment. Intractable nausea or vomiting is rarely seen with pelvic radiation alone and is usually the result of another process, i.e., bowel obstruction. Increased bowel activity with diarrhea usually can be controlled with low- fiber, low-fat, bland diets, and anti-diarrhea medications. Should G.I. toxicity become severe, hospitalization may be required, at which time the treatment is interrupted temporarily until the patient's condition improves.

Hematological: Hematological toxicity is seen infrequently, unless pelvic radiation is accompanied by chemotherapy. A CBC should be obtained weekly during radiotherapy. If the ANC falls below 1,000 /mcl or the platelet count below 50,000/mcl, the CBC should be obtained twice weekly. Radiotherapy should be stopped when ANC < 500 and/or platelets < 25,000. Radiotherapy should be temporarily halted if on successive measurements the platelet count declines rapidly below 50,000. Radiotherapy may be resumed when ANC > 500/mcl and platelets > 50,000/mcl. **(06/22/09)**

Brachytherapy:
If a vaginal brachytherapy boost is to be given based on the criteria given in Section 4.59, it should commence within 2 weeks of completion of the external beam RT. It should be delivered with a vaginal cylinder (HDR or LDR) or colpostats (LDR), and in the absence of gross residual disease following surgery the treating physician must choose one of the following:

A) HDR: 600 cGy x 2-3, weekly, prescribed at the vaginal surface. Dose optimization should be used in an effort to create reasonable homogeneity of dose around the surface of the applicator. A minimum of 4 cm of vaginal length should be treated.

B) LDR 2000-3500 cGy prescribed at the vaginal surface in 1 insertion at a dose rate of 40-100 cGy/hr. A minimum of 4 cm of vaginal length should be treated.

In cases where the patient has small volume (≤2 cm) residual disease in the vagina following surgery, the patient may have intra-cavitary treatment as described above only if the residual thickness following external RT is less that 0.5 cm. If the residual lesion is greater than 1 cm in thickness, a low dose-rate interstitial implant is recommended to deliver approximately 3500 cGy to the residual volume.

Physical Factors

If an intravaginal boost is to be used, it should be delivered with an intravaginal cylinder (HDR or LDR). Acceptable isotopes include cobalt or iridium for HDR, radium or cesium for LDR.

Expected Toxicity

Gastrointestinal: Nausea and vomiting may occur after extended field (PAN) treatments, but can be effectively treated with an appropriate antiemetic in most cases. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is not commonly seen as a result of radiation alone.

Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic radiation. It is recommended that instructions be given to patients for low-fiber, low-fat, bland diet. Most patients will require anti-diarrheal medications such as diphenoxylate HCL with atropine sulfate (Lomotil) or loperamide HCL to control diarrhea.

Hematological toxicity of a mild nature will be seen frequently with a decline in WBC and platelet count.

Radiation Therapy Quality Control and Documentation

The Radiological Physics Center is funded by the NCI to support clinical trials employing radiation therapy and will supervise the dosimetry quality control for this clinical trial. To participate in the trial, the institutions must demonstrate the ability to achieve an accuracy of ±3% in measuring the output of their sources and ±5% in delivering the prescribed dose.

## CARBOPLATIN DOSE CALCULATION

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).

2) Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.

3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to "non-IDMS" conversion) is also available, if needed for dose modifications (see below).

**Dosing of Carboplatin:**
The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment.

For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

**Maximum** carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

**The maximum allowed doses of carboplatin are:**
**AUC 6 = 900 mg**
**AUC 5 = 750 mg**
**AUC 4 = 600 mg**

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:
1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
   c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
   d. Adjusted weight calculation:
      Ideal weight (kg) = (Height (cm)/2.54) – 60) x 2.3) + 45.5

      **Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight**

   e. If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

**At the time of a dose modification for toxicity**:

1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.

| DRUG | INITIAL DOSE | Dose Reduction | UNITS |
|---|---|---|---|
| Cisplatin | 50 | 40 | Mg/m2 |

## TREATMENT MODIFICATIONS

Early and late toxicities encountered during treatment will be evaluated and graded according to the NIH common toxicity criteria outlined in CTCAE v3.0.

