PROTOCOL GOG-0238

A RANDOMIZED TRIAL OF PELVIC IRRADIATION WITH OR WITHOUT CONCURRENT WEEKLY CISPLATIN IN PATIENTS WITH PELVIC-ONLY RECURRENCE OF CARCINOMA OF THE UTERINE CORPUS

NCT# 00492778 **(04/21/2014)**

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POINTS:
PER CAPITA – 20
MEMBERSHIP – 6

Lead Organization: NRG / NRG Oncology **(04/21/2014)**

Participating Organizations (04/21/2014)

ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

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CONTACT INFORMATION (04/21/2014)		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. GOG Statistical and Data Center Roswell Park Cancer Institute, Carlton and Elm Streets, Buffalo, New York, 14263-0001 716-845-5702 FAX: 716-845-8393 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) *Contact the Study PI of the Lead Protocol Organization*		

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
The CTSU Website is located at https://www.ctsu.org.

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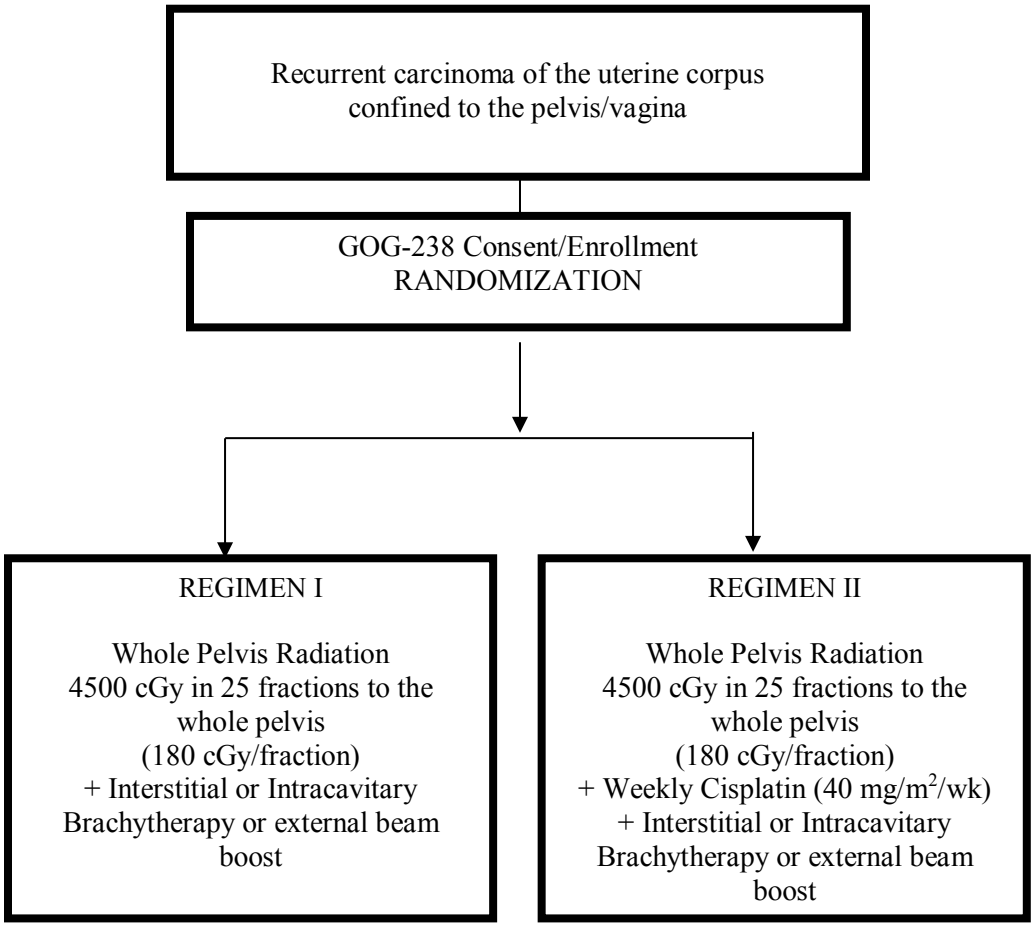
REVISED May 28, 2019.

SCHEMA

Institutional IMRT Credentialing is required before registering any patient on this trial.
Knowledge Assessment must be completed by the treating radiation oncologist.



Patients with tumors involving the distal vagina with 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.

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1.0 OBJECTIVES

1.1 Primary Objectives

1.11 To assess whether pelvic radiation therapy with concurrent cisplatin is more promising with respect to progression-free survival than pelvic radiation therapy alone in the treatment of recurrent uterine carcinoma limited to the pelvis and vagina.

1.2 Secondary Objectives

1.21 To capture the sites of recurrence subsequent to treatment with pelvic radiation with or without concurrent weekly cisplatin in women with recurrent uterine carcinoma.

1.22 To estimate overall survival of patients with recurrent uterine carcinoma treated with pelvic radiation therapy with or without concurrent weekly cisplatin.

1.23 To estimate the prognostic significance of the location (central pelvis versus vagina) and size of the recurrence in addition to the prognostic significance in the salvage setting of the histological subtype, grade, patient age, race, performance status, and the presence of lymph-vascular space involvement of the original tumor at the time of initial hysterectomy

1.24 To evaluate toxicity derived from the combined cisplatin and radiation compared with radiation alone in this patient population.

2.0 BACKGROUND AND RATIONALE

Endometrial cancer (EC) is the most common gynecologic malignancy. An estimated 41,200 new cases of EC are expected to be diagnosed in 2006.[1] After increasing from 1988 to 1998, incidence rates of EC leveled off through 2001. An estimated 7,350 deaths from uterine corpus cancer are expected in 2006.[1] The majority of these patients present with early stage disease, with survival rate over 80% after primary surgery. Unfortunately, most patients with advanced EC generally die from progression of their disease.

Two recently published large randomized trials, GOG-0099[2] and PORTEC,[3] evaluated the role of adjuvant pelvic radiation therapy (RT) in patients with early stage EC, endometrioid histologies, after surgery with or without complete surgical staging. In both trials, the pelvis alone (including regional-nodal, pelvic and vagina) was the most common site of initial failure in non-irradiated patients (8.9% in GOG-0099 and 14% in the PORTEC trial). In these two trials and others [4] adjuvant pelvic RT is associated with an improvement in loco-regional control, but does not statistically significantly impact

the overall survival or distant failure rate within the entire study population. The most common site of pelvic recurrence is the vagina, accounting for almost two thirds of the pelvic recurrences in the GOG-0099[2] and PORTEC[3] trials. Neither one of these trials, however, were powered to show a difference in survival in their low and/or intermediate risk patient populations which have competing risks of death. In both trials, adjuvant RT was associated with increased treatment-related morbidity. The lack of impact of pelvic RT on overall survival has led to many centers to abandon adjuvant radiation in patients with intermediate risk EC. A commonly espoused justification for abandoning adjuvant radiotherapy in the intermediate risk group is the belief that most women with isolated pelvic recurrence will be cured with salvage therapy. Unfortunately, prospective clinical trial data establishing the success rate for this salvage therapy is limited.

In GOG-0122, a Phase III randomized trial comparing "Whole Abdominal Radiotherapy (WAR) versus Combination Doxorubicin-Cisplatin (AP) Chemotherapy in Advanced Endometrial Carcinoma"[5] chemotherapy significantly improves progression-free survival (PFS) and overall survival when compared with WAR. Although the risk of death was reduced by 32% in the chemotherapy arm, 18% of these patients experienced an isolated vaginal or pelvic recurrence[5] as their initial site of recurrence.

STUDY	GOG #0099 (NFT vs. RT)	PORTEC (NFT vs. RT)	GOG # 0122 (WAR vs. AP)
Site of Failure			
Vagina	7.6% vs. 1.1%	10.2% vs. 2.3 %	5% vs. 5.7%
Pelvis	3.0% vs. 0.5%	3.4% vs. 2.0 %	8.4% vs. 12.3%
Distant	6.4% vs. 5.3%	7.0% vs. 7.9%	22% vs. 18%

NFT: No further therapy; RT: Radiation therapy; WAR: Whole abdominal radiotherapy; AP: Adriamycin + Platinum chemotherapy

The rates of pelvic recurrence in patients with early stage disease after surgery alone range between 5-15%, most of which are isolated vaginal recurrences. The reported salvage rate with radical irradiation is 65-80% in patients with isolated vaginal relapses.[6, 7] The results are less favorable in patients with pelvic and/or regional recurrences (<50% salvage rate).[6, 7] Ackerman et al[6] performed a retrospective analysis of 54 patients with vaginal recurrence of their endometrial cancer identifying patterns of relapse, determining the outcome of salvage treatment and examining the factors predictive of effective salvage. Initial therapy was surgery alone in 32 patients and surgery plus adjuvant pelvic irradiation (RT) in 22 patients. Isolated pelvic recurrences occurred in 72% of patients who underwent surgery alone and 23% of patients who received adjuvant RT in addition to surgery. Twenty-eight of the 54 patients in her study had isolated pelvis only recurrence. Sixteen of 28 patients with pelvic relapses recurred in the vagina only. With a minimum follow-up of 5 years, 67% had pelvic control until death (79% of patients with vaginal recurrences and 43% of patients with pelvic recurrences), after definitive RT.

Updated treatment and salvage therapy results of the PORTEC trial were published by Creutzberg et al in 2003[7] with 8-year local control and survival rates after relapse in patients with pathological stage I endometrial cancer. With a median follow-up of 73 months, 8-year actuarial locoregional recurrence (LRR) rates were 4% (13 patients) and 15% (46 patients) in the adjuvant RT and control groups, respectively ($p<0.0001$). Again, there was no difference in the actuarial overall survival rates (71% and 77%, respectively) or distant metastasis rates (10% and 6%, respectively) between the two groups. The majority of the locoregional recurrences in the control group were in the vagina (32/46 patients). Subsequent subset analysis indicated that patients with grade 1-2 disease with < 50% myometrial infiltration and patients less than 60 years old, had a LRR rate of <5%. However, patients with deep myometrial invasion (> 50%) and patients with grade 3 disease had a LRR between 7-15%. As expected, adjuvant RT eliminates the risk of LRR after surgery.

