

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0418

A Phase II Study of Intensity Modulated Radiation Therapy (IMRT) to the Pelvis +/- Chemotherapy for Post-operative Patients with either Endometrial or Cervical Carcinoma

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SCHEMA (9/20/06)

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Diagnosis:

1. Endometrial Carcinoma
2. Cervical Carcinoma

**R
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1. Endometrial cancer patients: IMRT 28 fractions over 5.5 weeks.
2. Cervical cancer patients: IMRT 28 fractions over 5.5 weeks and concurrent cisplatin starting on a Monday or a Tuesday for 5 weeks.

Patient Population: (See Section 3.0 for Eligibility)

-Patients who have had a hysterectomy for carcinoma of the uterine cervix or endometrium; and have a Zubrod performance status of 0–2.

Required Sample Size: 92

ELIGIBILITY CHECKLIST (3/20/2006, 5/15/07)

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RTOG Institution # _____

Case # _____

(page 1 of 4)

- _____(Y) 1. Does the patient have histologically proven endometrial or cervical cancer?
- _____(Y) 2. Did the patient have a hysterectomy (total abdominal, vaginal, radical, or laparoscopic-assisted vaginal hysterectomy) within 7 weeks prior to study entry (did the patients with endometrial carcinoma also have a bilateral salpingo-oophorectomy)?
- _____(N) 3. Does the patient have histology consisting of papillary serous, clear cell, or neuroendocrine (either large or small cell), endometrial stromal sarcoma, leiomyosarcoma or malignant mullerian mixed tumor?
- _____(Y) 4. Does the patient meet the eligibility staging criteria in either Section 3.1.3 or 3.1.4?
- _____(Y) 5. Will the patient require post-operative radiation or chemoradiation?
- _____(N) 6. Will the patient require extended field radiotherapy beyond the pelvis?
- _____(N) 7. Does the patient have para-aortic nodal disease?
- _____(N) 8. Is there evidence of metastatic disease outside of the pelvis?
- _____(N) 9. Has the patient received prior radiotherapy to the region of the study cancer resulting in overlapping of radiation therapy fields?
- _____(Y/N) 10. Has the patient had prior invasive malignancies other than non-melanomatous skin cancer?
_____(Y) if yes, has the patient been disease free for a minimum of 3 years?
- _____(Y) 11. Is the patient's age ≥ 18 ?
- _____(Y) 12. Is the patient's Zubrod Performance status 0-2?
- _____(Y) 13. Are the patient's lab values within the limits specified in Section 3.1.7?
- _____(Y) 14. Was a chest x-ray or chest CT performed within 8 weeks prior to study entry?
- _____(Y/N/A) 15. Was a CT/MRI/PET-CT of the abdomen/pelvis performed pre- or post-operatively?
(Cervix patients only)
- _____(N) 16. Does the patient's weight/size exceed the size limits of the treatment table or CT scanner?
- _____(N) 17. Does the patient have any mental status changes or bladder control problems that would not enable the patient to comply with bladder-filling instructions?
- _____(N) 18. Has the patient had unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months?
- _____(N) 19. Has the patient had a transmural myocardial infarction within the last 6 months?

(Continued on the next page)

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ELIGIBILITY CHECKLIST (3/20/2006)

RTOG 0418

RTOG Institution # _____

Case # _____

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- _____(N) 20. Does the patient have an acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?
- _____(N) 21. Does the patient have Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration?
- _____(N) 22. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects?
- _____(N) 23. Does the patient have Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition?
- _____(N/N/A) 24. Has the patient ever been treated with platinum-based chemotherapy or had an allergic reaction to cisplatin? **(Cervix patients only)**
- _____(Y) 25. Has the patient signed a study-specific informed consent prior to study entry?

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ELIGIBILITY CHECKLIST (3/20/2006)

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RTOG Institution # _____

Case # _____ (page 3 of 4)

The following questions will be asked at Study Registration:

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (above) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date [This question will be protocol specific, defining the calendar base date.]
- _____ 17. Registration date: This date will be populated automatically.
- _____ 18. Medical Oncologist or Gynecologic Oncologist (**Cervix patients only**)

(Continued on the next page)

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ELIGIBILITY CHECKLIST (3/20/2006)

RTOG 0418

RTOG Institution # _____

Case # _____ (page 4 of 4)

