A PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH DEFINITIVE RADIOTHERAPY AND CISPLATIN CHEMOTHERAPY IN UNTREATED PATIENTS WITH LOCALLY ADVANCED CERVICAL CARCINOMA

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0417

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SCHEMA (5/11/07)

Pelvic RT:
45 Gy given in 25 once-daily fractions (1.8 Gy/fraction) Monday-Friday over 5 weeks
↓
LDR x 2 or HDR x 5
↓
Parametrial boost (if indicated)

Bevacizumab (Avastin®): IV Q2 weeks (Days 1, 15 and 29, total of 3 doses) during chemoradiation, given before cisplatin, on the same day as cisplatin

Cisplatin: Weekly infusion x 6 weeks

Proton pump inhibitor (PPI) medications must be administered to all patients. See Section 9.4.1.

Patient Population: (See Section 3.0 for Eligibility)
- Patients with advanced adenocarcinoma, squamous, or adenosquamous carcinoma of the uterine cervix, FIGO stage IIB-IIIB or patients with FIGO stage IB-IIA with biopsy-proven pelvic node metastases and/or tumor size ≥ 5 cm
- Zubrod Performance Status 0-2

Required Sample Size: 57
ELIGIBILITY CHECKLIST (8/11/06, 8/27/08)
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1. Does the patient have histologic proof of squamous, adenocarcinoma or adenosquamous carcinoma of the uterine cervix?

2. Is the FIGO stage IIB to IIIB?

If no, then is the FIGO stage IB to IIA with biopsy-proven pelvic node metastases and/or tumor size ≥ 5 cm?

3. Did the patient have a confirmed diagnosis of carcinoma by cervical biopsy?

4. Is the Zubrod performance score 0-2?

5. Has the patient met all the lab requirements as described in Section 3.1.4.?

6. Has the patient’s baseline urine protein been screened within 21 days of study entry?

If urine analysis for urine protein creatinine (UPC) ratio > 0.5, was a 24-hour urine protein performed and found to be < 1000 mg?

7. Has the patient had a chest x-ray, chest CT or PET-CT within 8 weeks of study entry?

8. Has the patient had an evaluation of para-aortic lymph nodes by contrast-enhanced CT, MRI or PET-CT within 8 weeks of study entry as indicated in Section 3.1.7?

9. Is there suspicion of para-aortic lymph node disease as defined by imaging in Section 3.1.7?

If yes, was a biopsy by fine needle aspirate or laparoscopy or laparotomy performed and found to be negative?

10. Has the patient had a contrast-enhanced CT, MRI or PET-CT of the pelvis that includes evaluation of the abdomen to at least the level of the renal vessels within 8 weeks prior to study entry (MRI of the pelvis is strongly preferred in order to allow tumor measurement in 3D)?

11. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer)?

If yes, has the patient been disease free for a minimum of 3 years?

12. Does the patient have any medical illness preventing full dose chemotherapy?

13. Is there evidence of bleeding diathesis or coagulopathy?

14. Does the patient require use of > 1 mg warfarin sodium?

15. Does the patient have any previous medical or psychiatric illness, which would prevent informed consent?

16. Has the patient had prior surgery for carcinoma of the cervix other than biopsy?

17. Has the patient had previous pelvic radiation, including transvaginal irradiation to control bleeding?

18. Has the patient had prior systemic chemotherapy?
ELIGIBILITY CHECKLIST (8/11/06, 8/27/08, 1/6/09)
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19. Does the patient have an active GI ulcer, GI bleeding, or active inflammatory bowel disease?

20. Is the patient pregnant or lactating?

21. If the patient is of childbearing potential, is she using an adequate contraception?

22. Does the patient have clinically significant cardiac disease (e.g., uncontrolled hypertension [blood pressure of > 160/90 mmHg on medication])?

23. Does the patient have a history of myocardial infarction or unstable angina within 12 months, New York Heart Association (NYHA) Class II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication (chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia)?

24. Does the patient have a history of aneurysms, arteriovenous malformations and/or a cerebrovascular accident (CVA)?

25. Does the patient have a history of arterial thromboembolic event(s), including transient ischemic attack (TIA) or clinically significant peripheral artery disease within the past 6 months?

26. Has the patient had a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to start of treatment, or anticipation of need for major surgical procedure during the course of the study?

27. Does the patient have serious, non-healing wound, ulcer, or current healing fracture?

28. Has the patient had an organ transplant?

29. Does the patient have known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies or any known sensitivity to bevacizumab or any of the excipients of this product?

30. Does the patient have a history of any type of fistula (vesicovaginal, gastrointestinal, etc.) or gastrointestinal perforation?

31. Does the patient have a history of an intra-abdominal abscess within 6 months of study entry?

32. Is the patient known to be HIV positive? (NOTE: HIV testing is not required)

33. Is there evidence of tumor outside of the pelvis?

34. Has the patient signed a study-specific informed consent prior to study entry?
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

1.1 Cervical Cancer and Chemoradiation Therapy

It is estimated that there will be 12,900 new cases of cervical cancer in the United States each year.\(^1\) Of these 4400 will die from this disease. For small tumors in early stage (IB, IIA), radiation therapy or surgery yields overall survival rates of 85-90%. For women with more advanced disease, the 5-year survival rates are significantly worse.

Concurrent cisplatin-based chemotherapy has improved outcome compared to radiotherapy alone. Chemoradiotherapy has been shown in RTOG 90-01 and several GOG studies to be more effective in terms of overall survival and local control, than radiation therapy alone in the treatment of women with locally advanced carcinoma of the cervix.\(^2\)\(^-\)\(^7\) The combination of cisplatin and 5-fluorouracil decreased both local and distant recurrence rates and improved overall survival in RTOG 90-01.\(^8\) GOG 120 demonstrated superior survival for weekly cisplatin and radiotherapy compared with radiotherapy alone, and weekly cisplatin and radiotherapy resulted in less grade 3 and 4 toxicity compared with the combination of radiotherapy, cisplatin, 5-FU and hydroxyurea.\(^5\) In the arm that received radiotherapy and cisplatin, the rate of progression-free survival was 67%, which meant that 33% of the patients with advanced cervical cancer had failed therapy within two years, and thus there is need for improvement. Adding other chemotherapy agents or increasing the dose of radiotherapy is precluded because of excessive toxicity. Addition of a biomodulator to chemotherapy may improve outcomes without increasing toxicity. An example of such biomodulator is bevacizumab (Avastin), a monoclonal antibody to vascular endothelial growth factor (VEGF).

1.2 Concurrent Chemoradiotherapy and VEGF Blockade (5/11/07)

Vascular endothelial growth factor (VEGF) signaling is an attractive target for cancer therapy due to its role in tumor angiogenesis and its potential role in tumor cell survival. Bevacizumab (Avastin) is a humanized antibody to VEGF-A and was the first key regulator of angiogenesis to receive marketing approval by the US FDA. Numerous investigators have demonstrated high expression of VEGF in solid tumors.\(^6\)\(^-\)\(^10\) One recent study by Gaffney showed that cervical cancer patients who had increased expression of VEGF and COX-2 treated with definitive radiotherapy, had diminished disease-free survival on multivariate analysis.\(^11\) Furthermore, a direct correlation was observed between VEGFR and EGFR expression and risk of death, further supporting the addition of VEGF targets such as bevacizumab to combined modality therapy for advanced cervical cancer. One study also showed that expression of VEGF was associated with increased angiogenesis and metastasis regulated by hypoxia,\(^12\) which is known to be present in locally advanced cervical carcinoma. Hypoxic tumors are known to be substantially more resistant to radiation than oxygenated tumors, and even a small hypoxic fraction may affect the overall response to radiation therapy. This might serve as a mechanism of radiation and chemotherapy resistance and therefore represents a rational target. Willett and colleagues evaluated the addition of low dose bevacizumab (5mg/Kg Q 2 weeks) to standard preoperative 5-FU based chemotherapy and pelvic radiation for patients with locally advanced rectal cancer and preliminary results show no increased toxicity.\(^13\) Willett was able to show that low doses of bevacizumab alone decreased microvascular density, perfusion and interstitial fluid pressure and decreased the number of circulating epithelial cells. Additionally, there was increased fraction of vessels with pericyte coverage supporting the vessel normalization hypothesis.\(^14\) Normalization or pruning of the neovascularure may retard the shedding of metastatic cells in the circulation and improve delivery of therapeutic agents to tumors and work synergistically with radiation by improving tumor oxygenation. The combination of ionizing radiation and antiangiogenic agents seems counterintuitive because oxygen is a potent radiosensitizer and a reduction in oxygen concentration would be expected following a reduction in tumor vasculature due to antiangiogenic treatment. However, some recent studies indicate that tumor oxygen levels may increase after treatment with antiangiogenic agents and ionizing radiation, and these tumor oxygen levels may not be critical at the time of antiangiogenesis treatment. This in part is through a "normalization of tumor associated blood vessels" after treatment with an antiangiogenic agent. Combined modality treatment with radiation plus antiangiogenesis agents may be an effective strategy to enhance radiotherapy (RT), either through direct radiosensitization of tumor or stromal tissue or through targeting of aspects of the tumor microenvironment, such as hypoxia.

In most trials combining bevacizumab or other biologic targeting agents with radiation therapy, a loading/initial dose or course of the targeting agent is given. In this trial, bevacizumab will be
started at the same time as chemoradiation treatment. Patients with locally advanced cervical cancer often have bleeding at presentation, and therefore an initial loading dose of bevacizumab might exacerbate bleeding.

There is a need for development of surrogate markers to improve our ability to select patients likely to benefit from antiangiogenesis therapy. Changes in these markers during and after the course of therapy might be predictive of outcome and/or late effects.\textsuperscript{15}

Gene expression utilizing microarray technology has been evaluated in a wide variety of cancers.\textsuperscript{16,18} Microarray technology allows for the simultaneous evaluation of over 20,000 gene sequences that have been sequence-verified for over 4000 known genes. In addition, evaluation of tumor specimens for COX-2, VEGF, bFGF, MVD and TUNEL-staining for apoptosis prior to treatment and at the time of first implant might provide powerful insights into the response of particular genes or genetic pathways after therapy with radiation, cisplatin and bevacizumab. In RTOG trials, we have recently demonstrated the feasibility of RNA extraction for microarray gene expression analysis in the cooperative group setting.\textsuperscript{19}

The cervix is easily accessible for biopsy of tissue which can be used to correlate VEGF expression and other biologic markers with observed response to therapy with bevacizumab and chemo-radiotherapy. Therefore, for consenting subjects in this study, we will perform tumor tissue microarray testing for gene expression, proteomics and immunohistochemistry for protein expression prior to treatment and at the time of first brachytherapy implant.

The majority of studies evaluating molecular prognostic variables in general, have focused on evaluation of tumor tissue obtained at the time of initial biopsy and/or resection. This approach is limited to evaluation of molecular pre-treatment prognostic markers. The investigation of post-treatment and during-treatment factors has been more limited but might be important. Cervical cancer is well suited to biopsy during treatment as brachytherapy (OR procedure with the patient sedated) is a standard component of definitive radiotherapy. Biopsy will be obtained at the time of first brachytherapy for consenting patients.

Prognostic markers in urine and serum can be obtained with minimally invasive procedures and therefore will also be evaluated prior to treatment, during treatment and post treatment for correlation with tissue markers and clinical outcome for consenting patients.

The NCI Radiation Oncology Branch (ROB) previously evaluated serum and urine markers prior to, during and following definitive radiation therapy.\textsuperscript{20} Chan and colleagues reported some preliminary findings regarding urinary VEGF and MMP levels as they correlated with outcome. These patients were enrolled in the ROB blood and urine collection protocol, (NCI protocol 02-C-0064). Serum and urine were collected from patients with various cancers undergoing radiation therapy. The levels of serum and urine angiogenic factors were evaluated to determine if these levels were prognostic of outcome following radiation therapy.

Urinary VEGF level at presentation were different between patients with local-regional cancer and normal controls, and between patients with metastatic prostate cancer and local-regional disease, (p = 0.04 and 0.01, respectively). Similar results were found with MMP measurement (p = 0.03 and p< 0.0001, respectively).

Of those patients subsequently treated with radiation, VEGF levels at presentation between patients with no evidence of disease after radiation (NED) and those who had persistent or recurrent disease following radiotherapy were also different (p = 0.039). The comparison between angiogenic factor levels taken at least 1 month post-radiotherapy and the last on-treatment level was the strongest predictor of patient 1-year progression-free survival (p = 0.004). Similarly, overall MMP trending was also significantly associated with one-year progression-free survival, as was individual MMP-2 trending (p = 0.004 and 0.001, respectively). Step-wise logistic regression revealed that the VEGF trend comparing post-radiation levels to last on-treatment levels was an independent predictor of progression-free survival (p = 0.02). This study was exploratory and therefore hypothesis testing and requires further evaluation in groups of patients with similar cancers treated in a uniform way.
Serum samples for consenting subjects will be collected before, during, and after treatment per the collection schedule described in Section 10. These samples will be banked for future cytokine analysis.

Urine samples will be collected before, during, and after treatment per the collection schedule described in Section 10. Urine samples will be evaluated for VEGF and MMP levels and correlated with outcome measures.

1.3 Image-Guided Brachytherapy

There has been increasing interest in using image-guided brachytherapy to guide dose specification and modification during brachytherapy for cervical cancer. Though used routinely to guide external beam field design, there has been little use of imaging for brachytherapy except for prostate implant analysis. Applicator and software design have made this difficult in gynecologic brachytherapy because of ambiguity and disagreement over tumor and normal tissue definitions and dose-volume parameters. Recent improvements in software tools, the availability of DICOM transmission of image-guided dosimetry, and the development of published guidelines for tumor and normal tissue contouring definitions and dose/volume parameters now make this a reality. By collecting such data it is hoped that ultimately a better understanding of dose-volume relationships for tumor control and normal tissue complications will be gained. More immediate objectives include the need to assess the feasibility of implementation of image-guided dosimetry and DICOM transmission at contributing institutions and the consistency in guideline application amongst varied participants. This protocol has an imaging companion study, and will allow for collection of image-guided dosimetry for later analysis for participating investigators and consenting patients. The companion study is not mandatory for enrollment on RTOG 0417. There will be a half of a case credit to participating institutions.

1.4 Bevacizumab (5/11/07, 8/27/08)

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 (kd = 1.1 nM). 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 [AvastinTM (bevacizumab) Investigators Brochure, 2004].

Of known proangiogenic factors, VEGF is one of the most potent and specific, and it has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flik-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 decrease microvessel density and interstitial pressure in tumor xenografts in vivo. In patients, preliminary 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.

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.

To date, over 3000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens [AvastinTM (bevacizumab) Investigator's Brochure, 2004].

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.
The predicted time to reach steady state is 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 has been associated with severe headaches. The dose schedule of either 10 mg/kg q2w, or 15 mg/kg q3w is used in most phase 2 or 3 trials with only a few exceptions (e.g., the pivotal phase 3 trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg q2w). There is no consensus on the optimal dose and regimen of bevacizumab administration when combined with chemotherapy or combined chemoradiotherapy.

Clinical proof of principle for anti-VEGF therapy with bevacizumab has been provided by the pivotal phase 3 trial of bevacizumab (5 mg/kg q2w) in combination with bolus irinotecan/5-FU/leucovorin (IFL) in patients with untreated advanced colorectal cancer (CRC). In that study, the addition of bevacizumab to IFL was associated with an increase in objective responses (45% vs. 35%) and significant prolongations of both time-to-progression (TTP) (10.6 vs. 6.2 months) and overall survival (20.3 vs. 15.6 months) as compared to IFL. However, in the phase 3 trial in previously treated metastatic breast cancer, the addition of bevacizumab to capecitabine did not show a difference in TTP despite an increase in the response rate from 9% to 20%.

The selection of 10 mg/kg in this phase II trial (powered for toxicity) is based on the compilation of trials to date (with chemotherapy alone and the combination of chemoradiotherapy). The two published studies to date evaluating bevacizumab in combination with chemoradiotherapy (Willet, Crane) suggest improved response. Willet performed a dose escalation trial of bevacizumab in combination with continuous infusion 5-FU and pelvic radiation therapy in patients with locally advanced rectal cancer. Bevacizumab was given as an initial dose (monotherapy) and then with infusional 5-FU (225 mg/m^2) and radiation therapy (50.4 Gy/28) every 2 weeks for 3 doses (total of 4 doses). The MTD was determined to be 5 mg/kg owing to 2 of 5 cases of grade 3 and 4 diarrhea and colitis in the 10 mg/kg cohort. Crane reported the phase I trial results of the same regimen bevacizumab (initial dose as monotherapy and then Q2 weeks during chemoradiation, total 4 doses) with preoperative capecitabine (825 mg/m^2 BID) and abdominal radiotherapy (5040 cGy/28) for locally advanced pancreatic cancer. A small number of patients experienced bleeding and ulceration in the radiation treatment field that might have been related to bevacizumab but more likely was due to tumor involvement of the duodenum. Bevacizumab was not associated with increased acute toxicity with capecitabine and abdominal radiotherapy when capecitabine was given Monday through Friday at 825 mg/m2 BID (weekends excluded). We don't anticipate gastrointestinal dose limiting toxicity like what was experienced in one of the 2 reported studies to date, (Willet, diarrhea and colitis in 2 patients) as bowel toxicity is not considered dose limiting for cisplatin in contrast to 5 FU and its analogues. We do have a stringent early stopping rule built in for unexpected toxicity with the combination of bevacizumab (Q2 weeks, total 3 doses), weekly cisplatin (6 doses), and pelvic radiotherapy.

1.5 Safety Profile (5/11/07)

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 most serious adverse events (AEs) include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

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 v3.0 terms is included in Section 7.1.14 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 are uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include 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% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, although rare, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

**Proteinuria:** Proteinuria has been observed in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the phase 2 randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

**Hemorrhage:** The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal. In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

**Arterial Thromboembolic Events:** The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Schilling et al, ASCO 2005). In patients > 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

**Gastrointestinal Perforation/Fistula:** GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI 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.