It has been postulated by many that the lack of survival benefit of adjuvant RT is due to the high rate of successful salvage after relapse, primarily in patients with isolated vaginal relapses, and the increased incidence of distant failures. However, it is important to recognize that in Creutzberg's series, of the 46 (13%) LRR in the control group only 22 were salvaged and remained without evidence of disease at the time of the last follow up (48%). Furthermore, evaluation of the patients who died from endometrial cancer due to LRR alone, demonstrates an incidence of 10% (3/29) in the RT group vs. 25% (6/24) in the control group. The actuarial survival after first relapse is lower for the RT group when compared with the control group (3-year survival of 19% and 51% for each group, respectively, $p=0.004$), however, this type of comparison can be considered biased as it selects out of the RT arm nearly all local recurrences due to the effectiveness of RT on local control. In addition, Creutzberg et al.[7] have shown significantly better 3-year survival rates after vaginal recurrence alone when compared with pelvic or distant relapse (73%, 8%, and 14%, respectively, $p<0.01$). Furthermore, the survival after vaginal relapse was significantly better for patients in the control group compared with women who received adjuvant RT (65% vs. 43%, respectively). Of course, this is an expected finding since the former group was able to receive full doses of salvage RT while the latter group would have dose limitations due to prior pelvic RT.

Phase II chemotherapy trials in women with advanced or recurrent endometrial cancer have identified doxorubicin, cisplatin, carboplatin, and paclitaxel [8-16] as active agents with response rates of 30-35%. In addition, there is extensive clinical experience combining cisplatin with external beam irradiation in cervical cancer. A number of large randomized studies evaluating concurrent platinum-based chemoradiotherapy treatment in cervical cancer have shown superior rates of loco-regional control, disease-free survival, and overall survival when compared with RT alone.[17-20] Further support for the use of concurrent cisplatin and radiation in the treatment of endometrial cancer comes from two GOG studies. A Phase I study of weekly cisplatin and whole abdomen radiation (WAR) for the treatment of stage III and IV endometrial cancer reported by Reisinger et al[21] found that this regimen was well-tolerated acutely, and late toxicity was similar to that seen with WAR alone. The rationale for the use of cisplatin in conjunction with radiation in this setting included the radiation-sensitizing properties of cisplatin, the

cytotoxic activity of cisplatin in endometrial cancer, and the relatively limited bone marrow toxicity of cisplatin compared with other agents active in EC. While too few patients were treated to make definitive conclusions, it is interesting to note that no isolated recurrences were seen in the radiation treatment field following this regimen.[21] A subsequent study reported by Soper et al[22] treated patients with the same chemotherapy regimen followed by four cycles of subsequent doxorubicin and cisplatin every three weeks in an attempt to control systemic disease. Patients again tolerated the WAR and concurrent cisplatin confirming the tolerability reported for the GOG study by Reisinger, et al.

The only prospective clinical trial data documenting the salvage rate of radiotherapy in women with endometrial cancer is from the PORTEC[7] study. With an actuarial survival of only 51% at three years for the 46 women with pelvic recurrence of endometrial cancer without prior radiotherapy, it is imperative that we develop better strategies for managing these patients. Several retrospective series have shown that the prognosis of patients with regional recurrences from endometrial cancer is very poor, with low salvage rates with RT alone, and high risk for distant failures.[6, 23-29]

The adoption of chemo-radiation using the well-established regimen of weekly cisplatin is the most logical first step. As adjuvant chemotherapy is increasingly prescribed instead of adjuvant radiotherapy for women with endometrial cancer the likelihood of developing pelvic recurrence is increased. Mundt et al[30] found a 39.5% rate of pelvic recurrences in 43 patients with high-risk pathological stage I-IV endometrial cancer after adjuvant chemotherapy alone without pelvic RT.

We have designed a randomized Phase II screening study to estimate the relative benefit on progression-free survival of the addition of cisplatin to external pelvic irradiation, estimate overall survival and toxicity, and evaluate clinical, host and pathologic factors at study entry and from the original hysterectomy as potential prognostic factors.

2.1 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the endometrial cancer population with recurrent disease limited to the pelvis treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 All patients must have undergone complete hysterectomy and bilateral salpingo-oophorectomy at the time of the original therapy for their uterine carcinoma.

3.12 Patients must have a biopsy with histologically confirmed diagnosis of recurrent endometrial cancer confined to the pelvis and/or vagina and no evidence of extrapelvic disease.

3.13 Patients must have endometrial carcinoma including endometrioid adenocarcinoma, adenocarcinoma with squamous differentiation, mucinous adenocarcinoma, squamous cell carcinoma, mixed carcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, and serous adenocarcinoma histologies.

3.14 Patients must have no evidence of extrapelvic disease. Complete workup staging should be performed prior to initiation of therapy to rule-out presence of metastatic disease. This should include: CT scan of the thorax with IV contrast, as well as a CT of the pelvis and abdomen with IV and PO contrast performed using multi-detector CT and equal or less than 5 mm slice thickness. If the patient is unable to tolerate contrast, then MRI with IV gadolinium should be performed. A chest x-ray should be done first, and if abnormal, then a CT scan of the chest should be done. **(10/8/08)**

3.15 Primary surgical debulking before protocol therapy is permissible. This would include removal of gross symptomatic disease in the pelvis and/or vagina.

Exenterative surgery is not permissible. Patients enrolled subsequent to revision 11 with complete resection of gross recurrent disease are eligible. **(05/14/2012)**

3.16 Patients may have received prior hormone therapy and/or systemic chemotherapy. Such therapy must have been completed at least 6 months prior to study entry and the patient has clear evidence of disease subsequent to such therapy. Patients must not have received neoadjuvant chemotherapy for the present recurrent disease.

3.17 Patients must have GOG performance status 0, 1, or 2.

3.18 Patients must have an estimated survival greater than or equal to 3 months

3.19 Patients must have adequate:

3.191 Bone Marrow Function: Absolute neutrophil count (ANC) ≥ 1,500/mm^3, equivalent to Common Toxicity Criteria (CTCAE v 3.0) grade 1. Platelets ≥ 100,000/mm^3 (CTCAE v3.0 grade 0-1).

3.192 Renal Function: Creatinine ≤ institutional upper limit normal (ULN), CTCAE v 3.0 grade 0. **Note: If creatinine > ULN, creatinine clearance must be >50 mL/min.**

3.193 Hepatic Function: Bilirubin ≤ 1.5 x ULN (CTCAE v3.0 grade 1). SGOT and alkaline phosphatase ≤ 2.5 x ULN (CTCAE v3.0 grade 0-1).

3.194 Neurologic Function: Neuropathy (sensory and motor) ≤ CTCAE v3.0 grade 1.

3.110 Patients with ureteral obstruction must undergo stent or nephrostomy tube placement prior to study entry.

3.111 Patients who have met the pre-entry requirements specified in Section 7.0.

3.112 Patients must have signed an approved informed consent and HIPAA authorization.

3.2 Ineligible Patients

3.21 Patients with evidence of disease outside of the pelvis, including presence of positive periaortic or inguino-femoral nodes.

3.22 Patients who have received previous vaginal, pelvic, or abdominal irradiation.

3.23 Patients who received chemotherapy directed at the present recurrence.

3.24 Patients with septicemia or severe infection.

3.25 Patients who have circumstances that will not permit completion of this study or the required follow-up.

3.26 Patients with renal abnormalities, such as pelvic kidney, horseshoe kidney, or renal transplantation, that would require modification of radiation fields.

3.27 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of

other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.28 Patients enrolled prior to revision 11 who have undergone complete surgical resection of the recurrent tumor and have no evidence of residual disease evaluable clinically and by CT or MRI imaging, following resection. **(05/14/2012)**

3.29 Patients who have a significant history of cardiac disease, i.e., uncontrolled hypertension, unstable angina, congestive heart failure, or uncontrolled arrhythmias within 6 months of registration.

3.210 Patients with history of active collagen vascular disease.

3.211 Patients with GOG Performance Grade of 3 or 4.

4.0 STUDY MODALITIES

4.1 Cisplatin (Cis-diamminedichloroplatinum, Platinol)

4.11 Formulation: Cisplatin is available in aqueous solution in 50 mg and 100 mg vials with 9 mg/mL of sodium chloride.

4.12 Preparation: Aluminum reacts with cisplatin causing precipitation formation and loss of potency, therefore, needles, or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

4.13 Storage: The aqueous solution should be stored at room temperature and protected from light.

4.14 Adverse effects:

4.141 Frequent: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions.

4.142 Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

4.143 NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

4.144 Severe renal toxicity can be largely avoided by induction of a diuresis before, during, and after treatment.

4.145 Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if creatinine > 1.5 x institutional upper limit normal (ULN) develop.

4.146 Mild or severe electrolyte abnormalities may occur (5%) as acute or chronic complications, especially hypokalemia or hypomagnesemia. Monitoring of electrolytes and electrolyte replacement will usually correct these abnormalities. Rarely, severe hypomagnesemia and hypocalcemia may require replacement therapy and discontinuation of treatment with cisplatin.

4.147 Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment.

Patch or skin tests are recommended for patients with suspected allergy to cisplatin. An emergency set for the treatment of allergic reactions should be available in the treatment area.

4.148 Local necrosis and thrombophlebitis can be avoided by careful administration.

4.149 Neurotoxicity may be related to cumulative dose and severe toxicity can be largely avoided by careful monitoring for evidence of paresthesias and timely discontinuation of treatment. Ataxia has been described.

4.150 Ototoxicity may occur. NOTE: Eighth (VIII) nerve toxicity resulting in hearing loss and (less commonly) vestibular symptoms is a well-documented complication of cisplatin treatment and is usually related to total cumulative dose. It is advised that patients placed on cisplatin, whether as a single agent therapy or combination, be questioned concerning hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow-up audiometry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each course of cisplatin.

4.15 Drug Interactions
Phenytoin: cisplatin decreases the effect of phenytoin
Aminoglycosides, amphotericin B; increased renal toxicity
Loop Diuretics (furosemide): increased risk of ototoxicity

4.16 Supplier: Commercially available.

4.17 Administration: See Section 5.44 **(10/8/08)**

Refer to package insert for additional information.

4.2 Radiation Therapy **(05/14/2012)**

4.21 Patients will receive a random treatment assignment of either pelvic radiation therapy daily Monday-Friday for approximately 5 weeks followed by brachytherapy, or the same external beam irradiation to the pelvis in combination with intravenous cisplatin given on a weekly basis x 5 weeks, to be followed by brachytherapy. When brachytherapy is not to be used, a three dimensional treatment or intensity modulated radiotherapy (IMRT) boost is allowed. IMRT credentialing is required (see Section 5.0). All the external beam irradiation must be completed within 6 weeks of its initiation. Brachytherapy should be completed within 4 weeks of completion of external beam irradiation.