Radiation Therapy

GI Toxicity: Gastrointestinal toxicity greater than Grade 2 requires temporary discontinuation of treatment until toxicity resolves to Grade 1 or less.

Hematological Toxicity: CBC should be obtained weekly during radiation therapy. If the ANC falls below 1,000 /mcl or the platelet count below 50,000/mcl, the CBC should be obtained twice weekly. If the ANC falls below 500/mcl or the platelet count below 25,000/mcl, then treatments should be stopped temporarily to allow recovery to ANC > 500/mcl and platelet count > 50,000/mcl. Radiotherapy should be temporarily halted if on successive measurements the platelet count declines rapidly below 50,000.

Recurrent Disease: Treatment will be discontinued in patients with progressive disease. Consideration for other therapies should be given.

Chemotherapy-Hematological Toxicity

REGIMEN I: Cisplatin dose modifications

Dose reduction levels:

Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white blood cell count (WBC). Administration of the second dose of cisplatin on Day 29 will be a dose Level 1 if the ANC is $\geq$ 1,500 cells/mcl and the platelet count is $\geq$ 100,000 cells/mcl, or at dose Level 2 if ANC 1,000 to 1,500 cells/mcl and/or platelet count is 70,000-100,000 cells/mcl. The second dose on Day 29 will be held until Day 36 if these parameters are not met. If on Day 36, the hematological parameters are not met, the second dose of cisplatin will be omitted.

G-CSF and erythropoietin should not be used during chemo-radiation treatment. Transfusions can be administered at the discretion of the treating physician.

REGIMENS I and II: Carboplatin and paclitaxel dose modifications:

Dose reduction levels:

| DRUG | INITIAL DOSE | 1ST DOSE REDUCTION | 2ND DOSE REDUCTION | UNITS |
|---|---|---|---|---|
| Carboplatin | 6.0* | 5.0 | 4.0 | AUC |
| Paclitaxel | 175 | 175 | 135 | Mg/m2 |

* For patients randomized to Regimen I, the initial dose of carboplatin will start at an AUC of 5. The first dose reduction for patients receiving carboplatin at an AUC of 5 will correspond to the second dose reduction described in the table above. Subsequent carboplatin doses will be escalated to an AUC of 6 as outlined below in Section 6.229.

Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC). Subsequent cycles of therapy will not begin until the ANC is ≥ 1,500/mcl and the platelet count is ≥100,000/mcl. Therapy will be delayed on a week-by-week basis until these values are achieved.

Treatment modifications will be employed in a sequential manner using cycle delay and dose reduction.

Patients who experience Grade 4 thrombocytopenia (≤10,000 plts/mcl) will have a 1-level dose reduction of carboplatin, without a change in paclitaxel dosage.

There will be no dose modifications based on uncomplicated ANC nadirs.

On Regimen II, patients who experience febrile neutropenia will receive G-CSF with subsequent cycles according to ASCO guidelines and no dose reduction. As all patients in Regimen I will receive G-CSF with systemic chemotherapy, if febrile neutropenia occurs despite the use of G-CSF, then dose reduction will be necessary.

Patients who require a delay of > 7 days will receive a dose reduction of one level in accordance with the table above and without addition of G-CSF.

Protocol therapy will be discontinued in patients who require a delay of > 21 days.

There will be no dose re-escalations in the study, <u>except the following</u>: Patients randomized to Regimen I will be started at a reduced dose of carboplatin after radiotherapy (AUC 5). Their subsequent carboplatin dose will be escalated to an AUC of 6, provided that these patients do not develop any of the following: Grade 4 thrombocytopenia; greater than Grade 3 neutropenia that does not recover to Grade 1 by Day 21 of the first cycle; or other Grade 3 or higher non-hematological toxicity that does not recover to Grade 1 by Day 21 of the first cycle (except alopecia). Individual assessment by the treating physician is recommended prior to dose escalation of patients randomized to Regimen I after the first cycle of carboplatin and paclitaxel.

Transfusions and erythropoietin can be administered at the discretion of the treating physician.