**Wound Healing Complications:** Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a
very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/Bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/Bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

**Congestive Heart Failure:** The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

**Venous Thrombosis:** Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL + bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

**Fertility and Pregnancy:** Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

**Immunogenicity:** As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome:** RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnose and typically demonstrated vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

**Neutropenia:** When combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase III trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevacizumab + IFL arm vs. 14% in the IFL arm (grade 4 neutropenia was 3% vs. 2%). In a phase III trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutropenia (27% vs. 17%), febrile neutropenia (5.4% vs. 1.8%), and an increased rate of infection with neutropenia (4.4% vs. 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs. none in the chemotherapy control arm.
2.0 OBJECTIVES

2.1 Primary
2.1.1 To determine treatment-related serious adverse event rates and adverse event rates (as defined in Section 13.1), within first 90 days from treatment start, in patients with locally advanced carcinoma of the cervix treated by intravenous bevacizumab, intravenous weekly cisplatin and concurrent pelvic radiation therapy.

2.2 Secondary
2.2.1 To evaluate treatment-related serious adverse events and adverse events at any time.
2.2.2 To evaluate disease-free survival (failure: local, regional or distant failure, or death due to any cause).
2.2.3 To evaluate overall survival (failure: death due to any cause).
2.2.4 To collect tissue to perform future immunohistochemical analyses for angiogenic markers to correlate with clinical outcome; to collect tissue to perform future microarray testing for evaluation of gene expression.
2.2.5 To collect urine and serum for future cytokine analysis.
2.2.6 To implement the image-based brachytherapy guidelines proposed by the Transatlantic Image-guided Brachytherapy Working Group and collect CT or MRI-based dosimetry of brachytherapy applications used during the course of treatment for later analysis of feasibility and consistency as well as dose/volume assessments of tumor control and complications.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (5/11/07, 8/27/08)
3.1.1 Histologic proof of squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, including FIGO (International Federation of Gynecologists and Obstetricians) stage IIB to IIIB or patients with FIGO stage IB to IIA who have biopsy-proven pelvic node metastases and/or tumor size ≥ 5 cm.
3.1.1.1 Pelvic lymph nodes are considered those below the superior border of the sacrum. Those above the top of the sacrum are peri-aortic lymph nodes. Patients with positive peri-aortic lymph nodes are ineligible for this trial.
3.1.2 All patients must have confirmation of diagnosis by cervical biopsy.
3.1.3 Zubrod Performance Status 0-2.
3.1.4 Laboratory values must be as follows (Within 21 Days of registration)
- White blood cell count: ≥ 3,000/mm³
- Absolute granulocyte count: ≥ 1,500/mm³
- Platelets: ≥ 100,000/mm³
- Total bilirubin: ≤ 1.5 mg/dl
- Serum creatinine: ≤ 1.5 mg/dl
- AST and ALT: ≤ 2.5 x institutional upper normal limit
- Serum calcium: ≤ 1.3 x institutional upper normal limit
- INR: < 1.5
- Serum Pregnancy: Negative
- Hemoglobin: > 10 – Transfusion may be used to meet this criterion.

3.1.5 Urine protein screening must be performed within 21 days of study entry:
3.1.5.1 If urine analysis for urine protein creatinine (UPC) ratio > 0.5, then a 24-hour urine protein must be performed and must be < 1000 mg
3.1.5.2 UPC is calculated using one of the following formulas:
   - [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
   - [(urine protein) x 0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.1.6 Chest X-Ray, Chest CT, or PET-CT within 8 weeks prior to study entry
3.1.7 Evaluation of para-aortic lymph nodes is required to at least the level of the renal vessels by contrast-enhanced CT, MRI or PET-CT within 8 weeks prior to study entry. All patients with suspicious para-aortic lymph nodes on CT, MRI or PET-CT must have biopsy by fine needle aspirate or laparoscopy or laparotomy. FDG-PET scanning can be used to supplement cross
sectional imaging for determination of nodal involvement or distant metastases. PET imaging is encouraged, but not required.

3.1.8 CT, MRI or PET-CT of the abdomen/pelvis that must include evaluation of the abdomen to at least the level of the renal vessels, with contrast-enhancement, within 8 weeks prior to study entry. MRI of the pelvis is strongly preferred in order to allow tumor measurement in three dimensions.

3.1.9 Signed study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (8/27/08, 1/6/09)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.
3.2.2 Medical illness preventing the use of full-dose chemotherapy.
3.2.3 Evidence of bleeding diathesis or coagulopathy, INR>1.5
3.2.4 Patients who require the use of warfarin sodium > 1 mg.
3.2.5 Previous medical or psychiatric illness that would prevent informed consent or limit survival to less than six months.
3.2.6 Prior surgery to treat carcinoma of the cervix other than biopsy.
3.2.6.1 Patients who have undergone surgical debulking of pelvic or para-aortic nodes.
3.2.7 Patients with positive para-aortic disease
3.2.8 Previous pelvic radiation therapy including transvaginal irradiation to control bleeding.
3.2.9 Prior systemic chemotherapy.
3.2.10 Patients with active Gl ulcers, Gl bleeding, or active inflammatory bowel disease.
3.2.11 Pregnant, nursing or woman of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception.
3.2.12 Clinically significant cardiac disease (e.g., uncontrolled hypertension [blood pressure of >160/90 mmHg on medication], history of myocardial infarction or unstable angina within 12 months of registration), New York Heart Association (NYHA) Class II (See Appendix II) or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication (subjects with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia) are not eligible.
3.2.13 Patients with a history of aneurysms, cerebrovascular accident (CVA) and arteriovenous malformations
3.2.14 Patients with arterial thromboembolic events, including transient ischemic attack (TIA), or clinically significant peripheral artery disease within 6 months of registration.
3.2.15 Tumor outside the pelvis.
3.2.16 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to start of treatment, or anticipation of need for major surgical procedure during the course of the study.
3.2.17 Serious, non-healing wound, ulcer, or current healing fracture.
3.2.18 Patients with a history of any type of fistula (vesicovaginal, gastrointestinal, etc) or gastrointestinal perforation.
3.2.19 Intra-abdominal abscess within 6 months of study entry.
3.2.20 Patients who have had an organ transplant.
3.2.21 Patients with known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies.
3.2.22 Patients who are known to be HIV positive who have a CD4 cell count less than 350 cells/mm$^3$ within 21 days of registration; note, however, that HIV testing is not required for entry into this protocol. Excluding HIV positive patients with invasive cervical cancer and low CD4 cell counts is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

(In addition to the mandatory pre-testing for eligibility in Section 3.0)

Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient’s eligibility for this study, please contact RTOG HQ immediately (215) 574-3189
4.1 **Required Evaluations/Management**

See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 History and physical examination including height, weight, body surface area and Zubrod Performance Status (ZPS). Documentation of the nature and size (including measurements in three dimensions) of the primary tumor is required. Initial examination should be performed by a gynecologic oncologist and radiation oncologist.

4.1.2 Patients who have consented to take part in the Optional Imaging Component of this trial must not be allergic to iodinated contrast if undergoing a contrast-enhanced CT scan of the pelvis with the applicator in place. Patients must not be allergic to the contrast agent (gadolinium) and have no contraindications to MRI scanning and may be sedated if claustrophobic.

4.2 **Highly Recommended Evaluations/Management (5/11/07, 8/27/08)**

4.2.1 It is highly recommended (but not mandatory) that patients have biopsies for fresh tissue acquisition within 14 days prior to starting treatment and at the first implant (see Sections 8.0, 10.2) as well as urine and plasma for future cytokine analysis at these same time points in addition to the first post-treatment follow-up visit at 4-8 weeks.

4.2.2 Cystoscopy and sigmoidoscopy are suggested for bulky lesions at the discretion of the radiation and gynecologic oncologist and in concert with imaging findings.

5.0 **REGISTRATION PROCEDURES**

5.1 **Pre-Registration Requirements (8/31/06, 5/11/07, 8/27/08)**

5.1.1 **LDR/HDR Brachytherapy Credentialing**

Only physicians who have completed the Knowledge Assessment Questionnaire available from the RPC website (http://rpc.mdanderson.org) may enter patients onto this study.

Upon review and successful completion, the Radiological Physics Center will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter subsequent patients onto this study. Notification will then be given to the institution from the RTOG RT Quality Assurance Department.

5.1.1.1 The first intracavitary implants performed on two patients (both LDR and HDR) at each institution will be reviewed directly by the Radiological Physics Center (RPC). The following data needs to be submitted to the RPC: For HDR, submit an RTOG Gynecological Brachytherapy Protocol Compliance Form (see RPC website http://rpc.mdanderson.org for instructions and forms), treatment plan, isodose plots, treatment media and images for CT-based planning (AP and lateral); For LDR, submit an RTOG Gynecological Brachytherapy Protocol Compliance Form (see RPC website http://rpc.mdanderson.org for instructions and forms), treatment plan, isodose plots, source activity, source loading, treatment time and films (AP and lateral). The films and dosimetry will be sent within 2 working days to the RPC at MD Anderson Cancer Center.

5.1.2 **Regulatory Pre-Registration Requirements**

5.1.2.1 **U.S. sites and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSU-IRBcertif_Final.pdf, prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.1.2.1.1 **Pre-Registration Requirements FOR CANADIAN INSTITUTIONS**

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.

5.1.2.1.2 Note: 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/Researchers/InternationalMembers.aspx.
Approved international sites fax copies of the documentation below, along with the completed International REC Certification Form, http://www.rtog.org/Researchers/InternationalMembers/RECCertification.aspx to RTOG Headquarters (215-574-0300) prior to registration of the institution's first case:

- REC approval letter;
- Informed Consent (English Version);
- Federalwide Assurance (FWA) number.

### 5.1.3 Online Registration

Patients can be registered only after eligibility criteria are met.

Institutions 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 must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at (http://www.rtog.org/LinkClick.aspx?fileticket=--BXerpBu5AQ%3d&tabid=219) (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 (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.

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

Note: Intensity Modulated RT (IMRT) is Not allowed

This study also contains an optional imaging component. Patients are encouraged, but not required to participate in the component by contributing additional CT or MR images to the RTOG Imaging Library - Institution Registry Study of CT and MR Image-Based Intracavitary Brachytherapy for Cervical Carcinoma.

Participation in this optional imaging component requires institutions to demonstrate the ability to perform electronic data submission to the Image-Guided Therapy Center (ITC) prior to enrolling patients on this study. Additional information on electronic data submission can be found on the ATC web site at http://atc.wustl.edu/.

The images will be transmitted electronically to ITC. Details regarding this component are available in Appendix VIII or on the ATC website at http://atc.wustl.edu.

6.1 Dose Specifications

Whole pelvis will be treated to a total dose of 45 Gy in 5 weeks prescribed to the isocenter (or 100%) where isocenter is defined as the intersection of 4 beams in a 4-field technique or midplane (and midline) for AP-PA. The goal is to keep prescription points consistent with previous trials. Four-field technique (AP-PA and lateral opposed fields) is recommended, particularly when treatment is delivered with a beam energy of < 15 MV. Patients will be treated once a day, 5 days a week with a daily fraction size of 1.8 Gy. The whole pelvis should receive a dose of 45 Gy. If the patient has extensive tumor that precludes intracavitary treatment, shrinking field techniques should be performed to bring gross tumor volume with adequate margins to a minimum of 65 Gy. The involved lateral parametrium and/or involved pelvic nodes should be boosted with fields tailored to encompass known areas of disease to achieve a total dose (including the intracavitary treatment) of 60 Gy ± 5%. See Section 6.4.3 for parametrial fields. IMRT is not allowed.

The parametrial and/or nodal boost fields will be treated with 1.8 Gy per day prescribed to Point B at midplane (see Appendix VII) to bring the cumulative dose (including initial pelvic fields and contribution from brachytherapy) to Point B to 60 Gy ± 5%.

6.2 Technical Factors (5/11/07)

A megavoltage beam of 6 MV or greater (4-6 MV acceptable if treating groin nodes), with a minimum source-axis distance of 100 cm will be used. Isocentric technique will be used. MLC or custom Cerrobend blocks are acceptable for field shaping.

6.3 Localization, Simulation, and Immobilization (5/11/07, 8/27/08)

All fields treated require simulation and portal verification on the treatment unit. Copies of these images will be submitted to RPC. At simulation, techniques to limit irradiation of the small bowel should be employed including: simulation and treatment in the prone position (supine acceptable if prone is not tolerated or per institution preference) and a full bladder (if tolerated; empty bladder acceptable if not tolerated). If a four-field technique is used, use of a belly board with the patient in the prone position and contrast opacification of the small bowel is recommended. The distal (inferior most) aspect of cervico-vaginal disease should be marked using radio-opaque seeds or using a radio-opaque vaginal tampon (or using a barium soaked Texas Q-tip). Barium or other radio-opaque device should be used to localize the rectum. The tumor volume including gross nodal disease should be delineated on the simulation films (AP and lateral projections) or digitally reconstructed radiographs (DRRs) if CT treatment planning is used. CT treatment planning is preferred.

6.4 Treatment Planning/Target Volumes (5/11/07, 8/27/08)

Initial pelvic fields will be prescribed to isocenter or the 100% isodose (isocenter must be placed as defined above and the prescription point is 100%, no renormalizing allowed). Heterogeneity correction must be turned off.

6.4.1 Pelvic Field

6.4.1.1 AP-PA Portals:
Superior Border: A transverse line between L4 and L5 (or 1 cm margin on the superior extent of the uterus, whichever is higher).

Inferior Border: Transverse line below the lowest extent of the obturator foramen or 3 cm below the most distal vaginal disease (whichever is most inferior), to include the introitus if necessary.

Lateral Border: 2 cm lateral to widest true bony pelvic diameter.

Custom Blocking: To shield small bowel and femoral heads while maintaining a margin of at least 1 cm from common iliac nodes and should not shield the obturator foramina (there should be at least 1.5 cm from the obturator foramen to block edge on the AP and PA fields).

6.4.1.2 Lateral Portals:

Superior/Inferior Borders: Identical to AP-PA fields.

Anterior Border: A straight line drawn 5 mm anterior to the symphysis pubis and at least 1 cm anterior to common iliac nodes at L4-L5.

Posterior Border: In most cases, the entire sacrum should be included in the lateral fields. Posterior block should be designed so that the gross tumor is encompassed by at least 3 cm margins. In cases with small volume of disease, a line through the posterior sacrum may be used to include the cervical disease with a margin of 3-4 cm.

Stage IIIA (or IIIB with lower third vaginal involvement): The inguinofemoral lymph nodes will be covered electively (to 45 Gy). AP-PA or 4 field are acceptable techniques as long as the inguinofemoral lymph nodes, defined as 2 cm margin around inguinofemoral vessels, receive 45 Gy. The lower border of the inguinofemoral region will be the lesser trochanter. The inferior border in the midline might have to be lower than this (to get adequate margin on the cervical and or vaginal tumor). A 2-cm margin on the inferior extent of tumor is required. The tumor will be contoured and viewed on the DRRs that are submitted.

6.4.2 Reduced Fields: Parametrial/Nodal Boost (for Stage IIB and IIIB or involved pelvic lymph nodes. Note: Pelvic lymph nodes are considered those below the superior border of the sacrum. Those above the top of the sacrum are periaortic lymph nodes. Patients with positive periaortics lymph nodes are ineligible for this trial.)

6.4.3 Parametrial Boost

AP-PA fields with the lateral borders identical to pelvic fields.

Superior Border: 9-12 cm above inferior border, tailored to the position of the cervix and uterus from radio-opaque markers and intracavitary films. Central blocking should measure at least 4.5 cm at midplane and should be tailored to the position of the intracavitary system.

6.4.3.1 Nodal Boosts

At least 4x4 cm and maintain a margin of 1-1.5 cm from involved nodes.

6.4.3.2 Treatment Technique

In general, parametrial and/or nodal boosts will be given with AP-PA (≥ 10 MV) technique (to avoid overlap with brachytherapy). However, other techniques including CT simulated multi-field plans are acceptable (especially if nodal disease is high in the pelvis and therefore not getting contribution from brachytherapy). In this latter situation, 1 cm margin will be added in all directions on the GTV to define the PTV (PTV to be covered by prescription dose). Boost dose will be such that the total dose will be 60Gy (+/- 5%). All fields will be treated on a daily basis.

6.4.4 LDR Brachytherapy

Cesium will be used with standard intracavitary systems preferably in two intracavitary applications. An effort should be made to deliver a minimum cumulative external and intracavitary dose to Point A of 85 Gy (See Appendix VII). Occasionally, normal tissue tolerance limits may demand a lower dose when vaginal and uterine anatomy does not permit optimal brachytherapy. If tumor and normal tissue anatomy permit acceptable intracavitary geometry, treatment may be performed as soon as the fourth week of external beam therapy. The interval between the two applications will be 1-3 weeks. It is recommended that the total course of treatment be completed in less than 56 days. Interstitial brachytherapy may be used to treat distal vaginal disease that cannot be adequately covered with intracavitary treatment.

6.4.5 HDR Brachytherapy

6.4.5.1 Iridium-192 is the source most commonly used for HDR brachytherapy. For patients receiving HDR brachytherapy, 5 fractions of 6.0 Gy each to Pt. A is the preferred
fractionation scheme. See Section 6.4.6.8 for guidelines of vaginal surface dose, normal tissue tolerances, packing and imaging.

6.4.5.2 **Timing**

HDR brachytherapy may start as early as week two. When HDR brachytherapy begins, one insertion will be performed per week with no external beam therapy on the same day as HDR brachytherapy. If the majority of the external beam radiation has been given, then two insertions per week can be done separated by at least 48 hours in order to complete all treatment within eight weeks (56 days). No more than two HDR brachytherapy treatments will be given per week.

6.4.5.3 **HDR Instruments**

It is strongly recommended that tandem and ovoids or a tandem and ring be used for HDR brachytherapy. For patients with lower third vaginal involvement, tandem and cylinder may be most appropriate and will be at the discretion of the treating radiation oncologist. A tandem and cylinder or tandem alone is allowed only for patients where tandem and ovoid application is not possible due to extent of disease or poor anatomy (obliterated fornices).

