RADIATION THERAPY ONCOLOGY GROUP

RTOG 0921

A PHASE II STUDY OF POSTOPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT) WITH CONCURRENT CISPLATIN AND BEVACIZUMAB FOLLOWED BY CARBOPLATIN AND PACLITAXEL FOR PATIENTS WITH ENDOMETRIAL CANCER

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SCHEMA

R E G I S T E R	PELVIC IMRT WITH OPTIONAL BOOST AND CONCURRENT CISPLATIN AND BEVACIZUMAB
	FOLLOWED WITH ADJUVANT CHEMOTHERAPY OF CARBOPLATIN AND PACLITAXEL

See Section 6.0 for complete details on radiation therapy
See Section 7.0 for complete details on systemic therapy

Patient Population: (See Section 3.0 for Eligibility)

- Patients must have undergone a hysterectomy (total abdominal hysterectomy, vaginal hysterectomy, robotic-assisted hysterectomy, radical hysterectomy or laparoscopic-assisted vaginal hysterectomy) for carcinoma of the uterus within 56 days prior to study entry. Patients must also have had a bilateral salpingo-oophorectomy.
    - Endometrioid endometrial adenocarcinoma, clear cell carcinoma, papillary serous adenocarcinoma, adenosquamous carcinoma or other adenocarcinoma variant
    - Patients must have Zubrod performance status 0-1

Required Sample Size: 34

____(Y) 1. Did the patient have a hysterectomy (total abdominal, vaginal, robotic-assisted hysterectomy, radical, or laparoscopic-assisted vaginal hysterectomy) and bilateral salpingo-oophorectomy for endometrial carcinoma within 56 days prior to study entry?

____(Y) 2. Does the patient have histologically proven endometrial cancer?

____(Y) 3. Does the patient have histology consisting of endometrioid endometrial adenocarcinoma, clear cell carcinoma, papillary serous adenocarcinoma, adenosquamous carcinoma, or other adenocarcinoma variant?

____ (N) Is the histology carcinosarcoma?

____(Y) 4. Does the patient have endometrial cancer with one of the following? (**Note**: Overlap of disease characteristics below may occur and is permitted)

- Grade 3 carcinoma with greater than 50% myometrial invasion; all papillary serous and clear cell carcinoma will be considered grade 3.
- Grade 2 or 3 carcinoma with any cervical stromal invasion
- Known extra-uterine disease confined to the pelvis, any grade

_____(N) 5. Does the patient have positive common iliac or positive para-aortic disease (defined as lymph nodes ≥ 2cm in any dimension or biopsy proven)?

____(N) 6. Is there evidence of metastatic extrauterine disease, gross/residual (not including pelvic nodal) disease, or distant metastases?

_____(N) 7. Has the patient received prior external beam radiotherapy to the pelvis resulting in overlapping of radiation therapy fields?

____(Y/N) 8. Has the patient had prior invasive malignancies other than non-melanomatous skin cancer?

____(Y) If yes, has the patient been disease-free for a minimum of 3 years?

____(Y) 9. Is the patient's age ≥ 18?

____(Y) 10. Is the patient's Zubrod performance status 0-1?

____(Y) 11. Are the patient's lab values/UPC ratio value within the limits specified in Section 3.1.7 and 3.1.8

____ (Y/N) 12. Was the patient treated with Warfarin within 14 days prior to study entry?

____(Y) If yes, is the INR less than 1.5?

____(N/NA) 13. Does the patient require more than 1mg/day of Warfarin?

____(Y) 14. Has the patient had a history/physical examination including normal postoperative exam within 56 days prior to study entry?

____(Y) 15. Was a chest x-ray, CT, or PET/CT performed within 56 days prior to study entry?

____(Y) 16. Has the patient had a CT or PET/CT of the abdomen and pelvis within 56 days of study entry?

_____(N) 17. Does the patient have neuropathy > grade 1?

_____(N) 18. Does the patient have ototoxicity > grade 2?

_____(N) 19. Has the patient had prior systemic chemotherapy for uterine cancer?

_____(N) 20. Does the patient have a history of arterial thromboembolic events, including transient ischemic attack (TIA), or clinically symptomatic peripheral artery disease within 12 months of study entry?

_____(N) 21. Has the patient had any major surgical procedure requiring open biopsy incision or significant trauma within 28 days prior to study entry or anticipation of the need of any surgical activity during the course of the study excluding vascular access to device placement or procedures that do not require significant incision?

_____(N) 22. Does the patient have a history of abdominal fistula, GI perforation or intra-abdominal abscess within 6 months prior to study entry?

_____(N) 23. Has the patient had an organ transplant?

_____(N) 24. Does the patient have any history of hypertensive crisis or hypertensive encephalopathy?

_____(N) 25. Does the patient have a history of stroke/cerebrovascular event (CVA) within 6 months of study entry

_____(N) 26. Does the patient have a known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies?

Continued on next page

____(N) 27. Does the patient have mental status changes or bladder problems that make her unable to comply with bladder filling instructions?

_____(N) 28. Has the patient ever had an allergic reaction to bevacizumab, cisplatin, carboplatin or paclitaxel?

_____(N) 29. Is the patient breast feeding?

_____(N) 30. Has the patient had prior therapy with Anti-VEGF compounds?

_____(N) 31. Does the patient have any of the comorbidities described in Section 3.2.7?

_____(Y) 32. Has the patient signed a study-specific informed consent prior to study entry?

The following questions will be asked at Study Registration:

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

_____ 18. Medical oncologist's name [for trials that include a drug component]

_____(Y/N) 19. Have you obtained the patient's consent for her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact her in the future to take part in more research?

_____(Y/N) 24. Is use of brachytherapy intended?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION (2/21/11)

Endometrial cancer is the most common cancer of the female reproductive organs in the United States. Approximately 41,000 women are diagnosed annually, with the majority presenting with early-stage disease curable by surgery alone. Nevertheless, more than 7,000 women die of the disease each year (ACS, 2008). Prior randomized trials in early-stage disease show that radiation reduces the risk of local-regional failures by approximately two-thirds, from 6-14% without to 1.5-5% with pelvic radiation (Aalders 1980; Creutzberg 2000; Keys 2004; ASTEC Study Group 2009), though distant failures persist (5-10%) even in the favorable group of stage I and II patients. From these randomized trials, specific sub-groups of higher risk early stage patients were identified. The PORTEC trial suggested a higher risk of recurrence for older patients (> 60 years old), and for those with stage IC, grade 3 disease or lymphovascular invasion. The GOG-99 trial hypothesized that a high-intermediate risk could account for two-thirds of the recurrences, with factors including age, depth of myometrial invasion, grade, and lymphovascular invasion. In this high-intermediate risk group, pelvic radiation reduced the 4-year cumulative incidence of local recurrence from 13% to 5%. These trials define a group of higher-risk stage I and II patients for whom pelvic radiation therapy may be considered standard treatment to prevent pelvic relapse.

Overall, patients with stage IC grade 3 disease have an increased risk of pelvic and distant relapses compared to those with stage IB or grade 2 disease (Straughn 2003, Greven 1990). In the PORTEC trial, patients with stage IC grade 3 disease received adjuvant pelvic external-beam radiation alone (Creutzberg 2004); the 5-year rate of pelvic relapse was 14%, distant relapse was 31%, and overall survival at 5 years was 58%. Similar to the high-intermediate risk group category, patients with cervical involvement, clear-cell or papillary serous adenocarcinoma, or extra-uterine pelvic confined disease, including pelvic nodal spread, have an increased rate of both local and distant metastases and require pelvic radiation to reduce the risk of a pelvic recurrence. Given the risk of local and distant relapse with high-intermediate-risk stage I, stage II, and stage III uterine cancer, chemotherapy combined with radiation may be considered for these patients.

Patients with stage IC to stage IVA endometrial cancer treated with chemotherapy alone have a high rate of local relapse. In a series of 43 high risk stage I-IV patients treated with chemotherapy alone, Mundt et al. reported a 40% pelvic relapse rate (Mundt 2001). Patients with lymph node involvement had a 3-year actuarial 46% risk of vaginal and a 41% risk of pelvic relapse. The use of adjuvant chemotherapy versus radiation in high-intermediate or advanced-stage endometrial cancer patients has been reported in three randomized trials. Table 1 depicts the results comparing chemotherapy to radiation therapy; the chemotherapy-alone arms demonstrate a local relapse rate of 18% for stage III and IV disease (Randall 2006), and 11% (Maggi 2006) or 7% (Susumu 2008) for those with stage IC through IIIC. In the GOG 122 trial, women with stage III or IVA endometrial cancer after a hysterectomy with optional nodal sampling and no single site of residual disease > 2cm were randomized to whole abdomen radiation or chemotherapy with Adriamycin and cisplatin for 8 cycles (Randall 2006). The primary outcome was progression-free survival (PFS); significant improvements in PFS and overall survival (OS) were found in the chemotherapy arm after adjustment for stage. An Italian trial randomized women with stage IC to IIIC endometrial carcinoma to pelvic radiation versus chemotherapy using cyclophosphamide, doxorubicin, and cisplatin (CAP) but found no difference in overall or progression-free survival (Maggi 2006). Similarly, a Japanese randomized trial of women with stage IC to IIIC endometrial carcinoma showed no benefit from chemotherapy when compared with radiation. Retrospective subset-analysis identified a possible benefit in progression-free survival for high-risk patients, including stage IC patients over 70 years of age or with Grade 3 disease and those with stage I or IIIA with deeper than 50% myometrial invasion; however, the authors do not report local recurrence results for this group. (Susumu 2008).

Table 1. Results of randomized trials utilizing chemotherapy compared to radiation in patients with endometrial carcinoma

	Randall et al. (n=420)		Maggi et al. (n=345)		Susumu et al. (n=385)	
	RT	CH	RT	CH	RT	CH
LR	13%	18%	7%	11%	7%	7%
DR	22%	32%	21%	16%	13.5%	16%
5 yr PFS	38%	42%	63%	63%	84%	82%
5 yr OS	42%	53%	69%	66%	85%	87%

Key: RT=Radiation therapy; CH=chemotherapy; LR=local recurrence; DR=distant recurrence; PFS= progression-free survival; OS=overall survival

For patients with high-intermediate and advanced disease, a combination of chemotherapy and radiation offers potential reductions in both local and distant relapses. The GOG 0184 randomized patients treated with surgery and pelvis and/or para-aortic radiation to cisplatin and doxorubicin with or without paclitaxel; 10% had a local regional recurrence and 30% had a distant recurrence (Homesley 2009). A phase II trial of concurrent cisplatin with radiation and 4 cycles of cisplatin (50 mg/m2)/paclitaxel (175 mg/m2 every 4 weeks) after RT in RTOG 9708 showed a 4 year pelvic recurrence rate of 2%, regional recurrence rate of 2% and distant recurrence rate of 19% (Greven 2006). No recurrences occurred in the 13 stage IC, IIA, or IIB patients, Acute toxicity during chemo-RT was Grade 1 in 27%, Grade 2 in 43%, Grade 3 in 27%, and Grade 4 in 2%; a total of 20 of 45 patients (44%) had any Grade 3+ non-hematologic toxicity. The maximum late toxicity rates were 41% (Grade 2), 16% (Grade 3), and 5% (Grade 4). During adjuvant chemotherapy, the acute toxicity was Grade 1 in 7%, Grade 2 in 7%, Grade 3 in 21%, and Grade 4 in 62% (Greven 2004). These studies indicate the efficacy of combined chemo-radiation at improving local control, but demonstrate the need for novel agents to reduce the rate of distant relapses.

A recent trial by the GOG (GOG 209) of chemotherapy alone among patients with stage III and IV endometrial cancer required an amendment, with a standard dose reduction of the chemotherapy to paclitaxel 135 mg/m^2 and carboplatin AUC 5 every 3 weeks, given the toxicities seen at higher doses in patients who had received pelvic radiation. Based on these studies, chemotherapy doses of cisplatin 50 mg/m^2 during radiation and carboplatin AUC 5 and paclitaxel 135 mg/m^2 every 3 weeks as adjuvant treatment were chosen for this protocol.

1.1 IMRT

Intensity-modulated radiotherapy (IMRT) treats regions at risk for disease spread while sparing adjacent normal tissues. This may allow for dose escalation. A recent study demonstrated that 93% of the primary target region was covered by the 45 Gy isodose line in contrast to 75% coverage with a 4-field plan (Bouchard 2008). In addition to optimizing target coverage, IMRT reduces the dose to normal tissues, decreasing acute and chronic toxicity (Roeske 2003, Mundt 2003). Retrospective studies with pelvic IMRT indicate that the volume of small bowel treated over 45 Gy is smaller with IMRT than with whole pelvic radiation. Portelance et al. showed a >60% reduction in volume of small bowel radiated to more than 45 Gy with IMRT (Portelance 2001). A second study by Roeske showed a 50% reduction in volume of small bowel radiated to more than 45 Gy (Roeske 2000). Retrospective reports show a lower rate of acute Grade 2 GI toxicity (16% versus 91%, p=0.002) compared with whole pelvic radiation. Fewer anti-diarrheal medications were required in the IMRT group. There were also lower chronic toxicities (11% versus 54%, p=0.02) (Salama 2004). To standardize IMRT contouring, the RTOG developed an atlas based on consensus guidelines (Small 2008). Utilizing these guidelines, the RTOG 0418 trial assessed the feasibility of IMRT in post-operative patients; results for endometrial cancer patients indicate an acute Grade 2 or higher bowel toxicity of 28% in a multi-institutional setting (Jhingran ASTRO abstract 2009). Given the Grade 3+ non-hematologic acute toxicity rate in RTOG 9708 of 44%, the hope is that IMRT will reduce RT-related side effects.

1.2 Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity (k_d = 1.1 nM) (Presta 1997). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1 (Avastin™ [bevacizumab] Investigators Brochure; Kim1993; Presta 1997). Bevacizumab binds to and inhibits

the biologic activity of human vascular endothelial growth factor (VEGF) in in vitro and in vivo assays.

1.2.1 Mechanism of Action

Of known proangiogenic factors, VEGF is one of the most potent and specific, and has been identified as a crucial regulator of both normal and pathologic angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms and whose action is primarily mediated through binding to the receptor tyrosine kinases VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells in vitro, and to decrease microvessel density and interstitial pressure in tumor xenografts in vivo. Results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab (Willett 2004).

The mechanism of action of bevacizumab in combination with chemotherapy and radiation therapy may be through one or more of the following: inhibiting growth of new vessels, regression of newly formed blood vessels, normalization of vasculature leading to improved delivery of systemic therapy or improved oxygenation (and improved efficacy of radiation), or direct effects on tumor cells.

1.2.2 Clinical Studies

To date, more than 7,000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens (Bevacizumab Investigator's Brochure 2008).

1.2.3 Pharmacokinetics and MTD

The pharmacokinetics (PK) of bevacizumab have been characterized in several phase 1 and phase 2 clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution.