IMRT will be allowed for the entire course of therapy, this is for the treatment of the whole pelvis and/or the boost in those cases not undergoing brachytherapy.

If IMRT is to be used, treatment plans for such patients must be electronically submitted for a rapid review PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. Before ANY patient is enrolled on this study the treating radiation oncologist must complete a Knowledge Assessment Questionnaire found on the IROC Houston (formerly the Radiological Physics Center [RPC]) website (http://irochouston.mdanderson.org). **(10/8/2008) (04/21/2014)**

All IMRT plans need to be submitted for a rapid review prior to delivering any protocol treatment for the first patient treated at any particular institution

4.211 The investigators will submit a brief radiation treatment plan for each patient at time of study entry, to ensure that sites do not modify their radiation plan if the patient is randomized to chemoradiation. This brief summary of the planned radiation must include a description of the external beam radiation fields and dose, as well as the plan for brachytherapy boost (intracavitary and/or interstitial). When brachytherapy is not to be used, a three dimensional treatment or intensity modulated radiotherapy (IMRT) boost is allowed and plans for such therapy must be submitted, as well. **(10/8/2008)**

4.212 Institutions that are considering administering an IMRT MUST be credentialed by IROC Houston. Instructions for credentialing are available at the IROC Houston website, http://irochouston.mdanderson.org (see Section 5.0 for details). **(10/8/2008) (05/14/2012) (04/21/2014)**

4.2121 When IMRT is to be used each institution must submit and successfully complete a protocol-specific plan for the first patient treated at that institution on this protocol. A rapid review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by IROC Houston and suggestions regarding protocol compliance will be forwarded from IROC Houston to the radiation oncologist at the participating institution. IMRT treatment plans for subsequent patients enrolled at a particular site will not be required to go through the rapid review process via IROC Houston prior to treatment, but a review of the treatment plan for each

patient will be performed by the GOG for each patient. For instructions on the rapid review process, please see section 4.21112. **(10/8/2008) (04/21/2014)**

4.2122 Institutions may NOT submit a plan for 3D conformal treatment and then switch to IMRT treatment during the course of the study. **(10/8/2008)**

Each institution is to determine if IMRT for the pelvis +/- boost is to be used at the time of the randomization. This remains the same except that it would refer to the entire IMRT plan rather than just the boost. **(05/14/2012)**

4.22 Physical Factors

4.221 External beam radiation will be delivered using a linear accelerator with a nominal photon beam energy of 6 MV or greater. SAD of 100 cm is required unless the Tomotherapy device is used. Institutions using IMRT must use megavoltage equipment capable of delivering static IMRT with a multileaf collimator or dynamic IMRT using either an MLC or tomotherapy. Forward or inverse treatment planning methods are acceptable.

4.222 Intracavitary Low dose rate (LDR) and High dose rate (HDR) intracavitary brachytherapy alone, in combination with external beam irradiation, is allowed only in patients with minimal vaginal disease limited to the mucosa or for lesions with an estimated thickness less or equal than 5 mm. Interstitial LDR or HDR brachytherapy is required for patients with isolated vaginal recurrences with an estimated thickness over 5 mm.

4.23 <u>Localization and Simulation:</u>

4.231 Primary to simulation it is recommended that radiopaque marker seeds are inserted into the vaginal apex or at the edges of the gross disease as delineated by pelvic exam, 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 L1-2 level to below the perineum. Care should be taken to scan the entire volume of both kidneys during the CT simulation for patients undergoing IMRT.

Patients can be immobilized in the Belly Board in prone position with full bladder as per Institutional guidelines. **(05/14/2012)**

4.232 CT simulation is required to define gross tumor volume (GTV), 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 2 hours 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.

4.2321 Planning of the external beam (3DRT or IMRT) should be done with a full bladder scan

4.233 Contouring the Target volumes:

4.2331 Please refer to the ***RTOG Gynecological Atlas for volume specification. The atlas may be accessed on the RTOG website at:*** http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx

4.2332 The primary gross tumor volume in the vagina and/or pelvis should be contoured as gross tumor volume (GTVp). This is defined as all gross disease based on clinical pelvic examination as well as CT and/or MRI findings. Any gross lymph node disease should be as well contoured independently as regional-gross tumor volume (GTVr).

4.2333 The clinical target volume (CTV1) is defined as the GTV in the vagina +/- pelvis plus the areas considered to contain potential microscopic disease. The primary CTV or CTV2 should include the GTV with 2 cm cranio-caudal and 1.5 cm axial margins. A minimum of 3 cm of normal vagina should be contoured distally to the gross disease in patients with vaginal recurrences. The distal margin of the external beam radiation fields (based on the CTV1) should be confirmed clinically as well as per CT using the most-distal seed marker placed in the vagina as a surrogate. The most inferior aspect of the external beam radiation field should be at least 1cm inferior to the obturator foramen, whatever margin is the most inferior one. The nodal CTV, included in the CTV1, should include the internal (hypogastric and obturator), external and common iliac lymph node regions. The CTV1 should be delineated using the contrast-

enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 7 mm axial margin around the vessels). On the pelvic wall side the margin will exclude the psoas and the piriformis muscles. Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 5 mm margin around the vessels) and providing adequate margin around GTV is obtained (margin can be reduced in the axial margin to 1 cm around the GTV, when in close proximity to small bowel).

Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) is usually added to the CTV1 for adequate coverage of presacral nodes. 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 CTV1 (nodal CTV should stop at the femoral head. Proximately, the CTV1 should end 7 mm from the L4-5 interspace to account for the PTV1.

4.2334 The PVT1 should provide a 7 mm margin in all directions around the CTV1. The PTV2 volume to be treated using 3D conformal techniques or IMRT in patients that are not candidate for brachytherapy boost should encompass the CTV2 as defined above with a 7 mm margin in all directions.

4.2335 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.

4.2336 Critical normal surrounding structures:

4.23361 Bladder will be contoured in each slice including the portion inferior to the PTV.

4.23362 Rectum will be contoured in each slice including the portion inferior to the PTV and superiorly to the level that leaves the posterior pelvis around the region of the recto-sigmoid colon.

4.23363 Small bowel will be contoured in each slice including at least 2cm above the PTV.

4.23364 Femoral heads and the sacrum will be contoured in all the slices.

4.23365 Kidneys should be contoured in all IMRT cases.

4.234 Constraints: participants are strongly encouraged to respect the following limits, including the 3D conformal or IMRT boost. **(05/14/2012)**

4.2341 Small bowel: <30% to receive ≥ 40Gy, minor deviation 30% to 40Gy.

4.2342 Rectum: < 60% to receive ≥ 55Gy, minor deviation 40% to 62Gy. **(02/08/10)**

4.2343 Bladder: < 60% to receive ≥ 55Gy, minor deviation 50% to 50Gy.

4.2344 Femoral heads: < 50% to receive ≥ 40Gy, minor deviation 50% to 50Gy. The maximum delivered dose to point is 54Gy. **(02/08/10)**

4.2345 Iliac crests: <50% to receive ≥30 Gy

4.2346 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 1cc (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV.

4.2347 Kidneys: < 33% to receive ≥ 15 Gy, minor deviation 33% receiving 15 Gy.

4.24 Treatment Plan, Dose Specification and Distribution

4.241 The volume irradiated with the whole pelvic fields will include the totality of the gross disease locally and regionally, as visualized by CT scan, the CTV and PTV as defined above.

4.242 The whole pelvis will receive a total dose of 4500 cGy in 25 fractions at 180 cGy/fx, encompassing the PTV, using a four-field technique throughout the entire treatment. The prescription dose is the isodose that encompassed 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 1cc (whichever is smaller) of

the tissue outside the PTV will receive >110% of the dose prescribed to the PTV.

4.243 In patients with tumors involving the distal vagina with clinically negative groins, the bilateral inguino-femoral lymph node regions should be treated to 4500 cGy. Planning CT is recommended to adequately determine the depth of the inguino-femoral nodes. A number of techniques have been used to treat the areas at risk without over-treating the femoral necks. Some of the most commonly used techniques include the use of unequal loading (2:1, AP/PA), a combination of low and high energy photons (6MV, AP, and 15-18 MV, PA), or equally weighted beams with a transmission block in the central AP field, utilizing small AP photon or electron beams to deliver a daily boost to the inguino-femoral nodes. A technique has been developed and implemented at Indiana University, which uses a narrow PA field to treat the pelvis, and a wider AP field encompassing the pelvis and inguino-femoral nodes, with daily AP photon boost to the inguinal nodes being delivered using the asymmetric collimator jaws.[31]

4.244 Patients with pelvic recurrence not amenable to brachytherapy, because not technically feasible, should undergo external beam boost using three-dimensional treatment planning, conformal radiotherapy or IMRT techniques to deliver a minimal total dose of 65 Gy to the GTV (2000 cGy boost at a dose/fraction of 200 cGy in 10 fractions). The prescription dose is the isodose that encompassed at least 97% of the PTV. No more than 20% of any PTV should receive > 110 % of the prescribed dose. No more than 1% or 1cc (whichever is smaller) of the tissue outside the PTV will receive > 110% of the dose prescribed to the PTV. **(02/08/10)**

IMRT is allowed for all patients independently if a brachytherapy boost is to be performed of not. In case that the patient is not undergoing brachytherapy the entire plan, including the boost with IMRT needs to be submitted. **(05/14/2012)**

4.245 If overall treatment time for external pelvic RT, whole pelvis irradiation to 4500 cGy, exceeds 42 days (6 weeks), or the entire external beam plus boost exceed 70 days (10 weeks), the reason for the delay must be documented. If interruption of radiation should occur for ≥5 consecutive treatment days the protocol Study Chair or Co-Chair must be notified.

4.25 <u>Low Dose Rate (LDR) Intracavitary Brachytherapy</u>

Recurrences limited to the superficial mucosa of less than 5 mm thickness, can be treated with LDR endocavitary brachytherapy techniques. Following the completion of external beam RT, to a dose of 45 Gy, the patient will receive intracavitary brachytherapy using vaginal ovoids or vaginal cylinders or, depending upon the location of the lesion, for an additional 30 Gy prescribed to a depth of 0.5 cm, in order to deliver a dose to GTV, as defined by physical exam and/or CT scan, of a minimum of 75 Gy estimated to a depth of 0.5 cm. In **very superficial lesions of maximum depth of 2-3 mm**, the dose can be prescribed to the vaginal surface, for an additional 35 Gy in order to deliver a total dose of 80 Gy including the contribution from external beam irradiation. The implant should adequately cover the involved area with a minimum mucosal margin of 3 cm.