6.4.6 **Intracavitary Radiotherapy Dosimetry**

6.4.6.1 Intra-uterine tandems and vaginal applicators (ovoids) such as the Fletcher-Suit-Delclos afterloading system are recommended. The dose to points A, B, rectal reference, bladder reference, and vaginal vault reference must be calculated and reported.

6.4.6.2 **Point A**: Measure 2 cm along the intrauterine tandem from the cervical os or flange of the tandem and 2 cm laterally in the plane of the intracavitary system.

6.4.6.3 **Point B**: Measure 5 cm lateral from a point 2 cm vertically superior to the cervical os or flange of the central tandem along the patients’ midline.

6.4.6.4 **Bladder Dose**: Calculated at the center (in the superior-inferior plane on AP view) of a contrast-filled balloon of a Foley catheter and closest to the applicator system on a lateral view, as defined by ICRU 38.

6.4.6.5 **Rectal dose**: In accordance with ICRU 38, mark the point 0.5 cm posterior to the vaginal surface (as demarcated by the opaque packing) at the midpoint of the applicator system or at the level of the flange if no ovoids are used.

6.4.6.6 **Vaginal Surface Dose**: Calculated at the vaginal surface lateral to the midpoint at the surface of the ovoid. If no ovoids are used (tandem only), the vaginal surface point will be placed just lateral to the packing at the level of the cervical os (cervical flange marking the os or marker seeds).

6.4.6.7 **Suggested maximum cumulative (external + brachytherapy) doses to sensitive structures for patients treated with LDR implant**: Small Intestine: 60 Gy; Bladder: 80 Gy; Rectum: 70 Gy; Vaginal Surface: 135 Gy.

6.4.6.8 **Suggested maximal doses to normal tissue for HDR**: It is recommended that the rectum and bladder for each fraction receive less than or equal to 70% and 80% of the point A dose, respectively. As in LDR brachytherapy, every attempt should be made to deliver tumoricidal doses, even if the late responding tissues receive a slightly higher dose. In order to stay below an LDR equivalent of 70 Gy to the rectum for five HDR insertions (120 Gy³), including the 45 Gy contribution from the external beam radiation, the rectum (rectal reference point) should receive less than 4.1 Gy for each HDR fraction of 6 Gy (68% of the prescribed dose to Point A). The dose to the bladder (bladder reference point) should be less than 4.6 Gy per each HDR fraction of 6 Gy (77% of the prescribed dose to Point A).

6.4.6.9 **Dosimetry to be Reported**:

- Total dose to point A
- Total dose to point B
- Total bladder dose (bladder point)
- Total rectal dose (rectal point)
- Maximal total vaginal reference surface dose
- Central axis isodose curve

6.5 **Documentation Requirements** *(8/31/06, 5/11/07)*

Institutions that have completed the following compliance review for brachytherapy cases in RTOG GYN protocols may enroll patients on this study without further patient review.

**Compliance**: Low dose rate (LDR) or high dose rate (HDR) brachytherapy can be employed in this study. The first intracavitary implants performed on two patients (both LDR and HDR) at each institution will be reviewed directly by the Radiological Physics Center (RPC) with rapid
feedback. The following data needs to be submitted to the RPC: for HDR, submit a completed RTOG Gynecological Brachytherapy Compliance Form (see RPC website http://rpc.mdanderson.org for instructions and forms), treatment plan, isodose plots, treatment tapes and images for CT-based planning (AP and lateral); for LDR, submit a completed RTOG Gynecological Brachytherapy Compliance Form (see RPC website http://rpc.mdanderson.org for instructions and forms), treatment plan, isodose plots, source activity, source loading, treatment time and films (AP and lateral). The films and dosimetry will be sent within 2 working days to the RPC at MD Anderson Cancer Center:

Radiological Physics Center
Attn: Joye Roll
Courier Address: 7515 S. Main Street
Green Park 1, Suite 300
Houston, TX 77030-4502
Phone: 713-745-8989

Low dose rate (LDR) or high dose rate (HDR) brachytherapy will be employed in this study. If the plan is found to be compliant, a letter will be sent to the institution indicating that the treatment plan was found to be protocol compliant. If the plan is not compliant, a phone call will be made to the institution from one of the reviewers.

6.6 Compliance Criteria

6.6.1 Radiation Treatment Interruption
There will be no specific guidelines regarding the holding of radiotherapy for toxicities including cytopenias. This will be left to the discretion of the treating radiation oncologist. Any radiotherapy treatment interruptions should be recorded including the reason for the treatment break. The radiation oncologist is encouraged to keep treatment breaks to a minimum. Usually radiotherapy will continue if cisplatin is held for mild/moderate cytopenias.

6.6.2 Protocol Compliance
Field Borders
- Per Protocol: Up to 1 cm beyond borders as stated in protocol
- Variation Acceptable: > 1 to 2 cm beyond borders as stated in protocol
- Deviation Unacceptable: > 2 cm beyond borders as stated in protocol
Total Dose
- Per Protocol: ≤ 5% of prescribed dose
- Variation Acceptable: > 5% or ≤ 10% of prescribed dose
- Deviation Unacceptable: > 10% of prescribed dose
Elapsed Days
- Per Protocol: ≤ 56 days
- Variation Acceptable: > 56 days but ≤ 63 days
- Deviation Unacceptable: > 63 days

6.7 R.T. Quality Assurance Reviews
The Radiation Oncology Principal Investigator, Tracey Schefter, MD, will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RPC. Dr. Schefter will perform the next review after complete data for the next 20 cases enrolled has been received at RPC. The final cases will be reviewed within 3 months after this study has reached the target accrual and/or as soon as complete data for all cases enrolled has been received at RPC. These reviews will be ongoing.

6.8 Radiation Adverse Events
6.8.1 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, low blood counts. Common long-term effects include vaginal narrowing, shortening, dyspareunia and induction of menopause. Long-term side effects, although uncommon, may include rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, vaginal vault necrosis.
Rare long-term effects include bowel obstruction, ureteral obstruction, and vesicovaginal or rectovaginal fistula.

6.8.2 All toxicities will be recorded on data collection forms.

7.0 DRUG THERAPY

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

7.1 Bevacizumab (rhuMAB VEGF, Avastin® NSC# 704865) (5/11/07, 8/27/08)

Bevacizumab (10 mg/Kg will be given intravenously every 2 weeks (Days 1, 15 and 29) for 3 doses during chemoradiation. Bevacizumab will be given on the same day as weekly cisplatin, and will be given before cisplatin.

7.1.1 Classification: Recombinant humanized monoclonal antibody

7.1.2 Molecular Weight: Approximate molecular weight is 149,000 daltons.

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

7.1.4 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.

7.1.5 How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes:

- Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
- Each 400 mg (25 mg/mL – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for injection, USP.

7.1.6 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 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, Room 7149, Bethesda, MD 20892. All forms can be accessed on the NCI web site, [http://ctep.cancer.gov/forms/index.html](http://ctep.cancer.gov/forms/index.html).

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.

7.1.7 Drug Inventory Records: The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD, using the NCI Drug Accountability Record Form (see the NCI Investigators Handbook for Procedures for Drug Accountability and Storage).

7.1.8 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.

7.1.9 Storage: Upon receipt, bevacizumab should be refrigerated (2º to 8º C). Do not freeze. Do not shake.

7.1.10 Stability: Shelf-life studies of rhuMAB VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Therefore vials should be discarded 8 hours after initial entry.
Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.

7.1.11 Route of Administration: Intravenous

7.1.12 Method of Administration: The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, the third dose can be administered between 30 and 60 minutes. 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, the IV infusion line must be flushed 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 50 mL 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 50 mL bag or 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.
### Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (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.cancer.gov/reporting/adeers.html](http://ctep.cancer.gov/reporting/adeers.html) for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Bevacizumab.

**Version 1.2, June 19, 2007**

<table>
<thead>
<tr>
<th>Category (Body System)</th>
<th>Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)</th>
<th>'Agent Specific Adverse Event List' (ASAEL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGY/IMMUNOLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</td>
<td>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</td>
<td></td>
</tr>
<tr>
<td><strong>BLOOD/BONE MARROW</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Leukocytes (total WBC)</td>
<td>Leukocytes (total WBC)</td>
<td></td>
</tr>
<tr>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td></td>
</tr>
<tr>
<td><strong>CARDIAC ARRHYTHMIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular arrhythmia NOS</td>
<td>Supraventricular arrhythmia NOS</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CARDIAC GENERAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>Cardiac ischemia/infarction</td>
<td></td>
</tr>
<tr>
<td>Cardiac troponin I (cTnl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CONSTITUTIONAL SYMPTOMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td></td>
</tr>
<tr>
<td>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10^9/L)</td>
<td>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10^9/L)</td>
<td></td>
</tr>
<tr>
<td>Rigors/chills</td>
<td>Rigors/chills</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DERMATOLOGY/SKIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus/itching</td>
<td>Pruritus/itching</td>
<td></td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>Rash/desquamation</td>
<td></td>
</tr>
<tr>
<td>Urticaria (hives, welts, wheals)</td>
<td>Urticaria (hives, welts, wheals)</td>
<td></td>
</tr>
<tr>
<td>Wound complication, non-infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Fistula, GI - Select</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heartburn/dyspepsia</td>
<td>Heartburn/dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Ileus (functional obstruction of bowel, i.e., neuroconstipation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leak (including anastomotic), GI: large bowel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Category (Body System)</td>
<td>Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)</td>
<td>'Agent Specific Adverse Event List' (ASAEL)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>HEMORRHAGE</strong>/BLEEDING</td>
<td>Perforation, GI - Select&lt;br&gt;Ulcer, GI - Select&lt;br&gt;Vomiting</td>
<td>Hemorrhage GI - Select&lt;br&gt;Hemorrhage, CNS&lt;br&gt;Hemorrhage, GU: vagina&lt;br&gt;Hemorrhage, pulmonary/upper respiratory: lung&lt;br&gt;Hemorrhage, pulmonary/upper respiratory: nose</td>
</tr>
<tr>
<td>INFECTION</td>
<td>Infection with normal ANC or Grade 1 or 2 neutrophils - Select&lt;br&gt;Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound)</td>
<td></td>
</tr>
<tr>
<td>METABOLIC/LABORATORY</td>
<td>Alkaline phosphatase&lt;br&gt;ALT, SGPT (serum glutamic pyruvic transaminase)&lt;br&gt;AST, SGOT (serum glutamic oxaloacetic transaminase)&lt;br&gt;Bilirubin (hyperbilirubinemia)&lt;br&gt;Creatinine&lt;br&gt;Proteinuria</td>
<td>Alkaline phosphatase&lt;br&gt;ALT, SGPT (serum glutamic pyruvic transaminase)&lt;br&gt;AST, SGOT (serum glutamic oxaloacetic transaminase)&lt;br&gt;Bilirubin (hyperbilirubinemia)&lt;br&gt;Creatinine&lt;br&gt;Proteinuria</td>
</tr>
<tr>
<td>NEUROLOGY</td>
<td>CNS cerebrovascular ischemia&lt;br&gt;Dizziness&lt;br&gt;Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS])</td>
<td>CNS cerebrovascular ischemia&lt;br&gt;Dizziness</td>
</tr>
<tr>
<td>PAIN</td>
<td>Pain - abdomen NOS&lt;br&gt;Pain - chest/thorax NOS&lt;br&gt;Pain - head/headache&lt;br&gt;Pain - joint&lt;br&gt;Pain - muscle&lt;br&gt;Pain - NOS</td>
<td>Pain - abdomen NOS&lt;br&gt;Pain - chest/thorax NOS&lt;br&gt;Pain - head/headache&lt;br&gt;Pain - joint</td>
</tr>
<tr>
<td>PULMONARY/UPPER RESPIRATORY</td>
<td>Bronchospasm, wheezing&lt;br&gt;Cough&lt;br&gt;Dyspnea (shortness of breath)&lt;br&gt;Fistula, pulmonary/upper respiratory - Select&lt;br&gt;Nasal cavity/paranasal sinus reactions&lt;br&gt;Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)&lt;br&gt;Pulmonary/Upper Respiratory - Other (nasal-septal perforation)</td>
<td>Cough&lt;br&gt;Dyspnea (shortness of breath)&lt;br&gt;Nasal cavity/paranasal sinus reactions&lt;br&gt;Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)</td>
</tr>
<tr>
<td>RENAL/GENITOURINARY</td>
<td>Fistula, GU - Select&lt;br&gt;Renal failure</td>
<td></td>
</tr>
<tr>
<td>SYNDROMES</td>
<td>Cytokine release syndrome/acute infusion reaction</td>
<td>Cytokine release syndrome/acute infusion reaction</td>
</tr>
<tr>
<td>VASCULAR</td>
<td>Thrombosis/thrombus/embolism&lt;br&gt;Visceral arterial ischemia (non-myocardial)</td>
<td>Thrombosis/thrombus/embolism</td>
</tr>
</tbody>
</table>

*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 ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.*
Also reported on bevacizumab trials but with the relationship to bevacizumab still undetermined:

BLOOD/BONE MARROW - Idiopathic thrombocytopenia purpura; platelets
CARDIAC GENERAL - Cardiac arrest; pericardial effusion; pulmonary hypertension
COAGULATION - DIC
DEATH - Sudden death (cause unknown)
DERMATOLOGY/SKIN - Hypopigmentation
GASTROINTESTINAL - Rectal abscess/necrosis; small bowel obstruction; taste alteration
METABOLIC/LABORATORY - Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia
MUSCULOSKELETAL/SOFT TISSUE - Aseptic necrotic bone; gait/walking; myasthenia gravis
NEUROLOGY - Aseptic meningitis; confusion; peripheral neuropathy; seizure; syncope
OCULAR/VISUAL - Cataract; watery eye
PULMONARY/UPPER RESPIRATORY - ARDS; pneumonitis/pulmonary infiltrates; pneumothorax
RENAL/GENITOURINARY - Urinary frequency

Note: Bevacizumab 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.

7.1.14 Dose Definition: The dose of bevacizumab is 10 mg/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 of > 10% from baseline.

7.1.15 Technique of Administration: The first dose of bevacizumab is administered by intravenous infusion over 90 minutes prior to cisplatin chemotherapy. If this is well tolerated, the next cycle of bevacizumab 2 weeks later can be administered over 60 minutes. Premedications are administered as per institutional protocol.

7.1.16 Duration of Treatment: Bevacizumab will be administered in 3 cycles, on days 1, 15, 29, and each cycle will be administered on the same day as cisplatin chemotherapy. Bevacizumab will be administered prior to cisplatin, and radiotherapy will follow completion of chemotherapy. 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. Bevacizumab treatment will only be administered during external beam radiotherapy. No further bevacizumab will be administered during brachytherapy or after completion of radiotherapy.

7.1.17 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) contained within the terms of award, apply to the use of the Agent(s) in this study:

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.

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"):

- 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.
• 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.

• 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.

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.

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.

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.

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(s) 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 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.

7.2 Cisplatin (8/27/08)

Cisplatin and external beam treatment should be initiated on a Monday or Tuesday (day 1) and given concurrently. It is also acceptable to initiate cisplatin and radiation on a Wednesday; however, for the second and subsequent weeks, cisplatin and bevacizumab should be moved to Monday or Tuesday. Cisplatin will be given weekly with external beam radiation therapy and once with LDR brachytherapy for a total of six doses. When given with LDR brachytherapy it should be administered after the applicators are placed. Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control Guidelines stated in the RTOG Procedure Manual.

7.2.1 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.

### 7.2.2 Administration

Patients will be prehydrated 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.

### 7.2.3 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.

### 7.2.4 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 of cisplatin. Renal adverse events have been noted in 28-36% of patients treated with a single dose of 50 mg/m². 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.

**Ototoxicity:** Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m². It is manifested by tinnitus and/or hearing loss in the high frequency range. Deafness has been reported 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 greater dose frequency 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 SGOT (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 occurred.

### 7.2.5 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.

### 7.2.6 Pharmaceutical data

Cisplatin (cis-diamminedichloroplatinum II) has the empiric formula NZ2Cl2 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.

### 7.2.7 Supply

This drug is commercially available.

### 7.2.8 Duration of administration

Cisplatin is administered once a week (starting on Monday, day 1) during external beam radiotherapy (Days 1, 8, 15, 22, 29) and during the parametrial boost.
Radiotherapy will continue if toxicity is specifically attributable to cisplatin. Cisplatin chemotherapy will not be administered after radiotherapy is completed.

7.3 Treatment

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.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab*</td>
<td>10 mg/kg</td>
<td>IV</td>
<td>Q2 weeks (Days 1, 15 &amp; 29) during chemoradiation; prior to cisplatin</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>40 mg/m²</td>
<td>IV</td>
<td>1 hour infusion weekly x 6 weeks</td>
</tr>
</tbody>
</table>

*See Section 9.4.1 - proton pump inhibitors are required.