The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (Cobleigh 2003). Dose schedules of 5 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks are used in most phase 2 or 3 trials.

1.2.4 Clinical Efficacy of Bevacizumab

Clinical proof of principle for anti-VEGF therapy with bevacizumab has been observed in several solid tumors, including metastatic colorectal cancer (Hurwitz 2004, Giantonio 2007), non-small cell carcinoma (NSCLC), and renal cell cancer (Yang 2003). Willett et al. performed a dose escalation study of bevacizumab in combination with continuous infusion 5-FU and pelvic radiation therapy in patients with locally advanced rectal cancer. The MTD was determined to be 5 mg/kg owing to 2 of 5 cases demonstrating grade 3 or 4 diarrhea and/or colitis in the 10 mg/kg cohort. We therefore have selected the 5 mg/kg dose given in combination with cisplatin (which has fewer gastrointestinal effects), and IMRT (which should also spare more of the bowel and other normal tissues than the standard external beam radiation fields). Additional clinical trials are ongoing on a variety of solid tumors and hematological malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biological agents.

1.2.5 Bevacizumab in Gynecologic Malignancies

Uterine tissue is highly vascular given the monthly growth of new spiral arteries. Angiogenesis or the development of new blood vessels has been well-described in tumor development. The newly developed vasculature is required for providing sufficient growth factors and nourishment to the developing cancer. Tumor growth requires the expression of pro-angiogenic factors such as VEGF. Studies have noted VEGF serum levels in patients with endometrial cancer are significantly elevated compared with those of that controls, but levels do not correlate with stage (Mazurek 2004, Gornall 2001). The extent of vascular proliferation as detected by KI-67/Factor-VIII and degree of pericyte coverage detected by alpha smooth muscle actin staining correlated with survival in a large endometrial cohort, indicating the importance of angiogenesis in endometrial cancer development (Stefansson 2006). As endothelial cell proliferation and

neovascularization are critical for growth of endometrial cancer, the inhibition of angiogenesis may be critical to halt tumor progression (Mazurek 2006, Kamat 2007).

Targeted biological anti-angiogenic therapy with cisplatin is being studied with pelvic radiotherapy in cervical cancer patients in RTOG 0417. Recurrent disease has been shown to respond to bevacizumab: therefore, there is promise for this novel therapy (Wright 2007). Bevacizumab is being investigated in an ongoing GOG phase III trial for recurrent and metastatic cervical cancer. Phase II studies (Cannistra 2007, Burger 2007) of bevacizumab in patients with persistent or recurrent ovarian cancer show activity as some patients had complete or partial tumor responses. Therefore, bevacizumab is also the investigational agent in two ongoing phase III trials in the post-operative treatment of ovarian cancer.

The goal of this phase II study in post-operative endometrial cancer patients at high risk of local and distant relapse is to evaluate toxicity with the addition of anti-angiogenic treatment with bevacizumab, given concurrently with IMRT and cisplatin chemotherapy followed by systemic adjuvant therapy with carboplatin and paclitaxel chemotherapy. The goal of IMRT is to decrease some of the toxicity that might be attributable to standard external-beam radiation. Toxicity will be evaluated as the primary end point, and the trial will include a transitional research component.

1.2.6 Safety Profile

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia.

The major bevacizumab-associated adverse events identified in phase I to phase III trials include hypertension, proteinuria, arterial thromboembolic events, hemorrhage, congestive heart failure (CHF), gastrointestinal perforations, and wound healing complications. Other serious adverse events (SAEs) observed with bevacizumab therapy include reversible posterior leukoencephalopathy syndrome and fistula formation.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE terms is included in Section (7.2.14) of the protocol. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

- *Infusion-Related Reactions*

  Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%) including rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

- *Hypertension*

  Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% (all grade) across trials, with a mean increase of +5.5mmHg to +8.4mmHg for systolic pressure, or +4.1mmHg to +5.4mmHg for diastolic pressure. Incidence of grade 3 (hypertension requiring initiation of or increase in hypertensive medications) ranges from 7.8 to 17.9%.

  Grade 4 hypertension (hypertensive crisis) occurred in up to 0.5% of bevacizumab-treated patients.

  Hypertension associated with bevacizumab can generally be controlled with routine oral drugs during treatment. However, rare incidents of hypertensive crisis with encephalopathy (including RPLS – reversible posterior leukoencephalopathy syndrome) or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with standard medical practice

(Chobanian 2003). Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

- *Proteinuria*
  Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from mild asymptomatic increase in urine protein (incidence of about 38%) to rare instances of grade 3 proteinuria (> 3.5gm/24-hour urine) (3%) or nephrotic syndrome (1.4%). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. The risk of proteinuria may be higher in patients with advanced RCC or history of hypertension. There is also evidence from dose-finding trials that the rate of proteinuria may be dose-related.

  Proteinuria will be monitored by urine protein: creatinine (UPC) ratio before each treatment. If the UPC ratio is not available, a dipstick urinalysis may be used before treatment is allowed to proceed.

- *Hemorrhage*
  Overall, there were grade 3 or 4 bleeding events in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types. The hemorrhagic events noted in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

  Tumor-associated hemorrhage: Serious tumor-associated bleedings has been observed in patients with lung, colorectal cancer, pancreatic and gastric cancer, CNS metastases, hepatoma, or varices treated with bevacizumab.

  Mucocutaneous hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

  There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as the vagina or gingival.

- *Arterial Thromboembolic Events (ATE)*
  The risk of arterial thromboembolic events is increased with bevacizumab therapy; such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction (MI), and other peripheral or visceral arterial thrombosis. A pooled analysis of five randomized studies showed a two-fold increase in these events (3.8% vs. 1.7%). ATE led to a fatal outcome in 0.8% patients with bevacizumab vs. 0.5% without bevacizumab. The rate of cerebrovascular accidents (including TIA) was 2.3% vs. 0.5%, and the rates of MI 1.7% vs. 0.7%. Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Skillings 2005). In patients $\geq$65 years of age treated with bevacizumab and chemotherapy, the rate of ATE was approximately 8.5%.

  Aspirin is a standard therapy for primary and secondary prophylaxis of ATE in patients at high risk of such events, and ≤325 mg daily was allowed in the five randomized studies discussed above, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and ATE events, retrospective analyses of the effect of aspirin on the risk of ATE were inconclusive. Further analyses of the effects of concomitant use of bevacizumab and aspirin are ongoing.

- *Venous Thromboembolism (VTE) (including deep venous thrombosis, pulmonary embolism and thrombophlebitis)*
  In the Phase III pivotal trial in metastatic CRC, there was a slightly higher rate of VTE in patients treated with chemotherapy + bevacizumab compared with chemotherapy alone (19% vs. 16%). The incidence of NCI-CTC Grade≥ 3 VTEs in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%).

In clinical trials across all indications the overall incidence of VTEs ranged from 2.8% to 17.3% in the bevacizumab arms compared to 3.2% to 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE compared with chemotherapy alone. However, patients with mCRC who receive bevacizumab and experienced VTE may be at higher risk for recurrence of VTE.

- *Gastrointestinal Perforation*
  GI perforations/fistula were rare but more frequent among patients whose therapy included bevacizumab. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab but 0.3% in patients receiving IFL alone. GI perforation has also been reported in non-CRC tumors (e.g. gastric/esophageal, pancreatic and ovarian cancers) or nonmalignant conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

- *Fistula*
  Fistula formations, including events resulting in death, have been observed in patients receiving bevacizumab in clinical studies and post-marketing reports. Fistulae in the GI tract are common (1-10% incidence) in patients with certain metastatic tumors such as colorectal cancer or ovarian cancer, but uncommon (0.1-1%) or rare (0.01-0.1%) in other conditions.

  In addition, fistulae that involve areas other than the GI tract have also been observed (e.g. tracheoesophageal, bronchopleural, urogenital, biliary). Events were reported at various time points during treatment, ranging from 1 week to 1 year following initiation of bevacizumab, with most events within the first 6 months of therapy.

- *Wound Healing Complications*
  Bevacizumab delays wound healing in rabbits and may also compromise or delay wound healing in humans. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab.

  The interval between surgery and initiation of bevacizumab required to avoid elevated risk of impaired wound healing has not been determined. Across metastatic CRC trials, at least 28 days must have elapsed following major surgery before bevacizumab could be initiated; data suggested that initiation of bevacizumab 29-60 days following surgery did not increase the risk of wound-healing complications compared to chemotherapy alone.

  If patients require elective major surgery, bevacizumab should be discontinued 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure. In the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, chemotherapy should be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery.

- *Congestive Heart Failure (CHF)*
  The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment.

  Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO showing a normal ejection fraction.

- *Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES) or similar leukoencephalopathy syndrome*
  RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely been reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and visual disturbance or cortical

blindness, with or without associated hypertension. MRI scans are required for diagnosis. [Typical findings are vasogenic edema (enhanced intensity in T2 and FLAIR sequences on non-contrast MRI) predominantly in the white matter of the posterior parietal and occipital lobes, and less frequently, in the anterior distributions and the gray matter].

RPLS/PRES is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important to prevent irreversible tissue damage. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker 2006; Oscan 2006).

- *Neutropenia*
  In the phase III trial with IFL +/- bevacizumab in colorectal cancer, Grade 3-4 neutropenia was 21% with bevacizumab + IFL vs. 14% with IFL (Grade 4 neutropenia was 3% vs. 2%). Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab. In a phase III trial in NSCLC, the carboplatin and paclitaxel + bevacizumab arm was associated with an increased rate of grade 4 neutropenia (27% vs. 17%), febrile neutropenia (5.4% vs. 1.8%), and infection with neutropenia (4.4% vs. 2.0%), with three fatal cases (Sandler 2006).

- *Additional Adverse Events*
  See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

- *Breastfeeding*
  As an IgG1 antibody, bevacizumab may also be secreted in human milk. Therefore, women should avoid breastfeeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, ranging from 11 to 50 days).

- *Immunogenicity*
  As a therapeutic protein, bevacizumab has the potential for immunogenicity. Given the limited sensitivity of the currently available assay, high titers of human anti-bevacizumab antibodies have not been detected in any of the approximately 500 patients treated with bevacizumab.

2.0 OBJECTIVES

2.1 Primary Objective

To assess the Grade 3+ non-hematologic treatment-related adverse event rate within 90 days from the start of treatment when administering concurrent bevacizumab, cisplatin and IMRT followed by carboplatin and paclitaxel chemotherapy in patients with high-risk endometrial cancer.

2.2 Secondary Objective(s)

2.2.1 To evaluate treatment-related adverse events occurring within 1-year from start of treatment
2.2.2 To evaluate all treatment-related adverse events
2.2.3 To evaluate disease-free and overall survival
2.2.4 To evaluate local, regional and distant failure

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (2/21/11)

3.1.1 Patients must have undergone a hysterectomy (total abdominal, vaginal, robotic-assisted, radical, or laparoscopic-assisted vaginal hysterectomy) for carcinoma of the uterus within 56 days prior to study entry. Patients must also have had a bilateral salpingo-oophorectomy.

3.1.2 Patients must have confirmed uterine cancer with one of the following: (**Note**: Overlap of disease characteristics below may occur and is permitted)
- o Grade 3 carcinoma with greater than 50% myometrial invasion; all papillary serous and clear cell carcinoma will be considered Grade 3.
- o Grade 2 or 3 carcinoma with any cervical stromal invasion
- o Known extra-uterine disease confined to the pelvis, any grade

3.1.3 Endometrioid endometrial adenocarcinoma, clear-cell carcinoma, papillary serous adenocarcinoma, adenosquamous carcinoma, or other adenocarcinoma variant histologies

3.1.4 Patients must have Zubrod performance status 0-1

3.1.5 Age ≥ 18

3.1.6 History/physical examination including normal post-operative exam within 56 days prior to study entry.

3.1.7 Patients must have adequate bone marrow, renal and hepatic function; as indicated by the following laboratory assessments within 21 days prior to study entry:
- ANC ≥ to 1500cells/mm³; without use of growth factors
- Platelets ≥ 100,000/mm^3;
- Serum creatinine ≤ 1.5 mg/dl
- Total bilirubin ≤ 1.5 times institutional upper normal limit
- Hemoglobin ≥ 10 g/dl; (transfusion may be used to meet this criterion)
- AST and ALT ≤ 2 times institutional upper normal limit.

3.1.8 Urine protein screened by the Urine Protein Creatinine (UPC) ratio within 14 days prior to study entry. Patients must have a UPC ratio <1.0.

3.1.8.1 Obtain at lease 4 ml of a random urine sample in a sterile container (does not have to be a 24-hour urine). Request separate urine protein and creatinine levels; the lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPC ratio is calculated using one of the following formulae:
- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.1.9 INR < 1.5 for patients treated with Warfarin within 14 days prior to study entry

3.1.10 To assess the abdomen and pelvis, CT or PET-CT of the abdomen and pelvis within 56 days of study entry.

3.1.11 To assess the chest for all patients regardless of stage, a chest x-ray or chest CT or PET-CT within 56 days of study entry.

3.1.12 Patients must sign a study-specific informed consent.

3.2 Conditions for Patient Ineligibility (2/21/11)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease-free for a minimum of 3 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

3.2.2 Carcinosarcoma

3.2.3 Metastatic extrauterine disease, gross/residual disease (not including pelvic nodal disease), or distant metastases

3.2.4 Positive common iliac or positive para-aortic nodal disease (radiologically LN ≥ 2cm in any dimension or biopsy-proven)

3.2.5 Prior systemic chemotherapy for uterine cancer; note that prior chemotherapy for a different cancer is allowable; see section 3.2.1. Patients on chemotherapy for a non-malignant condition at the time of initiation of trial chemotherapy will be excluded.

3.2.6 Prior external-beam radiotherapy to the pelvis that would result in overlap of radiation therapy fields

3.2.7 Severe, active comorbidity as follows:

3.2.7.1 Unstable angina and/or congestive heart failure (NYHA ≥ grade II) requiring hospitalization within the last 12 months

3.2.7.2 Transmural myocardial infarction within the last 12 months

3.2.7.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of study entry

3.2.7.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of study entry

3.2.7.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects

3.2.7.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. Excluding patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.2.7.7 Active GI ulcers, GI bleeding, inflammatory bowel disease, or GI obstruction.

3.2.7.8 Inadequately controlled hypertension defined as systolic >150 and/or diastolic > 90 on hypertensive medications

3.2.7.9 Significant vascular disease including aortic aneurysm, aortic dissection or arteriovenous malformation, within 12 months of study entry.