The use of vaginal ovoids is highly recommended in patients with superficial lesions limited to the apex of the vagina, since it allows the use of anterior and posterior packing with subsequent decrease in the dose to the bladder and rectum, respectively. For lesions involving the mid and lower vagina, vaginal cylinders should be used.

Rectal dose should be kept ≤ 70Gy and bladder dose ≤ 75Gy including the contribution from external beam (4500 cGy) and intracavitary brachytherapy.

4.26 High Dose Rate (HDR) Intracavitary Brachytherapy

Recurrences limited to the superficial mucosa of less than 5 mm thickness, can be treated with HDR endocavitary brachytherapy techniques.

The patient will receive 3 implants after completing 45 Gy external beam irradiation. At least the proximal 5 cm in length of the vagina should be treated for lesions involving the vaginal apex. The patient will receive a total of 3 fractions each one of 700 cGy prescribed to a depth of 5 mm. In case that the entire length of the vagina is to be treated, this should be done only with the first implant (700 cGy to a depth of 0.5 cm) and the remaining 2 fractions should treat only the proximal 3-5 cm (depending upon the extent of the disease at the vaginal apex, providing a distal margin of 3 cm).

4.27 Low Dose Rate Interstitial Brachytherapy

Recurrences limited to the superficial mucosa of more than 5 mm thickness, need to be treated with LDR interstitial techniques

Following the completion of external beam radiotherapy to 45 Gy, the patient will receive an interstitial implant to deliver a minimum dose of -80 Gy to the gross tumor volume, as defined by physical exam and/or CT scan, depending upon the size of the recurrence.

4.28 High Dose Rate (HDR) Interstitial Brachytherapy

Recurrences limited to the superficial mucosa of more than 5mm thickness, need to be treated with interstitial techniques, which can be utilizing HDR or LDR brachytherapy.

Following the completion of external beam RT, to a dose of 45 Gy, the patient may receive interstitial brachytherapy using templates and interstitial needles on an individualized basis depending on the location and extent of the disease. In addition to a documented clinical exam, all patients are required to undergo pre-treatment imaging using either CT or MRI to adequately document tumor size and location. It is recommended that interstitial brachytherapy be planned utilizing the diagnostic imaging obtained at the time of protocol enrollment, but when in the best interest of the patient, a repeat diagnostic study using either CT or MRI can be obtained in the final week of external radiation to guide applicator placement. Laparoscopy or laparotomy may be considered to help place needles and minimize risk for injury to the small bowel. If available, the use of transabdominal or trans-rectal ultrasound, CT scan, or MRI is strongly recommended for guidance during needle placement.
All patients will be required to undergo a post-procedure CT scan of the abdomen/pelvis with 2.5mm or smaller slice thickness to be used for HDR treatment planning. The gross tumor with a clinically based expansion should be contoured and designated as the High Risk CTV (HR-CTV) as a separate structure as delineated by marker seeds, CT scan, or MRI imaging. It is recommended that treating physicians perform an image fusion using the pre-implant imaging study that demonstrates the tumor volume best. The dose should be optimized to the CTV with the goals of achieving a D_{90} (dose to 90% of the CTV) $\geq$ 100% of the prescription dose while minimizing the dose to normal organs. The prescription for HDR interstitial brachytherapy will be 5 fractions of 4-6 Gy each, delivered to the gross disease as defined by physical exam, CT and/or MRI scans. Normal –tissue dosimetry should include descriptions of dose to volumes such as to $0.1cm^3$, $1cm^3$, and $2cm^3$ of the bladder, rectum, sigmoid, and small bowel. In all cases, the needle loading should be optimized to limit the cumulative dose delivered to $2cm^3$ of organs at risk from both external beam radiation therapy and brachytherapy as follows:

Organ at Risk	Equivalent Dose at 2Gy per Fraction (EQD2)
Rectum, $2cm^3$	< 70 Gy
Sigmoid, $2cm^3$	< 70 Gy
Small Bowel, $2cm^3$	< 65 Gy
Bladder, $2cm^3$	< 90 Gy

For reference regarding the calculation of EQD2 doses, please use the American Brachytherapy Society HDR Radiobiologic Dose Equivalent Worksheet at: https://www.americanbrachytherapy.org/guidelines/

It is strongly recommended that patients complete anesthesia and applicator placement in the morning, such to allow sufficient time for image confirmation and implant planning to occur and the subsequent delivery of the first fraction in the afternoon on that first day. The remaining fractions should be delivered over the next two days treating patients twice per day with a minimum interfraction interval of 6 hours. It is recommended that treating physicians use an anchoring mechanism such as the proprietary locking devise on interstitial applicators or adhesive glue if using a disposable template, to assure catheters are stable during treatment. For patients where the interstitial needles are fixed to the template, a pre-treatment CT scan immediately prior to the 1st fraction and a clinical exam with each remaining fraction is required to confirm applicator position. In situations where adhesive glue is not utilized, a CT image dataset should be obtained prior to each HDR fraction, and interstitial needles identified. In cases where the axial, coronal, or sagittal displacement is ≥ 5mm in ANY direction, an attempt should be made to correctly reposition. In situations where there is ≥ 5mm displacement and needles are unable to be corrected, the treating oncologist should re-plan and repeat the dwell position optimization in order to guarantee target coverage. In those cases where an HDR treatment is re-planned, the HR-CTV and organs at risk should be denoted with a subscript with sequential numbering indicative of the brachytherapy plan (ie. $HR\text{-}CTV_1$, $HR\text{-}CTV_2$, etc. or $Rectum\_HDR_1$, $Rectum\_HDR_2$, etc.).

4.29 Dose Distribution for All Regimens

A four-field box technique with parallel opposed AP/PA and two opposing lateral fields or IMRT should be used for the initial pelvic fields. AP/PA only fields are allowed in patients in whom inguino-femoral nodal irradiation is indicated. Dose distribution across clinical target volume should not vary more than 5% from the recommended dose. All fields must be treated daily.

Patients with pelvic recurrence not amenable to brachytherapy, because not technically feasible, should undergo external beam boost using three-

dimensional treatment planning, 3D conformal radiotherapy or IMRT techniques to deliver a minimal total dose of 65 Gy to the GTV (2000 cGy boost at a dose/fraction of 200 cGy in 10 fractions).

4.29 Radiation Equipment

4.291 External beam radiation will be delivered using a Linear Accelerator with a peak photon energy of 6 MV or greater. SAD of 100 cm is required unless the Tomotherapy device is used. For those institutions using IMRT, megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) using forward planned or inverse planned IMRT treatment planning methods is acceptable. All patients will undergo CT based simulation for localization, and verification of external RT treatment portals. MRI could be used in pre-treatment planning. All the structures, including gross tumor volume at the primary and regional sites (GTVp and GTVr), in addition to the clinical target volumes (CTV 1 and CTV2), planning target volumes (PTV1 and PTV2) and the normal critical surrounding structures should be contoured as above, and delivered doses documented. Dose-Vole Histograms (DVH) are to be submitted for each one of the indicated volumes and critical structures.

4.292 For Submission via TRIAD™ the structure names must match the following list exactly or resubmission will be required **(04/21/2014)**

Standard Name	**Description / Detailed Specification**
GTVp	Primary GTV. **Required**
CTVn	Nodal Lymph nodes as described in protocol **Required**
CTV_4500	CTV1 = CTVp+CTVn **Required**
PTV_4500	PTV1 : PTV expanded to encompass CTV1 by a 7 mm margin **Required**
PTV_6500*	PTV2: Primary PTV (When IMRT is used for boost) **Required when applicable**
Bladder	Bladder **Required**
Femurs	Femoral Heads **Required**
Kidneys	Kidneys

	Required
Rectum	Rectum **Required**
BowelSpace	Bowel **Required**
IliacCrests	Iliac Crests **Required**
NonPTV	Unspecfifed tissues (External minus PTVs) **Required**
External	External Skin **Required**
HR_CTV	Primary GTV + expansions for interstitial HDR Brachytherapy **Required where applicable (HDR Interstitial)**
Rectum_HDR	Rectum **Required where applicable (HDR Interstitial)**
Bladder_HDR	Bladder **Required where applicable (HDR Interstitial)**
Sigmoid_HDR	Sigmoid **Required where applicable (HDR Interstitial)**
Small Bowel_HDR	Small Bowel Loops **Required where applicable (HDR Interstitial)**

4.293 Intracavitary LDR brachytherapy should be delivered using Cesium-137.

Intracavitary HDR brachytherapy should be delivered with a single Iridium-192 source.

Interstitial LDR brachytherapy should be delivered using Iridium-192.

Interstitial HDR brachytherapy should be delivered with a single Iridium-192 source.

Orthogonal or computed tomography films should be performed for each implant to confirm applicator geometry. For patients where the interstitial needles are fixed to the template, a pre-treatment CT scan immediately prior to the 1st fraction and a clinical exam with each remaining fraction is required to confirm applicator position. In situations where a locking mechanism or adhesive glue is not utilized, a CT image dataset should be obtained prior to each HDR fraction.

4.210 External Radiation Fields

4.2101 Whole Pelvis Field: The external RT target volume should encompass, with adequate margins, the gross disease in the pelvis and any gross extension to the vagina as well as possible microscopic extension to pelvic lymph nodes. See Section 4.233 for detailed description of GTV, CTV and PTV.

4.21011 GTVp= Primary GTV in the vagina and/or pelvis. This is defined as all gross disease based on clinical pelvic examination as well as CT and/or MRI findings. Any gross lymph node disease should be as well contoured independently as regional-gross tumor volume (GTVr).

4.21012 CTV2= GTVp + 2 cm cranio-caudal and 1.5 cm axial margins. A minimum of 3 cm of normal vagina should be contoured distally to the gross disease in patients with vaginal recurrences.

4.21013 CTV1= CTV2 + the nodal CTV, including the internal (hypogastric and obturator), external and common iliac lymph node regions. The CTV1 should be delineated using the contrast-enhanced (preferably IV contrast administered) iliac vessels, in addition to the perinodal soft tissue (minimum of 7 mm axial margin around the vessels). On the pelvic wall side the margin will exclude the psoas and the piriformis muscles. Bone and intraperitoneal small bowel should be excluded from the CTV as much as possible (leaving at least 5 mm margin around the vessels) and providing adequate margin around GTV is obtained (margin can be reduced in the axial margin to 1 cm around the GTV, when in close proximity to small bowel). Approximately 1-2 cm of tissue anterior to the sacrum (S1-S3) is usually added to the CTV1 for adequate coverage of presacral nodes. 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 CTV1 (nodal CTV should stop at the femoral head. Proximately, the CTV1 should end 7 mm from the L4-5 interspace to account for the PTV1.