_____ (Y/N) 19. Tissue/Blood kept for cancer research?

_____ (Y/N) 20. Tissue/Blood kept for medical research?

_____ (Y/N) 21. Allow contact for future research?

_____ 22. Primary tumor (endometrial vs cervical)?

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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 Background

Radiation therapy is commonly used in the treatment of gynecologic tumors, notably cervical and endometrial carcinomas. In most cases of endometrial carcinoma and/or in early-stage cervical carcinoma, patients are treated with an initial hysterectomy and lymph node dissection; however, if findings in the surgical specimen suggest a high-risk of pelvic recurrence, post-operative radiation therapy is often recommended. Randomized trials have demonstrated that whole pelvic radiation therapy (WPRT) reduces the rate of pelvic disease recurrence in patients who have undergone hysterectomy for uterine or cervical cancer. Recently, a randomized study by Peters, et al evaluated post-operative radiation therapy compared to concurrent chemotherapy and radiation in high-risk cervical carcinoma patients, and found that concurrent chemoradiation therapy was superior to radiation alone in this population.¹

Unfortunately, conventional WPRT results in the irradiation of large volumes of small bowel, rectum and bladder. Conventional techniques used to treat the pelvis with radiation therapy after hysterectomy for carcinoma of the uterine cervix or corpus involve either two (AP-PA) or four (AP, PA, Right lateral, and Left lateral) photon fields. These techniques expose most of the contents of the true pelvis to the prescribed dose (usually 45-50 Gy in 25-28 fractions). After hysterectomy, small bowel tends to fall into the vacated space in the true pelvis, increasing the amount of bowel treated to high dose. This in turn increases the risk of acute and late small bowel complications, limiting the dose that can be delivered to paracervical and nodal tissues that are at risk for recurrence. Although several studies have suggested that genitourinary side effects may be increased, the most consistent finding of toxicity after whole pelvic radiation is a marked increase in the incidence of small bowel complication in patients after a hysterectomy. Even with modest doses of radiation therapy (45-50 Gy), the risk of severe injury from postoperative radiation therapy is between 5% and 15%. Acute GI symptoms typically involve varying degrees of diarrhea, cramping, and abdominal discomfort.^{2,3} Chronic (late) toxicity may arise months to years after WPRT. Although severe chronic toxicities (proctitis, obstruction, fistulas) are uncommon, many women treated with WPRT suffer from a variety of chronic problems including intermittent diarrhea, intolerance to certain foods, and malabsorption of vitamins, lactose and bile acids.^{2,3}

Recently, intensity-modulated radiotherapy (IMRT) has evolved as a technique that can treat certain areas such as the tumor or areas at risk of recurrence while sparing adjacent normal tissues from high-dose irradiation. IMRT is an advanced form of 3D-conforming radiotherapy that produces a high-dose volume of radiation, which may be irregularly shaped to conform to the clinical target volume; by conforming more closely to the target volume, normal pelvic tissues (i.e., small bowel, bladder, rectum) are relatively spared. IMRT is currently being used in many clinical settings to achieve more conformal treatment of irregular treatment volumes, including the treatment of prostate, and head and neck carcinomas.

The major potential advantage of IMRT in the treatment of gynecological carcinomas, in the postoperative setting, is the ability to shape a dose distribution that delivers a lower dose to intraperitoneal pelvic contents (i.e., small and large bowel) than to the surrounding pelvic lymph nodes. This should make it possible to reduce the acute and late side effects of treatment. Recently, two groups have shown in planning studies that IMRT reduces the volume of small bowel irradiated to ≥ 45 Gy during WPRT for both cervical and uterine cancer. Portelance et al⁴ compared 4-, 7- and 9-field plans delivered by Dynamic Multileaf Collimation (DMLC) with 4-field box technique and showed a 58-67% reduction in the volume of small bowel irradiated to more than 45 Gy with IMRT that increased with the number of fields, but not beyond 7 fields. Roeske et al⁵ reported similar results in 10 patients with cervical or uterine carcinoma, treating the proximal vagina, parametrial tissues, uterus and pelvic nodes to 45 Gy in 25 fractions. A 50% reduction in the volume of small bowel irradiated to more than 45 Gy was observed with a 9-field Corvus plan when compared with 4-field 3D conformal plan.