3.2.7.10 Serious cardiac arrhythmia on medication (well-controlled atrial fibrillation on medication is allowed)

3.2.7.11 Serious non-healing wound, ulcer, or bone fracture

3.2.8 Neuropathy > CTCAE Grade 1 (per section 7.9) at the time of study entry

3.2.9 Ototoxicity > CTCAE Grade 2 (per section 7.9) at time of study entry.

3.2.10 History of arterial thromboembolic events, including transient ischemic attack (TIA), or clinically symptomatic peripheral artery disease within 12 months of study entry

3.2.11 Major surgical procedure requiring open biopsy incision or significant trauma within 28 days prior to study entry or anticipation of need of any surgical activity during the course of the study excluding vascular access to device placement or procedures that do not require significant incision

3.2.12 History of abdominal fistula, GI perforation or intra-abdominal abscess within 6 months prior to study entry.

3.2.13 History of organ transplant

3.2.14 Any history of hypertensive crisis or hypertensive encephalopathy

3.2.15 History of stroke/cerebrovascular event (CVA) within 12 months of study entry

3.2.16 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies

3.2.17 Mental status changes or bladder problems that make patient unable to comply with bladder-filling instructions.

3.3.18 Mental or psychiatric illness that would prevent informed consent.

3.2.19 Prior allergic reaction to bevacizumab, cisplatin, carboplatin or paclitaxel

3.2.20 Patients who require the use of warfarin sodium >1 mg daily. Low-molecular weight heparin is allowed at prophylactic dosages at any time during this protocol.

3.2.21 Breastfeeding

3.2.22 Prior therapy with Anti-VEGF compounds

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (2/21/11)

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

See Appendix II; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 Alkaline phosphates, Mg, BUN, and electrolytes, (Na, K, Cl, HCO3), must be obtained and recorded ≤21 days prior to study entry.

4.1.2 Audiogram when there is a history of hearing loss

4.2 Highly Recommended Evaluations/Management

4.2.1 Lymphadenectomy is encouraged, but not required.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for IMRT Treatment Approach

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Institutions granted previous approval by RTOG to participate in RTOG IMRT head and neck or RTOG IMRT pelvis studies may enroll patients on this study without further credentialing. Please note all institutions must complete a "Dry-Run" test as

described in Section 5.1.2. Visit http://rpc.mdanderson.org/rpc and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.1.2 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Each institution must submit and successfully complete a protocol-specific Dry-Run Test (the treatment plan for the FIRST PATIENT to be treated at the site on this protocol), and a Rapid Review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The Dry-Run Test will be reviewed by the ITC. The Rapid Review will be conducted by the RTOG and suggestions regarding protocol compliance will be forwarded to the participating institution.

The treatment plans for subsequent patients enrolled at a site are required to be reviewed prior to treatment, but a review will be performed for protocol compliance at a later date. Instructions for submitting the dry run can be found on the ATC website (http://atc.wustl.edu). RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients into this study.

5.2 Pre-Registration Requirements for LDR or HDR Brachytherapy Treatment Approach

Only physicians who have completed the Knowledge Assessment Questionnaire for LDR or HDR Brachytherapy available from the RPC website (http://rpc.mdanderson.org) may treat patients with LDR or HDR brachytherapy on this study.

Upon review and successful completion, the Radiological Physics Center (RPC) will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter subsequent patients into this study.

5.3 Regulatory Pre-Registration Requirements (7/14/10)

5.3.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
  IRB/REB approved consent (English and native language versions*)
  ***Note**: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

All pre-registration requirements must be met before registering the first case.

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.3.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.3.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.3.3.1 **For institutions that do not have an approved (letter of Intent) LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.3.3.2 **For institutions that have an approved LOI for this protocol:**
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

Please refer to your LOI Approval Notification.

Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

5.4 Registration

5.4.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

IMRT treatment is mandatory on this protocol.

Radiation should begin no sooner than 29 days and no later than 56 days after hysterectomy

Please refer to the RTOG Gynecological Atlas for volume specifications. The Atlas may be accessed on the RTOG website at: http://www.rtog.org/gynatlas/main.html.

GTV=gross tumor volume (nodal boost)
PTV=planning target volume (vaginal and nodal)
CTV=clinical target volume (nodal)
ITV=internal target volume (vaginal)

6.1 Dose Specifications

6.1.1 Prescription dose will be according to the following specifications:

6.1.1.2 The vaginal planning target volume (PTV) (ITV with 7mm margin) and nodal PTV (nodal CTV with 7-mm margin) will receive 45 Gy in 25 fractions. Treatment will be delivered once daily, 5 fractions per week, over 5 weeks. Both target regions will be treated simultaneously with the same dose. Breaks in treatment should be minimized.

6.1.1.3 The dose is prescribed to cover 97% of the vaginal PTV and nodal PTV. A volume of 0.03 cc within any PTV should not receive > 110% of the prescribed dose. No more than 0.03 cc of any PTV will receive < 93% of its prescribed dose. Any contiguous volume of 0.03 cc or larger of the tissue outside the vaginal/nodal PTVs must not receive > 110% of the dose prescribed to the vaginal/nodal PTV.

6.1.1.4 Patients who have enlarged pelvic lymph node(s) that are ≥ 2cm in any dimension on the diagnostic or planning CT or biopsy proven to be positive may receive 8 additional fractions (at the discretion of the treating radiation oncologist) to the enlarged node(s) in 1.8Gy daily fractions for a total dose of 59.4 Gy to the nodal boost PTV.

6.2 Technical Factors

6.2.1 Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. The use of custom-made compensators is acceptable as long as dose specifications and constraints are satisfied.

6.2.2 A megavoltage beam of 6 MV or greater must be used, with a minimum source-axis distance of 100 cm. The exception is the use of a tomotherapy unit that uses 80 cm.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patients will be immobilized in the supine position in an immobilization device. Patients should be immobilized in a cradle that fixes the position of at least the upper body, trunk and proximal legs. Patients will be treated in the immobilization device.

6.3.2 Treatment planning CT scans will be required to define tumor, clinical and planning target volumes. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment

6.4 Treatment Planning/Target Volumes (7/14/10)

6.4.1 Two separate treatment-planning CT scans (full-bladder and empty-bladder CT scans, as described below) are required (must be submitted) and then should be fused together prior to outlining target volumes. If two CT scans cannot be performed, the patient cannot participate in this protocol. The patient will be instructed to drink 32 ounces of fluid 30-60 minutes before simulation:

- A CT scan simulation will be performed with the full bladder, and
- A second CT will be performed after the patient has voided for the empty-bladder scan.
- Both CT scans must be submitted (see Section 12.2)

6.4.2 For post-operative patients with no gross disease, there should not be a gross tumor volume (GTV). Patients with residual nodal disease will have a nodal boost GTV (section 6.4.13).

6.4.3 The Clinical Target Volume (CTV) is defined as regions at risk for harboring potential microscopic disease, delineated by the treating physician.

6.4.4 Internal Target Volume (ITV) is defined as the volume of the vagina that is in both the empty- and full-bladder CT scans that are done at the time of simulation and fused together. This volume accounts for internal organ motion. Institutions that cannot acquire two CT scans (full- and empty-bladder) and delineate an ITV will not be allowed to enroll patients into this protocol. It will be considered an unacceptable deviation if the institution is unable to do two scans but uses IMRT.

6.4.5 The Planning Target Volume (PTV) will provide a 7-mm margin around the ITV to compensate for the variability of treatment setup. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

6.4.6 IMRT planning will be done on the full-bladder scan with full heterogeneity correction enabled in the treatment planning system.

6.4.7 The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose volume histogram (DVH) analyses of the vaginal ITV and nodal PTV and critical normal structures. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissues.

6.4.8 Planning Priorities

- Dose to nodal PTV and vaginal ITV are the most important planning priorities, followed by the goal dose to critical structures.
- The priorities in addressing the protocol aims and constraints are in Critical Structures (see section 6.5)

6.4.9 Nodal CTV

The nodal CTV should include lymph nodes that drain the involved site and adjacent perinodal soft tissue, including the internal (hypogastric and obturator), external, and common iliac lymph nodes to the level of L4/5.

Identification of the nodal CTV begins with the identification of the iliac vessels. The nodal CTV will include the vessel, perinodal tissue, and pertinent clips. The CTV of the nodes should end 7 mm from L4/L5 interspace to account for the PTV. The PTV for nodes should stop at the L4/L5 interspace.

For patients with cervical involvement (stage II disease), presacral lymph nodes and soft tissues should be included as well, down to the level of S3.

(See GYN atlas for examples: http://www.rtog.org/gynatlas/main.html.)

Exclusions from the nodal CTV contour (these structures should be removed from the nodal CTV contour):

- Psoas and piriformis muscle on the pelvic side wall or adjacent to clinically negative lymph nodes
- Bone
- Intraperitoneal small bowel
- The most antero-lateral external iliac lymph nodes that lie just proximal to the inguinal canal should be excluded from the CTV (i.e., the nodal CTV should stop immediately at the level of the femoral head).

Patients with enlarged nodes contoured (nodal GTV) will not have these exclusions; however, if small bowel lies within 2cm of the nodal GTV, this bowel will be excluded.

6.4.10 The vaginal CTV will account for internal organ motion as an ITV (section 6.4.4). The ITV should encompass the vagina and paravaginal soft tissues drawn after fusion of the full and empty bladder scans. The inferior limit of the vaginal ITV should cover at least 3 cm of the vagina, or at least 1 cm below the obturator foramen. The inferior limit may be individualized based on inferior spread of the patient's tumor on prior pre-operative physical examination and post-operative pathology reports. The lateral margin of the vaginal PTV (ITV + 7mm) should be to the obturator muscle. Patients should be treated with a full bladder, as this may push small bowel out of the field.

6.4.11 The nodal PTV will provide a 7-mm margin (anterior, posterior, lateral, superior and inferior) around the nodal CTV. The vaginal PTV will be 7.0 mm around the vaginal ITV (anterior, posterior, lateral, superior and inferior) around the vaginal ITV.

6.4.12 The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing Recording and Reporting Photon Beam Therapy and 1999 ICRU Report #62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50).

6.4.13 The nodal GTV will consist of the enlarged node (≥ 2 cm in any dimension) contoured as seen on the planning CT scan. The nodal boost PTV will provide a 7-mm margin (in all dimensions)

around the nodal boost GTV. The nodal boost PTV will NOT exclude the structures listed in section 6.4.9 except for small bowel.

6.5 Critical Structures (2/21/11)

6.5.1 Critical Structure Contouring

Normal structures will be contoured using the full-bladder CT scan.

6.5.1.1 *Bladder*

Bladder will be outlined on every slice, including the portion inferior to the planning target volume.

6.5.1.2 *Rectum/Sigmoid*

Rectum will be outlined on every slice, including the portion inferior to the planning target volume and superior to include the sigmoid to the level that it leaves the posterior pelvis.

6.5.1.3 *Bowel*

Bowel (small and large) excluding the rectum/sigmoid will be outlined on every slice, including up to 2 cm above the planning target volume and no more. It will include the volume surrounding loops of bowel out to the edge of the peritoneum because the bowel may lie within this space at any time during the course of treatment.

6.5.1.4 *Femur*

The femoral heads should be contoured on all slices.

6.5.2 Critical Structure Treatment Planning Dose Constraints

Per protocol:

- Bowel (small and large): 30% of the entire bowel volume must not receive more than 40 Gy.
- Rectum/Sigmoid: 60% of the recto-sigmoid volume must receive ≤ 40 Gy.
- Bladder: 35% of the bladder volume must receive ≤ 45 Gy
- Femoral head: 15% of the femoral head volume must receive less than 35 Gy

6.5.3 Use of Contrast to Identify Critical Structures

IV contrast may be used during simulation to help better define the vessels; however, it is not required. Oral contrast to opacify the small bowel is allowed at the physician's discretion. Rectal contrast is not allowed, because it may cause anatomical distortion.

6.5.4 All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 3 mm or smaller through the region that contains the primary target volumes and at least 4 mm in the regions above and below the target volumes. The superior limit will be at least at the L3/4 interspace and inferior limit will be below the perineum.

6.5.5 The ITV and CTV and normal tissues must be outlined on all CT slices in which the structures appear on the full-bladder scan. ITV contours will be drawn to include the excursion of target tissues as demonstrated on the empty-bladder scan (ITV). Using the full-bladder scan, all normal tissues will be outlined on all CT slices in which the CTV and ITV appear and on at least 7 slices (21 mm) above and below the target

6.5.6 Lymph node groups at risk to be contoured for the nodal CTV include the following:

- The lower common iliac nodes: the CTV should be contoured up to 7 mm from the top of L5. Therefore, the superior limit of the contoured common iliac PTV will be at the top of the L5 vertebral body.
- Internal iliac (obturator and hypogastric) nodes in entirety
- External iliac nodes - the CTV contour will stop at the most superior aspect of the femoral heads
- For patients with cervical involvement (FIGO stage II), the presacral node CTV contour will extend posteriorly to the S2/S3 interspace.
- The obturator nodes: the CTV contour will extend inferiorly to the upper third of the obturator fossa

6.5.7 The following contours must be submitted for evaluation:

- *Vaginal CTV bladder full*
- *Vaginal CTV bladder empty*
- *Vaginal ITV*
- *Vaginal PTV*
- *Nodal CTV*
- *Nodal PTV*
- *Bladder*
- *Rectum*

- *Bowel*
- *Femoral Heads*

6.6 Documentation Requirements

Verification orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal images that localize the isocenter placement shall be obtained and digitally submitted to the ITC. The portal imaging process should be repeated every five days. The initial set of images should be digitally submitted. Another set of portal images should be submitted from the middle of the patient's fractionated treatment, and images from the final portal imaging process should also be digitally submitted to the ITC. Though institutions are discouraged from using radiographic film if radiographic film is used, it must be scanned and submitted as jpeg images. For data submission, please refer to Section 12.2.

6.6.1 The ITC will display isodose distributions through the planning target volume to verify correct digital submission and conversion.

6.6.2 The ITC will compare the submitted digital dose-volume histograms (DVHs) for the PTVs, the designated critical structures and unspecified tissues with the DVHs calculated by the ITC.

6.7 Compliance Criteria (11/6/09)

6.7.1 Compliance Criteria for Treatment Interuptions

Per Protocol: Interruption of 0 days

Variation Acceptable: Interruption of 1-7 consecutive days

Deviation Unacceptable: Interruption of > 8 consecutive days

6.7.2 Compliance Criteria for Target Volumes

All maximum dose limits are stated for a volume 0.03 cc (approximately 3x3x3 mm) or larger.

Vaginal PTV

- Per protocol: The prescription criteria in Section 6.1.1.2 and 6.1.1.3 are fulfilled.
- Variation Acceptable: The 0.03 cc volume for the PTV exceeds 110% of the prescribed dose but remains at or below 115%. The minimum dose within any PTV (defined for a volume that is 0.03 cc or larger) falls below 93% but is ≥ 91% of prescribed dose.
- Deviation Unacceptable: A total of 0.03 cc of the PTV receives a dose that is over 115% of the prescribed dose. The minimum dose within any PTV (defined for a volume that is 0.03 cc or larger) falls below 91%.