4.21014 The PVT1 should provide a 7 mm margin in all directions around the CTV1. The PTV2 volume to be treated using 3D conformal techniques or IMRT in patients that are not candidate for brachytherapy boost should encompass the

CTV2 as defined above with a 7 mm margin in all directions.

4.2102 General guidelines in designing the Whole Pelvic Fields

4.21021 AP/PA pelvic fields: The superior border will be through the L4-5 interspace unless the target volume (e.g. common iliac nodes or local disease) would not be encompassed adequately in a cephalad direction. In the latter case, a 2 cm margin should be added to the highest level of pathologic abnormality, but should not be cephalad to the L-3/L-4 interspace. The lateral border will be 2 cm beyond the lateral margins of the bony pelvis. The inferior border will be inferior to the obturator foramen or the lowest extension of disease with at least a 3 cm margin. If possible, any attempt should be made to spare the vulva and perineum particularly in patients with upper and mid-vaginal lesions. If tumor extends to the introitus then the fields should "flash" the perineum and vulva.

4.21022 Lateral Pelvis Fields: The anterior border should be determined by the PTV1 as defined above, generally anterior to the symphysis pubis. The posterior border should be placed at least 1.5 cm behind the anterior surface of the sacrum. Attention should be paid to exclude as much as possible of the sacral plexus). The posterior wall of the rectum should be excluded providing that the gross tumor volume with a 2.5 cm (1.5 cm axial margin to the CTV2 and 7 mm additional margin to define the PTV2) margin is adequately included in the radiation field. Superior and inferior borders will be the same as for the anterior and posterior fields. If clips are present from the lymph node dissection to document the position of the lymph nodes, then these should be used as a guide when anterior blocks are designed to shield small bowel. At least 3 cm should not be blocked anterior to the L-5 vertebral body. Also, the anterior two-thirds of the L-5 vertebral body should not be blocked in order to adequately cover the common iliac nodes with 1.5-2 cm margins.

4.211 Radiation therapy quality control and documentation

4.2111 As per Section 4.2.

4.2112 Digital reconstructed radiographs (DRR) of the treatment fields with the three-dimensional reconstruction of the GTVp and GTVr as well as CTV are to be obtained and submitted for evaluation.

4.2113 Localization or block-check -images of the 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 to be used. This applies to the whole pelvic radiotherapy fields when IMRT is not used for boost of the GTV.

4.2114 For the IMRT boost plans orthogonal films or images with isocenter localization shall be obtained. The length of the treatment fields should be indicated in the films. These films will not be collected but should be held by the institution and available for review if requested.

4.2115 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.

4.2116 Tumor diagrams and detailed description of the vaginal lesions are required, as some lesions are visible neither by CT or MRI.

4.2117 Polaroid pictures of all treatment portals with the patient in the treatment position are recommended.

4.2118 Portal films will be obtained and submitted to the GOG Statistical and Data Center with the patient records for the whole pelvic field.

4.2119 Orthogonal simulation films will be taken following the interstitial +/- intracavitary brachytherapy implants for planning purposes, and CT and/or MRI scans will be required for treatment planning in those patients who are treated with HDR interstitial brachytherapy. The films and calculations of the intracavitary insertion will be submitted to the GOG Statistical and Data Center with the patient records. A digital treatment plan will need to be submitted for each patient treated with HDR interstitial brachytherapy including dwell positions and times, and dose volume histograms for organs of interest.

4.21110 Copies of the CT or MRI scan showing the relevant tumor volume should be submitted to the Statistical and Data Center as well.

4.21111 IROC Houston (at U.T. M.D. Anderson Cancer Center 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 machines and ±5% in delivering the prescribed dose. **(04/21/2014)**

4.21112 Rapid Review Data Submission for IMRT via TRIAD:

The following patient treatment data must be electronically submitted via TRIAD: Digital Data Submission Information Form (DDSI), http://www.rtog.org/CoreLab/TRIAD.aspx Digital treatment planning data (digital patient data CT scans, critical normal structures, including "unspecified tissue" as per NCI-IMRT guideline, all CTV/ITV/PTV contours, doses for all fraction groups, DVHs for total dose plan), Color Isodose Distribution **(04/21/2014)**

4.212 Expected Toxicity

Gastrointestinal toxicity: Nausea and vomiting may occur, especially after the first few treatments. Intractable nausea and vomiting beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is rarely seen as a result of radiation alone. Consider stool sample for Clostridium difficile toxin. Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic and peri-aortic radiation. It is recommended that instructions be given to patients for a low fiber, low fat, and soft diet. Most patients will require antidiarrheal medications during therapy.

Should GI toxicity become severe enough to require hospitalization or outpatient IV fluid replacement, all treatment should be discontinued temporarily until the patient's condition improves. Study Chair must be notified.

Hematological toxicity: is frequently seen when using a combination of pelvic irradiation and concurrent cisplatin. Decline in WBC and platelet count should be carefully monitored on a weekly basis. The guidelines for dose and treatment modifications are described in Section 6.0.

5.0 TREATMENT PLAN AND ENTRY

IMRT credentialing for this protocol will be handled by IROC Houston (formerly the Radiological Physics Center [RPC]). All information regarding credentialing can be found on the IROC Houston website (http://irochouston.mdanderson.org) by selecting "Credentialing", then "GOG". (**10/8/2008) (04/21/2014)**

5.1 Before any patient is enrolled on this study the treating radiation oncologist must complete a Knowledge Assessment Questionnaire found on the IROC Houston website. (**10/8/2008) (04/21/2014)**

5.11 **IMRT credentialing requirements when IMRT is planned:**

Institutions must be credentialed for IMRT by IROC Houston for this protocol prior to enrolling patients on to this study when IMRT is planned. Each institution must successfully irradiate a standardized phantom available from IROC Houston. Instructions for requesting and irradiating the phantom are available on the IROC Houston website. The treatment plan for irradiation of the phantom must be submitted electronically via TRIAD (see Section 5.13). Institutions that have been previously credentialed for IMRT via the Head and Neck phantom or the Pelvic phantom can determine which additional requirements must be completed by filling out the "Credentialing Status Inquiry" form on the IROC Houston website. IROC Houston will then issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center.

Institutions that have not been credentialed for IMRT by IROC Houston at M.D. Anderson Cancer Center for this protocol must apply for IMRT certification as described in the following sections. **(04/21/2014)**

5.12 Each Institution must complete the IMRT Facility Questionnaire available on the IROC Houston web site by selecting "protocol 0238". Each institution must submit the completed IMRT Facility Questionnaire online. **(04/21/2014)**

Institution and/or peer-reviewed documentation of target position reproducibility [planning treatment volume (PTV) and clinical target volume (CTV)] must be consistent with Section 4.29.

5.13 Each institution must complete the following process to access TRIAD PRIOR to any patient enrollment: **(04/21/2014)**

5.131 **Digital RT Data Submission Using TRIAD (04/21/2014)**

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by IROC

Houston (RPC). TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred. The following process must be completed prior to enrolling patients on the trial.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster, and should follow their procedures for assignment of roster roles.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the IROC Houston web site.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.2 Registration Procedures **(04/21/2014)**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

5.21 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

5.22 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

5.221 IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

5.222 Downloading Site Registration Documents:

Site registration forms may be downloaded from the GOG-0238 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.
Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
Click on the Protocols tab in the upper left of your screen
Click on the *NCTN NRG* link to expand, then select trial protocol # 0238
Click on the Site Registration Documents link

5.223 Requirements For GOG-0238 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in IROC Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

5.224 Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

5.225 Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
Click on the Regulatory tab at the top of your screen
Click on the Site Registration tab
Enter your 5-character CTEP Institution Code and click on Go

5.3 Patient Entry and Registration **(04/21/2014)**

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the GOG web menu page by clicking on the OPEN link.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

  Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

  Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.31 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

5.4 Randomization and Treatment Plan

5.41 Radiation Therapy Plan: **(04/21/2014)**

Please note that all institutions must electronically submit the treatment plan for all patients via TRIAD when IMRT is planned. See section 5.131 for details on setting up a TRIAD account. After the data has been submitted via TRIAD, complete a DDSI information form found as http://www.rtog.org/CoreLab/TRIAD.aspx. The case will be processed in preparation for rapid review. A rapid review will be performed on all patients to receive IMRT PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The rapid review will be conducted by IROC Houston in collaboration with a GOG designated radiation oncologist and suggestions regarding protocol compliance will be forwarded to the participating institution‘s radiation oncologist.

5.42 Patients with recurrent endometrial carcinoma, limited to the pelvis, after surgery with or without adjuvant chemotherapy, who have fulfilled the eligibility requirements according to Section 3.0 will receive random treatment allocation to one of the following treatment arms:

Regimen I: Whole pelvic external beam radiation followed by vaginal brachytherapy

versus

Regimen II: Whole pelvic external beam radiation with concurrent weekly cisplatin followed by vaginal brachytherapy

5.43 Radiation treatment will be administered daily, Monday through Friday, for approximately five weeks followed by brachytherapy treatments, all in accordance with Section 4.2.

The patients randomized to receive cisplatin will receive it weekly, preferably on Mondays, for 5 weeks at a dose of 40 mg/m^2 /week (maximum total dose of 70 mg/week).

5.44 Concurrent Cisplatin Administration

500 ml of normal saline should be infused intravenously one hour before cisplatin. Increased oral intake of water should be encouraged starting the day before treatment. Additional fluid may be given as needed for symptomatic support.

Patients enrolled will receive 40 mg/m^2 of cisplatin (maximum total dose of 70 mg/week). Drug will be diluted in 250 cc 0.9% sodium chloride and administered over one or two hours (**rate of 1 mg of cisplatin per minute)**. Details of pre- and post-hydration are left to the discretion of the treating physician, but at least 1000 cc 0.9% sodium chloride prior to cisplatin and another 500-1000 cc 0.9% sodium chloride after cisplatin are recommended. **This is the minimum fluid administration recommendation and more fluid may be given at the discretion of the treating physician**.

Cisplatin will be given on the first day of external radiation therapy (day 1), preferably approximately four hours prior to radiation therapy, cisplatin will be repeated as above on Days 8, 15, 22, and 29 (preferably Mondays) of external radiation therapy.

5.441 Recommended Pre-medications for Cisplatin

All pre-medications should be administered at least 15 to 30 minutes prior to cisplatin administration.