Recently, Mundt et al has published several reports looking at toxicity including acute⁶ and chronic GI toxicity⁷ as well as hematologic toxicity⁸ in 40 patients with cervical and endometrial carcinoma treated with IMRT compared to patients treated in the institution with traditional conventional WPRT. They found in this group of patients a lower rate of acute grade 2 GI toxicity (60% vs. 91%, $p = 0.002$) compared with patients treated with conventional WPRT.⁶ Moreover, the percentage of patients requiring no or only infrequent anti-diarrhea medications were 75% in patients treated with IMRT compared to 34% in patients treated with conventional WPRT ($p = 0.001$).⁶ In this same group of patients, patients treated with IMRT had a lower rate of chronic GI toxicity compared to patients treated with conventional WPRT (11.1% and

54%, respectively, $p = 0.02$).⁷ A reduction in hematological toxicity was also observed in the chemo-IMRT treated patients when compared with standard WPRT (31% vs. 60% grade 2 or greater white blood cell toxicity).⁸ This was attributed to a significant reduction of bone marrow irradiated, particularly within the iliac crests. This reduction in hematological toxicity may improve patient compliance and increase the number of courses of chemotherapy given to a patient as well as reduce treatment delays due to hematological toxicity. While the results from this single institution are very promising, the uses of IMRT for gynecological carcinomas need to be tested in a multi-institutional setting.

However promising IMRT may seem there are several issues of concern and caution. The most important of these concerns is the accurate definition of target volume and organ motion. In a recent study by Ahamad et al,⁹ a variety of different parameters on the CTV were used to generate IMRT plans. They found that the volume of the normal tissues spared by IMRT relative to conventional techniques was very sensitive to small increases of the margin size used to generate the PTV. For example, with increase in margin size around the CTV by 5 mm, the volume of small bowel spared 30 Gy or more by IMRT was reduced by as much as 40%. Also, the vaginal vault and central pelvic tissues can move during treatment either due to random internal organ motion, or changes in filling of the rectum and bladder. When compared to standard techniques, the very tight and conformal isodose curves around the outlined target volumes in IMRT increase the risk of missing areas containing sub-clinical disease when the volumes are not accurately drawn. As a result, there is an increased risk of marginal or out-of-field recurrence. Therefore, even though a single institution's results of using IMRT for the treatment of gynecological carcinoma are very promising, this needs to be verified in a multi-institutional setting.

Rationale of this phase II study: the primary purpose of this study is to test the feasibility of delivering IMRT in a multi-institutional setting for the treatment of gynecological carcinoma in the post-operative setting. The rationale is that a potential reduction in radiation side effects, especially acute GI and hematological side effects, using IMRT will increase patient compliance and reduce long-term side effects without compromising local-regional control.

2.0 OBJECTIVES

- 2.1 To determine the transportability of IMRT to a multi-institutional setting.
- 2.2 To test the hypothesis that there is a reduction in short-term bowel injury with this regimen compared to standard treatments.
- 2.3 To assess adverse events related to this regimen.
- 2.4 To estimate the rates of local-regional control, distant metastasis, disease-free and overall survival.
- 2.5 To evaluate chemotherapy compliance with this regimen for the cervical carcinoma patients.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (3/20/06, 4/21/06, 9/20/06, 5/15/07)

- 3.1.1 Patients must have undergone a hysterectomy (total abdominal hysterectomy, vaginal hysterectomy or radical hysterectomy or laparoscopic-assisted vaginal hysterectomy) for carcinoma of the cervix or endometrium within 7 weeks prior to study entry. Patients with endometrial carcinoma must also have had a bilateral salpingo-oophorectomy.
- 3.1.2 Patients must require postoperative radiation therapy (endometrial cancer) or chemo/radiation therapy (cervical cancer).
- 3.1.3 Endometrial Cancer:
 - 3.1.3.1 Patients with stage IB, grade 3, IC grade 1-3, IIA or IIB requiring post-operative pelvic radiation therapy are eligible for this trial.
 - 3.1.3.2 Patients with unstaged (no lymph node dissection or sampling) Stage IB, grade 2 are eligible for this trial.
 - 3.1.3.3 Patients with Stage IIIC, pelvic lymph node positive only, para-aortic nodes sampled and negative and not going to receive chemotherapy are eligible for this trial.
- 3.1.4 Cervical Cancer:
 - 3.1.4.1 Patients with cervical cancer initially treated with a radical hysterectomy and lymph node dissection that require post-operative pelvic radiation therapy are eligible for this study.
 - 3.1.4.2 Patients with cervical cancer treated with a simple hysterectomy with negative margins and negative nodes by CT/MRI/PET-CT are eligible for this study.
 - 3.1.4.3 Post-radical hysterectomy – if the patient has positive pelvic nodes (negative para-aortic nodes) they are eligible for this study.