7.4 Dose Modifications (8/27/08)

7.4.1 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:

Treatment Modification for Bevacizumab-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>CTCAE.v3.0 Grade</th>
<th>Action to Be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions, or Acute infusional reactions/ cytokine release syndrome</td>
<td>Grade 1-3</td>
<td>If infusion-related or allergic reactions occur, premeds should be given with the next dose, and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in the Section 7.1.12 for bevacizumab administration. For patients with Grade 3 reactions, bevacizumab infusion should be stopped and not restarted on the same day. At the physicians’ discretion, bevacizumab may be permanently discontinued or re-instituted with premeds and at a rate of 90+15 min. If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions. Grade 4: Discontinue bevacizumab</td>
</tr>
<tr>
<td>Arterial Thrombosis</td>
<td>&gt; Grade 2</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>• Cardiac ischemia/ infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CNS ischemia (TIA, CVA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• any peripheral or visceral arterial ischemia/thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous Thrombosis</td>
<td>Grade 3 OR asymptomatic Grade 4</td>
<td>Discontinue bevacizumab if full-dose anticoagulation is required (warfarin, unfractionated heparin, or low-molecular weight heparin)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 4 (symptomatic)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td></td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Controlled BP</td>
<td></td>
<td>Continue bevacizumab</td>
</tr>
<tr>
<td>Symptomatic or persistent HTN with systolic</td>
<td>Hold bevacizumab</td>
<td></td>
</tr>
<tr>
<td>&gt;160 or diastolic &gt;90 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td>Discontinue bevacizumab.</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td>Discontinue bevacizumab.</td>
</tr>
<tr>
<td>[Proteinuria should be monitored by urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>analysis for urine protein creatinine (UPC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio prior to every dose of bevacizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPC ratio &lt; 3.5</td>
<td>Continue bevacizumab.</td>
<td></td>
</tr>
<tr>
<td>UPC ratio &gt; 3.5</td>
<td>Hold bevacizumab until</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UPC recovers to &lt; 3.5.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 or nephrotic syndrome</td>
<td>Discontinue bevacizumab.</td>
<td></td>
</tr>
<tr>
<td>Wound dehiscence requiring medical or</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td>surgical intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI perforation, GI leak or ANY fistula</td>
<td>Discontinue bevacizumab</td>
<td></td>
</tr>
<tr>
<td>(GI or other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Within the radiation field Grade &gt; 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td>Patients who require full-dose anticoagulation should discontinue bevacizumab.</td>
</tr>
<tr>
<td>Outside the radiation field Grade 3</td>
<td></td>
<td>For patients not requiring full-dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anticoagulation, hold bevacizumab until</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALL of the following criteria are met:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- the bleeding has resolved and Hg is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- there is no bleeding diathesis that</td>
</tr>
<tr>
<td></td>
<td></td>
<td>would increase the risk of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- there is no anatomic or pathologic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>condition that could increase the risk of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hemorrhage recurrence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients who experience recurrence of grade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 hemorrhage should discontinue study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>therapy.</td>
</tr>
<tr>
<td>Other clinically significant AEs</td>
<td></td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>attributable to bevacizumab (except</td>
<td></td>
<td></td>
</tr>
<tr>
<td>controlled nausea/vomiting)</td>
<td>Grade 3</td>
<td>Hold bevacizumab until symptoms resolve to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; grade 1. If treatment delay is &gt;2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>due to toxicity, discontinue bevacizumab.</td>
</tr>
</tbody>
</table>
| 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 unlikely to recur with retreatment.** |
| 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.** |
### Dose Modifications for Cisplatin

Based on blood work performed prior to each cycle

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Threshold</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>≥ 1.5 mg/dl</td>
<td>Hold chemotherapy, repeat blood chemistry in one week; if below threshold then resume at 40 mg/m²; if not hold for 1 more week. If more than 2 treatments missed then discontinue chemotherapy.</td>
</tr>
<tr>
<td>ANC</td>
<td>&lt; 1000 mg/m</td>
<td>Hold for that week and use G-CSF for 3 days, repeat CBC diff. next week. If above threshold then treat with 40 mg/m², otherwise hold, use G-CSF for 3 days and repeat CBC &amp; diff next week. If more than 2 treatments missed then discontinue chemotherapy.</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt; 100,000</td>
<td>Hold for that week, repeat CBC diff. next week; if above threshold treat 40 mg/m², otherwise hold and repeat CBC diff. next week. If more than 2 treatments missed then discontinue chemotherapy.</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≥ 2 x ULN*</td>
<td>Hold for that week and repeat blood chemistry next week; treat 40 mg/m² only if below threshold; if more than 2 treatments missed then discontinue chemotherapy.</td>
</tr>
<tr>
<td>ALT</td>
<td>≥ 3 x ULN*</td>
<td>Hold for that week and repeat blood chemistry next week; treat 40 mg/m² only if below threshold, if more than 2 treatments missed then discontinue chemotherapy.</td>
</tr>
<tr>
<td>Platinum-related neuropathy</td>
<td>≥ grade 2</td>
<td>Discontinue chemotherapy</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>≥ grade 2</td>
<td>Discontinue chemotherapy</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Temp 38.5°C w/ AGC &lt; 1,000</td>
<td>Hold chemotherapy, use G-CSF for 3 days; if AGC &gt;1,000 the following wk, resume chemotherapy</td>
</tr>
</tbody>
</table>

* ULN = upper limit of institutional normal.
7.4.3 If chemotherapy is held, radiation therapy will continue. (If chemotherapy is held for toxicity the missed treatments are not completed after RT ends. Chemotherapy stops at the completion of RT.)

7.4.4 If radiation therapy is held, then chemotherapy will also be held.

7.5 Criteria for Removal from Protocol Treatment
See Section 11.3

7.6 Modality Review
The Gynecologic Oncology Co-Chair, Janice Kwon, MD will perform a Chemotherapy Assurance Review of all patients. 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. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.7 Adverse Events (8/17/2011)
Beginning October 1, 2011 this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE v4.0. All AE reporting on the study case report forms will continue to use CTCAE version 3.0. 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/ResearchAssociates/AdverseEventReporting.aspx 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.

7.7.1 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: Expedited Adverse Event Reporting Requirements. December 2004.]

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 7.8 also must be reported via AdEERS.

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.

7.7.2 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 drug 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 drug experience, 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. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.] Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically sponsored 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 study/case numbers and 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. **Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

**7.7.3 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 via the AdEERS system. 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.

**7.8 AdEERS Expedited Reporting Requirements (8/27/08)**

CTEP defines expedited AE reporting requirements for phase 2 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 Trial Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agent (bevacizumab) in this Study**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected with Hospitalization</td>
<td>Unexpected</td>
<td>Expected</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

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.

**8.0 SURGERY (5/11/07, 8/27/08)**

A biopsy confirming primary cervical cancer (squamous, adenocarcinoma, or adenosquamous histology) must be obtained prior to patient registration. In addition, see Section 10.1 concerning optional biopsies for biological correlative studies.

Planned hysterectomy is not allowed. Hysterectomy for salvage of recurrent/persistent cervical cancer is allowed but must not occur sooner than 8 weeks after completion of chemoradiation.
Unrelated elective surgery must not occur sooner than 8 weeks after the last dose of bevacizumab.

9.0 OTHER THERAPY

During treatment: If Hgb < 10 g/l it is recommended to transfuse to Hgb > 10 g/l.

9.1 Permitted Supportive Therapy/Procedures

9.1.1 Antiemetics
9.1.2 Low molecular weight heparin at prophylactic (not therapeutic) doses.
9.1.3 Warfarin at < 1 mg
9.1.4 Antidiarrheals
9.1.5 Analgesics
9.1.6 Hematopoietic Growth Factors except erythropoietin.
9.1.7 Herbal products except St John’s Wort
9.1.8 Nutritional supplementation
9.1.9 Upper endoscopy should be performed as clinically directed.

9.2 Permitted Post-Treatment Therapy

9.2.1 Warfarin sodium may be used beginning 2 weeks after chemoradiation is completed.

9.3 Non-permitted Supportive Therapy

9.3.1 Erythropoietin
9.3.2 St. John’s Wort
9.3.3 Anticoagulants at therapeutic doses
9.3.4 Transvaginal irradiation or any external beam to control bleeding

9.4 Required Concomitant Medications (8/27/08)

9.4.1 All patients must be on a proton pump inhibitor (any proton pump inhibitor is acceptable, but examples include lansoprazole, omeprazole, pantoprazole sodium, rabeprazole sodium). If any new epigastric pain develops, ulceration should be expected and sucralfate should be started.

10.0 PATHOLOGY (8/27/08)

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each specimen is preserved through careful 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. These 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.

TISSUE/SPECIMEN SUBMISSION

In this study, tissue submission for banking is highly encouraged but not mandatory for participation in this protocol. The RTOG Biospecimen Resource will provide a kit with all applicable instructions for the submission of the samples in this protocol. The samples, which are optional, include fixed tissue; fresh tissue in RNA later; serum, plasma anduffy coat aliquotted into cryovials; and frozen urine samples. Collection kits will be provided at no charge by contacting the Biospecimen Resource (see 10.1.5 for contact information). Kit contents and collection instructions can be found in Appendix IX.

10.1 Fixed Tissue/Specimen Submission for Banking (Optional) (8/11/06, 8/27/08)

For consenting patients, tissue from two biopsies for biological correlative studies will be obtained: one prior to treatment; and one at the time of first brachytherapy. (For tissue banking purposes, the biopsy performed for tissue diagnosis may be combined with the pretreatment biopsy.)

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

10.1.1 One H&E slide
10.1.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Biospecimen Resource. The Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.1.3 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.

10.1.4 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.

10.1.5 Submit materials for Tissue Banking and Translational Research to:

**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, DHL, 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

10.2 Fresh Tissue Submission for Banking/Translational Research (Optional) (8/11/06, 5/11/07, 8/27/08)

In this study, for consenting subjects, we will perform tumor tissue microarray testing for gene expression, proteomics, and immunohistochemistry for protein expression prior to treatment (within 14 days of starting chemoradiation) and at the time of the first implant. We may also perform RNA profiling and DNA SNP and methylation studies before treatment to study signatures associated with outcome. The microarray procedure allows for the simultaneous evaluation of over 20,000 separate gene sequences that have been sequence-verified. This includes over 4000 known genes. To accomplish these studies, biopsies of the cervix are highly recommended (but not mandatory) prior to treatment and at the first implant.

Gene expression utilizing microarray technology has been evaluated in a wide variety of neoplasms. Microarray technology allows for the simultaneous evaluation of thousands of genes. In addition, evaluation of tumor specimens for COX-2, VEGF, bFGF, MVD, and TUNEL staining for apoptosis prior to treatment and at the time of the first implant will provide powerful insights into the response of particular genes or genetic pathways after therapy with radiation, cisplatin, and bevacizumab. Genetic mutational analysis on the tumor DNA as well as RNA profiling tissue will also be done and correlated with long-term outcome and toxicities of treatment.

10.2.1 After the patient has been registered on the study and has consented to fresh tissue banking, the participating institution will contact the RTOG Biospecimen Resource (Section 10.1.5) to obtain the RNALater™ media. Institutions must have IRB approval and the RTOG case number before requesting the media from the Biospecimen Resource. Two vials of RNALater™ and instructions will then be mailed overnight to the requesting institution. One vial will be used for tissue collection prior to treatment, and the other vial will be used for tissue collection at the time of the first implant. RNA later may be stored in the refrigerator until the second specimen is obtained.

10.2.2 To perform the tumor tissue biologic endpoints, > 300 mg of cervical tumor tissue (2 mm core) is collected both prior to treatment and at the time of the first implant. Usually, this amount of tissue can be obtained with three passes of a Tischler biopsy forceps. The sample should be placed in RNALater™ for microarray analysis and immunohistochemistry, and mailed via overnight mail to the RTOG Biospecimen Resource (see Section 10.2.2.3). In select patients, a core biopsy, Novak endometrium suction curette, or a Kevourkian-Younge endocervical biopsy curette may be more appropriate secondary to location of tumor.

10.2.3 The following must be provided for the fresh tissue submission:
10.2.3.1 A sample in RNAlater™. The sample must be clearly labeled with the study and case numbers as well as the pathology identification number that corresponds to the Pathology Report.

10.2.3.2 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.

10.2.3.3 Submit materials for Tissue Banking and Translational Research to:

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, DHL, 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

10.3 Peripheral Blood Collection for Banking/Translational Research (Optional) (8/11/06, 5/11/07, 8/27/08)

Serum samples for consenting subjects will collected according to Section 10.3.1 and will be banked for future cytokine analysis. Future analysis will include RNA and DNA studies as described in Section 10.2.

Cytokine analysis will be performed using commercially available ELISA kits according to manufacturer’s instructions.

For 2-D electrophoresis, serum samples will be pre-cleared with Protein G and anti-HSA spin columns to remove IgG and serum albumin, respectively. Samples will be desalted and concentrated using Microcon centrifugal filters (Millipore) and the protein concentrations will be determined. For electrophoresis, 300 µg of protein will be separated in the first dimension by isoelectric focusing (IEF), followed by size separation with SDS-PAGE. Gels will be silver-stained, and variant proteins will be identified by MALDI-TOF MS.

10.3.1 Peripheral blood specimens recommended for submission include three serum-separator tubes (8-10 mL tubes with clot activator) collected at the following time points:
- Within 14 days prior to starting chemoradiation (preferably, at the time of biopsy);
- At the time of the first implant;
- Mid-treatment (at approximately week 4);
- During the last week of chemoradiation; and
- 4 to 8 weeks following completion of chemoradiation.

10.3.2 Keep serum collection tubes at 4°C until processing (tubes may be on ice up to 2 hrs). Centrifuge specimens at 1000 x g (approximately 2500 RPM for standard clinical centrifuge) at 4°C for 10 minutes.

10.3.3 Using sterile techniques to avoid contamination, aliquot 0.5-1 mL serum into nine (9) cryovials and freeze. Take great care to collect only serum and avoid collecting any solid particulate matter into the cryovials.

For plasma and buffy coat:
- Collect blood into two 3–5 mL purple-topped tubes (these should contain EDTA), using a 19–21 gauge needle to minimize hemolysis.
- Store blood tubes vertically at 4°C, avoiding any kind of agitation. Ideally these should be processed within 30 minutes.
- Centrifuge at a gravity (RCF) 3,000G (NOT AT SPEED, rpm) for 30 minutes with the brake off and at 4°C.
For plasma, take only the top two-thirds of supernatant and aliquot to a 0.5 mL/vial. The tip of the transfer pipette should be kept far away (at least 0.5 cm) from the buffy coat (this is very important in order to avoid platelet contamination).

For buffy coat, collect this after collecting the plasma supernatant. **Buffy coat only needs to be collected at one time point.** Inclusion of a small amount of the remaining supernatant and the red cells below the coat is acceptable to maximize the yield of the buffy coat. Aliquot to a 0.5 mL/vial.

10.3.4 Label each aliquot with study protocol and case numbers, the date and time of collection, and the time point taken.

10.3.5 Place specimens in freezer or ship immediately on dry ice.

10.3.6 The following materials must be provided to the RTOG Biospecimen Resource:

10.3.6.1 A Specimen Transmittal Form documenting the date and time of collection of the specimen; the RTOG protocol number, the patient’s case number, and method of storage, for example, stored at -20°C, must be included.

10.3.6.2 Blood samples should be sent to:

**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, DHL, 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

10.4 **Urine Specimens for Banking/Translational Research (Optional) (8/11/06, 8/31/06, 5/11/07, 8/27/08)**

Urine samples will be tested using a commercial Elisa system for VEGF, (R&D systems). Urine samples will also have creatinine levels measured by the clinical pathology department for standardization of the VEGF levels in the urine.

Urine will be evaluated by the laboratory of Marsha Moses for MMP activity using gel zymography. These results will be evaluated by two observers blinded to the clinical profile of the patient who supplied the sample. A binary evaluation of low-MW MMP, MMP-2, MMP-9 and high MW-MMP will be made. Each of the five MMPs will be scored as absent (0) or present (1). The five values for each MMP will be cumulated for each patient to create an MMP score from 0-5.

10.4.1 A minimum of 20 ml urine should be collected in a sterile collection cup, then aliquotted into 4 tubes (each with a minimum of 5 ml) labeled with patient ID, date and time of collection, and placed into a freezer (-20°C) for storage.

10.4.2 Urine specimens will be collected at the following time points:

- Within 14 days prior to starting chemoradiation (preferably, at the time of biopsy);
- At the time of the first implant;
- During the last week of chemoradiation; and
- 4 to 8 weeks following completion of chemoradiation.
10.4.3 Urine samples should be sent to:

**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, DHL, 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

From there, the Biospecimen Resource will forward the samples to Dr. Camphausen, NCI, for VEGF testing and to Marsha Moses, Children’s Hospital, Harvard Medical School for MMP testing.

10.5 Specimen Collection for Central Review

There will be no central review of pathology materials.

10.6 Specimen Shipping (8/27/08)

All patient specimens should be shipped to the RTOG Biospecimen Resource at the University of California San Francisco. Patient specimens must be scheduled to arrive at the Biospecimen Resource ONLY at a time when the lab is open. Thus, ship the specimen Monday-Thursday only. Do not mail any specimen so that it is scheduled to arrive on days or at times when the lab is closed, e.g., holiday, weekends, or after hours. This requirement may impact the scheduling of the biopsy or may require additional preparation or processing to preserve the specimen. Call the Biospecimen Resource if contingencies are not covered by these instructions.