Palonosetron 0.25 mg IV
Granisetron 2 mg or Ondansetron 12 mg IV
Dexamethasone 20 mg IV
Diphenhydramine 50 mg IV
Ranitidine 150 mg IVPB PRN
Lorazepam 1 mg IV/PO PRN

5.442 Recommended medication for delayed nausea and vomiting

Dexamethasone 4 mg PO bid x 2 days and 2 mg PO bid x 2 days
Aprepitant 125 mg, 80 mg, 80 mg PO daily x 3 days
Compazine 10 mg PO q 4-6 h PRN

5.5 Criteria for removal from treatment

5.51 Inability to tolerate the therapy because of toxicity.

5.52 Patients may withdraw from the study at any time for any reason.

5.53 Development of disease progression.

5.54 Any clinical adverse event or intercurrent illness, which, in the opinion of the treating physician, indicates that continued treatment with all study therapy (radiation therapy with/without cisplatin) is not in the best interest of the patient.

6.0 TREATMENT MODIFICATIONS

It is in the patient's best interest to receive the radiation therapy on time. Every effort should be made to encourage the patient to comply with the treatment prescribed where possible. When toxicity is encountered, the chemotherapy and radiation will be held as indicated in Tables 1 and 2, on those patients randomized to receive chemo-radiation therapy, until resolution. Restart radiation therapy and chemotherapy at that point, at full doses.

6.1 Hematologic Adverse Effects

6.11 Radiotherapy

A decline in ANC and platelet counts to Grade 2 (<1500-1000/mm^3, ANC and <75,000-50,000/mm^3, platelets) may frequently occur. A CBC should be obtained weekly during radiation therapy, and if the ANC < 1000/mm^3 or platelet count <50,000/mm^3, Grade 3 or worse toxicity, a CBC should be obtained at least every other day while radiation is on hold until recovery to Grade 2 or less.

Radiation therapy will not have to be interrupted for uncomplicated hematological toxicity (ANC > 1000/mm^3, platelets > 50,000/mm^3, no neutropenic fever). **(10/08/08)**

6.12 Cisplatin

Febrile neutropenia requiring intravenous antibiotics or thrombocytopenia with bleeding requiring platelet transfusion will require holding cisplatin and radiation therapy until symptoms resolve (fever or bleeding) and neutropenia is resolved to Grade 2 or less (ANC ≥1000/mm^3) and thrombocytopenia is resolved to Grade 2 or less (platelets ≥ 50,000/mm^3). Resume treatment as planned.

Neutropenia, which is uncomplicated, Grade 4 ANC <500/mm^3, or Grade 3-4 thrombocytopenia, <50,000 mm^3, lasting less than 7 days requires holding only chemotherapy until only Grade 3 neutropenia, ANC <1000-500/mm^3, and only Grade 2 thrombocytopenia, <75,000-50,000/mm^3. Radiation therapy will be interrupted until ANC≥1000/mm^3, Grade 3 or less, and thrombocytopenia ≥ 50,000/mm^3, Grade 2 or less. Resume chemotherapy as planned.

Prolonged Grade 4 neutropenia or Grade 3-4 thrombocytopenia lasting more than 7 days past the interruption of chemotherapy (14 days since the last dose received) should cause interruption of radiation therapy until ANC > 500/mm^3 (Grade 3 or better) and platelets > 50,000/mm^3 (Grade 2 or better).

Patients must have no worse than Grade 3 neutropenia (ANC > 500/mm^3) and Grade 2 thrombocytopenia (platelets > 50,000/mm^3) to receive their next weekly dose of chemotherapy.

Treatment toxicities will be reported using the NCI CTCAE v3.0.

Table 1. Treatment Modifications for Hematologic Toxicity

Toxicity NCI CTCAE v3.0 Grade	**Radiation (both regimens)**	**Cisplatin**
Neutropenia		
1 (1500/mm^3 - LLN)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Maintain dose level	Maintain dose level
4 (< 500/mm^3) **Uncomplicated**	Hold treatment for maximum of 2 weeks until recovered to ≤ grade 3	Hold treatment for a maximum of 2 weeks until recovered to grade ≤ grade 3 Resume full dose[1]
Neutropenic fever	Hold treatment for a maximum of 2 weeks until recovered to ≤ grade 2.	Hold treatment for a maximum of 2 weeks until recovered to ≤ grade 2. Resume full dose[1]
Thrombocytopenia		
1 (75,000/mm^3 - LLN)	Maintain dose level	Maintain dose level
2 (50,000- 74,999/mm^3)	Maintain dose level	Maintain dose level
3 (25,000- 49,999/mm^3)	Hold treatment for a maximum of 2 weeks until recovered to ≤ grade 2.	Hold treatment for a maximum of 2 weeks until recovered to ≤ grade 2. Resume full dose[1]
4 (< 25,000/mm^3)	Hold treatment for a maximum of 2 weeks until recovered to ≤ grade 2.	Hold treatment for a maximum of 2 weeks until recovered to ≤ grade 2. Resume full dose[1]

[1]Repeat lab work twice weekly and resume treatment based on this table.

6.2 Gastrointestinal Adverse Effects

Grade 1-2 nausea/vomiting with the onset of concomitant cisplatin and radiation therapy, and Grade 1 diarrhea after 1-2 weeks of radiation therapy may be expected. Patients may receive the investigator's choice of drugs for the control of nausea and vomiting associated with the cisplatin administration. Nausea, vomiting, and diarrhea during the course of radiation therapy may be treated symptomatically by antiemetic and antidiarrheal medications, and dietary modifications. Intractable nausea and vomiting beyond the first few days after

cisplatin chemotherapy should arouse suspicion of other causes such as bowel obstruction. Consider sending stool sample for Clostridium difficile toxin.

6.21 Radiotherapy

Radiation therapy will be interrupted in patients where hospitalization or IV fluid replacement is necessary (Grade ≥ 2). Radiation therapy should be resumed as soon as the patient has improved to allow oral intake and not require IV hydration (Grade ≤ 1). Every effort should be made to control diarrhea by dietary restriction and antiperistaltic drugs. This interruption should preferably be for no longer than one week.

Study Chair or Co-Chair must be called whenever interruption of radiation therapy has lasted more than 5 treatment days.

6.22 Cisplatin

Antiemetics should be used prophylactically (See Section 5.442). **(08/08/08)**

Table 2. Dose Modifications for Gastrointestinal Toxicity

Toxicity NCI CTCAE v3.0 Grade[1]	**Radiation (both regimens)**	**Cisplatin**
Diarrhea		
2 despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2
3 despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2
3, recurrent despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2
4 despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2
Nausea/Vomiting		

Toxicity NCI CTCAE v3.0 Grade[1]	**Radiation (both regimens)**	**Cisplatin**
2 despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2
≥3 despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2
≥3, recurrent despite maximal medical management	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2	Hold treatment for a maximum of 2 weeks, until recovered to ≤ grade 1. Resume treatment as planned, providing no other toxicities ≥ grade 2

[1] For ≤ CTCAE v3.0 Grade 2 toxicity not described above, maintain dose level of all agents.

6.3 Renal/Genitourinary Adverse Effects

Increased frequency with dysuria may occur in some patients. This may be treated symptomatically with antispasmodics and increased fluid intake. Urinary tract infection should be ruled out if the symptoms persist.

6.31 Radiotherapy

Radiation therapy may be interrupted for up to one week for Grade 3 or 4 bladder toxicity at the discretion of the investigator. Study Chair must be called whenever interruption of radiation therapy is considered.

6.32 Cisplatin

Renal Adverse Effects

If creatinine rises to greater than 2.0 mg/dl, obtain creatinine clearance (CrCl). Consider renal ultrasound. If CrCl is greater than or equal to 50 ml/min, continue therapy. If CrCl is less than 50 ml/min, hold treatment and check CrCl weekly. When the CrCl is greater than or equal to 50 ml/min, or the serum creatinine is less than 2.0 mg/dl, resume therapy at 75% of the planned dose. Persistence of CrCl less than 50 ml/min or serum creatinine greater than 2.0 mg/dl for more than two weeks requires notification of the Study Chair, and patient's study therapy will be stopped.

Selective renal tubular defects are sometimes observed. Hypocalcemia with hypomagnesemia and hypokalemia are common and potentially

severe. Replacement of magnesium, calcium, and potassium are usually effective. Severe tubular defects, although rare, may require chronic replacement therapy.

Diagnostic tests for alternative mechanisms of hypocalcemia (for example, GI or metabolic) are suggested.

The formula for calculating the creatinine clearance is:

$$\boldsymbol{CrCl} = 0.9 * \left[\frac{98 - (0.8 * (\boldsymbol{Age} - 20))}{\boldsymbol{Scr}} \right]$$

where *CrCl* = creatinine clearance in ml/min
Age = patient's age in years (from 20-80)
Scr = serum creatinine in mg/100 ml

6.4 Cutaneous Adverse Effects

6.41 Radiation

Grade 1-2 skin reactions may occur especially in the intertrigonous and peri-anal regions within the radiation fields. The skin reaction may be more prominent in those patients requiring irradiation of the inguino-femoral lymph node areas. Use of skin care as well as adequate hygiene measures are to be discussed with the patient at the initiation of therapy.

Radiation therapy may be temporarily interrupted for up to one week for Grade 3-4 skin toxicity at the discretion of the radiation oncologist.

6.42 Cisplatin

Chemotherapy will be resumed at the planned dose once toxicity has resolved.

6.5 Treatment of Hypersensitivity Reactions to Cisplatin:

6.51 In each case of a hypersensitivity reaction to cisplatin the infusion should be stopped and tubing disconnected. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Cisplatin will be discontinued following the first hypersensitivity reaction.

6.6 Radiotherapy Treatment Method Modifications **(10/8/2008)**

Institutions may NOT submit a plan for non-IMRT treatment and then switch to IMRT treatment during the course of the study. If IMRT is planned initially and an institution is considering administering another type of radiotherapy, then the study chair must be consulted before any other radiotherapy treatment plan begins.