Systemic Chemotherapy: Non-Hematologic Toxicity

Paclitaxel hypersensitivity reaction: If hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur, it will usually be during the first few minutes of infusion. Appropriate symptomatic therapy should be given. Continued treatment may be considered if the reaction is not life threatening; however, patients must be cautioned about potential recurrences of the reaction. Should the patient decide to continue with treatment, it is preferable that this be done on the same day of the occurrence. A suggested procedure would be to administer the drug first with 1 ml of the original IV solution diluted in 100 ml over one hour, then 5 ml in 100 ml over one hour, then 10 ml in 100 ml over one hour, and finally, the original solution at the original speed. Patients who elect not to have continued treatment with paclitaxel after experiencing a hypersensitivity reaction may continue on protocol therapy with carboplatin only.

Cardiac arrhythmias: Asymptomatic bradycardia associated with paclitaxel treatment is not an indication to discontinue therapy. For symptomatic arrhythmia, paclitaxel infusion should be discontinued, and the arrhythmia managed according to standard practice. The patient will be removed from protocol treatment and will require further cardiac assessment.

Ototoxicity: For clinically significant hearing loss or tinnitus, cisplatin will be discontinued. Audiograms are indicated in patients with pre-treatment hearing loss.

Myalgias: Myalgias can occur during the several days following paclitaxel treatment and may be severe. They should receive aggressive symptomatic treatment, including NSAIDs, narcotics, or steroids, as deemed appropriate by the treating physician. Myalgias are not an indication for dose reduction.

Neurological toxicity: Grade 2 or greater peripheral neuropathy requires delaying therapy until symptoms resolve to ≤ Grade 1. When treatment is resumed, paclitaxel dose should be reduced one dose level to 135mg/m$^2$. Recurrent Grade 2 neurotoxicity will require delay of treatment until neuropathy resolves to Grade 1. A delay exceeding three weeks for neurological function recovery will require discontinuation of protocol treatment. Patients will be removed from protocol therapy for recurrent Grade 3 or for Grade 4 neurological toxicity.

Renal toxicity
Serum creatinine will be obtained at enrollment and with each cycle of treatment. For creatinine levels ≥1.6 mg/dl prior to treatment, cisplatin will be held. Patient may remain on protocol therapy with the omission of cisplatin at the discretion of the treating physician. If the creatinine level subsequently returns to < 1.6 mg/dl, cisplatin may be

reinstated in subsequent cycles. Hydration before and after cisplatin infusion is recommended for all patients (2 liters of fluid). Use of mannitol is optional. Selective renal tubular defects are observed with cisplatin. Hypocalcemia, hypomagnesemia, and hypokalemia are common and potentially severe. Replacement of calcium, magnesium, and potassium is usually effective. Severe defects, although uncommon, may require chronic replacement therapy. Discontinuation from protocol in cases of severe renal tubular dysfunction resulting in dyselectrolemia can be done at the discretion of the treating physician.

Gastrointestinal toxicity
Nausea and Vomiting: Increased antiemetic support, sedation, and prophylactic hospitalization should be performed. Dose reductions are generally not needed for nausea and vomiting.
Stomatitis or diarrhea: If any grade mucositis is present on Day 21 of a cycle, the next cycle of treatment should be withheld until the mucositis has cleared. Grades 3 or 4 mucositis or diarrhea require one dose level reduction for paclitaxel.
Hepatic Toxicity

Liver function tests will be obtained prior to treatment and before each cycle of therapy (Bilirubin, SGOT and SGPT).

Bilirubin must return to $\leq$1.5 ULN prior to further therapy.

Transaminases (AST and ALT) should be $\leq$ 2.5 times ULN prior to each cycle of treatment.

Other toxicities: For any other Grade 3 or 4 toxicities not mentioned above, protocol treatment should be withheld until patients recover completely or to Grade 1 toxicity status. The next dose of the agent believed responsible for the adverse event will be given at a one dose level reduction. In general, unusual toxicities should be discussed with the Study Chair.

Discontinuation from protocol

Patients may withdraw from the protocol at any time for any reason.

Patients whose treatment is delayed over three consecutive weeks because of any toxicity should be removed from protocol therapy.

At the discretion of the treating physician, protocol treatment may be withdrawn because of serious toxicity or lack of compliance.