10.7 Reimbursement (8/27/08)

RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue; $200 per case for a block or core of material; $300 per case for complex material (blood, serum, buffy coat cells); $50 per time point for urine up to $150. After confirmation from the Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.8 Confidentiality/Storage (8/31/06, 5/11/07, 8/27/08)


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 for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the specimen is consumed/exhausted or when 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, the material will be returned to the institution that submitted it.
### Optional Specimens for Tissue Banking Evaluation

<table>
<thead>
<tr>
<th>Specimens taken from patient</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One H&amp;E stained slide of the primary tumor</td>
<td>H&amp;E stained slide</td>
<td>Slide shipped ambient</td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a skin punch</td>
<td>Paraffin-embedded tissue block or punch biopsy</td>
<td>Block or punch shipped ambient</td>
</tr>
<tr>
<td>&gt;300mg (2mm core) surgical sample from tumor taken prior to treatment and before 1st implant</td>
<td>1 sample of fresh tissue in RNAlater</td>
<td>Tissue in RNAlater shipped refrigerated via overnight carrier</td>
</tr>
<tr>
<td>5-10 mL of whole blood in Serum Separator Tube (SST) and centrifuge for serum <strong>NOTE</strong>: Collected at 4 different time points (Within 14 days prior to starting chemoRT; at the time of the first implant; during the last week of chemoRT; and 4 to 8 weeks following completion of chemoRT)</td>
<td>Nine (9) serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials</td>
<td>Serum sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>A minimum of 20 mL urine per time point <strong>NOTE</strong>: Collected at 4 different time points (Within 14 days prior to starting chemoRT; at the time of the first implant; during the last week of chemoRT; and 4 to 8 weeks following completion of chemoRT)</td>
<td>A minimum of 20 mL unpreserved urine in a sterile collection container per time point, aliquotted into 4 tubes (each with a minimum of 5 ml)</td>
<td>Urine sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>6-8 mL of plasma</td>
<td>Six (6) samples of plasma containing a minimum of 0.5 mL per aliquot in 1 mL cryovials.</td>
<td>On dry ice via overnight carrier</td>
</tr>
<tr>
<td>2 samples of buffy coat. <strong>NOTE</strong>: Only needs to be collected at one time point.</td>
<td>Two (2) samples of buffy coat in 1 mL cryovials.</td>
<td>On dry ice via overnight carrier</td>
</tr>
</tbody>
</table>
### 11.1 Study Parameters (5/11/07, 8/27/08, 1/6/09)

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>Pre-treatment</th>
<th>Weekly during CRT &amp; radioactive insertions</th>
<th>Prior to each brachytx procedure</th>
<th>Prior to each bev</th>
<th>4-6 wks Post RT</th>
<th>F/U every 3 mos to yr 2</th>
<th>F/U every 4 mos yr 3</th>
<th>F/U every 6 mos yrs 4-5</th>
<th>F/U yearly &gt; 5 years</th>
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<tbody>
<tr>
<td>History and PE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>ZPS</td>
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<td>X</td>
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<tr>
<td>Pelvic exam</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Diagnostic biopsy</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray, CT, or PET-CT</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CT/MRI/PET-CT of pelvis/abdomen to include para-aortic lymph node evaluation</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>INR</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/differential/platelet count</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>U/A calculation of Urine Protein Creatinine Ratio</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Creatinine, total bilirubin, AST and ALT, calcium</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Magnesium, electrolytes, BUN, alk phosphatase</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count (for patients known to be HIV positive)</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Serum Pregnancy test&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adverse events Assessment</td>
<td>X</td>
<td></td>
<td></td>
<td>_</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor response</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tbody>
</table>
Optional Banking Studies (for consenting patients)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>At Time of 1st Implant</th>
<th>At CRT Midpoint (approx. wk 4)</th>
<th>During Last Wk of CRT</th>
<th>4-8 Wks Post CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue(^a)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood(^f)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine(^g)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- a. Within 8 weeks prior to study entry.
- b. Within 21 days prior to study entry.
- c. All women of childbearing age.
- d. Every 6 mos for 3 yrs and then annually.
- e. See Section 10.1 for timing details.
- f. See Section 10.3.1 for timing details.
- g. See Section 10.4.2 for timing details.
11.2 Response Assessment (RECIST Criteria)

11.2.1 Measurement of Response


Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

- **Measurable disease** - the presence of at least one measurable lesion; If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter $\geq 20$ mm using conventional techniques or $\geq 10$ mm with spiral CT scan.

- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter $< 20$ mm with conventional techniques or $< 10$ mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

**Response Criteria: Evaluation of target lesions**

- **Complete Response (CR):** Disappearance of all target lesions
- **Partial Response (PR):** At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.3 Criteria For Discontinuing Study Treatment

- **11.3.1** Progressive disease as defined in Section 11.2.1.
- **11.3.2** The development of unacceptable treatment toxicity as defined in 7.4.1 and 7.4.2.
- **11.3.3** Delay in chemotherapy of more than 2 weeks.
- **11.3.4** Delay in radiotherapy of more than 2 weeks.
**DATA COLLECTION**

Data should be submitted to:

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

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 (8/11/06)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>At the end of 6 cycles (6 cycles constitutes one course); Due within 1 wk of systemic tx end</td>
</tr>
<tr>
<td>Chemotherapy Treatment Form (TF)</td>
<td>q 3 mos from Day 1 of RT start to year 2; q 4 mos year 3; q 6 mos years 4-5; then yearly. Also at progression/relapse and at death</td>
</tr>
<tr>
<td>Follow up Form (F1)</td>
<td></td>
</tr>
</tbody>
</table>

External Beam Dosimetry

Radiotherapy Form (T1) (Copy to RPC)

Within 1 week post radiotherapy to RTOG

### 12.2 Summary of Data Submission to Radiological Physics Center (RPC) (8/31/06, 5/11/07)

Radiological Physics Center  
Attn: Joye Roll  
Courier Address: 7515 S. Main Street  
Green Park 1, Suite 300  
Houston, TX 77030-4502  
Phone: 713-745-8989

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDR/HDR Brachytherapy Dosimetry (*Refer to Section 6.5 for submission of first implant)</td>
<td>Within 1 week post radiotherapy to RPC</td>
</tr>
<tr>
<td>Final Dosimetry</td>
<td></td>
</tr>
<tr>
<td>Images (simulation and portal) (T3)*</td>
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</tr>
<tr>
<td>Calculations (T4)</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Images (T8) (if applicable)*</td>
<td></td>
</tr>
<tr>
<td>Gynecological Brachytherapy Compliance Form (I9)</td>
<td>Each implant</td>
</tr>
<tr>
<td>Intracavitary Images (T0)*</td>
<td>Each implant</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) (Copy to RTOG)</td>
<td></td>
</tr>
</tbody>
</table>

*CT on disc preferred.
13.0  STATISTICAL CONSIDERATIONS

13.1  Study Endpoints

13.1.1  Primary Endpoint

- Treatment-related serious adverse events (SAEs) and adverse events (AEs), specified below and defined by the CTCAE v. 3.0 criteria, occurring within 90 days of treatment start:

**Serious Adverse Events (SAEs):**

- ≥ Grade 4 vaginal bleeding
- ≥ Grade 4 thrombotic event
- ≥ Grade 3 arterial events (including vessel injury, visceral arterial ischemia, cardiac ischemia/infarction)
- ≥ Grade 3 GI bleeding (except transfusion due to tumor-related bleeding needed solely to optimize radiotherapy treatment)
- ≥ Grade 3 bowel or bladder perforation
- Any grade 5 treatment-related adverse event

**Adverse Events (AEs):**

- All SAEs defined above and:
- Grade 3 and 4 nausea, vomiting or diarrhea persistent for > 2 weeks despite medical intervention
- Grade 4 neutropenia or leukopenia which persists for > 7 days
- Febrile neutropenia defined as a temperature > 38.5 ºC and granulocytes < 1000/mm³
- Grade 3 and 4 hematologic toxicity with the exception of neutropenia and leukopenia
- Grade 3 and 4 GI, renal, cardiac, pulmonary, hepatic and neurological adverse events

13.1.2  Secondary Endpoints

13.1.2.1  Treatment-related SAEs and AEs at any time.

13.1.2.2  Disease-free survival (failure: local, regional or distant failure or death due to any cause).

13.1.2.3  Overall survival (failure: death due to any cause).

13.1.2.4  To collect tissue to perform future immunohistochemical analyses for angiogenic markers to correlate with clinical outcome; to collect tissue to perform future microarray testing for evaluation of gene expression.

13.1.2.5  To collect urine and serum for cytokine analysis.

13.1.2.6  To implement the image-based brachytherapy guidelines proposed by the Transatlantic Image-guided Brachytherapy Working Group and collect CT- or MRI-based dosimetry of brachytherapy applications used during the course of treatment for later analysis of feasibility and consistency as well as dose/volume assessments of tumor control and complications.

13.2  Sample Size

13.2.1  Sample Size Derivation:  The primary objective of this study is to estimate the rate of treatment-related SAEs and AEs, as defined in Section 13.1.1, for patients with locally advanced cervical carcinoma receiving radiation and weekly cisplatin and bevacizumab. Based on Lanciano’s study,34 an SAE rate of 5% and an AE rate of 35% are considered tolerable and an SAE rate ≥ 20% and an AE rate ≥ 55% will be considered excessive. With 51 evaluable cases (defined as eligible cases that begin protocol treatment), we have a 5% chance of rejecting the treatment when the SAE rate is 5% and the AE rate is 35%, and 90% chance of rejecting the treatment when the SAE rate is 20% and the AE rate is 55%. Adjusting this figure by 10% to allow for patient ineligibility or loss, a total sample size of 57 patients will be required for this study.

13.2.2  Patient Accrual:  RTOG Phase II (0128) and Phase III (9001) cervical cancer studies accrued an average of 4 patients per month. Based upon this accrual rate, and allowing 4 months for institutional IRB review and approval, accrual should be completed in approximately 19 months. If after the 4-month start-up time, the average monthly accrual is less than 2 cases per month, the study will be re-evaluated with respect to feasibility.

13.3  Suspension of Accrual Due to Excessive Treatment Related SAEs and AEs

13.3.1  Rate of Treatment-Related Serious Adverse Events (SAEs)

The rate of treatment-related SAEs (as defined in 13.1.1) will be evaluated at two time points during accrual: after 10 and 27 patients have been entered that are evaluable. After the first 10 evaluable patients have been entered, patient accrual will be temporarily suspended pending the results of this first interim adverse event analysis. The study chairs have determined that a rate of 20% or greater will be considered to be excessive. According to
Flemming’s method\textsuperscript{35} with a maximum overall significance level of 0.05 if there are: 1) 3 or more of the specified treatment related SAEs out of the first 10 evaluable patients, or 2) 4 or more of the specified treatment related AEs out of the first 27 evaluable patients the study will have exceeded the limit for the specified treatment related SAEs. If the number of specified AEs crosses a boundary, as described in the rules above, then the conclusion will be that the treatment-related specified SAE rate is greater than 20%. If this occurs, the study chairs, RTOG Gynecological Cancer Working Group Chair and the statistician will review the adverse event data and make appropriate recommendations to the RTOG Executive Committee about the study. These stopping rules provide > 93% power for concluding that the unacceptable adverse event rate is equal to or exceeds 20% when in fact that is the true rate.

RTOG HQ will send the results of the interim SAE analyses to the Protocol Information Office (PIO) at NCI.

13.3.2 Rate of Treatment-Related Adverse Events (AEs)
The rate of treatment-related AEs (as defined in 13.1.1) will be evaluated at two time points during accrual: after 10 and 27 patients have been entered that are evaluable. After the first 10 evaluable patients have been entered, patient accrual will be temporarily suspended pending the results of this first interim adverse event analysis. The study chairs have determined that a rate of 55% or greater will be considered to be excessive. According to Flemming’s method\textsuperscript{35} with a maximum overall significance level of 0.05 if there are: 1) 9 or more of the specified treatment related AEs out of the first 10 evaluable patients, or 2) 14 or more of the specified treatment related AEs out of the first 27 evaluable patients the study will have exceeded the limit for the specified treatment related AEs. If the number of specified AEs crosses a boundary, as described in the rules above, then the conclusion will be that the treatment-related specified AE rate is greater than 55%. If this occurs, the study chairs, RTOG Gynecological Cancer Working Group Chair and the statistician will review the adverse event data and make appropriate recommendations to the RTOG Executive Committee about the study. These stopping rules provide > 85% power for concluding that the unacceptable adverse event rate is equal to or exceeds 55% when in fact that is the true rate.

RTOG HQ will send the results of the interim AE analyses to the Protocol Information Office (PIO) at NCI.

13.3.3 Fatal Treatment Morbidity
If any fatal treatment-related adverse events occur, the event will be reported to the study chairs, the RTOG Gynecological Cancer Working Group Chair and the RTOG Executive Committee for review.

13.4 Analysis Plan (1/6/09)
13.4.1 Interim Reports
Interim reports will be prepared every six months until the primary endpoint results have been presented. In general, these reports include:
- the patient accrual rate with projected completion date
- institutional accrual
- pretreatment characteristics
- compliance rates of treatment delivery with respect to the protocol prescription
- the frequency and severity of SAEs and AEs due to protocol therapy

13.4.2 Analysis for Reporting the Initial Treatment Results
In the absence of early stopping (see Section 13.3.1), this analysis will be performed after all patients have been entered and followed for a minimum of 90 days. All eligible patients (as per Section 3.0) that begin protocol treatment will be included in the analysis. Based on Flemming’s method,\textsuperscript{35} if at this third and final look (assuming the early stopping rules per Section 13.3 were not met) we observe 6 or more cases with SAEs defined in Section 13.1.1 and/or 22 or more cases with the AEs defined in Section 13.1.1, we will reject treatment due to excessive SAEs and/or AEs. Otherwise, the treatment will be considered as acceptable with respect to SAEs and AEs. The initial treatment report will contain the following:
1. institutional accrual and study accrual rate
2. tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion
3. distribution of important prognostic baseline variables
4. compliance rates of treatment delivery with respect to the protocol prescription
5. observed results with respect to the primary endpoint described in Section 13.1.1.

13.4.3 Analysis for Reporting the Long-term Treatment Results
The second analysis of treatment results will be performed after all patients have been followed for at least 2 years. All eligible patients (as per Section 3.0) that begin protocol treatment will be included in the analysis. The focus of this analysis will be on disease recurrence patterns and long-term adverse events. Disease-free and overall survival rates will be estimated using the Kaplan-Meier method.36

13.4.4 Clinical Data Update System (CDUS) Monitoring
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.

13.4.5 RTOG Data Safety Monitoring Board
The RTOG Data Safety Monitoring Board (DSMB) for phase I and II trials will review this study twice per year in conjunction with the RTOG semi-annual meetings with respect to patient accrual and morbidity.

13.4.6 Inclusion of Women and Minorities
The study was designed to test the efficacy under the assumption of the same efficacy across all races. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, if the distributions allow, the possible difference in any of the above endpoints among racial groups will be investigated. Summary statistics of the percentage of minorities entered will be reported. Based on accrual statistics from RTOG 9001 and 0128, the following table provides the projected number of patients for each racial group.

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
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<td>12</td>
<td>N/A</td>
<td>12</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
<td>45</td>
<td>N/A</td>
<td>45</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td>0</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects*</td>
<td></td>
<td>57</td>
<td>N/A</td>
<td>57</td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
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<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>1</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Black or African American</td>
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<td>20</td>
<td>N/A</td>
<td>20</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
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<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>35</td>
<td>N/A</td>
<td>35</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects*</td>
<td></td>
<td>57</td>
<td>N/A</td>
<td>57</td>
</tr>
</tbody>
</table>

PROJECTED DISTRIBUTION OF GENDER AND MINORITIES
REFERENCES (5/11/07)


APPENDIX I (5/11/07, 8/27/08)

SAMPLE INFORMED CONSENT

RTOG 0417

A Phase II Study of Bevacizumab in Combination with Definitive Radiotherapy and Cisplatin Chemotherapy in Untreated Patients with Locally Advanced Cervical Carcinoma

This is a clinical trial, a type of research study. The study doctor will explain the clinical trial to you. You have the choice to participate in this clinical trial. Please take your time to make your decision about participating. 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 the study doctor for more explanation.

You are being asked to take part in this study because you have locally advanced cervical cancer. This means that you have cervical cancer that is advanced but still confined to the pelvis and it is best treated with radiation and chemotherapy instead of surgery.

Why is this study being done? (8/27/08)

The purpose of this study is to find out what effects, good and bad, the anti-cancer drug bevacizumab has when added to chemotherapy and radiation for your type of cervical cancer.

Standard treatment for locally advanced cervical cancer involves the use of radiation and cisplatin 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 FDA for use in colon cancer. The use of bevacizumab with chemotherapy and radiation in cervical cancer is experimental. Bevacizumab is the common name for the commercial drug Avastin®.

How many people will take part in the study?

About 57 people will take part in this study.

What will happen if I take part in this research study?

If you agree to participate in this study, you will receive bevacizumab, cisplatin and radiation therapy. The treatment will be given as follows:

Radiation Therapy and Cisplatin: you will receive an external radiation treatment lasting a few minutes a day, five days a week, for a period of five weeks. Once a week, 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.
Depending upon the size of the tumor, you may get additional external radiation treatments or one to two treatments of internal radiation (insertion of radioactive “seeds” in hollow tubes) into your uterus and vagina. These treatments will require a 2 to 3 day hospital stay, and these will happen 2 to 3 weeks apart. An alternative could include having five internal radiation treatments as an outpatient (without being admitted into the hospital). The study doctor will discuss these options with you.

**Bevacizumab**: On the same day as your first treatment with radiation and cisplatin, you will have your first treatment of bevacizumab by intravenous (IV) over 90 minutes as an outpatient at your institution. 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 by intravenous (IV) for 30-60 minutes.

**Before you begin the study you will need to have the following exams, tests or procedures to find out if you can participate in the study.** These exams, tests or 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 the study doctor.

1. Diagnostic biopsy
2. History and physical exam
3. Pelvic exam
4. Chest X-Ray, CT scan or PET-CT scan (PET scans or positron-emission tomography uses a combination of X-rays and computing equipment to create an image to see the exact size and location of your cancer)
5. CT scan, MRI or PET-CT scan of the abdomen, pelvis and lymph glands
6. Surgery under anesthetic-- biopsies of lymph glands if indicated by your physician
7. Pregnancy test, if applicable
8. Blood tests and urine analysis
9. Blood pressure screening

**During Chemotherapy, External Radiation Treatment, and Radioactive Insertions (5/11/07):**

- Weekly clinical exams
- Pelvic exam before each internal radiation (insertion of radioactive “seeds” in hollow tubes) into your uterus and vagina
- Blood tests weekly
- Urine analysis before each bevacizumab dose
- Blood pressure weekly

**At Completion of Treatment:**

a. Clinical exams
b. Blood pressure screening

**During Follow-up (8/27/08):**
- Clinical exam 4-6 weeks after the completion of radiation and every 3 months for the first 2 years, then every 4 months for the 3rd year, every 6 months for the next 2 years, then annually
- Blood tests every 6 months for the first 3 years, then every year
- Chest x-ray, CT or MRI 4-6 weeks after treatment
- CT, MRI or PET-CT of your pelvis and abdomen 4-6 weeks after treatment
- PET scan, if recommended by your doctor
- Biopsies if necessary to check for disease
- Blood Pressure Screening 4-6 weeks after the completion of radiation and every 3 months for the first 2 years, then every 4 months for the 3rd year, every 6 months for the next 2 years, then annually

How long will I be in the study?