- 3.1.4.4 Post-radical hysterectomy – if the patient has microscopic parametrial invasion and negative margins they are eligible for this study.
- 3.1.4.5 Post-radical hysterectomy – if the patient qualifies by having met the Sedlis criteria for post-surgery for pelvic radiation therapy they are eligible for this study. The patient must have two of the following risk factors for this criterion:
- 3.1.4.5.1 *1/3 or more stromal invasion*
- 3.1.4.5.2 *lymph-vascular space invasion*
- 3.1.4.5.3 *large clinical tumor diameter (≥ 4 cm)*
- 3.1.5 Age ≥ 18
- 3.1.6 Zubrod performance status 0-2
- 3.1.7 Patients with adequate bone marrow, renal and hepatic function (all labs are to be obtained \leq 14 days prior to registration)
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other interventions to achieve Hg ≥ 8.0 g/dl is acceptable.) **(Endometrial and cervix patients)**
 - WBC $\geq 4,000/\text{mm}^3$ **(Cervix patients only)**
 - ANC $\geq 1,800$ cells/ mm^3 **(Cervix patients only)**
 - Platelets $\geq 100,000$ cells/ mm^3 **(Cervix patients only)**
 - Serum Creatinine ≤ 2.0 mg/dl and calculated creatinine clearance ≥ 50 cc/min. Both tests must be within these limits. The creatinine clearance should be calculated using the Cockcroft-Gault formula **(Cervix patients only)**:

$$\frac{(140 - \text{age}) \times (\text{ideal weight as kg})}{(\text{Serum Creatinine} \times 72)} \times 0.85$$
 - AST $\leq 2 \times$ ULN **(Cervix patients only)**
 - Bilirubin $\leq 2 \times$ ULN **(Cervix patients only)**
 - Alkaline phosphatase, Mg, BUN and electrolytes must be obtained and recorded **(Cervix patients only)**
- 3.1.8 Prior to registration CT/MRI/PET-CT of abdomen/pelvis, for initial radiological staging, must be performed pre- or post-surgery. **(Cervix patients only)**
- 3.1.9 Chest x-ray or chest CT must be performed within 8 weeks prior to study entry.
- 3.1.10 The patient must sign a study-specific informed consent.
- 3.2 Conditions for Patient Ineligibility (3/20/06)**
- 3.2.1 Patients with para-aortic nodal disease or who require extended field radiotherapy beyond the pelvis.
- 3.2.2 Patients with histology consisting of papillary serous, clear cell or neuroendocrine (either large or small cell), endometrial stromal sarcoma, leiomyosarcoma or malignant mullerian mixed tumor.
- 3.2.3 Patients who exceed the weight/size limits of the treatment table or CT scanner.
- 3.2.4 Mental status changes or bladder control problems that make the patient unable to comply with bladder-filling instructions.
- 3.2.5 Patients with evidence of metastatic disease outside of the pelvis.
- 3.2.6 Patients with microscopic involvement of the resection margin (< 3 mm) will be excluded.
- 3.2.7 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.
- 3.2.8 Prior radiation therapy to the pelvis that would result in overlap of radiation therapy fields.
- 3.2.9 Patients with active inflammatory bowel disease will be excluded.
- 3.2.10 Severe, active co-morbidity, defined as follows:
- 3.2.10.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- 3.2.10.2 Transmural myocardial infarction within the last 6 months
- 3.2.10.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- 3.2.10.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- 3.2.10.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory test coagulation parameters are not required for entry into this protocol
- 3.2.10.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this

protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients.

- 3.2.11 Cervical cancer patients with prior allergic reactions to cisplatin will be excluded.
- 3.2.12 Cervical cancer patients with prior treatment with platinum-based chemotherapy will be excluded.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

(In addition to required evaluations in Section 3.0)

- 4.1 Complete history and general physical examination completed within 14 days prior to study entry.
- 4.2 Audiogram (for cervical cancer patients) at the discretion of the treating physician.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements

Institutions must be credentialed by RTOG prior to enrolling patients into this study. Credentialing will be facilitated by the Advanced Technology Consortium (ATC) consisting for this study of the Image-Guided Therapy Center (ITC) at Washington University, the Radiological Physics Center (RPC) at M.D. Anderson Cancer Center, and RTOG RT Quality Assurance.