Nodal PTV

- Per Protocol: The prescription criteria are fulfilled.
- Variation Acceptable: A volume of 0.03 cc of the PTV exceeds 110% of the prescribed dose but remains at or below 115%. The minimum dose within any PTV (defined for a volume that is 0.03 cc or larger) falls below 93% but is ≥ 91% of its prescribed dose.
- Deviation Unacceptable: A volume that is 0.03 cc of the PTV receives a dose that is over 115% of the prescribed dose. The minimum dose within any PTV (defined for a volume 0.03 cc or larger) falls below 91%.

6.7.3 Compliance Criteria for Normal Tissues

6.7.3.1 *Bowel*

Per Protocol: 30% of the volume must not receive more than 40 Gy

Variation Acceptable: 30% to receive more than 40Gy but less than 45 Gy

Deviation Unacceptable: 0.03 cc or larger above 65 Gy and more than 30% > 45 Gy

6.7.3.2 *Rectum*

Per Protocol: 60% of the rectal volume must receive ≤ 40 Gy

Variation Acceptable: 60% to receive 40 Gy but less than 45 Gy.

Deviation Unacceptable: 0.03 cc or larger above 65 Gy and more than 60% > 45 Gy

6.7.3.3 Bladder

Per Protocol: 35% of the bladder volume must receive ≤ 45 Gy

Variation Acceptable: 35% to receive 45 Gy but less than 50 Gy.

Deviation Unacceptable: 0.03 cc or larger above 65 Gy and more than 35% > 50 Gy

6.7.3.4 *Femoral Head*

Per Protocol: 15% of the femoral head volume must receive less than 35 Gy

Variation Acceptable: no more than 50% > 35 Gy

Deviation Unacceptable: 0.03 cc or larger above 65 Gy and more than 50% > 35 Gy

All maximum dose limits are stated for a volume 0.03 cc (approximately 3x3x3 mm) or larger.

These dose constraints allow for the increased dose given with the nodal boost for patients with gross nodal disease.

6.8 Intracavitary Radiotherapy Technique and Dose Specifications (optional treatment) (7/14/10)

6.8.1 If a vaginal brachytherapy boost is given, it should follow the external beam irradiation and be started within two weeks of completion of the pelvic irradiation. Either high-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy may be used. For HDR brachytherapy, more than one insertion may be performed per week. External-beam radiation and intracavitary treatment should not be given on the same day. Iridium (HDR) or cesium (LDR) sources are to be used for intracavitary application with vaginal applicators.

6.8.2 The length (in cm) of treated vagina is at the discretion of the treating physician.

6.8.3 For LDR applications: a dose of 25 Gy prescribed to the vaginal surface at a dose rate of 0.8 to 1.2 Gy per hour. Colpostats or cylinders may be used. The largest possible cylinder diameter should be selected. Colpostats should be secured with maximal packing in order to minimize dose to the adjacent bladder and rectum.

6.8.4 For HDR applications, three applications of 6 Gy should be prescribed to the vaginal surface. This will give a total of 18 Gy.

6.8.5 A report on the source specifications, strengths, spacings relative to the applicators, size of applicator, and dosimetry calculations for all points is mandatory. Dwell times and dwell positions for all HDR insertions are also required. For all films that are submitted, the points of dose calculations should be marked on the film (vaginal surface points) as well as the rectal point if calculated. If cylinders are used and source specification and applicator size do not change, dose distributions may be made on only the first cylinder if desired. Dose to the vaginal surface from ovoid (colpostat) should include the contribution from both ovoids.

- Vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid or cylinder (Appendix VII).
- Dose points 0.5 cm posterior to the cylinder or colpostat should be calculated and recorded as the rectal dose point (Appendix VII).

6.9 R.T. Quality Assurance Reviews (11/6/09)

The Radiation Oncology Chair, Akila Viswanathan, M.D., MPH, will perform a rapid RT Quality Assurance Review PRIOR TO START OF RADIATION TREATMENT after complete data for the first case enrolled from each institution has been received (see Section 12.0). Remaining cases will be reviewed on an ongoing basis as RT treatment data is received. The RT Quality Assurance Review must be completed before the primary endpoint results can be submitted for presentation at a meeting (or if going directly to manuscript, before submission to a journal).

6.10 Radiation Therapy Adverse Events

Side effects expected from radiation therapy include fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, darkening of skin in the treatment portal, and low blood counts. Common long-term effects include vaginal narrowing, shortening and dyspareunia. Long-term side effects, although uncommon, may include rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, and vaginal vault necrosis. Rare long-term effects include bowel obstruction, urethral obstruction, and vesicovaginal or rectovaginal fistula.

All toxicities will be recorded on data collection forms.

6.11 Radiation Adverse Event Reporting

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. These types of events involving RT only must be reported via the AdEERS RT-only pathway.

The following must be reported via the AdEERS RT-only pathway:

	Grade 3		Grade 3		Grade 4 & 5	Grade 4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

Note:
- All grade 4 and 5 adverse events (AEs) that occur during or within 30 days after the completion of radiation therapy (RT), regardless of causation, must be reported within 5 days;
- Grade 4 and 5 AEs that occur in follow up (beyond 30 days after the completion of RT but still within the timeframe of follow up of the patient on study) and that are thought to be probably or definitely related to RT (e.g., radiation-induced spinal cored myelopathy) must be reported within 5 days.

7.0 DRUG THERAPY (11/6/09)

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Concurrent treatment must begin no sooner than 29 days and no later than 56 days after hysterectomy.

7.1 Treatment (2/21/11)

Note: The dose will be calculated using the patient's actual body weight; the dose will be recalculated if there is a weight change of ≥ 10% from baseline.

Bevacizumab will be administered prior to cisplatin, and radiotherapy may be given either before or after chemotherapy

If Bevacizumab or Cisplatin is held for toxicity the missed treatments are not completed after RT ends. No further bevacizumab or Cisplatin will be administered during brachytherapy or after completion of external radiotherapy.

Refer to section 7.2.10 for method of administration for Bevacizumab

7.1.1 Concurrent Chemoradiation

Agent	Dose	Route	Schedule
Bevacizumab	5 mg/kg	IV	every 2 weeks (on days 1, 15, & 29) during chemoradiation; prior to cisplatin Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose (DAY 15) over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer the final dose (DAY 29) over a minimum of 30 minutes.
Cisplatin	50 mg/m^2	IV	1-hour infusion days 1 and 29.

7.1.2 Adjuvant Chemotherapy

To start 4-6 weeks following completion of radiation therapy. A cycle is defined as 21 days.

Drug	Dose	Schedule
Paclitaxel	135 mg/m^2, maximum dose at BSA 2 m^2	IV over 3 hours, every 21 days x 4; to be given prior to carboplatin
Carboplatin	AUC 5	IV over 1-hour, every 21 days x 4

7.2 Study Agent: Bevacizumab (rhuMAb VEGF, Avastin®) NSC# 704865 (2/21/11)

7.2.1 Classification

Recombinant humanized monoclonal antibody

7.2.2 Molecular Weight

Approximate molecular weight is 149,000 daltons

7.2.3 Mode of Action

Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

7.2.4 Description

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions

7.2.5 How Supplied

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection, USP.

7.2.6 Preparation

Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

7.2.7 Storage

Upon receipt, refrigerate bevacizumab (2^o to 8^o C). Do not freeze. Do not shake.

7.2.8 Stability

Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry. Once diluted in 0.9% sodium chloride, administer solutions of bevacizumab within 8 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

7.2.9 Route of Administration

Intravenous

7.2.10 Method of Administration

Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose (DAY 15) over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer the final dose (DAY 29) over a minimum of 30 minutes. Premedications are administered as per institutional protocol.

If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

1. When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

Please note: the flush is not included in the total recommended infusion times.

7.2.11 Dose Definition

The dose of bevacizumab is 5mg/kg of actual body weight. The dose will be calculated using the patient's actual body weight; the dose will be recalculated if there is a weight change > 10% from baseline.

7.2.12 Duration of Treatment

Bevacizumab will be administered in 3 cycles, on days 1, 15, and 29. Cycles 1 and 3 will be administered on the same day as cisplatin chemotherapy. Bevacizumab will be administered prior to cisplatin, and radiotherapy may be given either before or after chemotherapy.

7.2.13 Special Precautions/Safety Issues (7/14/10)

- Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and RPLS. Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in (Section 7.6.1).
- Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.
- Infusional reactions: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.
- Hypertension: Patients should have BP monitored prior to each infusion of bevacizumab. Hypertensive mediation should be initiated or increased for optimal BP control according to standard public heath guidelines.
  - Proteinuria: Proteinuria should be monitored by urine protein: creatinine (UPC) ratio before each treatment.
    - If the UPC ratio is < 3.5 treatment will be continued, if the UPC is > 3.5 bevacizumab will not be given, but held until the UPC ration has declined to < 3.5. If the patient completes external beam radiation prior to the UPC ratio recovering to < 3.5, bevacizumab will be discontinued. No bevacizumab will be administered after the completion of radiation.
- Surgery and wound complication issues: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high-risk procedures such as liver resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

7.2.14 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. Below is the CAEPR for bevacizumab (rhuMAb VEGF).

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	***Myocardial infarction***
	Supraventricular tachycardia		***Supraventricular tachycardia***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Colitis		
	Constipation		***Constipation***
Diarrhea			***Diarrhea***
	Dyspepsia		***Dyspepsia***
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage[3]***
		Gastrointestinal perforation[4]	
		Gastrointestinal ulcer[5]	
	Ileus		
	Mucositis oral		***Mucositis oral***
Nausea			***Nausea***
Vomiting			***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
	Infusion related reaction		***Infusion related reaction***
	Non-cardiac chest pain		***Non-cardiac chest pain***
	Pain		***Pain***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[6]		***Infection[6]***
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		***Wound dehiscence***
INVESTIGATIONS			
	Alanine aminotransferase		***Alanine aminotransferase***

	increased		***increased***
	Alkaline phosphatase increased		***Alkaline phosphatase increased***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased***
	Blood bilirubin increased		***Blood bilirubin increased***
	Cardiac troponin I increased		
	Neutrophil count decreased		***Neutrophil count decreased***
	Weight loss		***Weight loss***
	White blood cell decreased		***White blood cell decreased***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[7]		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
Headache			***Headache***
		Intracranial hemorrhage	***Intracranial hemorrhage***
		Ischemia cerebrovascular	***Ischemia cerebrovascular***
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Hematuria		***Hematuria***
	Proteinuria		***Proteinuria***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Renal and urinary disorders - Other (renal failure)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Epistaxis		***Epistaxis***
	Hoarseness		***Hoarseness***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
	Respiratory, thoracic, and mediastinal disorders - Other (rhinitis)		***Respiratory, thoracic, and mediastinal disorders - Other (rhinitis)***
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus***
	Skin and subcutaneous tissue		***Skin and subcutaneous tissue***

	disorders - Other (rash)		***disorders - Other (rash)***
	Urticaria		***Urticaria***
VASCULAR DISORDERS			
Hypertension			***Hypertension***
	Thromboembolic event		***Thromboembolic event***
		Vascular disorders - Other (arterial thromboembolic event)[8]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal ulcer includes: Duodenal ulcer, Esophageal ulcer, Gastric ulcer and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[7]Metaphyseal dysplasia was observed in ***young patients who still have active epiphyseal growth plates.***

[8]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GASTROINTESTINAL DISORDERS - Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Osteonecrosis of jaw
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin ulceration

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2.15 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

Accountability and Supply

The Principal Investigator (or authorized designee listed by the Investigator on the site's most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution may request bevacizumab from NCI's Pharmaceutical Management Branch (PMB). The updated version (11/10/03) of each institution's Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time. PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612.

Investigator's Brochures may be obtained from PMB for investigational agents where CTEP holds the IND. To receive an Investigator's Brochure, you must be an active participant on an NCI-sponsored clinical trial and have an active investigator registration status. Contact the IB Coordinator at IBCoordinator@mail.nih.gov or 301-496-5725, Monday through Friday, from 8:30 a.m. to 4:30 p.m. Eastern time.

7.2.16 Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.3 Study Agent: Cisplatin (2/21/11)

7.3.1 Source and Formulation

Cisplatin is commercially available from Bristol-Myers Oncology as a dry powder supplied in 10 mg and 50 mg vials, and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride; 10 mg/vial. The 10 mg and 50 mg vials should be reconstituted with 10 mL or 50 mL sterile water for injection USP, respectively. Each mL of the resulting solution will contain 1 mg of cisplatin. Reconstitution of powder results in a clear colorless solution when completed as recommended.

NOTE: 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.

7.3.2 Administration

Patients will be pre-hydrated per institutional guidelines. Cisplatin will be dissolved at a concentration of 1 mL of sterile water/mg of drug, and the solution will be administered intravenously. Supportive treatment will be given according to institutional policy.

7.3.3 Storage and Stability

Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature. The aqueous solution should be stored at room temperature and protected from light. The reconstituted solution is stable for 20 hours at room temperature.

NOTE: Once reconstituted, the solution should be kept at room temperature. If the reconstituted solution is refrigerated, a precipitate will form.

7.3.4 Adverse Events

Incidence rates of adverse events associated with cisplatin are provided in the product package insert. The following events are expected with the administration of cisplatin:

- *Nephrotoxicity:* Dose-related and cumulative renal insufficiency is the major dose-limiting adverse events associated with cisplatin. Renal adverse events have been noted in 28-36% of patients treated with a single dose of 50 mg/m^2. It is first noted in the second week after a dose and is manifested as elevated BUN, creatinine, and serum uric acid, or as a decrease in creatinine clearance. Because renal adverse events become more prolonged and severe with repeated courses of cisplatin, renal function must return to normal before another dose can be given. Serum magnesium levels should be monitored and kept within normal limits
- *Ototoxicity:* Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m$^{2.}$ It is manifested by tinnitus and or hearing loss in the high-frequency range. Deafness has been reported only rarely.
- *Hematologic Toxicity:* Myelosuppression occurs in 25-30% of patients treated with cisplatin. Nadirs in circulating platelets and leukocytes occur between days 18 and 23 with most patients recovering by day 39. Thrombocytopenia, anemia, neutropenia, and fever are also possible adverse events.
- *Gastrointestinal Toxicity:* Marked nausea and vomiting occur in almost all patients treated with cisplatin. Diarrhea and anorexia have also been reported.
- *Neurotoxicity:* Neurotoxicity usually characterized by peripheral neuropathies, has been reported. Neuropathy usually occurs after prolonged therapy (4 to 7 months); however, symptoms have been reported after a single dose. Muscle cramps, loss of taste, seizures, autonomic neuropathy, dorsal column myelopathy, and Lhermitte's sign have also been reported.
- *Ocular Toxicity:* Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or dose frequencies higher than those recommended in the package insert.
- *Anaphylactic-like Reactions:* Anaphylactic-like reactions have occasionally been reported in patients previously exposed to cisplatin. Symptoms include facial edema, wheezing, tachycardia, and hypotension.
- *Hepatotoxicity:* Transient elevations in liver enzymes, especially serum glutamic oxaloacetic transaminase (SGOT) or aspartate transaminase (AST) and bilirubin have been reported.