## Disease Assessment and Schedule of Events

| Tests & Observations | Prior to study | During radiation therapy weekly | At the end of radiotherapy, prior to starting combination chemotherapy (Regimen I only) | Prior to each cycle of chemo-therapy | Follow-up | Within 4 weeks of completion of protocol therapy |
|---|---|---|---|---|---|---|
| History | 1 | | X | X | 4, 12 | X |
| Physical Examination | 1 | | X | X | 4 | X |
| Toxicity assessment | 1 | X | X | X | 14 | X |
| Pelvic Examination | 1 | | X | 7 | 4 | X |
| HGB or HCT | 2 | X | X | 3 | 13 | X |
| ANC | 2 | 5 | X | 3 | 13 | X |
| Differential | 2 | X | X | 3 | 13 | X |
| Platelets | 2 | 5 | X | 3 | | X |
| Creatinine | 2 | 8 | X | 3 | | X |
| Bilirubin | 2 | | X | 3 | 13 | X |
| SGOT, SGPT | 2 | | X | 3 | 13 | X |
| Alkaline Phosphatase | 2 | | X | | 13 | X |
| Chest X-ray | 9 | | | | 6 | |
| Urinalysis | 2 | | | | | |
| Abdomen and pelvis CT | 9 | | | | 6 | |
| Chest CT scan | 10 | | | | 10 | |
| Quality of Life Assessments | 11 | | 11 | | 11 | |

1. Must be obtained within 28 days of initiating protocol therapy.
2. Must be obtained within 14 days of initiating protocol therapy.
3. Must be obtained within 4 days of re-treatment with protocol therapy.
4. Every 3 months for first 2 years, then every 6 months until 5 years post treatment.
5. Weekly, and twice a week if ANC < 1,000 or platelet count < 50,000 mcl.
6. Must be obtained at the end of therapy, then every 6 months for first 2 years, and then annually for an additional 3 years
7. Every other cycle of chemotherapy, or as clinically indicated.
8. Within 3 days from Day 29 cisplatin
9. Must be obtained after surgery and within 28 days prior to initiating protocol therapy.
10. Must be obtained if Chest x-ray is abnormal. Chest CT is acceptable in place of CXR for baseline screening; however, the same modality that was used for baseline imaging studies must be used for all follow-up studies.
11. The QOL assessments to be administered are as follows: FACT-G Physical Well-being (PWB) and
    Functional Well-being (FWB) subscales (14 items), FACT-En additional concerns subscale (16 items),
    FACT/GOG-NTX-4 subscale (4 items), and items C3 and C5 from the FACT-C.
    Patients will complete the QOL assessments at 4 times:
    1) At baseline (within 14 days prior to starting protocol therapy)
    2) 6 weeks from start of protocol treatment (1 week post completion of RT for Regimen I or three weeks post completion of 2 cycles of chemotherapy for Regimen II)
    3) 18 weeks from start of protocol treatment (three weeks after completion of protocol therapy)

4) 70 weeks from start of protocol treatment (1 year from completion of protocol therapy)

NOTE: QOL assessments should be administered at ALL 4 assessment times, regardless of whether the patient progresses or is removed from the study for any reason.

12. After 5 years, information about survival will be obtained yearly by phone calls.
13. At the end of protocol-directed therapy and yearly for the first 5 years.
    If abnormal, evaluate with appropriate diagnostic testing to exclude the presence of systemic metastatic disease.
14. Every 6 months for 3 years (report on Form TLC).

## STUDY MONITORING AND REPORTING PROCEDURES

### ADVERSE EVENT REPORTING FOR ALL REGIMENS (COMMERCIAL AGENTS AND RADIATION THERAPY ADMINISTRATION)

#### Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

#### Reporting Expedited Adverse Events

Depending on the phase of the study, the use of investigational or commercial agents, and the role of the pharmaceutical sponsor, an AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG. Submitting a report through AdEERS serves as notification to GOG and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

#### Phase 2 and 3 Trials Utilizing a Commercial Agent: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the AdEERS system.

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS).