Treatment will take approximately seven to eight weeks. During this time you will have weekly clinical exams and blood tests. You will also have urine tests before each dose of bevacizumab. Follow-up visits will be every three months for the first two years, every four months for the third year, and every six months for the fourth and fifth year, then annually.

Can I stop being in the study?

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 bevacizumab can be evaluated by your doctor. Another reason to tell your 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 your disease becomes worse; the side effects of treatment become very severe; 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?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. 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 the study doctor about any side effects that you have while taking part in the study.
Risks associated with Radiation Therapy to the Pelvis

**Very Likely**
- Low blood counts causing easy bruising
- Shortening and narrowing of the vagina
- Pain with sexual intercourse
- Tiredness near the end of treatment
- Diarrhea
- Nausea and/or vomiting
- Stomach pain that feels like bad heartburn or an ulcer and that may make eating or drinking difficult (in rare cases, if you become dehydrated, you may need to receive fluids through your vein)
- Poor digestion of food
- Weight loss (in rare cases, if this is severe, you may need a tube placed into your stomach to provide nutrition)
- Rectal irritation
- Urinary frequency and difficulty
- Loss of pubic hair
- Reddening and irritation of the skin in the treatment area

**Less Likely But Serious**
- Rectal ulcer
- Bleeding or narrowing of the rectum
- Bloody urine
- Pain, bleeding, and/or blockage of the stomach or other parts of the digestive system
- Ureteral (tube connecting kidneys to the bladder) obstruction
- Fistula (opening) forming between pelvic tissues

**Reproductive risks**
This study may be harmful to an unborn child. Therefore, participants who are still menstruating and have not had a tubal ligation (tubes tied) must have a negative pregnancy test prior to participating in this study. The results will be made available to you prior to the initiation of this study. Ask about counseling and more information about preventing pregnancy. You should not nurse a baby while on this study.

Radiation to the pelvis will cause infertility, and you will not be able to become pregnant after treatment. Young women will go through menopause, and medication will be given to help with the symptoms of menopause.

**Risks Associated with Cisplatin**

**Very Likely**
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
• 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
- Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet
- Facial swelling

**Less Likely, But Serious**
- A decrease in the kidneys’ ability to handle the body’s waste, which may be permanent
- Allergic reactions which can cause difficulty breathing, fast heartbeat, and sweating
- Decrease in liver function
- Another cancer called Acute Leukemia
- Blindness, blurred vision or altered color perception that may or may not return to normal after stopping cisplatin

**Risks Associated with Bevacizumab (8/27/08)**

**Very Likely**
- Nose bleeds
- High blood pressure - In most patients, blood pressure can be controlled with routine medications. Rarely, uncontrolled hypertension may lead to damage to the brain and other vital organ functions.
- Fatigue
- Rash
- Headache
- Soreness in mouth or throat

**Less Likely**
- Dizziness
- Decrease in blood counts, which can lead to a risk of infection
- Anemia
- Low blood pressure
- Loss of appetite
- Weight loss
- Itching, hives, welts of the skin
- Ulcers (open sores of the skin or mucus membrane that shed inflamed dead tissue)
- Nausea and/or vomiting
- Constipation
- Inflammation of the colon, which can result in stomach cramps and/or diarrhea
- Obstruction of the bowel
- Mild to moderate bleeding in the tumor, stomach, intestines, vagina, or other parts of the body
- Blood clots in the veins: blood clots can occur in the veins of the leg and the lungs or
other organs. These events can be life-threatening.

- Clots in the arteries, including stroke or heart attack; these conditions can be life-threatening or fatal:
- When several studies were looked together, problems due to clots in arteries were increased about two-fold (up to 4-5%) in patients receiving chemotherapy plus bevacizumab compared to chemotherapy alone (about 2%). Elderly patients with past history of clots in the arteries were at a greater risk for these problems.
- Leakage of protein in the urine, which rarely can lead to damage to the kidney
- Reactions associated with infusion of the bevacizumab: rash, chills, fever, rigor
- Watery eyes, nasal stuffiness
- Shortness of breath, cough, wheezing
- Pain in the stomach, chest, joints or muscles and/or pain at the tumor site
- Hoarseness and/or change in or loss of voice

Rare but serious

- Serious or fatal bleeding from the tumor, brain, intestines, vagina, or the lungs
- Fistulas (abnormal openings or passages between internal organs or from an internal organ to the surface of the body) in the lung and/or intestinal tract
- Nasal septum perforation: a hole in the wall that divides the inside of the nose, which could result in crusting in the nose, bleeding and/or discharge from the nose, and/or whistling on intake of air and which would require surgery to repair
- Bowel perforation and bowel anastomotic dehiscence. Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the abdomen. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events are rare but can lead to serious infection and require surgery to repair.
- Heart problems (including irregular heartbeat, fluid collections surrounding the heart, heart attack or heart failure)
- Delayed or poor wound healing
- Acute and/or severe allergic reactions that result in difficulty breathing or drop in blood pressure
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (<1%): RPLS is a medical condition related to leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening and may have long-term effect on the brain function.
- Reversible changes in liver functions
- Kidney failure
- Sudden death of uncertain relationship to bevacizumab

**Risks Associated with Bevacizumab, Chemotherapy, and Radiation Therapy**

The combination of bevacizumab with chemotherapy and radiation therapy could increase the likelihood and/or severity of the side effects of chemotherapy and radiation therapy, such as the severity of mouth sores or risk of infection, bleeding, or anemia.

Low blood count (neutropenia) with increased risk of infection is a common side effect of chemotherapy drugs. This side effect may be increased when bevacizumab is added to chemotherapy. In some studies of bevacizumab plus chemotherapy, there also has been an increase in neutropenia-related fever and infections, including rare instances of infections leading to death.
Reproductive risks: You should not become pregnant while on this study because the drugs in this study may affect an unborn baby. Women should not breast feed a baby while on this study because the drugs may affect an infant. Bevacizumab remains in your body for weeks to months, therefore you should avoid nursing a baby for at least 3-4 months after your last dose of bevacizumab, although the exact duration of bevacizumab remaining in the body is not predictable for each individual patient. You will likely become infertile because of your treatment, and therefore you will not be able to have children in the future. It is important you understand that you need to use birth control while on this study in case you become pregnant early on during treatment. We do not know how the drugs in your treatment will affect an unborn baby. Check with the study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that this treatment will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the treatment of locally advanced cervical cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

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; (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, your tumor would continue to grow and your disease would spread.

The study doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

Will my medical information be kept private?

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 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), involved in keeping research safe for people

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

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 you with bevacizumab free of charge for this study. Every effort will be made to ensure adequate supplies of bevacizumab, free of charge for all participants. If bevacizumab becomes commercially available for this indication, there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should this situation arise.

The study agent, bevacizumab, will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI for use in this study 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 the 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 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.

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?

You can talk to the study doctor about any questions or concerns you have about this study. Contact the 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 studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.
Consent Form for Use of Tissue, Blood and Urine for Research

About Using Tissue for Research (8/27/08)

You have had or will have a biopsy (or surgery) to see if you have cancer. Your doctor removed or will remove a small portion of tissue from your cancer (about half the size of a pea) to do some tests. The results of these tests were given to you or will be given to you by your doctor and will then be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If there is no tissue left over, we would like to obtain your permission to do another biopsy of your tumor before you start treatment on the main part of the study.

In addition, we would like to obtain your permission to do a second biopsy of your tumor. We would do this biopsy at the same time that we place applicators to do the internal radiation (brachytherapy).

If you agree, this tissue will be kept and may be used in research to learn more about cervical 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.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf.

The research that may be done with your tissue 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 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 affect on your care.

Making Your Choice

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

1. If tissue is left over from my diagnostic biopsy, this tissue may be used in future research.
   
   Yes  No  Not Applicable

2. If tissue is not left over from my diagnostic biopsy, an additional pre-treatment biopsy may be taken and used in future research.
   
   Yes  No  Not Applicable

3. A biopsy may be taken of my tumor during brachytherapy and may be used for future research.
   
   Yes  No

4. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
5. My tissue 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).

Yes  No

About Using Blood for Research (8/31/06, 5/11/07, 8/27/08)

As a result 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 cervical 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 protocol treatment,
- On the day of your first brachytherapy (internal radiation) treatment,
- At the middle of your protocol treatment (at about the 4th week of your treatment),
- During the last week of your protocol treatment,
- 4-8 weeks after you have finished protocol treatment

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

1. Additional blood may be taken for use in future research.

   Yes  No

2. My blood may be kept for use in research to learn about, prevent, or treat cancer.

   Yes  No

3. My blood 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).

   Yes  No

About Using Urine for Research (8/31/06, 5/11/07)

The study doctor will take samples of your urine during your treatment to see how you are handling the treatment. In addition to that, we would like to collect some extra urine from you to use for future research. If you agree, small samples of your urine will be shipped to researchers who work in laboratories at the National Cancer Institute and Harvard University, so that they can analyze the genetic make-up of the samples. You will be asked to give additional urine samples at the following times:

- Before you begin protocol treatment,
- On the day of your first brachytherapy (internal radiation) treatment,
- During the last week of your protocol treatment, and
- 4-8 weeks after you have finished protocol treatment

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

1. My urine may be used in additional testing for research related to cancer cell growth.
   Yes   No

2. My urine may be kept for use in research to learn about, prevent, or treat cancer.
   Yes   No

3. My urine 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).
   Yes   No

If you agree that your tissue, blood and urine can be collected and 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.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf

**Things to Think About**
The choice to let us collect and keep your tissue, blood and urine for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue, blood and urine 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, blood and urine. Then any tissue that remains will be returned to the institution that submitted it, and any blood and urine that remains will be destroyed.

In the future, people who do research may need to know more about your health. While these researchers may have reports about your health, they will not have your name, address, phone number, or any other information that will let them know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue, blood and urine are used for this kind of research, the results will not be put in your health records.

Your tissue, blood and urine will be used only for research and will not be sold. The research done with your tissue, blood and urine may help to develop new products in the future.

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

**Risks**
The greatest risk to you is the release of information from your health record. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.
In addition to being a part of the study to treat your cancer, you are also being asked to have additional images taken of your pelvis to be used for future research by the Transatlantic Image-guided Brachytherapy Working Group conducted by the Radiation Therapy Oncology Group (RTOG).

Please note: This part of the informed consent form explains the option of having extra images taken of your pelvis to be used in future research. This part of the protocol is up to you. You do not have to have these additional images taken if you don’t want to. You can still be in the main study, to treat your cancer, even if you say “no” to allow the additional images to be taken of your pelvis.

Why are these additional images being collected?
The purpose of this optional component is to take special images using CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) of the radiation implants that you will receive during your cervical cancer treatment. The images will be taken before and after you receive your first implant, and may be before or after each one of your other implants are inserted. You may have from 2 to 10 additional images taken, depending on how many inserts you will receive. These images will allow the study doctor and other doctors to see how the radiation is distributed in your pelvis, including to your tumor and your internal organs. Your internal organs include your bladder, vagina, small intestine, and rectosigmoid (rectum and colon).

How are the images taken?
An MRI is used, which is an imaging technique that uses radio waves and a magnetic field to take pictures of your pelvis. Or a CT scan is used, which is a special X-ray that allows the study doctors to better visualize both normal (internal organs) and abnormal (tumor) tissues in your pelvic area. The CT scan may be done with contrast that requires an IV and a rectal contrast that requires a special applicator to be placed in your rectum during the scan. The MRI scan may require a glucagon injection in the muscle of your arm to decrease bowel activity and a contrast agent called gadolinium which helps to make the tumor more visible.

Risks of Imaging
MRI: The MRI test is painless. The only discomfort involved is lying in a confined space while the image is taken. The machine is shaped like a long tube and your body will be moved inside of the tube on a moving table. If you are claustrophobic (fear of closed-in spaces) you may be given medications to help calm you. Once inside the machine there will be some loud noises while the images are being taken.

There are some risks of injury due to MRI, such as:
- Damage to electronic devices (like cardiac pacemakers).
- Hemorrhage if an aneurysm clip is present. (If you have a pacemaker or aneurysm clip, you are not eligible for the MRI examination.)
- There is a risk of trauma if metal is introduced into the room (this risk is minimal in a properly administered site).
- Also, there is a risk of ear damage, which is minimized by ear plugs.
• An allergic reaction to contrast medicine (gadolinium) if an injection is used. The side effects may vary from mild flushing, itching and rash, and in rare cases, a severe life-threatening anaphylaxis (difficulty breathing, drop in blood pressure, shock, and kidney failure).

• If used, sedatives (drugs used to calm you) can cause drowsiness, decreased respiratory (breathing) rate, tachycardia (fast heart beat), brachycardia (slow heart beat), irregular heart beat, and occasionally nausea and vomiting.

CT Scan: Potential risks include an allergic reaction to the contrast dye which may vary from mild flushing, itching, and rash to severe life threatening anaphylaxis (difficulty breathing, drop in blood pressure, shock, and kidney failure).

Venipuncture and/or Injections: Risks of administration of intravenous contrast, and Intramuscular injections include; pain, discomfort, irritation from the needle stick, infection, bleeding or bruising at the needle site, lightheadedness, and fainting.

Your Participation
Either before or after your radiation implant, the study doctor will have you undergo a CT scan or MR scan of your pelvis, with your radiation applicator in place. The study doctor may use a special "CT/MR-compatible" applicator in place of the usual metal applicator when the scans are scheduled. This special applicator will give the same radiation dose to your tumor as the regular applicator, but it will allow clear, streak-free MR and CT pictures of your pelvic organs and applicator. Your scans will be transmitted electronically to the RTOG QA Center at Washington University to be analyzed at a later date. These scans will help analyze how the radiation dose is distributed in your normal organs and tumor. Your insurance will be billed for the CT and MRI scans. If your insurance does not cover the cost of these scans, you will need to discuss this ahead of time with your Radiation doctor.

Your participation is voluntary and you may choose not to participate in this part of the study. If you decide to be in this optional part of the study, you can withdraw at any time. If you choose not to take part, or if you choose to leave this part of the study at any time, your decision will not affect the cancer care provided by your health care team. There will be no penalty or loss of benefits to you if you choose not to take part.

Measures will be taken to protect the privacy of your records and your identity. Your identity will not be revealed in any publication that may result from this part of the study. The confidentiality of all study-related records will be maintained in accordance with State and Federal laws. There is a possibility that your medical research record, including identifying information, may be inspected and photocopied by officials of the Federal and State government agencies and your hospital, or University Human Studies Committee. Since the study is sponsored by the RTOG, which is funded by the National Cancer Institute (NCI), representatives of the NCI or RTOG may inspect these research records.

Benefits
The CT and/or MRI pictures taken before or after your implant will help to evaluate the relationship of the applicator and radiation dose to your pelvic organs and tumor. By allowing more accurate assessment of the radiation dose, the study doctor may be able to alter the radiation dose to improve tumor control and reduce complications. It is not possible to predict whether you will personally benefit from the results of the study, however, this research may
improve the treatment of future patients by allowing physicians to more accurately analyze and alter radiation doses to organs and tumors from the scans sent to the QA Center.

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

1. I would like to take part in the optional CT/MRI component of this study.
   Yes   No

2. 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 ________________________________
## ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death (Karnofsky 0).</td>
</tr>
</tbody>
</table>

## KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

## NEW YORK HEART ASSOCIATION (NYHA) CLASS DEFINITIONS

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>
### TNM CATEGORIES

#### Primary Tumor (T)

<table>
<thead>
<tr>
<th>TNM</th>
<th>FIGO</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>-</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>-</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T/s</td>
<td>0</td>
<td>Carcinoma <em>in situ</em></td>
</tr>
</tbody>
</table>
| T1   | I    | Cervical carcinoma confined to uterus  
       * extension to corpus should be disregarded* |
<p>| T1a  | IA   | Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions—even with superficial invasion—are T1b/IB. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification. |
| T1a1 | IA1  | Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread. |
| T1a2 | IA2  | Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less. |
| T1b  | IB   | Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2. |
| T1b1 | IB1  | Clinically visible lesion 4.0 cm or less in greatest dimension. |
| T1b2 | IB2  | Clinically visible lesion more than 4.0 cm in greatest dimension. |
| T2   | II   | Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina |
| T2a  | IIA  | Tumor without parametrial invasion |
| T2b  | IIB  | Tumor with parametrial invasion |
| T3   | III  | Tumor extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney |
| T3a  | IIIA | Tumor involves lower third of the vagina, no extension to pelvic wall |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Stage</th>
<th>Regional Lymph Nodes</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>T1a1</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>IA2</td>
<td>T1a2</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>IB1</td>
<td>T1b1</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>IB2</td>
<td>T1b2</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2aN0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2bN0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3aN0</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1  N1</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2  N1</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a  N1</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3b  Any N</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4  Any N</td>
<td>M0</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T Any N</td>
<td>M1</td>
<td>M1</td>
</tr>
</tbody>
</table>
Sample Treatment Diagram

Whole Pelvis
APPENDIX V (p.2)

Sample Treatment Diagram

Parametrial Boost with 5-6 cm Midline Shield
Definitions of Points A & B

APPENDIX VI
ICRU #38 Point Dose Definition
Description of ICRU Bladder/Rectal Dose Reporting Points

The bladder reference point is obtained as follows. A Foley catheter is used. The balloon must be filled with 7 cm³ of radio-opaque fluid. The catheter is pulled downwards to bring the balloon against the urethra. On the lateral radiograph, the reference point is obtained on an anterio-posterior line drawn through the center of the balloon. The reference point is taken on this line at the posterior surface of the balloon. On the frontal radiograph, the reference point is taken at the center of the balloon.

The point of reference for the rectal dose is obtained as follows. On the lateral radiograph, an anterio-posterior line is drawn from the lower end of the intrauterine source (or from the middle of the intravaginal sources). The point is located on this line 5 mm behind the posterior vaginal wall. The posterior vaginal wall is visualized, depending upon the technique, by means of an intravaginal mould or by opacification of the vaginal cavity with a radio-opaque gauze used for the packing. On the AP radiograph, this reference point is at the lower end of the intrauterine source or at the middle of the intravaginal source(s).