- *Other Toxicities:* Other infrequent toxicities that have been reported include cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, and asthenia. Rare cases of local soft tissue adverse events have also been reported.

7.3.5 Mechanism of Action

Primarily causes inhibition of DNA synthesis and, to a lesser degree, inhibition of RNA and protein; it has not been shown to be cell cycle-specific.

7.3.6 Pharmaceutical Data

Cisplatin (cis-diamminedichloroplatinum II) has the empiric formula N2CL2 PtH6. It is a planar inorganic compound with a molecular weight of 300; soluble in water at a concentration of 1 mg/mL. The (II) nomenclature denotes the (active) valence state of the platinum. The interatomic distance of the chlorides is 3.3A, which is different from the 5-7A interatomic distance of the classic alkylating agents. Only the dis-isomer is therapeutically active.

7.3.7 Supply

This drug is commercially available.

7.3.8 Duration of Administration

Cisplatin is administered on days 1 and 29 during external-beam radiotherapy. Radiotherapy will continue if toxicity is specifically attributable to cisplatin. Cisplatin chemotherapy will not be administered after radiotherapy is completed.

7.3.9 Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.4 Study Agent: Paclitaxel

Paclitaxel is a natural product obtained via a semi-synthetic process from *Taxus baccata*. As the study will be using generic paclitaxel, please consult the appropriate package insert for details on administration of the brand of paclitaxel used, including any pre-medication information.

7.4.1 Dose Definition

The dose of paclitaxel is 135 mg/m^2, with maximum body surface area (BSA) of 2.0 m^2. The dose will be recalculated if there is a weight change ≥10% from baseline.

7.4.2 Formulation

The following information is provided for Taxol® (paclitaxel). Paclitaxel is supplied as a nonaqueous solution that must be diluted prior to use. It is available in 5 mL (30 mg) single-dose vials, and 16.7 mL (100 mg) and 50 mL (300 mg) multi-dose vials. Each mL contains 6 mg of paclitaxel, 527 mg of Cremophor EL (polyoxyethylated castor oil) and 49% (v/v) dehydrated alcohol, USP.

7.4.3 Preparation

Paclitaxel should be diluted to a final concentration of 0.3 to 1.2 mg/mL in either 0.9% sodium chloride or 5% dextrose. The diluted paclitaxel solution will show a slight haziness that is proportional to the concentration of drug and the time elapsed since preparation. A solution that exhibits excessive particulate formation should be discarded.

The paclitaxel solution must be prepared in glass, polypropylene, or polyolefin due to the leaching of diethylhexylphthalate (DEHP) plasticizer when polyvinyl chloride bags are used. Non-PVC tubing and connectors, such as those that are polyethylene-lined, must be used during administration of paclitaxel. In-line filtration should be performed using a hydrophilic; microporous filter of pore size not greater than 0.22 microns (e.g., IVEX-HP and IVEX-II, Abbot).

7.4.4 Storage and Stability

Intact vials of paclitaxel are stable until the date indicated on the package if stored at temperatures ranging from 2-25˚C (36-77˚F) and protected from light. The product can be refrigerated or frozen without affecting quality; any precipitates that form upon refrigeration will redissolve upon reaching room temperature. If the solution remains cloudy after agitation, it should be discarded.

When prepared as described above, 0.3-1.2 mg/mL solutions of paclitaxel are stable for 27 hours.

7.4.5 Supply

Commercial supplies of paclitaxel will be used for this trial.

7.4.6 Adverse Events Associated With Paclitaxel

Incidence rates of adverse events associated with paclitaxel are provided in the product package insert. The following events are expected with the administration of paclitaxel:

- *Hematologic*: Myelosuppression is the major dose-limiting toxicity. Neutropenia is both dose- and schedule-dependant and typically resolves rapidly. Fever is common, and infectious episodes are seen in about 1/3 of the patients receiving paclitaxel. Thrombocytopenia is uncommon and the cases that occur are usually mild to moderate. Bleeding episodes may occur. While anemia is common, it is severe in only 16% of cases.
- *Allergic reactions*: Although patients are premedicated, hypersensitivity reactions still occur in approximately 40% of patients receiving paclitaxel (20% of cycles). Severe reactions are rare and generally occur within the first hour of administration; no severe reactions have been reported after the third cycle. The most common symptoms observed in severe reactions include dyspnea, flushing, chest pain, and tachycardia. Minor hypersensitivity reactions include flushing, rash, hypotension, dyspnea, tachycardia, and hypertension. Desensitization per the allergy team is allowed.
- *Cardiovascular*: Cardiovascular events observed with paclitaxel therapy include hypotension and bradycardia; typically, neither discontinuation of Paclitaxel® nor specific therapy for the event is required. Cardiovascular events possibly related to paclitaxel therapy occur in approximately 1% of patients and include syncope, rhythm abnormalities (asymptomatic ventricular tachycardia, bigeminy, and complete AV block requiring a pacemaker), hypertension, and venous thrombosis.
- *Neurologic*: The frequency and severity of neurologic events are dose- and schedule-dependent. Mild peripheral neuropathy is seen frequently, but severe symptoms are rare and may cause of paclitaxel discontinuation in 1% of patients. Sensory symptoms usually improve or resolve within several months of discontinuation. Serious neurologic events, such as grand mal seizures, syncope, ataxia, and neuron-encephalopathy, are rare.
- *Gastrointestinal*: The most common GI toxicities, which include nausea, vomiting, diarrhea, and mucositis, are typically mild or moderate. Mucositis is schedule-dependent and occurs more frequently with a 24-hour infusion than a 3-hour infusion of paclitaxel.
- *Other*: Although 60% of all patients experience arthralgia and myalgia, there is no consistent relationship between the dose or schedule of paclitaxel and the frequency of these events. The symptoms, which usually begin 2 or 3 days after paclitaxel treatment, are generally transient. Injection site reactions are more common with the 24-hour infusion of paclitaxel and are typically mild, consisting of erythema, tenderness, skin discoloration, or swelling at the injection site. Almost all of the patients receiving paclitaxel experience alopecia, but nail changes are uncommon. Edema may occur, but it is rarely severe enough to lead to discontinuation of treatment.

7.4.7 Administration

The regimen can be administered in an outpatient setting. Paclitaxel will be administered in a 3-hour infusion followed by carboplatin over 30 minutes. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin)which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. An antiemetic regimen is recommended. The antiemetic regimen used should be based on peer-reviewed consensus guidelines per institutional protocol. It is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen could include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine) given prior to administration of paclitaxel.

7.4.8 Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.5 Study Agent: Carboplatin (PARAPLATIN®) (10/14/10)

Carboplatin is a platinum compound used as a chemotherapeutic agent.

7.5.1 Formulation

Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol.

7.5.2 Supply

Commercial supplies of Carboplatin® will be used in this trial.

7.5.3 Preparation

When available, prediluted vials of carboplatin should be utilized. Otherwise, the preparation of carboplatin should proceed as described below:

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL:

Vial size	Diluent volume
50 mg	5mL
150 mg	15 mL
450 mg	45 mL

Carboplatin reacts with aluminum to form a precipitate and cause a 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 carboplatin.

7.5.4 Storage and Stability

Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30˚C or 59-86˚F) and protected from light. When prepared as described above, Carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

7.5.5 Adverse Events Associated With Carboplatin

- *Hematologic*: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leucopenia, and anemia are common, but typically resolve by Day 28 when carboplatin is given as a single agent.
- *Allergic reactions*: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy. Desensitization per the allergy team is allowed.
- *Neurologic*: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.
- *Gastrointestinal*: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.
- *Hepatic toxicity*: Elevated alkaline phosphatase, total bilirubin, and SGOT have been reported.
- *Other*: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

7.5.6 Carboplatin Administration

Carboplatin will be infused intravenously over 1-hour. The dose of carboplatin is area under the curve (AUC) 5. The dose of carboplatin is calculated as follows, using the Calvert formula based on creatinine clearance: Total dose (mg) = Target AUC (in mg/mL per min) x (Estimated GFR + 25). The GFR used in the Calvert formula should not exceed 125 ml/min, so the maximum carboplatin dose should not be more than the target AUC x 150, which is 750 mg of carboplatin for an AUC of 5 and 600 mg for an AUC of 4 in this protocol.

In the absence of new renal obstruction or other renal toxicity greater than or equal to CTCAE (per Section 7.9) grade 2 (serum creatinine >1.5 x ULN), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification as noted. If the creatinine at the time of a dose modification is lower than the original creatinine value used to

calculate the previous dose, use the previous (higher) creatinine. If the creatinine at the time of dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine.

In patients with an abnormally low serum creatinine (≤ 0.6 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.6 mg/dl. If a more appropriate baseline creatinine value is available within 4 weeks of treatment that may also be used for the initial estimation of GFR, but again the minimum value to be used for calculation of the GFR should be 0.6 mg/dl.

Note:
The carboplatin dose is calculated in mg, not mg/m^2.
The initial target AUC for carboplatin treatment in this trial is AUC=5.
Do not use any correction factors to calculate the carboplatin dose, use only the Cockcroft – Gault and Calvert formula as described in this paragraph.
Creatinine clearance (CrCL) can either be measured, or estimated using the Cockcroft-Gault formula.

Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = 0.85 \times \frac{(140\text{-age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}$$

When concerned about safety in a specific patient, measure the GFR

Carboplatin AUC of 5 over 1-hour, Day 1, q 21 days for 4 cycles, administered after paclitaxel. Do not exceed the maximum total dose of 750 mg

7.5.7 Non-Canadian International Institutions
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.6 Dose Modifications for Concurrent Therapy (7/14/10)

7.6.1 Dose Modification for Bevacizumab
Note: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below:

If a scheduled dose of bevacizumab is missed because of a holiday period, it may be resumed (along with cisplatin) as soon as possible within 1 week. Holding the treatment for more than 2 weeks indicates significant toxicity and the patient should then be considered off protocol treatment.

Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE Grade (per Section 7.9)	Action to be Taken
Allergic reactions, Or Acute infusional reactions / cytokine release syndrome	Grade 1 – 2	If bevacizumab causes an infusion related or allergic reaction, the following steps should be taken: For patients with Grade 1 and 2 reactions, premeds (H1 and H2 blocker, Decadron 10 mg I.V. or institutional protocol) should be given with the next attempted dose on the following day and again before the next regularly scheduled infusion; the infusion time may not be reduced for the subsequent infusion. Follow the guidelines in the Section 7.2.10 for bevacizumab administration.

	Grade 3	For patients with Grade 3 reactions, bevacizumab infusion should be stopped and the patient observed for an hour. Plans should be made to administer the drug the following day with these precautions: Dexamethasone 10 mg p.o. 12 and 6 hours before the planned infusion, H2 blocker famotidine 20 mg IV/p.o. or alternative 1 hour before bevacizumab, H1 blocker diphenhydramine 25-50 mg IV or p.o. or alternative 1 hour prior to treatment. Bevacizumab infusion time should be increased by 30 minutes and should not be decreased for the subsequent treatments. The patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.
	Grade 4	Discontinue bevacizumab
Arterial Thrombosis • Cardiac ischemia/infarction • CNS ischemia (TIA, CVA) • Any peripheral or visceral arterial ischemia / thrombosis	≥ Grade 2	Discontinue bevacizumab
Venous Thrombosis	Grade 3 OR Asymptomatic Grade 4	Discontinue bevacizumab if full-dose anticoagulation is required (warfarin, unfractionated heparin, or low-molecular weight heparin)
	Grade 4 (symptomatic)	Discontinue Bevacizumab
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice.]	
	Controlled BP	Continue bevacizumab
	Symptomatic or persistent HTN with systolic >160 or diastolic >90 mm Hg	Hold bevacizumab. If treatment is delayed for >2 weeks due to uncontrolled hypertension, discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Wound dehiscence requiring medical or surgical intervention		Discontinue bevacizumab
GI perforation, GI leak, or ANY fistula (GI or other)		Discontinue bevacizumab
Hemorrhage	Outside the radiation field Grade 3	• For patients not requiring full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hg is stable for 3 days at 10.0 g/dl - There is no bleeding diathesis that would increase the risk of therapy. - There is no anatomic or pathologic condition that could increase the

		risk of hemorrhage recurrence. Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
Other clinically significant AEs attributable to bevacizumab (except controlled nausea/vomiting)	Grade 3	Hold bevacizumab until symptoms resolve to ≤ grade 1. If treatment delay is >2 weeks due to toxicity, discontinue bevacizumab.
	Grade 4	• Discontinue bevacizumab • Upon consultation with the study chair, resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to ≤ grade 1 and is unlikely to recur with further treatment.
Reversible posterior leukoencephalopathy syndrome (RPLS)		Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.
UPC ratio < 3.5 UPC ratio ≥ 3.5 Nephrotic syndrome	 Grade 4	Continue bevacizumab Hold bevacizumab until UPC recovers to < 3.5 Discontinue bevacizumab

7.6.2 Dose Modifications for Cisplatin
Based on blood work performed prior to each cycle

Toxicity	Threshold	Modification
Serum creatinine	≥ 1.5 mg/dl	Hold chemotherapy, repeat blood chemistry in one week; if below threshold then resume at 40 mg/m^2; if not, hold for 1 more week. If still above threshold, discontinue chemotherapy.
ANC	< 1000 mg/m	Hold chemotherapy, re-check in 1 week, if patient still on radiation therapy proceed at 50 mg/m^2, otherwise omit this dose
Platelets	< 100,000	Hold chemotherapy, re-check in 1 week, if patient still on radiation therapy proceed at 50 mg/m^2, otherwise omit this dose
Bilirubin	≥ 2 x ULN*	Hold for that week and repeat blood chemistry 2 days before next scheduled dose; treat only if below threshold
ALT/AST	≥ 3 x ULN*	Hold for that week and repeat blood chemistry 2 days before next scheduled dose; treat only if below threshold.
Platinum-related neuropathy	≥ grade 2	Discontinue chemotherapy
Ototoxicity	≥ grade 2	Discontinue chemotherapy
Febrile neutropenia	Temp 38.5˚C w/AGC < 1,000	Hold chemotherapy, use G-CSF for 3 days; if AGC>1,000 the following week, resume chemotherapy 50 mg/m2

*ULN = upper limit of institutional normal

7.6.2.1 If chemotherapy is held, radiation therapy will continue.

7.6.2.2 If radiation therapy is interrupted and held, chemotherapy will also be held.

7.6.2.3 If bevacizumab or cisplatin is held for toxicity, the missed treatments will not be completed after RT ends. No further bevacizumab or cisplatin will be administered during brachytherapy or after completion of external radiotherapy.