7.0 STUDY PARAMETERS

7.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s):

Parameter	Prior to study entry/Pre-Therapy	Weekly during therapy	Upon completion of study therapy	Every month for the first 3 months after completion of therapy	Every 3 months after therapy for the 1st 2 years then every 6 months for the next 3 years.
History & Physical	1	X	X		X
Radiation treatment plan	1*				
GOG Performance Status	2	X	X		X
Toxicity Assessment		X	X	X	X
CT scan of Chest, abdomen, pelvis	1**		X		8
CBC/Differential/ Platelets	2	3	X		4
Electrolytes, BUN, Creatinine, Creatinine Clearance (CrCl), Calcium (CA), Magnesium (Mg), Phosphorous (PO_4)	2	X	X		X
Bilirubin, SGOT, Alkaline Phosphatase, LDH	2		X	X	X
Pap Smear			5		5
Barium enema	6				
Proctoscopy	6				
Cytoscopy	6				
Renal Ultrasound	6				
EKG	1				
Audiogram	7				7

* Radiation Therapy summary plan should be known prior to entry. Specify type of boost on the Fast Fact Sheet (FFS).

** X-ray of chest may be done first, and if abnormal a CT scan of the chest should be done. If the patient is unable to tolerate contrast, then MRI with IV gadolinium should be performed **(10/8/08)**

1. Must be obtained within 28 days prior to initiating protocol therapy.

2. Must be obtained within 14 days prior to initiating protocol therapy.
3. If Grade 4 neutropenia is documented (ANC <500/mm^3), obtain twice per week until resolved to no worse than Grade 3.
4. When clinically indicated
5. Recommended
6. Optional
7. Required in all patients with a history of hearing loss. Must be obtained within 28 days prior to initiating protocol therapy. Repeat during therapy every other cycle or more frequently as clinically indicated.
8. Every 6 months during follow-up. **(10/8/08)**

7.2 PATHOLOGY REQUIREMENTS **(10/18/2010)**

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating the primary site, histologic cell type, and grade will be required, as well as at least one representative slide documenting the recurrent tumor. Recurrent disease in the pelvis must be histologically documented for eligibility for this protocol.

When submitting pathology material to the GOG Statistical and Data Center, individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting stained slides, pathology reports and Form F to the GOG Statistical and Data Center. Please see Section 10.2 for additional requirements and instructions.

7.3 TRANSLATIONAL RESEARCH **(10/18/2010)**

Not applicable.

7.4 QUALITY OF LIFE ASSESSMENTS **(10/18/2010)**

Not applicable.

8.0 EVALUATION CRITERIA

8.1 Parameters of Outcome – GOG RECIST Criteria

8.11 Measurable disease

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

8.12 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the progression of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

Measurement of the longest dimension of each target lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline.

8.13 Definition of disease progression

Progression for patients with measurable disease is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically

measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry

- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

Progression for patients with non-measurable disease is defined as increasing clinical, radiological, or histological evidence of disease since study entry.

8.14 Survival is the observed length of life from entry into the study to death or the date of last contact.

8.15 Progression-Free Survival is the period from study entry until disease progression, death, or date of last contact.

8.16 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE.

8.17 Classification of recurrence at study entry
The type of recurrence will be classified for each patient as either
1) an isolated vaginal recurrence, defined as a recurrence of endometrial carcinoma limited to the vagina with no evidence of pelvic recurrence as identified clinically and by CT scan or MRI, or
2) any recurrence situated in the pelvis. Recurrences that are evident in both the pelvis and the vagina are to be included in the pelvic recurrence group.

9.0 DURATION OF STUDY

The patient can refuse study treatment at any time. All patients will be followed (with completion of all required case report forms) for a minimum of 5 years after completion of therapy unless consent is withdrawn.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT **(04/21/2014)**

10.11 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.

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational or commercial agents, and 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 CTEP Adverse Event Reporting System (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through CTEP-AERS 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 signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS 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 June 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 CTEP-AERS system. **(5/23/2011)**

Beginning July 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the CTEP-AERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/c

tc.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). **(5/23/2011)**

	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 Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	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:

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

[2] Although a CTEP-AERS 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 CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005

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 CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete CTEP-AERS 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 expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital

anomalies, or birth defects must be reported to GOG via CTEP-AERS 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.

Additional Instructions or Exceptions to CTEP-AERSExpedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

- There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting: **(10/18/2010)**

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS 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.

Up until June 30, 2011, AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(5/23/2011)**

Starting July 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via CTEP-AERS (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. **(5/23/2011)**

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 CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.15 Automated CDUS reporting

For studies using commercial agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through CTEP-AERS will also be included with the quarterly CDUS data submissions.

10.2 GOG DATA MANAGEMENT FORMS **(10/18/2010)**

The following forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. **Note: Pathology materials (Form F, path report, and slides) must be submitted together via postal mail or the forms may be uploaded using the Upload feature in SEDES. Additionally, radiation materials (forms, copies, films, reports, etc) must be submitted together via postal mail. (10/18/2010)**

Form	Due within		Copies*	Comments
	Weeks	Event		
Knowledge Assessment	0	Prior to Registration	1	Available at http://irochouston.mdanderson.org under 'Credentialing.' **(10/08/08) (04/21/2014)**
Brief Description of Radiation Therapy Plan	0	Registration	1	Specify type of boost planned on Fast Fact Sheet
Form R	2	Registration	1	Submit via SEDES
Form OSR	2	Registration	1	Submit via SEDES; report site of disease as vaginal, pelvic or both and report any disease resection prior to entry
Form DR Form BDR	4 4	Registration Registration	1 1	Submit via SEDES Available in SEDES for print only
Form D2M – baseline assessment	4	Registration	1	Submit via SEDES; report any tumor present at baseline as non-target lesions if non-measurable
Pathology requirements Primary diagnosis: Form F Pathology Report Slides Recurrence diagnosis: Form F Pathology Report Slides	 6 6 6 6 6 6	 Registration Registration Registration Registration Registration Registration	 2 2 ** 2** 2** **	All forms may be uploaded in SEDES or mailed via postal mail. All slides must be sent via postal mail. See below
Radiation Materials: - daily treatment reports - CT/MRI showing relevant tumor volume External beam:	4	Completion of therapy	 2 1	Forms G, HDRV, LDRV, and IR must be submitted via SEDES. Paper copies should also be submitted with radiation materials via postal mail.

Form	Due within		Copies*	Comments
	Weeks	**Event**		
- simulation films or digitally reconstructed radiograph			1	
- portal films				
- dosimetry calculation				
- Isodose distribution curves			1 2	
- Form G			2	
Brachytherapy:				
- orthogonal simulation films for each intracavitary placement			2 1	
- Implant films				
- dosimetry calculation				
- isodose distribution curves for each intracavitary placement			1 2 2	
- Form HDRV or Form LDRV				
Interstitial:				
- Films for all insertions			2	
- Activity of needles				
- A diagram locating each needle				
- Summary of active dwell positions and times for HDR insertions				
- Dosimetry calculations for reported doses				
- Dose distribution for each insertion				
- Form IR			1	
- Digital Treatment Plan for HDR interstitial implants			1	
- Dose Volume Histogram (DVH) for HDR interstitial insertions			1	
IMRT:				
- dosimetry calculations				
- Dose Volume Histograms (DVH)			1	

Form	Due within		Copies*	Comments
	Weeks	Event		
Form D2R***	2	Completion of each week of external radiation	1	Submit via SEDES
Form T****	2	Beginning of each subsequent week of external radiation and completion of all study therapy	1	Submit via SEDES
Form D2M	4	Chest, abdomen, and pelvis imaging and clinical tumor measurements	1	Submit via SEDES
Form Q0	2	Completion of study treatment	1	Submit via SEDES
Form TLC	2	Each 6 month follow-up toxicity assessment	1	Submit via SEDES until disease progression is documented
Form Q	2	Disease progression; death; normal follow-up; change in treatment	1	Submit via SEDES quarterly for 2 years, semi-annually for 3 more years

*The number of required copies including the original form, which must be sent to the Statistical and Data Center. No copies are required for forms submitted through SEDES. Additionally, forms submitted through SEDES should not be sent through postal mail or fax.

At least one representative stained slide (or slides) documenting the primary invasive endometrial tumor, cell type, and histologic grade. At least one stained slide will be required, along with the Form F and pathology report for the recurrent disease in the pelvis. **(10/18/2010)

***Not required for Regimen I.

****Only one T form is required for Regimen I subsequent to completing radiation therapy.

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested. **(5/23/2011)**

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study design overview and registration:

Chemotherapy consisting of the combination of doxorubicin, cisplatin, and paclitaxel (TAP) is a standard treatment in the GOG for women with advanced or recurrent measurable endometrial cancer in which surgery and/or radiation are no longer thought to be curative. Pelvic radiation following initial surgery is being used less frequently when disease is caught at an early stage. Subsequently investigators have noticed a growing number of patients with isolated vaginal or pelvic recurrences. Pelvic radiation is commonly given at recurrence and thought to be curative in a subset of these patients, however, data on efficacy of therapy for such patients are very limited; most of which are from retrospective studies. This screening trial will allow evaluation of the experimental arm given the lack of historical control data available. Additionally, evaluation of prognostic factors such as tumor size, site, and histology will be possible. Furthermore, these data will help to determine the feasibility of future studies in this population of patients.

This study is a randomized Phase II screening clinical trial.[32] This design will provide a preliminary assessment of the direct but non-definitive screening comparison of an intermediate endpoint between two therapeutic regimens: pelvic irradiation with or without weekly cisplatin. All patients on this study will be registered and randomized centrally at the GOG Statistical and Data Center. Prior to registration, eligibility will be reviewed via Fast Fact Sheet verification. The sequence of treatment assignments will be concealed from institutions and patients until registration with verification of eligibility. Randomization with equal probabilities to the two treatment regimens will be carried out following study registration. All reports will include a complete accounting of all patients registered to this protocol.

11.2 Data collection:

The principal parameters to be collected, analyzed, and reported to determine the relative therapeutic effect of the two treatment regimens are:

11.21 Outcome Variables:

Primary: Duration of progression-free survival
Secondary: Duration of overall survival

11.22 Tumor characteristics**:** site of measurable disease (vaginal, central pelvic), tumor size as measured by the maximum dimension of the tumor, histological cell type, tumor grade and the presence of lymph-vascular space involvement of the original tumor at the time of initial hysterectomy.

11.23 Host characteristics**:** age at entry, performance status, and race.

11.24 Adverse effects**:** frequency and severity of adverse effects graded by CTCAE Version 3.0.

11.25 Treatment**:** total dose of radiation received (external beam and brachytherapy); the number of cycles of protocol directed therapy administered; for those not completing study therapy, the reason for not completing the assigned treatment

11.3 Accrual**:**

The Gynecologic Oncology Group has not previously prospectively studied this population. The anticipated annual accrual is 40 patients. Accrual will be monitored on a quarterly basis. If the average accrual rate is 20 patients per year or less at the end of 2 years, the feasibility of this study will be reassessed. If the average annual accrual rate exceeds 60 patients at two years, then consideration for converting to a Phase III study will be given. This decision will be made only on the basis of accrual and the sample size, Type I and II errors, and error spending functions will be modified to that which is appropriate for a Phase III study.