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Unexpected | | Expected | | | |
| | Unexpected and Expected | Unexpected | Expected | With Hospitali-zation | Without Hospitali-zation | With Hospitali-zation | Without Hospitali-zation | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days |
| **Possible Probable Definite** | Not Required | 7 Calendar Days | Not Required | 7 Calendar Days | 7 Calendar Days | 7 Calendar Days | Not Required | 24-Hrs; 3 Calendar Days | 7 Calendar Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:

AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent."**

**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.**

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
    "7 calendar days" – A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported, regardless of attribution and designation as expected or unexpected, with the exception of any events identified as protocol-specific exclusions for expedited adverse event reporting.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via AdEERS if the event occurs following treatment with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Procedures for Expedited Adverse Event Reporting:

AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

# GOG PROTOCOL #258

Patient Initials (First, Middle, Last): _____

**IMPORTANT**

- USE NO. 2 PENCIL ONLY
- ERASE CHANGES COMPLETELY

EXAMPLES: RIGHT ● WRONG ✓ ✗ ◒ ⊙

DATE QUESTIONNAIRE COMPLETED: MO. | DAY | YEAR

Patient Study ID: 0258

**Scheduled time to obtain Quality of Life Questionnaire (Mark one)**

① Prior to starting study therapy (within 14 days)
② Regimen I: 1 week after completion of radiation therapy
Regimen II: Prior to cycle 3 (6 weeks after starting study therapy for those off study therapy prior to cycle 3)
③ 18 weeks after starting study therapy
④ 70 weeks after starting study therapy

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

## PHYSICAL WELL-BEING:

| | | NOT AT ALL | A LITTLE BIT | SOME-WHAT | QUITE A BIT | VERY MUCH |
|---|---|---|---|---|---|---|
| GP1. | I have a lack of energy. | ⓪ | ① | ② | ③ | ④ |
| GP2. | I have nausea. | ⓪ | ① | ② | ③ | ④ |
| GP3. | Because of my physical condition, I have trouble meeting the needs of my family. | ⓪ | ① | ② | ③ | ④ |
| GP4. | I have pain. | ⓪ | ① | ② | ③ | ④ |
| GP5. | I am bothered by side effects of treatment. | ⓪ | ① | ② | ③ | ④ |
| GP6. | I feel ill. | ⓪ | ① | ② | ③ | ④ |
| GP7. | I am forced to spend time in bed. | ⓪ | ① | ② | ③ | ④ |

## FUNCTIONAL WELL-BEING:

| | | | | | | |
|---|---|---|---|---|---|---|
| GF1. | I am able to work (include work at home). | ⓪ | ① | ② | ③ | ④ |
| GF2. | My work (include work at home) is fulfilling. | ⓪ | ① | ② | ③ | ④ |
| GF3. | I am able to enjoy life. | ⓪ | ① | ② | ③ | ④ |
| GF4. | I have accepted my illness. | ⓪ | ① | ② | ③ | ④ |
| GF5. | I am sleeping well. | ⓪ | ① | ② | ③ | ④ |
| GF6. | I am enjoying the things I usually do for fun. | ⓪ | ① | ② | ③ | ④ |
| GF7. | I am content with the quality of my life right now. | ⓪ | ① | ② | ③ | ④ |

## ADDITIONAL CONCERNS:

| | | NOT AT ALL | A LITTLE BIT | SOME-WHAT | QUITE A BIT | VERY MUCH |
|---|---|---|---|---|---|---|
| O1. | I have swelling in my stomach area. | ⓪ | ① | ② | ③ | ④ |
| O3. | I have cramps in my stomach area. | ⓪ | ① | ② | ③ | ④ |
| Hep 8. | I have discomfort or pain in my stomach area. | ⓪ | ① | ② | ③ | ④ |
| ES6. | I have vaginal bleeding or spotting. | ⓪ | ① | ② | ③ | ④ |
| ES4. | I have vaginal discharge. | ⓪ | ① | ② | ③ | ④ |
| Hep 1. | I am unhappy about a change in my appearance. | ⓪ | ① | ② | ③ | ④ |
| ES1. | I have hot flashes. | ⓪ | ① | ② | ③ | ④ |
| ES2. | I have cold sweats. | ⓪ | ① | ② | ③ | ④ |
| ES3. | I have night sweats. | ⓪ | ① | ② | ③ | ④ |
| HI7. | I feel fatigued. | ⓪ | ① | ② | ③ | ④ |
| ES8. | I have pain or discomfort with intercourse. | ⓪ | ① | ② | ③ | ④ |
| En1. | I have trouble digesting food. | ⓪ | ① | ② | ③ | ④ |
| B1. | I have been short of breath. | ⓪ | ① | ② | ③ | ④ |
| Cx6. | I am bothered by constipation. | ⓪ | ① | ② | ③ | ④ |
| BL2. | I urinate more frequently than usual. | ⓪ | ① | ② | ③ | ④ |
| En2. | I have discomfort or pain in my pelvic area. | ⓪ | ① | ② | ③ | ④ |
| C3. | I have control of my bowels. | ⓪ | ① | ② | ③ | ④ |
| C5. | I have diarrhea. | ⓪ | ① | ② | ③ | ④ |