7.6.2.4 If a scheduled dose of bevacizumab is missed because of a holiday period, it may be resumed (along with cisplatin) as soon as possible within 1 week. Holding the treatment for more than 2 weeks would otherwise indicate significant toxicity, and the patient should then be considered off protocol treatment.

7.6.2.5 In the event of a bevacizumab-related AE, standard therapy with cisplatin and radiation should continue as scheduled.

7.6.2.6 In the event of a cisplatin-related AE for an allergic reaction, tinnitus, neuropathy or hearing loss, bevacizumab should be continue on days 15 and 29 with radiation.

7.6.2.7 In the event of a cisplatin-related AE for creatinine elevation, neutropenia or thrombocytopenia, bevacizumab should be discontinued.

7.6.2.8 If cisplatin or bevacizumab-related AE result in a delay in RT beyond day 29, bevacizumab, cisplatin and RT will resume once RT resumes provided the side effects have resolved.

7.6.2.9 If cisplatin and radiation are permanently discontinued because the AE does not recover within 3 weeks, the patient will be removed from the protocol and no further protocol therapy will be administered.

7.7 Dose Modification for Adjuvant Therapy (2/21/11)

7.7.1 Dose Modification for Carboplatin/Paclitaxel

The adjuvant treatment course will not begin until all toxicities, (except anemia, ≥ grade 2) have resolved to grade 0 or 1. There will be no dose escalations in this study. Once a patient is dose-reduced, dose escalation is not permitted and the patient should continue on this dose for all subsequent cycles.

Initial treatment modifications will consist of cycle delay and/or dose reduction as directed. Treatment decisions will be based on absolute neutrophil count (ANC) not total white blood cell count (WBC). No treatment course will begin or resume until ANC is ≥ 1500 cells/mm^3 (CTCAE grade 1 (per Section 7.9)) and platelet count is ≥ 100,000/mm^3. Treatment will be delayed for a maximum of 21 days until values are achieved. A patient who fails to recover adequate counts in the 21-day period will not receive further protocol-directed chemotherapy.

7.7.1.1 *Delayed Hematologic Recovery*

If ANC is less than 1,500 cells/mm^3 (CTCAE grade 2 or worse (per Section 7.9)) within 24 hours prior to chemotherapy, therapy will be delayed. If platelet count is less than 100,000 cells/mm^3 within 24 hours prior to chemotherapy, therapy will be delayed. Patients who have a > 7-day delay in recovery of ANC to greater than 1500 cells/m^3 will receive G-CSF with the next cycle. Treatment will be delayed for a maximum of 21 days until values are achieved. Patients who fail to recover adequate counts in the 21-day period will not receive further protocol-directed chemotherapy.

7.7.1.2 Febrile neutropenia (ANC < 1000/mm3) or prolonged (> 7 days) grade 4 neutropenia after the previous treatment course should trigger growth factor administration after the following course. If the symptoms recur, the dose of paclitaxel and carboplatin will be decreased by one level in addition to the administration of growth factor. If the symptom recurs, the patient will not receive further chemotherapy.

7.7.1.3 *Paclitaxel Hypersensitivity Reaction*

Hypersensitivity reactions during administration of paclitaxel usually occur in the first few minutes of infusion. Appropriate symptomatic therapy should be given per the treating physician institution's protocol. Consideration for continued treatment should be given if the reaction is not considered life-threatening. If the patient decides to continue treatment, it is preferable to re-treat that same day, but treatment the following day is also acceptable. A suggested re-treatment would be to administer the drug first with 1 cc of the original IV solution diluted in 100 cc over 1 hour, then 5 cc in 100 cc over 1 hour, then 10 cc in 100 cc over 1 hour and finally the original solution at the normal speed. Patients who elect not to have immediate (same day/following day) re-treatment with paclitaxel may be given carboplatin only that day, but they would be candidates for paclitaxel hypersensitivity rechallenge at the next cycle per their institution's protocol.

Dose Level Modification for Carboplatin/Paclitaxel

Drug	Starting dose level	Dose Level -1
Paclitaxel	135 mg/m^2	110 mg/m^2
Carboplatin	AUC 5 (750 mg or less)	AUC 4 (600 mg or less)

* Patients who require more than 1 dose reduction will be removed from protocol treatment.

TOXICITY	PARAMETERS	MODIFICATION
Febrile neutropenia/ ANC and platelets	1st febrile neutropenia or ANC <500 mm^3 lasting >7 days AND grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding	Reduce carboplatin one dose level. No modification for Paclitaxel. Resume treatment when ANC > 1500 cells/m^3 and platelets > 100,000 cells/mm^3 Administer Neulasta 24-72 hours after the next course of chemo.
	2nd	Discontinue protocol therapy.
TOXICITY	PARAMETERS	MODIFICATION
Febrile neutropenia/	1st occurrence febrile	No dose reduction. Administer Neulasta 24-72hours

ANC only	neutropenia or ANC<500 mm^3 lasting >7 days	after this course of chemo.
	2nd occurrence	Reduce paclitaxel and carboplatin one dose level Resume treatment when ANC > 1500 cells/m^3 and platelets > 100,000 cells/mm^3 and administer Neulasta 24-72 hours after this course of chemo
	3rd occurrence	Discontinue protocol therapy.
Neutropenia	Grade 4 uncomplicated (no fever/infection) lasting <7 days	No dose modifications.
Platelets only	1st occurrence grade 4	Reduce carboplatin one dose level Resume treatment when ANC > 1500 cells/m^3 and platelets > 100,000 cells/mm^3
	2nd	Reduce paclitaxel one dose level Resume treatment when ANC > 1500 cells/m^3 and platelets > 100,000 cells/mm^3
	3rd	Discontinue protocol therapy.
	1st occurrence grade 3 associated with bleeding	Reduce carboplatin one dose level Resume treatment when ANC > 1500 cells/m^3 and platelets > 100,000 cells/mm^3
	2nd	Reduce paclitaxel one dose level Resume treatment when ANC > 1500 cells/m^3 and platelets > 100,000 cells/mm^3
	3rd	Discontinue protocol therapy.
	Grade 3 uncomplicated (absence of associated bleeding)	No dose modifications.
GI	Any grade	No dose modifications. Hold only if persistent nausea and vomiting occurs on the day of chemotherapy prior to treatment being given.
Serum creatinine	≥Grade 2 (less than 2.0 mg/dl)	Hold treatment; when recovered to Grade 1, resume, reducing carboplatin one dose level. If not recovered to ≤Grade 1 within 21 days, discontinue protocol therapy.
	>2.0 mg/dl	Discontinue protocol therapy.
	≥Grade 3	Discontinue protocol therapy and notify study chair.
TOXICITY	PARAMETERS	MODIFICATION
Neurotoxicity-peripheral neuropathy	≥Grade 3	Reduce paclitaxel and carboplatin one dose level and delay subsequent therapy for up to 21 days until recovered to Grade 1. If not recovered within 21 days, discontinue protocol therapy.
	2nd occurrence	Discontinue protocol therapy.
SGOT/SGPT/Total Bilirubin/ alkaline phosphatase	Grade 2	Hold treatment; when recovered to ≤ Grade 1, resume reducing paclitaxel one dose level.
SGOT/SGPT/Total Bilirubin/ alkaline phosphatase	≥Grade 3	Discontinue protocol therapy.
Alopecia, fatigue, myalgias	Any grade	No modification.

Other non-hematologic toxicity	≥Grade 3	Hold treatment until recovered to Grade 1. If not recovered to ≤Grade 1 within 21 days, discontinue protocol therapy.

7.7.1.4 *Dose Adjustments With Multiple Toxicities*
If patients experience multiple toxicities, the greatest dose reductions for one or both drugs should be used.

++Please note that if paclitaxel is held, carboplatin should also be held.

7.8 Modality Review

The Gynecologic Oncology Co-Chair, Brigitte Miller, M.D., will perform a Systemic Therapy Quality Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Miller will perform a review after complete data for the first 10 cases enrolled have been received at RTOG Headquarters and will continue the reviews on an ongoing basis until completion. The Systemic Therapy Quality Assurance Review must be completed before the primary endpoint results can be submitted for presentation at a meeting (or if going directly to manuscript, before submission to a journal).

7.9 Adverse Events (2/21/11)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.9.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.10 also must be reported via AdEERS.**

"In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site."

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.9.2 Serious Adverse Events (SAEs) — **All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.**

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the AdEERS ticket number, study/case numbers, the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.**

7.9.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or, 3) Treatment related secondary malignancy.

7.10 AdEERS Expedited Reporting Requirements

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent [Bevacizumab] in this Study

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 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 an agent under a CTEP IND require reporting as follows:

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

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

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

Please see exceptions below under section entitled "Additional Instructions or Exceptions."

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 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 via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND [Bevacizumab]:

The following SAEs will be exempted from expedited reporting through AdEERS (they should still be reported in the routine AE CRFs)

- G3-4 Venous thromboembolism
- G3-4 Neutropenia/febrile neutropenia, regardless of hospitalization
- G3-4 Diarrhea, Nausea, Vomiting, or Dehydration, regardless of hospitalization

7.11 Clinical Trials Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator (http://ctep.cancer.gov/industry/ipo.html) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for

immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator=s confidential/ proprietary information.

8.0 SURGERY

All patients will undergo surgery for their cancer within 56 days prior to enrolling in this protocol

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Antiemetics per the treating institution's protocol
9.1.2 Antidiarrheals per the treating institution's protocol
9.1.3 Analgesics, including aspirin per the treating institution's protocol
9.1.4 Hematopoietic Growth Factors, except erythropoietin, as specified in the protocol
9.1.5 Nutritional supplementation per the treating institution's protocol
9.1.6 Low-molecular weight heparin is allowed at prophylactic dosages at any time during this protocol.
9.1.7 Warfarin at <1mg dose until 2 weeks after radiation is completed
9.1.8 Herbal products except St John's Wort
9.1.9 Proton pump inhibitors per the treating institution's protocol
9.1.10 Upper endoscopy as clinically directed

9.2 Non-permitted Supportive Therapy

9.2.1 Warfarin > 1mg daily
9.2.2 Erythropoietin
9.2.3 St John's Wort
9.2.4 Anticoagulants at therapeutic doses
9.2.5 Aminoglycoside antibiotics
9.2.6 Amifostine

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies

integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking and translational research.

10.2 Fixed Tissue Specimen Collection for Banking and Translational Research (Highly Recommended) (2/21/11)

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I)

In this study, we will isolate RNA and DNA from FFPE tumor tissue for array analysis. In addition tumor tissue microarrays will be created from the FFPE blocks to allow and perform immunohistochemistry analysis for gene expression. Evaluation of tumor specimens and the possibility of creating a tissue array allows for easy simultaneous staining for proteins of interest and TUNEL staining for apoptosis. MicroRNA and gene expression utilizing microarray technology has been evaluated in a wide variety of neoplasms. Microarray technology allows for the simultaneous evaluation of hundreds of microRNAs and thousands of genes, creating a "snap shot" of the pathways activated in the tumor. The ultimate goal of these studies will be to identify tumor signatures that predict for patient outcomes such as toxicity, disease-free survival and overall survival. Better prediction of these outcomes could eventually help guide treatment and create a "genetically tailored' treatment approach.

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 One H&E stained slide

10.2.2 A paraffin-embedded tissue block of the tumor or three 2-mm diameter cores of tumor tissue, punched from the tissue block containing the tumor with punch tools and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or cores must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

See Appendix V for Specimen Plug Kit Instructions.

10.3 Peripheral Blood Collection for Banking and Translational Research (Highly Recommended) (7/14/10)

In this study from serum and plasma we will be able to measure levels of secreted factors, antibodies, microRNAs, tumor cells etc., giving insight into both initial levels of these factors as well as levels at the end of treatment, to determine if levels determine toxicity or outcome at either timepoint. Whole blood analysis will allow us to have the patient normal DNA to perform studies such as SNP (single nucleotide polymorphism) studies in each patient. SNPs are inherited differences in a person's DNA. There is mounting evidence that SNPs in genes important in DNA repair (oncogenes etc.) might either predict for a genetic predisposition to tumor formation itself or response to cytotoxic therapy.

For consenting patients, serum, plasma, and whole blood will be taken as follows:

- Serum and plasma: Prior to treatment and at the 6 month follow-up appointment.
- Whole blood: Prior to protocol treatment or at any time before, during, or after protocol treatment.

See Appendix V for Blood Collection Kit and Instructions.

10.4 Storage Conditions (7/14/10)

Store at –80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada: Mon-Tues).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only- Canada: Mon-Tues).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only- Canada: Mon-Tues).

10.5 Specimen Collection Summary (2/21/11)

Specimens taken from patient:	**Collected when:**	Submitted as:	Shipped:
One H&E stained slide of the primary tumor	Pre-treatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor or three 2 mm diameter cores of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsies	Block or punches shipped ambient
SERUM; 5-10mL of whole blood in 1 red-top tube and centrifuge for	Before treatment begins and at the 6 month follow-up	Frozen serum samples 0.5 mL per aliquot in 1 mL cryovials(five-ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Before treatment begins and at the 6-month follow-up	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) fand mix	At any time before, during, or after protocol treatment	Frozen whole blood samples containing 1mL per aliquot in 1mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

10.6 Submit materials for banking and translational research as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.7 Reimbursement (7/14/10)

RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement & Case Credit Schedule found on the RTOG Web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement

10.8 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.8.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.8.2 Specimens will be stored indefinitely. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, remaining material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix II.

11.2 Evaluation Criteria (2/21/11)

11.2.1 All patients will undergo weekly examinations during irradiation. Examination will include general physical assessment, performance status, assessment of bowel/bladder complaints and assessment of skin in the treated area.

11.2.2 At three months following the completion of radiation therapy, a pelvic examination will be performed to document the presence of disease. Suspected recurrent disease must be documented by biopsy

11.2.3 Complete blood count with differential and platelet count, total bilirubin, serum creatinine, AST, ALT, ALK PHOS, MG, BUN and electrolytes (Na, K, Cl, HCO3) every 6 months for 2 years then annually.

11.2.4 UPC ratio must be checked at the first post-treatment visit and must be checked at subsequent post-treatment follow-up visits only if the value is > 1.

See the bevacizumab dose modification table in Section 6.7.1 for UPC-related dose modifications.

11.2.5 Audiogram if there is a history of hearing loss.

11.2.6 Performance status will be defined according to the Zubrod Performance Scale. Toxicities from protocol treatment will be graded according to the revised NCI Common Toxicity Criteria, Version 4.0.

11.2.7 Efficacy Parameters

11.2.7.1 *Survival*: failure will be defined as death due to any cause and will be measured from date of study entry to death. Data for living patients will be censored at the date of last contact.

11.2.7.2 *Pelvic failure*: recurrence in the pelvis, which must be confirmed by histologic or cytologic biopsy of the recurrent lesion.