ICRU REPORT 38, March 1, 1985
APPENDIX VII (5/11/07, 8/27/08)

HIGH DOSE RATE INTRACAVITARY BRACHYTHERAPY GUIDELINES

Schedule (5/11/07)

- HDR brachytherapy may begin at a minimum whole pelvic dose of 1800cGy (week 2) for favorable vaginal geometry. If vaginal geometry is not favorable, the first HDR insertion should be performed after 4 weeks of external beam (3600 cGy). (If a midline block is used, other acceptable fractionation schemes are shown in Table 1).

- HDR procedures can be performed once or twice per week with a minimum separation of 2 days. It is important to avoid prolongation of the overall treatment time beyond 56 days. Whether one or two HDR fractions are given per week, the external beam irradiation to the whole pelvis should not be given the same day as the HDR fraction.

Dose Specification (5/11/07)

- Localization orthogonal images of the applicator system should be obtained for each fraction for dosimetry calculations and dose optimization with and without rectosigmoid contrast.

- Dose per fraction for the HDR brachytherapy course will be specified at POINT A. (Maximum dose to point will be 6 Gy. Every attempt should be made to get the two point As the same).

- The vaginal surface dose shall be defined opposite the dwell positions in each ovoid at a distance equal to the radius of the ovoid. For the ring applicator, the surface dose points on the ring are measured 6 mm laterally from each dwell position on each side of the ring. For the tandem and cylinder, the dose will be calculated at the cylinder surface, which generally has a radius between 1.0 and 1.5 cm.

- Normal tissue dose points will include 1 or 2 rectal dose points based on rectal contrast. A point adjacent to the applicator system at 0.5cm posterior to the vaginal packing in the lateral projection has previously been described in the RTOG protocols (the ICRU 38 rectal and bladder point definition should be used). Bladder dose may be calculated at a point on the surface of a contrast-filled balloon of a Foley catheter closest to the system on a lateral view.

Brachytherapy Dose (5/11/07, 8/27/08)  (The recommended brachytherapy dose in this study will be 30.0 Gy in 5 fx to Pt. A [6 Gy per fraction]. If a midline block is used, appropriate fractionation schemes are provided in Table 1.)

- The dose to point A will be based on the external beam dose (see Table 1).

- The vaginal surface dose should be approximately 140-200% of the Point A dose.

- Maximum doses to the bladder, and rectum should be less than or equal to 80% and 70% of the Point A dose, respectively. In order to stay below an LDR equivalent of 70 Gy to the rectum for five HDR insertions (120 Gy³), including the 45 Gy contribution from the external beam radiation, the rectum (rectal reference point) should receive less than 4.1 Gy for each HDR fraction of 6 Gy (68% of the prescribed dose to Point A). The dose to the bladder (bladder reference point) should be less than 4.6 Gy per each HDR fraction of 6 Gy (77% of the prescribed dose to Point A).
**Treatment Data Requirements (5/11/07)**

AP and lateral images of each brachytherapy fraction are with bladder contrast.

Copies of dosimetry and computer data for each brachytherapy fraction are required.

---

**Table 1-Equivalent Doses for Tumor and Late Effects for Doses of EBRT and HDR Brachytherapy used in Cervical Cancer**

<table>
<thead>
<tr>
<th>EBRT (Gy) @ 1.8 Gy/fx</th>
<th># of HDR fractions</th>
<th>HDR dose /fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.8</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>19.8</td>
<td>6</td>
<td>7.4</td>
</tr>
<tr>
<td>39.6</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>39.6</td>
<td>6</td>
<td>5.8</td>
</tr>
<tr>
<td>45</td>
<td>5</td>
<td>6.0-6.5**</td>
</tr>
<tr>
<td>45</td>
<td>6</td>
<td>5.3-5.8**</td>
</tr>
<tr>
<td>50.4</td>
<td>4</td>
<td>7.0*</td>
</tr>
<tr>
<td>50.4</td>
<td>5</td>
<td>6.0*</td>
</tr>
<tr>
<td>50.4</td>
<td>6</td>
<td>5.3*</td>
</tr>
</tbody>
</table>

**these doses are used in treating larger, more advanced tumors**

APPENDIX VIII

Proposal for Image-Based Intracavitary Brachytherapy for Cervical Carcinoma

Patients are encouraged, but not required to participate in this component by contributing additional CT or MR images to the RTOG Imaging Library - Institution Registry Study of CT and MR Image-Based Intracavitary Brachytherapy for Cervical Carcinoma.

1.0 Title: Institution Registry of CT and MR Image-Based Intracavitary Brachytherapy for Cervical Carcinoma

2.0 Objectives: The objectives of the additional component to this protocol are to:

2.1 Implement the image-based brachytherapy guidelines proposed by the Transatlantic Image-guided Brachytherapy Working Group for cervical cancer at multiple participating RTOG institutions.

2.2 Collect the CT- or MRI-based dosimetry generated and transmit it to the ATC repository for later analysis.

2.3 This analysis will allow the ability to:

- Investigate the relationship between the proposed dose-volume parameters and doses to conventionally specified points.
- Evaluate the feasibility of adopting the proposed guidelines for image-based brachytherapy in cervical cancer at multiple institutions.
- Compare the consistency of target and normal organ delineation amongst various investigators.
- Evaluate the defined dose/volume parameters in relationship to toxicity and local control.

3.0 Background

The current clinical practice for cervical cancer intracavitary brachytherapy in most centers is to use orthogonal film-based dosimetry and specify dose at point A, while assessing the normal tissue point doses. Point A is an empirical point and does not reflect dose to the tumor, as the tumor itself is not imaged. Additionally, the normal tissue dose points may not accurately represent the dose distributions in these organs. The International Commission on Radiation Units and Measurements, ICRU- Report 38 for dose specification of gynecological brachytherapy recommended that reference points such as point A not to be used because, “such points are located in a region where the dose gradient is high and any inaccuracy in the determination of the distance results in large uncertainties in the absorbed doses evaluated at those points.” Instead it recommended that doses be specified in terms of Total Reference Air Kerma and that the Reference Volume be determined, i.e. the tissue volume encompassed by a reference isodose surface, 60 Gy, for comparing intracavitary treatments performed in different institutions regardless of the applicator system, insertion technique and method of treatment, and prescription used. However, this practice has not been universally adopted.

In recent years, three-dimensional treatment planning systems have been increasingly used in most radiotherapy treatment facilities. This technology allows radiation oncologists to shape the spatial dose distribution to conform to the target volume and reduce the dose to normal tissues. With this approach, it is possible to decrease the probability of normal tissue toxicity and to escalate the dose to the tumor to produce higher rates of local control. While 3-D image-based dosimetry is extensively used in prostate brachytherapy, it has not been readily implemented in cervical brachytherapy.

In 2002, the RTOG and GOG organized committees to investigate the feasibility of image-based brachytherapy for future gynecologic protocols. One endpoint was to develop and collect a library of images at RTOG headquarters for later analysis using DICOM RT export function. Since other organizations had expressed interest in this subject and to obtain broader input while minimizing duplication of effort,
representatives from additional organizations (Radiological Physics Center (RPC), American Brachytherapy Society (ABS), American College of Radiology (ACR), American College of Radiology Imaging Network (ACRIN), American Association of Physicists in Medicine (AAPM), Radiation Therapy Oncology Group (RTOG) were invited to form the Image-guided Brachytherapy Working Group. This group recently published their recommendations for image-based intracavitary brachytherapy for cervical cancer. \textsuperscript{36} Subsequently, the Image-Guided Brachytherapy Working Group joined with the GYN GEC-ESTRO Working Group to form the Transatlantic Image-Guided Brachytherapy Working Group with joint guidelines for image-based brachytherapy for gynecologic cancers. The GEC-ESTRO GYN Group had developed their guidelines beginning in 2000 with subsequent publications detailing the specifics and feasibility of such a system. \textsuperscript{21-23} Given their encouraging results, this system is now to be piloted in the United States. The present proposal wishes to study the feasibility of implementing the recommendations of the Transatlantic Image-Guided Brachytherapy Working Group in RTOG trials at multiple participating institutions.

4.0 **Patient Eligibility**

4.1 Cervical cancer patients receiving intracavitary brachytherapy under existing RTOG protocols are eligible as a companion registry study.

4.2 Patient must sign informed consent. (See Appendix I)

4.3 Patient must be able to tolerate a CT or MRI. **MRI is the preferred imaging modality.**

4.3.1 CT: Patients must not be allergic to iodinated contrast if undergoing a contrast-enhanced CT scan of the pelvis with the applicator in place.

4.3.2 MRI: Patients must not be allergic to the contrast agent (gadolinium) and have no contraindications to MRI scanning.

4.4 Administration of sedatives must be permissible for claustrophobic patients.

5.0 **Methods**

5.1 Pretreatment MRI: High resolution, T2 weighted MRI with and without fat saturation is to be used for imaging. Other sequencing (e.g., T1 weighted MRI with Gd contrast) can be used to supplement these data sets. The details of protocol for MR imaging for cervical cancer is provided in Attachment I. Diagnostic CT scans pre-treatment can be performed within institutional guidelines.

5.2 **Applicators**

5.2.1 MRI-compatible applicators that simulate conventional applicators are required. When using CT, CT-compatible applicators are preferred. If unavailable, efforts to minimize artifact should be considered. Use of bone rather than soft tissue windows is helpful in minimizing artifact and assessing the surrounding soft tissues around the tandem. The vaginal portion of a non-CT compatible applicator may produce too much artifact to visualize the walls of the rectum, bladder, and vagina. If vaginal packing is used for CT-based planning, it should be saturated in a 1:10 dilution of iodinated contrast:water, or it should have radio-opaque stripe sewn into the gauze. When moving a patient between the imaging unit and the treatment room, a secure method of fixing the applicator with respect to the patient is required.

5.3 MRI at the time of (any) intracavitary brachytherapy with MRI compatible applicator in place. If MRI is not available, CT is acceptable. The MRI or CT should be performed at the time of each insertion if possible.

5.3.1 For MRI, inject 50 ml of sterile saline into the bladder via the catheter port after clamping the drainage tube. Additionally, the Foley catheter bulb should be filled with 7 ml of water. The bladder should be drained in the period between the MRI and the treatment. An additional 50 ml should be added to the drained bladder just before treatment to insure similar bladder distention as imaged on the MRI. For CT, inject a mixture of 40 ml of sterile saline with 10 ml of iodinated contrast into the bladder via the catheter port after clamping the drainage tube. The Foley catheter bulb should be filled with 7 ml of dilute contrast. The bladder should be drained in the period between the CT and treatment. An additional 50 ml of saline should be added to the drained...
bladder before treatment to insure similar bladder distention as imaged on the CT. For MRI, no rectal contrast is required. For CT, 50 ml of dilute gastrograffin (1:3 parts gastrograffin:water) should opacify the rectosigmoid. Another 50 ml can be added if there is not opacification of the sigmoid.

5.3.2 High resolution, T2 weighted MRI with and without fat saturation with applicator in place is to be used for imaging. Other sequencing (eg. T1 weighted MRI with Gd contrast) can be used to supplement these data sets. The details of protocol for MR imaging for cervical cancer is provided in Attachment I. If CT is used, contiguous slices of 3 mm or less are recommended. A table feed of 3 mm will be used for helical/spiral CT with a reconstruction interval of 3 mm. An AP and lateral scout should be obtained and can be used to assess proper applicator placement. IV and oral contrast are optional.

5.3.3 Imaging to define tumor and normal structures must be performed with the patient in the treatment position, with all treatment conditions duplicated as closely as possible. For example, if the patient is to be treated supine with the knees slightly elevated then imaging should be performed with the patient in the same position. Markers for localizing tumor margins or normal tissues, if used, must be MR/CT-compatible. Images must be obtained 2 cm superior to the most cephalad part of the brachytherapy sources to 2 cm inferior to the most caudad part of the brachytherapy sources. Imaging is to be performed for one or more brachytherapy insertions. Ideally, an MRI or CT should be obtained for each fraction.

5.4 Prescription

5.4.1 The prescription methods, doses, and dosimetry procedures will be according to the applicable RTOG/GOG protocol. The dose is to be prescribed to Point A as defined by the following ABS recommendations.

5.4.2 For tandem and colpostats, begin by drawing a line connecting the middle of each of the colpostat source positions. Then, from the intersection of this line with the tandem, move superiorly along the tandem 2 cm plus the radius of the colpostats and then 2 cm perpendicular to the tandem in the lateral directions. The dose shall be calculated and specified to point A on both the right and left. The average of the right and left doses can be taken if a single point A dose is needed.

5.4.3 In a tandem and ring insertion, finding point A begins with drawing a line connecting the mid-dwell positions of the ring. From the intersection of this line with the tandem, move superiorly along the tandem 2 cm plus half the thickness of the ring (including the cap), and then 2 cm perpendicular to the tandem in the lateral direction.

5.4.4 For applications using a tandem and vaginal cylinders, begin at the flange on the tandem (indicating the external cervical os) travel superiorly along the tandem 2 cm, and then laterally perpendicular to the tandem 2 cm to obtain point A.

5.5 Nomenclature: The delineation of GTV and CTV is performed at the time of each brachytherapy insertion. The delineation process is based on clinical examination at diagnosis and at brachytherapy and on a set of sectional images (MRI) taken at diagnosis and at brachytherapy with the applicator in place. For CT applications, there will be no GTV or CTV delineations given the poor soft tissue resolution of CT.

5.5.1 Gross tumor volume (diagnosis) (GTV\text{\textsubscript{D}}) includes the macroscopic cervical tumor and its extensions at diagnosis as detected by clinical examination (visualization and palpation) and as visualized on MRI. On MRI, the cervical tumor will appear as high signal intensity mass(es) at fast spin echo sequences (FSE) T2 with potential extension to the corpus, parametria, vagina, bladder, and rectum.
5.5.2 Gross tumor volume at brachytherapy (GTV\textsubscript{B1}, GTV\textsubscript{B2}, GTV\textsubscript{B3}...) includes the macroscopic cervical tumor and its extensions at the time of brachytherapy (BT) as detected by clinical examination and as visualized on MRI. On MRI, the cervical tumor will appear as high signal intensity mass(es) at fast spin echo sequences (FSE) T2 with potential extension to the corpus, parametria, vagina, bladder, and rectum.

In patients treated with upfront BT or with BT alone, GTV\textsubscript{B} is identical with GTV\textsubscript{D}.

5.5.3 High risk CTV for Brachytherapy: (HR CTV\textsubscript{B1}, HR CTV\textsubscript{B2},...) includes the tissues with a major risk of local recurrence because of residual macroscopic disease after radiation and includes the GTV\textsubscript{B1}, B2, etc. It always includes the whole cervix and the presumed extra-cervical tumor extensions at the time of (BT). In limited disease the GTV\textsubscript{B} is identical with the GTV\textsubscript{D}. In advanced disease, the presumed tumor extensions are defined by means of clinical examination (visualization and palpation) and by the MRI findings at the time of BT, taking into account tumor spread at diagnosis as defined on clinical examination and initial staging MRI (GTV\textsubscript{D}) (Fig. 1-2). Pathologic residual tissue(s) as defined by palpable indurations and/or residual grey zones visualized on MRI in the parametria, uterine corpus, vagina or rectum and bladder are included in the HR CTV\textsubscript{B}. No margins are added to the HR CTV. A total radiation dose is prescribed to the HR CTV to eradicate macroscopic disease.

5.5.4 Intermediate risk CTV for Brachytherapy (IR CTV\textsubscript{IR1}, IR CTV\textsubscript{B2}) includes the tissues with a major risk of local recurrence in areas that correspond to initial macroscopic disease extensions that have regressed to potential residual microscopic disease at the time of brachytherapy. This encompasses the high risk CTV with a margin of 5-15 mm. The amount of margin is chosen according to tumor size and location, potential tumor spread, tumor regression and treatment strategy.

* In limited disease (tumor size <4 cm), BT may be performed alone or as a combination treatment (upfront preoperative treatment/combination with EBT): the IR CTV\textsubscript{B} encompasses the HR CTV (including GTV\textsubscript{D} and the whole cervix) and different margins are added according to potential spread. In the anterior-posterior direction, a margin of up to 5 mm is taken, limited by the natural anatomical borders of the rectal and bladder wall. A margin of 10 mm is used cranially into the uterine corpus and caudally below the cervical os into the vagina. In the lateral direction, a 10 mm margin is applied into both parametria, usually representing the internal third of the parametrium (Fig. 1). In the case of endocervical or lateral macroscopic tumor growth, an additional margin of 5 mm is applied, in the direction of potential spread.

* In more extensive disease, patients are treated with a combination of external beam irradiation and BT: IR CTV\textsubscript{B} is based on macroscopic tumor extension at diagnosis (GTV\textsubscript{D}) which is superimposed on the anatomical area as it presents at time of BT taking the original anatomical tumor spread as a reference.

Different margins are used depending on the extent of disease at diagnosis and on the regression at the time of BT. These margins are confined by the anatomical borders of

\[\text{The authors are aware that the area of significant microscopic tumor load is situated around the area of macroscopic tumor load, and therefore IR CTV should be in principle a volume surrounding the HR CTV like a ring. However, for practical reasons, we contour the intermediate risk CTV as a volume including the high risk CTV and adding a safety margin following the contouring recommendations of ICRU (Report 50, 62) in external beam for different CTVs.}\]
rectal and bladder wall if these are not involved. In case of invasion, the margins should be restricted to the rectal and bladder wall only (no lumen included).

In the case of a complete remission, the IR CTV includes the HR CTV and the initial macroscopic tumor extension at diagnosis superimposed on the anatomy at the time of BT, without any margins (Fig. 3).

In the case of good remission, the IR CTV includes the HR CTV and the initial tumor extensions at diagnosis (Fig. 3 (a) and (b)). In the case of poor tumor remission of less than 10 mm including the extra-cervical residual disease (e.g. parametria), a margin of minimum of 10 mm into the direction of potential spread (parametria, vagina, uterus) is added to the HR CTV (Fig. 3).

In the case of stable disease, a margin of 10 mm is added to the initial tumor extension at diagnosis which is superimposed on the anatomy as it presents at the time of BT (Fig. 3).