Questions continue on the other side. Please turn page over. Thank you!

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

## FACT/GOG-NTX:

| | | NOT AT ALL | A LITTLE BIT | SOME-WHAT | QUITE A BIT | VERY MUCH |
|---|---|---|---|---|---|---|
| NTX1 | I have numbness or tingling in my hands. | ⓪ | ① | ② | ③ | ④ |
| NTX2 | I have numbness or tingling in my feet. | ⓪ | ① | ② | ③ | ④ |
| NTX3 | I feel discomfort in my hands. | ⓪ | ① | ② | ③ | ④ |
| NTX4 | I feel discomfort in my feet. | ⓪ | ① | ② | ③ | ④ |

## TO BE COMPLETED BY CLINICAL STAFF

QOL Contact person: _____

### Status of the QOL assessment (Mark Only One)

⓪ The questionnaire is complete.
① Patient kept appointment, but could not complete questionnaire due to illness.
② Patient kept appointment, but refused to complete questionnaire for reasons other than illness. specify reason: _____
③ Questionnaire not administered due to clinical staff error.
④ Patient off study treatment and cannot be contacted for follow-up.
⑤ Patient died.
⑥ Other, specify: _____

## Supplementary Materials and Methods

### Statistical Analysis:

The Kruskal-Wallis test corrected for ties was used to compare the maximum grade of acute and late adverse effects of therapy by treatment arm. A significance level of 0.01 was used for each AE term or category. No correction for multiple testing was employed. Competing risk analyses were carried out for vaginal, pelvic or PA nodes, and distant recurrences estimating the cumulative incidence of each to specific type of recurrence. Death in the absence of each of these events was considered a competing event.

**Quality of Life Analysis:**

The Trial Outcome Index of the Functional Assessment of Cancer Therapy for endometrial cancer (FACT-En TOI) and the FACT/GOG-neurotoxicity (NTX) subscale were used to measure quality of life and chemotherapy-induced neurotoxicity symptoms. Two items from the FACT-C combined with 4 items from the FACT-En TOI were used to explore gastrointestinal (GI) symptoms. Each item in the FACT-En TOI and the FACT/GOG-Ntx subscale were scored using a 5-point scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). For the negative statements (or questions), reversal was performed prior to score calculation. According to the FACIT measurement system, a subscale score was the summation of the individual item scores if more than 50% of subscale items were answered. When unanswered items existed, a subscale score was prorated by multiplying the mean of the answered item scores by the number of items in the subscale. The total FACT-En TOI score is calculated as the sum of the subscale scores if more than 80% of the FACT-En TOI items provide valid answers and all of the component subscales have valid scores. The total scores range 0-120 for FACT-En TOI and 0-16 for the FACT/GOG-Ntx subscale. A higher TOI, NTX, or GI score suggests better QOL or less symptoms.