Institutions that have been credentialed by RTOG to participate in RTOG IMRT head and neck studies or RTOG IMRT prostate studies may enroll patients on this study without further credentialing by RTOG. Please note that all institutions must complete the “Dry-Run” test as described in Section 5.1.4.

Institutions that have **not** been credentialed by RTOG to participate in RTOG IMRT head and neck studies or RTOG IMRT prostate studies must apply for IMRT certification as described in Sections 5.1.1-5.1.4.

- 5.1.1 Each institution must complete the IMRT Facility Questionnaire available on the ATC web site, <http://atc.wustl.edu/>. Each institution must submit the completed Facility Questionnaire by email, fax, or mail to:

Image-Guided Therapy Center (ITC)
Attn: Roxana Haynes
4511 Forest Park Avenue, Suite 200
St. Louis, MO 63108
E-mail: itc@castor.wustl.edu
Phone: 314-747-5415
FAX: 314-747-5423

Institutional and/or peer-reviewed documentation of target position reproducibility (gross tumor volume within planning treatment volume) must be consistent with Section 6.4.

Documented ability to transfer patient specific material and treatment planning parameters including CT-based dose deposition representations, dose-volume matrices and parameters, and stereotactic targeting representations to the ITC.

- 5.1.2 Each institution must contact the ITC (itc@castor.wustl.edu) and request an FTP account for digital data submission.
- 5.1.3 Each institution must successfully irradiate a standardized phantom provided by the Radiological Physics Center (RPC) at M.D. Anderson Cancer Center. Instructions for requesting and irradiating the phantom are available at the RPC web site, <http://rpc.mdanderson.org/rpc/> by selecting “Credentialing” and “RTOG.” The treatment plan for irradiation of the phantom must be submitted electronically to the ITC (see Section 5.1.2).
- 5.1.4 Each institution must submit and successfully complete a protocol-specific Dry-Run Test (the treatment plan for the first patient to be treated at the site on this protocol), and a Rapid Review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The Dry-Run Test will be reviewed by the ITC. The Rapid Review will be conducted by the RPC and suggestions regarding protocol compliance will be forwarded to the participating institution.

The treatment plans for subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed for protocol compliance at a later

date. Instructions for submitting the dry run can be found on the ATC website (<http://atc.wustl.edu>).

5.2 Registration

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met. The RA will 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. A username and password are required. 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. E.T.

6.0 RADIATION THERAPY

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

6.1 Dose Specifications (3/20/06, 5/15/07)

6.1.1 Prescription dose shall be according to the following specifications:

6.1.1.1 The vaginal planning target volume (PTV) (ITV with 7.0 mm margin) and nodal PTV will receive 50.4 Gy in 28 fractions. Treatment will be delivered once daily, 5 fractions per week, over 5.5 weeks. All targets will be treated simultaneously. Breaks in treatment should be minimized. Total treatment breaks exceeding 5 consecutive days will be considered a major violation.

6.1.1.2 The prescription dose is the isodose which encompasses at least 97% of the vaginal PTV and nodal PTV. No more than 20% of any PTV will receive > 110% of its prescribed dose. No more than 1% of any PTV will receive < 93% of its prescribed dose. No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTVs will receive > 110% of the dose prescribed to the primary PTV.

6.1.1.3 The vaginal cuff may be boosted with a high-dose rate dome cylinder at the discretion of the treating radiation oncologist. If a boost to the vaginal cuff is used, the dose should be limited to 600cGy x1-2 fractions prescribed to the vaginal surface. Only the top 1/3-1/2 of the vagina should be treated.

6.2 Technical Factors

6.2.1 Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. The use of three-dimensional conformal radiotherapy (3D-CRT) using forward-planned IMRT treatment planning methods is acceptable. The use of compensators or partial

transmission blocks are also acceptable as long as dose specifications and constraints are satisfied.

6.2.2 6-10 MV energy photon beam should be used

6.3 Localization, Simulation, and Immobilization

6.3.1 Prior to simulation, it is recommended that small radiopaque marker seeds are inserted into the vaginal apex to help identify the vaginal apex on the CT scan. Radiopaque markers that distend or otherwise alter the vaginal anatomy should not be used.