11.2.7.3 *Distant failure*: appearance of distant metastasis

11.2.7.4 *Progression-free survival*: failure will be defined as pelvic failure, distant failure, or death due to any cause and will be measured from date of study entry to date of first failure. Data for living patients without failure will be censored at the date of last contact.

11.3 Evaluation of Disease and Toxicity

Patients will be followed for disease status and for the appearance of chronic toxicity with history & physical examination that includes a pelvic exam. The follow-up examination schedule is every 3 months for 1 year, every 6 months for 2 years, and annually thereafter. A pap smear should be obtained at least yearly during follow-up. Appendix II lists all follow-up required. At each follow-up, every attempt should be made to document the histology of the recurrent tumor and clinical toxicities.

11.3.1 Toxicity Evaluation

Myelosuppressive toxicity shall be reported as the lowest observed WBC and platelet count. Anemia and red blood cell transfusions will be noted. Every effort will be made to obtain an autopsy on patients who die during or immediately after the study.

11.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease.
- Adverse events that require discontinuation of protocol treatment per protocol-specified dose modifications.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (11/6/09)

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

Item	Due
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Surgical Operative Report (S2)	
Surgical Pathology Report (S5)	
Concurrent Treatment Form (TF)	Within 1 week of completion of concurrent therapy
Adjuvant Treatment Form (SF)	Within 1 week of completion of adjuvant therapy
Follow-up Form (F1)	Every three months from end of RT for 1 year; then every six months for 2 yrs., then annually

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) (2/21/11)

Item	Due
Preliminary Dosimetry Information (DD)	
†Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist	Within 1 week of start of RT
Digital data submission includes the following:	
▪ CT data (include both empty and full bladder CT scans), critical normal structures, CTV, and PTV contours	
▪ Digital beam geometry for initial and boost beam sets	
▪ Doses for initial and boost sets of concurrently treated beams	
▪ Digital DVH data for all required critical normal	

structures, CTV, and PTVs for total dose plan	
▪ Three sets of portal or isocenter verification images (beginning, middle of fractionated treatment, and end) should be sent to the ITC in jpeg format.	
Digital Data Submission Information Form (DDSI) – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/ddsi/ddsi.html)	Within 1 week of start of RT
Hard copy isodose distributions for total dose plan (T6)	Within 1 week of start of RT
NOTE: Sites must notify ITC via e-mail (itc@castor.wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".	
Final Dosimetry Information	Within 1 week of RT end
Radiotherapy Form (T1) [copy to HQ and ITC]	Within 1 week of RT end
Daily Treatment Record (T5) [copy to HQ and ITC]	Within 1 week of RT end
Modified digital patient data as required through consultation with Image-Guided Therapy QA Center	Within 1 week of RT end

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@castor.wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

***Optional LDR or HDR Brachytherapy treatment (see section 6.8.5) data to be submitted to the RPC should include the complete brachytherapy treatment planning data and digital images or films INCLUDING AP and LATERAL views.**

Send by mail or FedEx to:

Radiological Physics Center (RPC)
Attention: Dosimetry
7515 South Main Street
Suite 300
Houston, TX 77030-4502

13.0 STATISTICAL CONSIDERATIONS (11/6/09)

13.1 Study Endpoints

13.1.1 Primary Endpoint

13.1.1.1 Treatment-related grade 3+ non-hematologic adverse events (CTCAE: per Section 7.9) occurring within 90 days after the start of treatment

13.1.2 Secondary Endpoints

13.1.2.1 Treatment-related grade 3+ non-hematologic adverse events (CTCAE: per Section 7.9) occurring within 1 year after the start of treatment

13.1.2.2 All treatment-related adverse events (CTCAE: per Section 7.9)

13.1.2.3 Overall survival (failure: death due to any cause)
13.1.2.4 Progression-free survival (failure: pelvic or distant failure or death due to any cause)
13.1.2.5 Pelvic failure (appearance of pelvic disease)
13.1.2.6 Distant failure (appearance of distant disease)

13.2 Study Design

13.2.1 Sample Size Derivation

This study is designed to estimate the rate of grade 3+ non-hematologic treatment-related adverse events (AEs), as graded by the CTCAE (per Section 7.9), occurring within 90 days from the start of IMRT+ cisplatin + bevacizumab. The rate of the acute specified AEs from RTOG 9708 (RT + cisplatin) was 44% and the hypothesis is that the addition of bevacizumab to IMRT + cisplatin will not increase this rate beyond 60%. This study will be designed with a 1-sided, upper bound confidence interval to estimate this AE rate. Twenty-seven evaluable patients will be required to have 95% confidence that the true grade 3+ non-hematologic treatment-related AE rate is not greater than 60%. To allow for ineligible/non-protocol treatment patients, **a total sample size of 34 patients will be required** for this study.

13.2.2 Patient Accrual

It is projected that there will be a period of approximately 6 months with very slow accrual at the beginning of this study to allow for both institutional IRB approval and IMRT credentialing by the RTOG QA center. Following this initial period, it is projected that the study will accrue 4 patients/month and that accrual will be completed in approximately 15 months from activation.

13.3 Fatal Adverse Event

If a fatal AE occurs (1) within 30 days of protocol treatment completion, regardless of relationship to protocol treatment or (2) at any time and is related to protocol treatment, the event will be reported to the study chairs and the RTOG GYN/Breast Committee Chair for GYN Cancer Trials for review. At this time it will be determined if accrual to the trial must be suspended pending this review for patient safety. The research associate will, after requesting additional supporting documentation if necessary, have all documents scanned and transmitted electronically to the study chairs and the head of the RTOG Data Safety Monitoring Board (DSMB) for their review. This will take place within 2 weeks of each reported adverse event if at all possible.

13.4 Analysis Plan

13.4.1 Interim Reports

Interim reports will be prepared every 6 months until the primary endpoint has been accepted for presentation or publication. Subsequently, these reports will be prepared yearly until collection of follow-up data is terminated. In general, these reports include:

- the patient accrual rate with projected completion date
- institutional accrual
- exclusion rates and reasons
- pretreatment characteristics
- compliance rates of treatment delivery with respect to the protocol prescription
- the frequency and severity of adverse events

13.4.2 CDUS Reports

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.3 Data Safety Monitoring Board (DSMB) Review

To monitor the safety of this study, it will be officially reviewed by the RTOG DSMB twice a year in conjunction with the RTOG semi-annual meeting and on an "as needed" basis in between meetings.

13.4.4 Analysis for Reporting the Initial Treatment Results

The analysis for reporting the initial primary endpoint results of treatment will be undertaken when each patient has been potentially followed for a minimum of 90 days from the start of treatment. Only patients that meet the eligibility requirements of this protocol and start protocol treatment will be included. The usual components of this analysis are:

- tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion
- patient accrual rate

- institutional accrual
- distribution of important prognostic baseline and other pretreatment variables
- frequency and severity of adverse events
- compliance rates of treatment delivery with respect to the protocol prescription
- observed results with respect to the endpoints described in Section 13.1.

13.4.5 Efficacy and Additional Adverse Event Analyses

Treatment-related grade 3+ AEs occurring within 1 year from start of treatment, all adverse events and the efficacy endpoints listed in 13.1.2, will be analyzed after each patient has been potentially followed for a minimum of 1 year. Pelvic failure and distant failure will be estimated using the cumulative incidence method (Kalbfleisch 1980). Progression-free survival and overall survival rates will be estimated using the Kaplan-Meier method (Kaplan 1958).

13.5 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered differences in prognosis by race and ethnicity. If the distributions allow, an exploratory statistical analysis will be performed to examine the possible differences between the among the race and ethnicity categories.

Gender and Minority Accrual Estimates

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	NA	2
Not Hispanic or Latino	32	NA	32
Ethnic Category: Total of all subjects	34	NA	**34**
Racial Category			
American Indian or Alaskan Native	0	NA	0
Asian	1	NA	1
Black or African American	3	NA	3
Native Hawaiian or other Pacific Islander	1	NA	1
White	29	NA	29
Racial Category: Total of all subjects	34	NA	**34**

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APPENDIX I

Informed Consent Template for Cancer Treatment Trials
(ENGLISH LANGUAGE)

RTOG 0921

A PHASE II STUDY OF POSTOPERATIVE INTENSITY-MODULATED RADIATION THERAPY (IMRT) WITH CONCURRENT CISPLATIN AND BEVACIZUMAB FOLLOWED BY CARBOPLATIN AND PACLITAXEL FOR PATIENTS WITH ENDOMETRIAL CANCER

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more information.

You are being asked to take part in this study because you have a newly diagnosed endometrial cancer and have had a hysterectomy.

Why is this study being done? (11/6/09)

The purpose of this study is to learn the effects (good and bad) of an anti-cancer drug called bevacizumab has when added to standard chemotherapy and intensity-modulated radiation therapy (IMRT) to treat your type of cancer.

Standard treatment for endometrial cancer involves the use of radiation and chemotherapy. This study adds bevacizumab to radiation and cisplatin. Bevacizumab may block cancer cells from making new blood vessels. It may also help standard chemotherapy and radiation work better.

Bevacizumab has been approved by the Food & Drug Administration for use in several other types of cancer. However, the use of bevacizumab with chemotherapy and radiation in endometrial cancer is experimental. Bevacizumab is the common name for the commercial drug Avastin®.

Standard radiation techniques cannot avoid delivering radiation to some of the normal tissues that surround the tumor. In this study, radiation will be given using a technique called IMRT. IMRT is an advanced delivery technique intended to lower the amount of radiation that the normal tissues receive, possibly reducing unwanted side effects. IMRT still delivers the desired amount of radiation to the areas that your doctor thinks may have cancer cells, such as lymph nodes.

How many people will take part in the study?

About 34 people will take part in this study

What will happen if I take part in this research study? (2/21/11)

Before you begin the study you will need to have the following exams, tests, or procedures. These procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical exam including height, weight, and your condition overall (called your performance status).
- Medical history review (questions about your health and current medications)
- Assessment by chest x-ray, CT scans (Computerized Tomography), or PET-CT within 8 weeks of your enrollment into the study.
- An assessment by CT or PET-CT of the abdomen
- Routine blood work.
- If you have a history of hearing loss, a hearing test called audiogram will be performed.

The following test is not a part of regular cancer care but is a normal test for people who receive the drug bevacizumab.

- A urine test to measure the amount of protein in your urine

If these tests show that you are eligible and you agree to participate, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

If you are entered onto this study, you will receive a combination of bevacizumab, cisplatin (a standard chemotherapy drug), and IMRT. After this treatment is completed you will also receive chemotherapy with two other drugs called paclitaxel and carboplatin. The treatment will be given as follows:

IMRT and Cisplatin: you will receive a radiation treatment lasting a few minutes a day, five days a week, for a period of five weeks. On days 1 and day 29, along with the radiation therapy, you will receive chemotherapy (as an outpatient) consisting of cisplatin through a tube in your vein (intravenously) over a one-hour period.

Your study doctor may decide that you should also receive a different type of radiation treatment known as a "vaginal cuff boost" or brachytherapy (insertion of radioactive "seeds" in hollow tubes) into your vagina. Brachytherapy comes in two forms, low-dose-rate and high-dose-rate. Low-dose-rate brachytherapy requires an inpatient hospital stay, whereas high-dose-rate brachytherapy is given as an outpatient (without being admitted into the hospital).

With a vaginal cuff boost, the physician temporarily places a radiation source inside your vagina to the treat the top of the vagina. The physician places an applicator, about the size of a large tampon containing a hollow tube, into the vagina, and then the radiation source goes through the hollow tube and treats the vagina. This internal treatment takes about 10 - 30 minutes for each of 3 high-dose-rate treatments and this procedure will be performed on an out-patient basis. One insertion occurs with low-dose-rate treatment, and the applicator stays in place while you are in the hospital for approximately 2 to 3 days. This type of radiation treatment is different from external

radiation treatment, and your study doctor will determine whether or not you should receive it.

Bevacizumab: On the same day as your first treatment with radiation and cisplatin, you will have your first treatment of bevacizumab. This is done by infusion into a vein over 90 minutes as an outpatient If you do not have any bad reactions to the first infusion, you will receive your second and third treatments of bevacizumab 2 and 4 weeks later using the same technique but each one will last only about 60 minutes.

Paclitaxel and Carboplatin: Approximately 4 to 6 weeks after you have completed your treatment with bevacizumab, cisplatin and radiation, you will receive your first dose of paclitaxel by infusion into a vein over 3 hours and carboplatin by vein over 1-hour. You will be given these treatments as an outpatient at 3-week intervals four times.

During the study: (7/14/10)

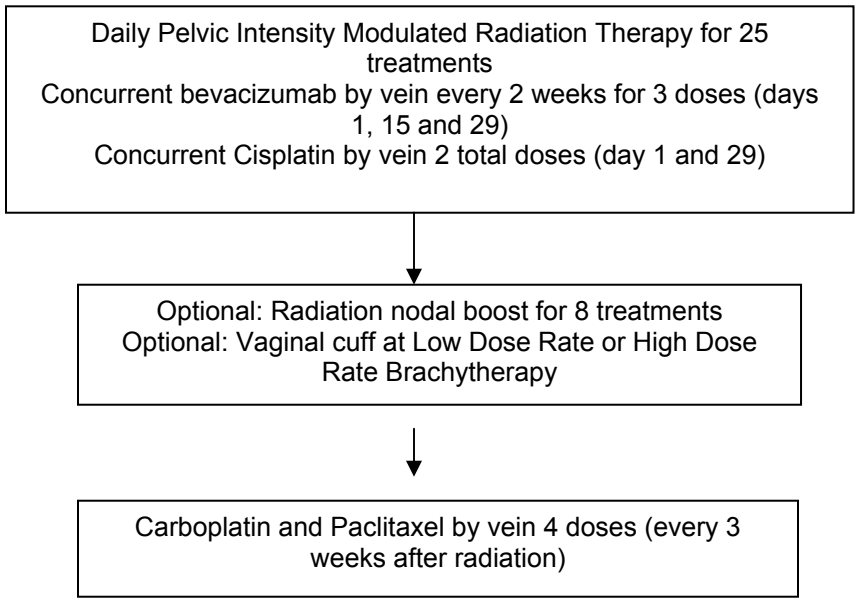
- You will be seen by your doctor before each chemotherapy session and after completion of all treatments to determine if you are having any side effects.
- You will be evaluated by the study doctor on a weekly basis during RT
- Your weight, vital signs and overall-well being will be recorded.
- A urine test will be done before the bevacizumab treatments to measure the amount of protein in your urine
- Blood tests will be done before the bevacizumab treatments and before each combination chemotherapy treatment.