The treatment difference in patient reported outcomes (PROs) was assessed with a linear mixed model adjusting for patient's pretreatment score, assessment time points, and age at enrollment. Patients were classified by their randomly assigned regimen rather than the treatment received. The assessment time

points were treated as categorical since they are not equally spaced. The covariance matrix among the repeated PRO scores reported by the same patient is assumed to be unstructured. To reflect the observed covariance pattern of the PROs scores, the 'empirical' variance was used in estimating the precision of parameter estimates. First, the interactions between assessment time points and treatment assignments were tested for the constant differential effects of treatments over time. If the interaction effect was not statistically significant, an overall treatment effect was estimated by a weighted average of estimates from each time point. If the testing for interaction was rejected treatment comparison was performed for each assessment time. In this case, the Hochberg's step-up method was used to adjust the p values for treatment differences at each assessment time points obtained from the fitted mixed model.

Since two PROs measures were tested in the primary PRO objective, the type I error was set at 0.025 for each of two PROs (FACT-En TOI or FACT-GOG/Ntx subscale) to ensure the overall type I error to be 0.05 (two-sided). Therefore, the Bonferroni method was used to adjust the p values for each PRO measure.

**Regulatory Approval Timeline and Conduct of GOG-0258**

2007-2009: Trial design and approval by the Uterine Corpus Committee (GOG), Protocol Development Committee (GOG), Uterine Cancer Task Force (NCI), Gynecologic Cancer Steering Committee (NCI), Central Institutional Review Board, and Clinical Trials Evaluation Program.