A total radiation dose is prescribed to this intermediate risk CTV appropriate for eradicating significant microscopic disease. Dose is selected according to tumor volume, stage of disease and treatment strategy (BT alone/combination treatment).

It is assumed that no extra margins are needed either for patient-related uncertainties (e.g. organ movement) or for set up uncertainties. Therefore, the PTV is identical to the CTV.

5.6 **Contours:** The following are to be contoured: GTV, HR CTV, IR CTV (MRI only). In addition, the organs at risk including the bladder, rectum and the sigmoid, as well as the small intestines (if within 2 cm of the uterus). For small intestines, contour the intestines (excluding the sigmoid colon) using the outermost limit of all the intestines, rather than individual bowel loops. For the bladder, rectum and sigmoid, contour the outer surface of the organ wall. The transition from rectum to sigmoid is defined when the straight rectum begins to take a turn to the left or right. The rectum and bladder and sigmoid should be contoured on all slices where the applicator is visible and 1 cm inferiorly and superiorly. For the rectum, the contours should include all parts from the anorectal junction to the rectosigmoid flexure. For the sigmoid, contour from the rectosigmoid flexure to a point 2 cm beyond the uterus and uterine tandem. The small bowel is contoured only if visible within 2 cm of the applicator.

5.7 **Dose Reporting:** Recommendations for recording and reporting 3D gynecological brachytherapy

5.7.1 Complete description of the presenting clinical situation including the cervical tumor and its extensions, the pathologic diagnosis, and imaging findings

5.7.2 Dimensions and volume of the GTV, HR CTV and IR CTV at diagnosis and at the time of each brachytherapy insertion

5.7.3 Complete description of the 3D sectional imaging techniques and contouring procedure (slice thickness, contrast, contoured targets and normal tissues).

5.7.4 Complete description of the brachytherapy technique including radionuclide; source type (wire, stepping source); source strength; applicator type; type of afterloading (manual or remote)

5.7.5 Prescribed Dose (point A or other dose specification point, vaginal cylinder surface)

5.7.6 Treatment prescription and treatment planning including applicator reconstruction technique, standard loading pattern, dose specification method; optimization method

5.7.7 Total Reference Air Kerma (TRAK)

5.7.8 Dose at Point A (right, left, mean)

5.7.9 D_{100}, D_{90} for GTV and HR CTV and IR CTV, respectively (Definition: dose to 100% or 90% of GTV, HR CTV, IR CTV)
V100 (Definition: volume enclosed by 100% of the prescription dose); V150 (Definition: volume enclosed by 150% of the prescription dose); V200 (Definition: volume enclosed by 200% of the prescription dose)

5.7.10 Dose to Organs at risk (OAR): bladder and rectum, sigmoid and small bowel
ICRU reference points: Based on standard localization film definitions or axial CT/MRI images following the ideals of ICRU 38 (rectum: 5 mm posterior to the posterior vaginal wall as referenced from the mid vaginal applicator surface; bladder: mid posterior catheter bulb surface on axial slice where bulb is at its largest cross sectional diameter).

Representative doses to the organs at risk: rectum, sigmoid, bladder and small bowel; based on localization films or axial CT scans identifying multiple points on the portions of contrast opacified normal organ walls closest to the applicator.

5.7.11 Cumulative Dose Volume Histograms (DVH): recommended for evaluation of the complex dose heterogeneity. DVH parameters for GTV, HR CTV and IR CTV are the minimum dose delivered to 90% and 100% of the respective volume: D90, D100. The volume, which is enclosed by 150% or 200% of the prescribed dose (V150, V200), is recommended for overall assessment of high dose volumes. V100 is recommended for quality assessment only within a given treatment schedule. For OAR the minimum dose in the most irradiated tissue volume is recommended for reporting: 0.1, 1, and 2 cm³; optional 5 and 10 cm³. Underlying assumptions are: full dose of external beam therapy in the volume of interest, identical location during fractionated brachytherapy, contiguous volumes and contouring of organ walls for >2 cm³.

\[D_{0.1cc}, D_{1cc}, D_{2cc}\] for organs at risk (e.g. rectum, sigmoid, bladder) when contouring outer wall of organs only

\[D_{5cc}, D_{10cc}\] for organs at risk if contouring of inner and outer organ walls is performed

5.7.12 Complete description of time-dose pattern: physical and biologically weighted doses
\[(\alpha/\beta = 10\text{ Gy for GTV and CTV}; \alpha/\beta = 3\text{ Gy for OAR}; T_{1/2} = 1.5\text{ h for GTV, CTV and OAR})\]

5.8 Investigate the relationship between the dose-volume parameters above and doses to conventionally specified points.

5.9 Compare the feasibility and consistency of target delineation amongst various investigators.

5.10 Data Transmission: Data is to be transmitted electronically to the ITC. DICOM RT is now available for the brachytherapy plan transmissions. The link for data transmission to the ITC is provided in the protocol. (http://atc.wustl.edu/protocols/rtog-devel/0417/0417.html)
ATTACHMENT I: MR Imaging of Cervical Carcinoma

1.0 Normal MR Appearance:
The zonal anatomy of the cervix is best demonstrated on T2-weighted sequences. The mucosa of the endocervix is seen as a central stripe of high signal intensity that is surrounded by low signal intensity stroma. The peripheral cervical tissue demonstrates intermediate signal intensity, similar to myometrium. On gadolinium contrast-enhanced T1-weighted images, the inner mucosal epithelium and the pericervical tissue enhance more than the inner cervical stroma. The parametrium, connective soft tissue that is adjacent and lateral to the uterus and not covered by peritoneum, is vascular and contains many efferent lymphatics. The uterine arteries and the distal ureters pass through the lateral parametrial tissues. The parametrium demonstrates intermediate signal intensity on T1-weighted images and varying degrees of high signal intensity on T2-weighted images.

2.0 MR Imaging Appearance of Cervical Carcinoma
The superior soft tissue contrast provided by MR imaging compared to CT or US makes it the best possible imaging modality for the assessment of tumor volume and extent. On T2-weighted sequences, cervical cancer is seen as a hyperintense mass relative to normal stroma. On T1-weighted images cervical cancer is usually isointense to normal stroma and may not be detectable. With dynamic contrast imaging, cervical cancer shows early contrast enhancement.

3.0 MRI Sequences:
Both T1- and T2-weighted sequences are required for evaluation of the female pelvis. T1-weighted imaging provides excellent contrast between fat and soft tissue and is the optimal sequence for assessment of lymphadenopathy. T1-weighted sequences are also useful for characterization of soft tissues. Both hemorrhage and fat demonstrate high signal intensity on T1-weighted images, and a fat-saturation sequence can be used to differentiate the two. With fat saturation techniques, fat appears dark (fat-saturated) and hemorrhage remains high in signal intensity. T2-weighted sequences are optimal for demonstrating the zonal anatomy of the uterus and cervix, identifying ovaries, and depicting pathologic conditions. Conventional spin echo T2-weighted imaging has been replaced by fast spin echo (FSE). T2-weighted techniques which require less imaging time and therefore reduce motion artifact. Breath-hold single-shot FSE pulse sequences, which decrease imaging time and motion even further, have recently been developed.

Intravenous contrast enhancement, with gadolinium chelates (0.1 mmole/kg), may be useful in characterizing and better depicting the extent of lesions as well as in assessing vascular anatomy. Gadolinium chelates can be used safely in patients with allergies to iodinated contrast media and/or renal impairment. Gadolinium is routinely used in the evaluation of endometrial and ovarian disease. Gadolinium is not routinely used in the staging of cervical cancer as it has not been shown to improve overall staging accuracy. However, it can help differentiate viable tumor from debris and areas of necrosis, and assess for bladder or rectal involvement.

4.0 MRI protocol for cervix cancer
Imaging will be performed on a high field strength 1.5 Tesla magnet with a phased array surface coil as it provides higher signal-to-noise ratio resulting in improved spatial resolution than the generalized body coil. For optimum imaging results, movement artifact must be kept to a minimum. Bowel motion is limited by having patients fast for 4-6 hours prior to the study and if there are no medical contraindications, administration of an anti-peristaltic agent (glucagon 1 mg IV or IM or buscopan 20 mg IV or IM) just before the examination. Respiratory compensation is used to minimize breathing artifact. A Foley catheter will be inserted into the bladder and 50 cc of sterile saline added prior to the examination and brachytherapy insertion. The degree of bladder distension will be the same as that during treatment. The area of coverage should extend from the aortic
bifurcation down through the introitus with 24-28 cm field of view (FOV), 5mm slice thickness with 1 mm gap, 16 kHz bandwidth, 256-521 x 256 matrix and NEX of 2. An echo train length (ETL) of 8 will be used for the FSE T2 sequences. The sequences for a diagnostic staging examination are as follows:

- Localizer, sagittal plane
- Sagittal plane of section, FSE T2-weighted image; repeat with single shot FSE T2 if motion artifact present.
- Axial plane of section, FSE T2-weighted image; repeat with single shot FSE T2 if motion artifact present.
- Axial plane of section, T1-weighted image; scan to renal hilum if pelvic lymphadenopathy present.
- Only if cancer extension to the urinary bladder or rectum is suspected after reviewing the non-contrast images, gadolinium will be administered and a sagittal plane of section, post-contrast T1 will be obtained.

Sequences required for assessing position of applicator:
- b) & c) as above with applicator in place. Can use single shot FSE T2, if adequate.

The MR imaging protocol is summarized in Table 1.
Table 1: Protocol for cervical carcinoma MRI for staging and brachytherapy

**POSITION:** Supine

**CENTERING POINT:**

**SPECIAL INSTRUCTIONS:**

<table>
<thead>
<tr>
<th>SEQ</th>
<th>COIL</th>
<th>PLANE</th>
<th>TR</th>
<th>TE</th>
<th>FLIPET</th>
<th>BW (kHz)</th>
<th>FOV (cm)</th>
<th>SLICE THICK</th>
<th>GAP</th>
<th>MATRIX Freq/phase</th>
<th>NEX</th>
<th>IMAGING OPTIONS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>FSE T2 pelvic</td>
<td>Sagittal</td>
<td>2000</td>
<td>85</td>
<td>16</td>
<td>36-48</td>
<td>10</td>
<td>0</td>
<td>256/256</td>
<td>1</td>
<td></td>
<td></td>
<td>Localizer.</td>
</tr>
<tr>
<td>2.</td>
<td>SE T1   pelvic</td>
<td>Axial</td>
<td>5-700</td>
<td>10-15</td>
<td>16</td>
<td>24-28</td>
<td>5</td>
<td>1</td>
<td>256/256</td>
<td>2 StSlap RC</td>
<td></td>
<td></td>
<td>Extend to renal hilum if pelvic nodes present</td>
</tr>
<tr>
<td>3.</td>
<td>FSE T2   pelvic</td>
<td>Axial</td>
<td>4000</td>
<td>85</td>
<td>8</td>
<td>16</td>
<td>24-28</td>
<td>5</td>
<td>1</td>
<td>512/256</td>
<td>2</td>
<td></td>
<td>Frq AP to reduce abd. wall motion artifact</td>
</tr>
<tr>
<td>4.</td>
<td>FSE T2   pelvic</td>
<td>Sagittal</td>
<td>4000</td>
<td>85</td>
<td>8</td>
<td>16</td>
<td>24-28</td>
<td>5</td>
<td>1</td>
<td>512/256</td>
<td>2</td>
<td></td>
<td>Frq AP to reduce abd. wall motion</td>
</tr>
<tr>
<td>Options</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1. SSFSE T2 pelvic</td>
<td>Sag+/Ax</td>
<td>∞</td>
<td>100</td>
<td>62.5</td>
<td>24-32</td>
<td>5</td>
<td>1</td>
<td>256/256</td>
<td>0.5</td>
<td>Breath hold salvage T2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. FSE T2 pelvic</td>
<td>Obl Cor</td>
<td>4000</td>
<td>85</td>
<td>8</td>
<td>16</td>
<td>24-28</td>
<td>5</td>
<td>1</td>
<td>512/256</td>
<td>2</td>
<td>If cervical mass not well seen on ax or cor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. SE T1post gad pelvic</td>
<td>Sag+ax</td>
<td>5-700</td>
<td>10-15</td>
<td>16</td>
<td>24-28</td>
<td>5</td>
<td>1</td>
<td>256/256</td>
<td>2</td>
<td>StSlap RC Post gad</td>
<td>NPW for sag. sequence. If suspect bladder &amp; rectal involvement.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. Schematic diagram for cervix cancer, limited disease, with GTV, high risk CTV and intermediate risk CTV for definitive treatment: coronal and transversal view (Courtesy of Haie-Meder et al, Radiotherapy and Oncology 74(2005):235-345.)
Fig. 2. Schematic diagram for cervix cancer. Extensive disease, poor remission after EBT with GTV, grey zones on MRI and high risk CTV and intermediate risk CTV for definitive treatment: cornnal and transversal view. (Courtesy of Haie-Meder et al, Radiotherapy and Oncology 74(2005):235-345.)
Fig 3. Schematic representation for high risk and intermediate CTV lateral parametrial limits for extensive disease; four different cases with regard to amount of remission after external beam radiotherapy combined with chemotherapy. (Courtesy of Haie-Meder et al, Radiotherapy and Oncology 74(2005):235-345.)
Fig. 4. Cumulative dose volume histograms of bladder, rectum and sigmoid (patient, Figs. 1, 3, 4 and 6) based on organ contouring indicating the minimum dose in the most irradiated tissue volume adjacent to the applicator ($D_{0.1cc}$, $D_{1cc}$, $D_{2cc}$ for 0.1, 1, and 2 cm$^3$).

Total EQD2 dose values for these OAR are given assuming four identical HDR fractions with an $a/b$ of 3 Gy. Treatment planning, for this example, was based on dose constraints for $D_{2cc}$ (bladder: 90 Gy$_{EQD2}$, rectum, sigma: 70 Gy$_{EQD2}$). 90 Gy$_{EQD2}$ is reached with four HDR fractions of 6.3 Gy (25.2 Gy), which is corresponding to 48 PDR pulses with 77 cGy/puls, 1 puls/h (37 Gy) and to LDR with 77 cGy/h in 48 h (37 Gy). For 70 Gy$_{EQD2}$ the dose per HDR fraction is 4.5 Gy (18 Gy). The same dose is reached with 48 PDR pulses with 54 cGy/puls, 1 puls/h (26 Gy), and LDR with 54 cGy/h in 48 h (26 Gy). (Courtesy of Potter et al Radiotherapy and Oncology 78 (2006) 67–77)
Fig. 5 Schematic anatomical diagram (sagittal view) indicating the most irradiated tissue volumes adjacent to the applicator for rectum, sigmoid and bladder: 0.1, 1, and 2 cm³ (identical patient as in Figs. 1 and 2, dose volume parameters for this schematic patient example can be taken from Fig. 5). (Courtesy of Potter et al Radiotherapy and Oncology 78 (2006) 67–77)
APPENDIX IX

Specimen Kit Description and Shipping Instructions (8/11/06, 8/27/08)

Each kit contains materials for 1 timepoint of collection:
- Nine (9) 1mL cryovials (for peripheral blood – Serum);
- One (1) urine collection cup;
- Two (2) 5 mL cryovials containing RNALater™ (For Fresh Tissue Collection)
- Biohazard bags;
- Absorbant shipping material;
- Styrofoam container (inner);
- Cardboard shipping (outer) box;
- Return shipping label.

Peripheral Blood:

Preparation of Serum:

- Using nine (9) 1ml cryovials, label them with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark cryovials “serum”.

Process:
- Place blood tubes on ice and allow blood to clot for 30 minutes.
- Spin in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
- Aliquot a minimum of 0.5ml serum into each of the nine, labeled 1mL cryovials.
- Place cryovials into biohazard bag.
- Use RTOG labels* to label bag.
- Store serum at –80°C Celsius until ready to ship.

Urine Specimens:

Preparation for collecting Urine:

- A clean catch urine specimen will be collected.

Process:
- Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
- After urinating a small amount into the toilet bowl, to clear the urethra of contaminants, collect a sample of urine in the collection cup.
- After 10-20 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
- Finish voiding the bladder into the toilet bowl.
- Aliquot 5 ml of urine into two-four 15-ml centrifuge tubes. Tighten tubes closed. If more urine is still present in the collection cup, place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen tubes and cup with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark specimen as “urine”.
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Store specimens frozen at -20°C Celsius until ready to ship on dry ice by overnight courier.

Fresh Tissue:

Process:
- Place the fresh tissue directly into the cryovials containing RNALater™ and seal the cryovial.
- Label each specimen with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark as “fresh tissue”.

Shipping Instructions for all specimens (8/27/08):

Serum/Urine Specimens: Cryovials containing serum, and urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Serum
and urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs. minimum). Seal the box with plastic tape. All paperwork should be placed in a plastic bag, sealed, and taped to the outside top of the Styrofoam box. Pack the Styrofoam box in a cardboard box. **Note:** Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box “biohazard”.

**Fresh Tissue:** Cyrovials containing fresh tissue should be wrapped in an absorbent material (e.g., paper towels) and placed in a biohazard bag. Fresh tissue samples should be sent in a separate refrigerated cooler (use refrigerant packs or other coolant material) overnight to the RTOG Biospecimen Resource. **Note:** Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box “biohazard”.

Send specimens by overnight express to the address below. If sending multiple coolers for a case, please mark coolers with number and total (e.g., 1 of 2, etc.). Specimens only should be shipped Monday through Thursday to prevent thawing due to delivery delays. Saturday or holiday deliveries will not be accepted. Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.

**Notes:**
- Include all RTOG paperwork in pocket of biohazard bag.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature).
- **Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.**

**For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource:**

Phone 415-476-RTOG (7864)  
FAX 415-476-5271  
RTOG@ucsf.edu

Sites must submit the required documentation with specimens. All specimens will be shipped to:

**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, DHL, etc.): For Frozen Specimens**
RTOG Biospecimen Resource  
University of California San Francisco  
1657 Scott Street, Room 223  
San Francisco, CA 94115