Post-treatment evaluations:

- A physical exam will be performed every 3 months for the first year after the end of radiation, then once every 6 months for 2 years and then yearly thereafter.
- Every year you will have a Pap smear examination to test for tumor cells.
- Blood tests will be done every 6 months for the first 2 years, then yearly.
- Any side effects of treatment will also be assessed at each follow-up visit.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study? (11/6/09)

You will be asked to take radiation plus bevacizumab and cisplatin chemotherapy for 5 to 6 weeks. You will wait 4-6 weeks and then receive additional chemotherapy with carboplatin and paclitaxel for about another 4 months. You will be closely followed and your health assessed every week during therapy.

After you are finished with treatment, the study doctor will ask you to visit the office for follow-up exams every three months for one year as part of this protocol, and every 6 months for 2 years, then once every year thereafter.

The study doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- There are any problems with research funding or drug supply
- Your condition worsens; or
- Other unforeseen reasons

If you are removed from the research study, the study doctor will explain to you why you were removed.

Can I stop being in the study? (11/6/09)

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study? (11/6/09)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know yet all the possible side effects. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking treatment. In some cases, side effects can be serious, long-lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the radiation include those that are:

Likely

- Tiredness
- Diarrhea
- Nausea and vomiting
- Rectal irritation
- Urinary frequency or difficulty in urination
- Loss of pubic hair
- Reddening and irritation of the skin in the radiated area
- Decrease in blood counts that may cause infection, bleeding, and bruising

Less Likely

- Painful intercourse
- Vaginal narrowing and shortening

Rare but Serious

- Poor nutrition
- Rectal ulcer
- Bleeding or narrowing of the rectum
- Blood in the urine
- Bowel obstruction
- Damage to the vaginal wall, which could lead to a fistula (abnormal passageway between the bladder and the vagina or between the rectum)

- Long-term kidney damage leading to dialysis (separation of blood and toxins) if the lymph nodes are radiated
- Spinal cord damage leading to paralysis (if the lymph nodes are radiated)

Risks and side effects related to cisplatin include those that are:

Likely

- Decrease in blood counts that can lead to a risk of infection and bleeding
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Hearing loss or ringing in the ears
- Numbness or tingling in the hands or feet

Less Likely

- Muscle cramps or spasm
- Loss of coordination
- Involuntary movements or shaking
- Rash
- Vision problems
- Hair loss
- Low mineral levels in your blood
- Decrease in liver function causing temporary elevation in blood tests

Rare but Serious

- Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet
- A decrease in the kidneys' ability to handle the body's waste, which may be permanent
- Allergic reactions that can cause difficulty breathing, fast heartbeat, and sweating
- Another cancer called acute leukemia

Risks and side effects related to bevacizumab (7/14/10, 7/19/10)

Likely

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Less Likely

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation

- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare but Serious

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.

- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Risks and side effects related to paclitaxel (7/19/10)

Likely

- Lowering of blood counts. This could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You might need treatment with antibiotics, require hospitalization or transfusions if these problems are severe.
- Nausea and vomiting
- Numbness or tingling in the hands or feet
- Fatigue
- Complete hair loss

Less Likely

- Muscle aches and joint pain
- Muscle cramps or spasms
- Loss of coordination
- Involuntary movements or shaking
- Rash, itchiness, redness, hives
- Diarrhea
- Sores in your mouth
- Sore throat
- Swelling of your stomach and/or stomach lining
- Swelling of your colon
- Low or high blood pressure
- Vision problems
- Decrease in liver function causing temporary elevation in blood tests
- Skin irritation
- Changes in taste
- Light-headedness

Rare but Serious

- Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet
- Allergic reactions, which can cause difficulty in breathing, fast heartbeat, and sweating
- Slowing of your heart or irregular heart rhythm
- Swelling and/or failure of your liver
- Inflammation of the lungs
- Swelling of the brain
- Seizures
- Mood changes

Risks and side effects related to carboplatin (7/19/10)

Likely

- Decrease in blood counts, which can cause infection, (white blood cell count) or bleeding or bruising (platelet count)
- Anemia (decrease in red blood cell count)
- Nausea
- Vomiting
- Diarrhea
- Loss of appetite and taste
- Fatigue
- Weight loss
- Hair loss

Less Likely

- Mouth sores
- Restlessness
- Tingling or numbness in your hands and feet , which may be long term or permanent
- Muscle cramps
- Weakness
- Hiccups
- Increase in blood uric acid level
- Inflammation of the liver resulting in rise in liver function tests
- Blurred vision
- Changes in body calcium, potassium, sodium, phosphate, and magnesium levels, which can cause muscle cramps, weakness, and abnormal heart rhythms

Rare but Serious

- Leukemia (another type of cancer that is likely to be fatal)
- Involuntary movements, loss of coordination, and seizures
- Severe allergic reaction with low blood pressure, shortness of breath, rash, swelling of the face, chest pain, and shock
- Damage to the ears, including hearing loss and ringing in the ears
- Kidney failure
- Death from allergic reaction
- Death from infection due to low white blood cell count
- Heart attack
- Stroke
- Irregular heart beat
- Blindness

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study? (11/6/09)

Taking part in this research study may or may not make your health better. While researchers hope the addition of bevacizumab to standard chemotherapy and IMRT will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We hope the information gathered in this research study will help doctors learn more about Bevacizumab as a treatment for endometrial cancer in the future.

What other choices do I have if I do not take part in this study? (11/6/09)

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; or (3) no treatment except medications to make you feel better. Radiation and chemotherapy could be given either alone or in combination with each other. If you choose to have no treatment, there is a high likelihood that your tumor would recur and your disease would spread

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Radiation Therapy Oncology Group (RTOG, the sponsor of this study)
- The Institutional Review Board (IRB) at your hospital
- Qualified representatives of Genentech (manufacturers of bevacizumab)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), who are involved in keeping research safe for people

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The Division of Cancer Treatment and Diagnosis, NCI, will provide bevacizumab free of charge while you participate in this study. However, if you should need to take bevacizumab much longer than is usual, it is possible that the NCI's supply of free bevacizumab could run out. If this happens, your study

doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it."

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be meeting regularly to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or any information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study? (11/6/09)

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

Consent Form for Use of Tissue and Blood for Research

About Using Tissue and Blood for Research (11/6/09)

You have had a hysterectomy to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://www.rtog.org/tissue%20for%20research_patient.pdf

The research that may be done with your tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

About Using Blood for Research (7/14/10)

As part of your participation in the trial, you will have blood tests performed. We would also like to collect additional blood from you for research to see how patients respond to radiation, chemotherapy and bevacizumab in the treatment of endometrial cancer. If you agree to let us take additional blood, you will be asked to give blood samples at the following times:

- Before you begin study treatment and at your 6-month follow-up visit
  AND/OR
- At any time before, during, or after study treatment in conjunction with one of you office visits for the main part of the study

Each sample will require approximately 10cc (1 tablespoon) of blood.

Things to Think About
The choice to let us keep the tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

Even if you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue and blood that remain will no longer be used for research. Remaining tissue will be returned to the institution that submitted it, and remaining blood will be destroyed.

In the future, people who do research may need to know more about your health. While the [*doctor/institution*] may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks (11/6/09)

The greatest risk from the use of your tissue for research is the release of information from your health records. We will do our best to make sure that your personal information is kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease) as follows:
    - Tissue ☐Yes ☐ No
    - Blood ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.

    ☐Yes ☐ No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II
STUDY PARAMETER TABLE (2/21/11)

	Prior to Registration			During Treatment			Follow up – From end of RT								Long-term Follow up
Assessment	≤ 56 days	≤ 21 days	≤ 14 days	WEEKLY DURING RT	PRIOR TO BEV	PRIOR to each adjuvant cycle	3mo	6mo	9mo	12 mo	18 mo	24 mo	30 mo	36 mo	Annually thereafter
Hysterectomy	x														
History/physical/pelvic exam	x			x	x	x	x	x	x	x	x	x	x	x	x
Pap Smear (see section 11.3)										x		x			x
Performance status	x			x											
CBC w/ Platelets and DIFF		x			x	x		x	x	x	x	x		x	x
INR (See section 3.1.8)			x												
Total Bilirubin, Serum Creatinine, AST,ALT		x			x	x		x	x	x	x	x		x	x
Urine Protein Creatinine (UPC) ratio			x*		x*		x								
ALK PHOS, MG, BUN, Electrolytes (Na,K, Cl, HCO3)		x			x	x		x	x	x	x	x		x	x
Chest X-ray/Chest CT or PET-CT	x														
CT or PET-CT of Abdomen and Pelvis (see section 3.0)	x														
Audiogram (see section 4.0)	x*														
Tissue Banking (for consenting pts)	Submitted from pre-treatment biopsy														
Serum Banking (for consenting pts)				Prior to treatment start				X							
Plasma Banking (for consenting pts)				Prior to treatment start				X							
Whole Blood Banking (for consenting pts)	At any time before, during, or after protocol treatment														

*SEE SECTIONS 3.1, 7.6.1, 11.2 & 11.3 FOR DETAILS

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled. Cannot carry on self-care. Totally confined to bed
5	Death

NEW YORK HEART ASSOCIATION CLASS DEFINITIONS

Cardiac	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

*To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

APPENDIX IV

STAGING FOR ENDOMETRIAL CANCER
(AJCC, 6th Edition, 2002)

Primary Tumor (T) (Surgical-Pathologic findings)

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma in situ
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium
T1b	IB	Tumor invades less than one-half of the myometrium
T1c	IC	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades cervix but does not extend beyond uterus
T2a	IIA	Tumor limited to the glandular epithelium of the endocervix. No evidence of connective tissue stromal invasion
T2b	IIB	Invasion of the stromal connective tissue of the cervix
T3	III	Local and/or regional spread as defined below
T3a	IIIA	Tumor invades serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b	IIIB	Vaginal involvement (direct extension or metastasis)
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient evidence to classify a tumor as T4).

Regional Lymph Nodes (N)

- NX - Regional lymph nodes cannot be assessed
- N0 - No regional lymph node metastasis
- N1 - IIIC Regional lymph node metastasis to pelvic and/or para-aortic nodes

Distant Metastasis (M)

- MX - Distant metastasis cannot be assessed
- M0 - No distant metastasis
- M1 - IVB Distant metastasis (Includes metastasis to abdominal lymph nodes other than para-aortic, and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa)

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

APPENDIX V (7/14/10)

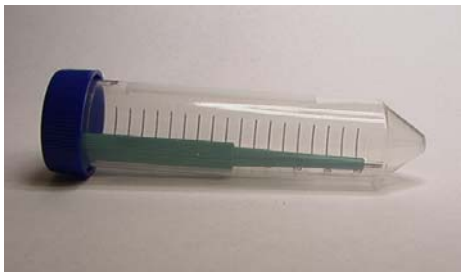
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label punch tool with proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or email us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the address below:

US Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115
Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

APPENDIX V
RTOG BLOOD COLLECTION KIT INSTRUCTIONS continued (2/21/11)

This Kit is for collection, processing, storage, and shipping of serum, plasma, or blood (as specified by protocol):

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty (20) 1 ml cryovials
- Biohazard bags (3)
- Absorbent shipping material (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD

(A)Serum: Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as serum collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot 0.5 ml serum into as many cryovials as serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(B)Plasma: Purple Top EDTA tube #1

- ❑ Label as many 1 ml cryovials (5 to 10) as necessary for plasma collected.Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma".
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

(C) Whole Blood For DNA: Purple Top EDTA tube #2

- ❑ Label as many 1 ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials labeled "blood" asnecessary for the blood collected (3 to 5), labeled with RTOG study and case numbers, date/time of collection and time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ☐ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

  - OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).

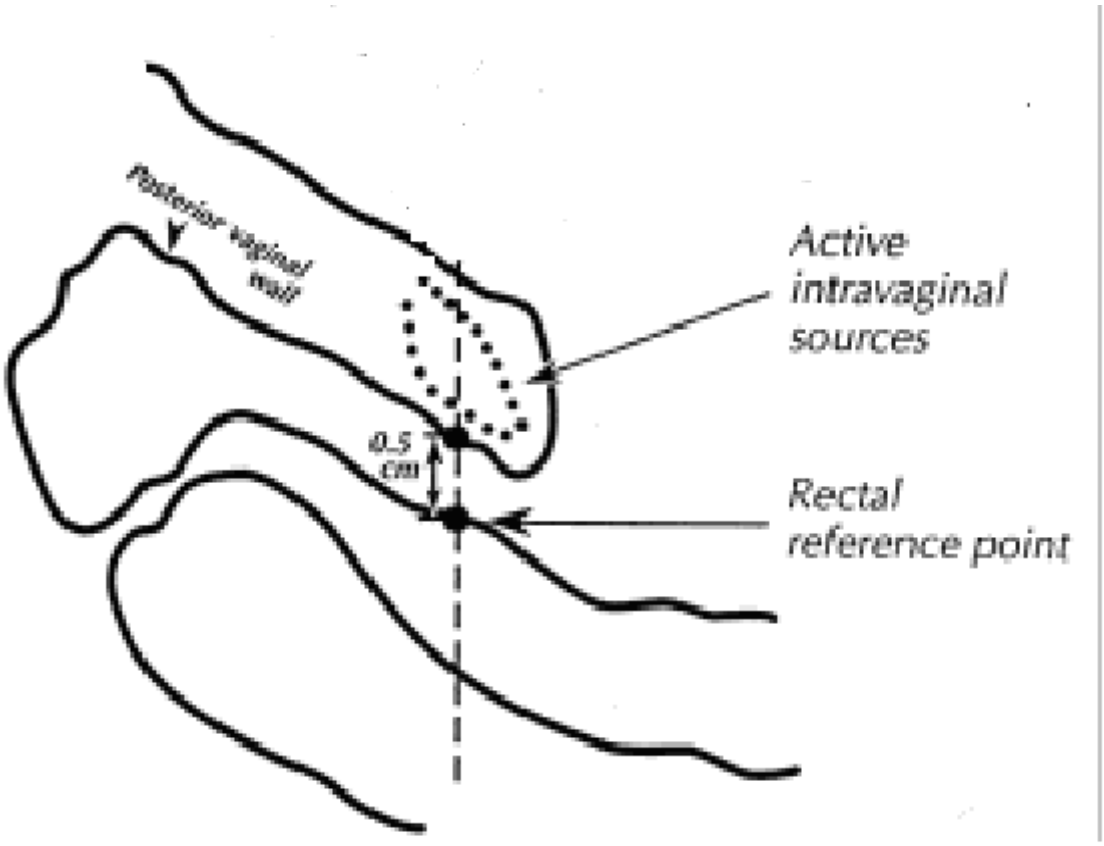
  - OR:
  - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864

Shipping Address :
Courier address (FedEx, UPS, etc.): (For all Frozen Specimens
RTOG Biospecimen Resource
Universtity of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115
For questions, call 415.476. RTOG (7864) or e-mail: RTOG@ucsf.edu

Appendix VI - Definition of Rectal Points



APPENDIX VII

Points of Calculation