June 29, 2009: Trial activation

September 2013: First DSMB review

July 28, 2014: Target accrual reached

January 2016: Second DSMB review

March 9, 2017: Data freeze and final analysis

**Major deviations related to radiation delivery (n=15):**

8– Shielding and/or field placement

4 – Dose or dose and field placement

1 – Pre-treatment was denied; patient treated off study

2 – Incomplete data submission; a complete evaluation was not possible

## Supplementary Tables and Figures

**Figure S1:** Patient enrollment, randomization, and treatment

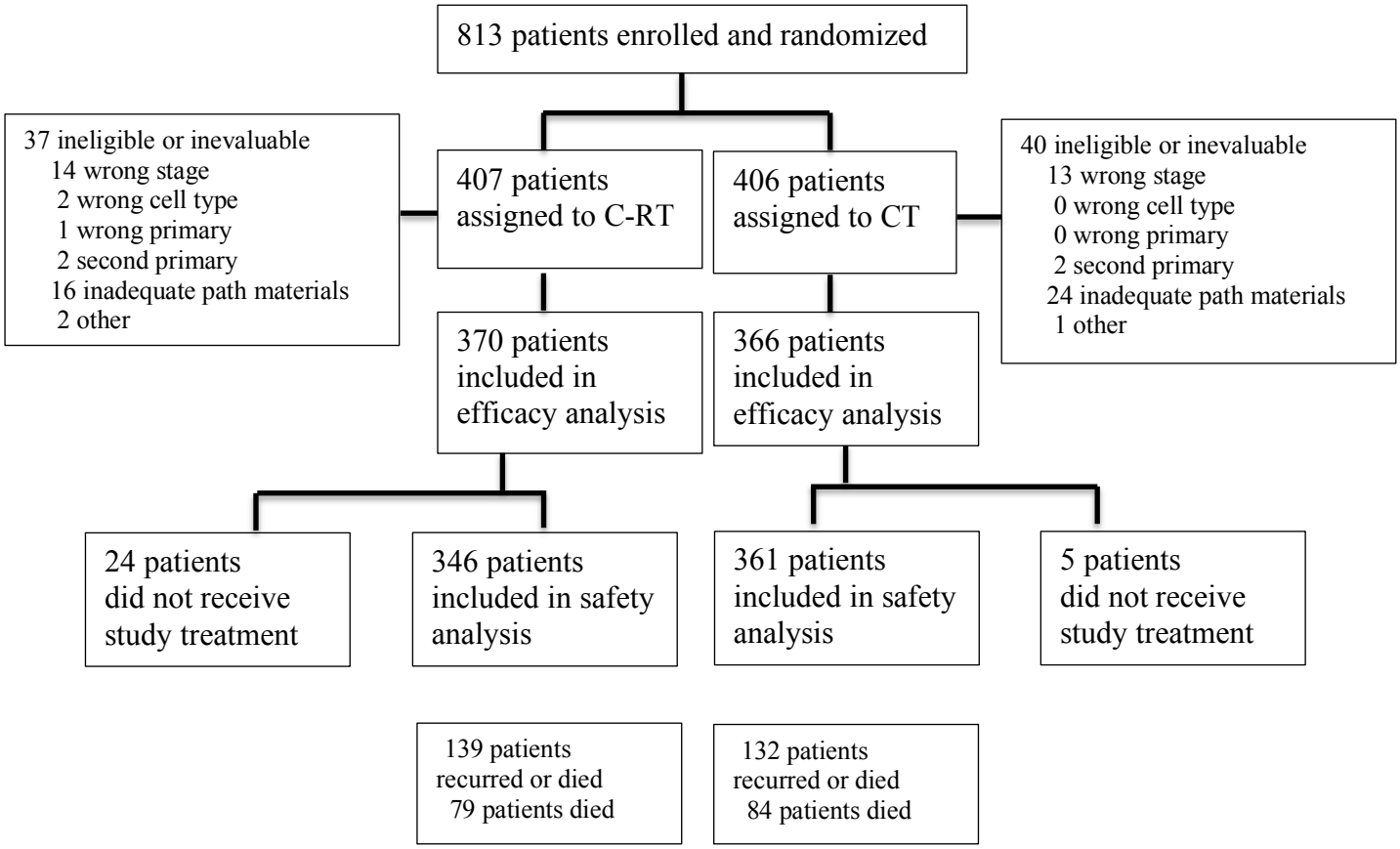


**Table S1:** Treatment allocation and delivery

| | C-RT | CT | Total |
|---|---|---|---|
| **Randomized** | 407 | 406 | 813 |
| Ineligible | 37 | 40 | 77 |
| Eligible | 370 | 366 | 736 |
| Never Treated | 24 | 5 | 29 |
| Withdrew Consent for Follow-up | 12 | 13 | 25 |
| Eligible, treated and not lost to follow-up | 334 | 348 | 682 |
| Received EBRT, no brachytherapy | 174 | | |
| Received EBRT, + Brachytherapy | 201 | | |
| Received >4 cycles of Carbo/Paclitaxel | 310 | 374 | 674 |
| Treatment length (median; weeks) | 21 | 17 | |

**Table S2:** Chronic toxicity in the two arms (C-RT and CT).* corresponds to $p<0.05$ and ** to $p<0.01$.

| **Adverse Event** | C-RT (n=346) % | | CT (n=361) % | |
|---|---|---|---|---|
| | All | Grade 3-5 | All | Grade 3-5 |
| Constitutional | 24 | 2 | 25 | 0 |
| Cardiac | 8 | 2 | 7 | 1 |
| Dermatologic | 9 | 0 | 14 | 0 |
| Gastrointestinal** | 21 | 5 | 25 | 2 |
| Renal | 8 | 2 | 12 | 1 |
| Blood/Bone marrow** | 8 | 2 | 11 | 2 |
| Lymphedema** | 7 | 1 | 15 | 0 |
| Musculoskeletal** | 7 | 2 | 9 | 0 |
| Metabolic | 12 | 3 | 12 | 2 |
| Neurological | 41 | 4 | 35 | 1 |
| Pulmonary | 8 | 0 | 10 | 1 |
| Pain | 23 | 2 | 24 | 2 |

**Table S3: Initial Recurrence Sites**

| Outcome | C-RT | | CT | | Total |
|---|---|---|---|---|---|
| | N | % | N | % | N |
| Site of Initial Recurrence | | | | | |
| No Recurrence | 253 | 68.4 | 236 | 64.5 | 489 |
| Vagina | 7 | 1.9 | 18 | 4.9 | 25 |
| Pelvis | 13 | 3.5 | 30 | 8.2 | 43 |
| Vagina and Pelvis | 0 | 0 | 1 | 0.3 | 1 |
| PA Node | 9 | 2.4 | 11 | 3 | 20 |
| PA Node + other* | 1 | 0.3 | 8 | 2.2 | 9 |
| Distant | 79 | 21.4 | 44 | 12 | 123 |
| Distant + any other | 8 | 2.2 | 18 | 4.9 | 26 |
| **Total** | 370 | 50.3 | 366 | 49.7 | 736 |

*vagina or pelvis