Revision # 11: Total accrual as of March 21, 2012 was 48 out of a projected 164 assuming an accrual rate of 40 patients per year. Annual accrual in 2011 was 15. In order to increase accrual several changes to this protocol are incorporated into this revision:

- A change in eligibility that favors a lower risk patient population – patients with completely resected vaginal metastasis are now eligible
- Use of IMRT for the entire radiation therapy prescription rather than just for the boost

Accrual scenarios are presented in a table below. **(05/14/2012)**

11.4 Hypotheses and sample size**:**

Primary Hypothesis*:* This screening study will evaluate an intermediate endpoint as a preliminary indication of activity; progression-free survival. The primary hypothesis of interest is "Is pelvic radiation with concurrent cisplatin active relative to pelvic radiation alone with respect to progression-free survival in patients with recurrent endometrial carcinoma limited to the pelvis and vagina?" The design of this study will provide preliminary evidence of efficacy with regard to progression-free survival. The type I error level will be set at 0.10 (one tail) which allows for a higher false positive rate than for a usual randomized study design. Since this rate is higher and an intermediate endpoint is chosen, the comparative results will be considered preliminary and in the event of a positive trial, a full-sized Phase III trial will be necessary to provide a definitive, more precise estimate of the treatment effect. However, if the resulting p-value is less than 0.005, similar to that used for Phase III interim analysis, attention will be given to estimate the effect with respect to overall survival. If the estimated effect

size is similar to that seen in PFS, then it may be regarded as compelling. In this event, the ability to conduct a Phase III trial may be severely limited.

Background information: Four recent studies provide estimates of 5 year overall survival among patients treated with radiation for vaginal recurrence of endometrial adenocarcinoma. [7,6,27,29] These estimates are 0.75, 0.65, 0.55 and 0.43. The average of these estimates, weighted by the number of deaths reported in each study, is 0.52. Assuming an exponential failure time distribution, the constant monthly hazard estimate is then –ln(0.52)/60=0.011. Under the assumption that the hazard of progression or death is 1.5 times that of survival, then the estimate of the monthly hazard of progression or death is 0.011*1.5=0.0165; translating into a median time to progression or death of 42 months. Similarly, the estimate of median overall survival among patients treated with radiation for pelvic recurrence of endometrial adenocarcinoma is 8 months.[7]

Sample Size***:*** It is anticipated that 75% of patients registered to this study will have a recurrence limited to the vagina. Among those with a vaginal recurrence, the median time to progression or death is assumed to be 42 months in the control arm. Additionally, among those with a recurrence that is not isolated to the vagina (25% of patients registered), the median time to progression or death is assumed to be 8 months. The relative decrease in the progression/death hazard of 0.645 translates into an increase in median progression-free survival to 65.7 months for vaginal recurrences and 12.5 for extra-vaginal recurrences. This difference requires observing at least 94 failures to provide 80% statistical power when type I error is limited to 0.10 (one tail test). [33] A proportional hazards model will be used to assess the equality of hazard rates between the two regimens. All eligible patients will be included in the analysis, regardless of the amount of study treatment received. The analysis will be stratified by initial performance status and type of recurrence at entry (vaginal only vs. all others). Potential confounders including tumor size, tumor histology (serous/clear cell v all others), age, race and tumor grade, will be considered in an exploratory model.

Revision # 11: Patients with surgically removed vaginal recurrences are thought to be at lower or similar risk of progression on average than similar patients with vaginal recurrences who fit the eligibility criteria prior to this revision. Assuming the hazard rates from the original statistical design but shifting the percentage of vaginal only recurrences to 100% or 85% from 75%, accrual and study durations are estimated under different accrual rate increase scenarios. The current accrual duration assumed for this table is 50 months.

Proportion with vaginal recurrence*	Annual accrual rate	Total accrual duration in months (sample size)	Additional follow-up (months)	Overall study duration (years)
85%	24	102 (154)	8	9.2
85%	36	84 (152)	18	8.5

85%	48	76 (154)	20	8.0
100%	32.4	90 (153)	24	9.5

*Following revision #11

Secondary Hypotheses***:*** Overall survival and identification of prognostic factors with respect to PFS and overall survival.

Overall survival (OS) will be analyzed as a secondary endpoint. This endpoint is not expected to have sufficient power for a definitive test and will therefore be treated as supportive evidence. All eligible patients will be included in the intent-to-treat analysis. The final analysis will be stratified by performance status and type of recurrence at entry (vaginal only vs. all others). Other potential confounders will be assessed.

This study will investigate the prognostic significance of tumor size, tumor location (vaginal only vs. all others) and histology in patients treated with radiation with or without cisplatin. Additionally, age, race, and tumor grade will be evaluated as prognostic factors. These analyses will help to define the appropriate population with sufficient risk for future studies involving therapy that is more aggressive. A proportional hazards model adjusted for performance status and treatment will be used to explore the relationship between these variables and PFS or survival.

Design assumptions: Assumptions made to determine sample size will be checked after two years of accrual and prior to the planned time of closing the study to patient entry. This will not involve a comparison of treatment arms but will be based upon aggregated data.

Revision #11: The accrual rate for this study has been monitored for several years. In response to an initial slow accrual rate, this study was added to the CTSU menu and endorsed by RTOG. Changes to the eligibility and flexibility in the radiation therapy prescription plan are now made to increase accrual beyond its current rate. (05/14/2012)

11.5 Study Duration**:**

The planned sample size is 164 eligible patients. It is anticipated that this study will require approximately 49 months of accrual assuming a uniform accrual rate of 40 patients per year. It is estimated that twenty months of post accrual follow-up will be necessary to observe the minimum number of failures required for the final primary analysis. To avoid the small loss in power due to the interim futility analysis, consideration will be given to extension of follow-up, if necessary, to observe five additional failures prior to the final analysis.

11.6 Interim Analyses**:**

There will be one planned interim futility analysis of progression-free survival data. The planned interim analysis will occur when approximately 60 failures have been reported. If the observed rate of recurrence or death, stratified by performance status and type of recurrence at entry, of the experimental arm is greater than that of the control arm, then accrual termination will be considered (if still active) with a conclusion that an advantage for the experimental regimen has not been established. This will result in a small loss in power for the current study, roughly, 0.005.[34]

Other factors to be assessed at the time of interim analysis will include frequency and severity of adverse effects, the frequency of treatment termination due to toxicity, the OS relative hazard estimate, and potential confounders.

The results of interim analyses are scheduled to be reviewed by the GOG Data Safety and Monitoring Board (DSMB) at its semi-annual meetings. This committee meets in January and July each year. The precise dates for these meetings are set more than one year in advance by individuals who have no knowledge of efficacy results. Approximately eight weeks prior to each of these meetings, the database is locked in order to prepare a progress report. If the prerequisite number of events has been attained, an interim analysis is also prepared and presented to the DMC at their next scheduled meeting. The decision to terminate accrual to any particular regimen includes consideration of toxicities, treatment compliance, overall survival and results from external studies. Additionally, the GOG Safety Review Committee (SRC) reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports on an ongoing basis (not efficacy results). This committee also reviews those deaths in which the study treatment may have been a contributing cause. The SRC reports to the DMC and may recommend study amendments pertaining to patient safety. (05/14/2012)

11.7 Anticipated Gender and Minority Inclusion**:**

This study restricts entry to women by nature of the site of disease. The table below lists the projected percentage of patients by racial/ethnic subgroup. Prior GOG studies of similar populations support no differences in the intervention effect between racial/ethnic subgroups. Therefore, the study design does not involve race. However, subsets defined by white and non-white will be analyzed in this study to investigate this important question with the current therapies.

0.1%	American Indian, Alaskan Native
1.7%	Asian
14.6%	Black
2.7%	Hispanic
80.9%	White
100.0%	Total

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APPENDIX I

CLINICAL STAGING - CARCINOMA OF THE CORPUS UTERI
FIGO CLASSIFICATION
(1988)

STAGE O: Carcinoma in situ. Histologic findings suspicious of malignancy.

(Cases of Stage 0 should not be included in any therapeutic statistics.)

STAGE I: The carcinoma is confined to the corpus.

STAGE IA: The length of the uterine cavity is 8 cm or less.
STAGE IB: The length of the uterine cavity is more than 8 cm.

The Stage I cases should be sub-grouped with regard to the histological type of the adenocarcinoma as follows:

G1 - Highly differentiated adenomatous carcinoma.
G2 - Differentiated adenomatous carcinoma with partly solid areas.
G3 - Predominantly solid or entirely undifferentiated carcinoma.

STAGE II: The carcinoma has involved the corpus and the cervix.

STAGE III: The carcinoma has extended outside the uterus but not outside the true pelvis.

STAGE IV: The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum. A bullous edema as such, does not permit a case to be allotted to Stage IV.

STAGE IA G123: Tumor limited to endometrium.
IB G123: Invasion to < 1/2 myometrium.
IC G123: Invasion > 1/2 myometrium.

STAGE IIA G123: Endocervical glandular involvement only.
IIB G123: Cervical stromal invasion.

STAGE IIIA G123: Tumor invades serosa and/or adnexae and/or positive peritoneal cytology.

STAGE IIIB G123: Vaginal metastases.
IIIC G123: Metastases to pelvic and/or para-aortic lymph nodes.

STAGE IVA G123: Tumor invasion bladder and/or bowel mucosa.
IVB: Distant metastases including intra-abdominal and/or inguinal lymph node.

CLINICAL STAGING - CARCINOMA OF THE CORPUS UTERI (con't)
FIGO CLASSIFICATION
(1988)

Histopathology -- Degree of Differentiation

Cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

G1 = 5% or less of a non-squamous or non-morular solid growth pattern.
G2 = 6-50% of a non-squamous or non-morular solid growth pattern.
G3 = More than 50% of a non-squamous or non-morular solid growth pattern.

Notes on Pathological Grading

(1) Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade I or grade II tumor by 1.

(2) In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.

(3) Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules Related to Staging

(1) Since corpus cancer is now surgically staged, procedures previously used for determination of stages are no longer applicable, such as the finding of fractional D&C to differentiate between stage I and stage II.

(2) It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply but designation of that staging system would be noted.

(3) Ideally, width of the myometrium should be measured along with the width of tumor invasion.