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

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

6.4 Treatment Planning/Target Volumes (9/20/06, 5/15/07)

6.4.1 Two separate treatment planning CT scans (full bladder and empty bladder CT scans, as described below) are required and then should be fused together prior to outlining target volumes. The patient will be instructed to drink 32 ounces of fluid 30-60 minutes before simulation:

6.4.1.1 A CT scan simulation will be performed with the full bladder, and

6.4.1.2 A second CT after the patient has voided for the empty bladder scan.

6.4.2 The Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, clinical information, and MRI. In this study, which is used for post-operative patients with no gross disease, there should not be a GTV.

6.4.3 The Clinical Target Volume (CTV) is defined as areas considered to contain potential microscopic disease, delineated by the treating physician. Please refer to Section 6.5 for details.

6.4.4 Internal Target Volume (ITV) is defined as the volume of the vagina that is in both the empty and full bladder CT scans that are done at the time of simulation and fused together. This volume accounts for internal organ motion.

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

6.4.6 Planning of the IMRT will be done on the full bladder scan.

6.4.7 The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose volume histogram (DVH) analyses of the PTV (CTV with a 7 mm margin) and critical normal structures. An inverse or forward-planning IMRT technique should be used. All planning must be done on the full-bladder CT scan. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of non-involved tissues.

6.4.8 The method used for tissue heterogeneity calculations shall be reported.

6.4.9 Planning Priorities:

- Critical normal structures constraints followed by the prescription goals are the most important planning priorities.
- The priorities in addressing the protocol aims and constraints are in Critical Structures (Section 6.5).

6.4.10 The nodal CTV should include lymph nodes that drain the involved site and adjacent perinodal soft tissue. This should include the internal (hypogastric and obturator), external, and common iliac lymph nodes; if the cervix is involved (even with endometrial cancer), presacral lymph nodes and soft tissues should be included as well, down to the level of S3. Identification of the CTV usually begins with the identification of the iliac vessels. The nodal CTV will include the vessel, perinodal tissue (on the pelvic wall side, the margin will exclude psoas and piriformis muscle) and pertinent clips. The average margin will be 7 mm. Bone and intraperitoneal small bowel should be excluded from the CTV; also, iliopsoas muscle that lies adjacent to clinically negative lymph nodes should also be excluded from the CTV. Approximately 1-2 cm of tissue anterior to the S1, S2 and S3 sacral segments is usually added to the CTV for patients with cervical carcinoma in order to include the presacral lymph nodes and uterosacral ligaments. The most antero-lateral external iliac lymph nodes that lie just proximal to the inguinal canal should be excluded from the CTV (i.e., nodal CTV should stop right at the level of the femoral head). The CTV of the nodes should end 7 mm from L4/L5 interspace to account for the PTV. The PTV for nodes to stop at L4/L5 interspace. (See GYN atlas for examples: <http://www.rtog.org/gynatlas/main.html>.)

- 6.4.11** The vaginal and parametrial CTV should actually be an ITV, which will account for internal organ motion. The ITV is drawn after the full and empty bladder scans are fused together, and it should encompass the vagina and paravaginal soft tissues from both scans. This is because patients are not able to maintain constant levels of bladder filling, despite careful counseling. Patients should, however, be treated with a full bladder, because full bladder pushes the small bowel up and out of the field. The inferior limit is usually around the level of the upper third of the symphysis pubis but can be individualized based on inferior spread of the patient's tumor on prior pre-operative physical examination and post-operative pathology reports. The lateral margin of the vaginal PTV should be to the obturator muscle. However, at least 3 cm of the vagina needs to be treated or at least 1 cm below the obturator foramen.
- 6.4.12** The Planning Target Volume (PTV) will provide a 7 mm margin (anteriorly, posteriorly, laterally, as well as in the superior and inferior directions) around the nodal CTV. The vaginal PTV will be 7.0 mm around the vaginal ITV anteriorly, superiorly, inferiorly, laterally, and posteriorly.
- 6.4.13** The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing Recording and Reporting Photon Beam Therapy and 1999 ICRU Report #62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50).

6.5 Critical Structures (9/20/06)

- 6.5.1** Normal structures will be contoured using the full-bladder CT scan.
- 6.5.2** Bladder – will be outlined on every slice, including the portion inferior to the planning target volume.
- 6.5.3** Rectum – will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid.
- 6.5.4** Small bowel – will be outlined on every slice, including at least 2 cm above the planning target volume. It includes the volume surrounding loops of small bowel out to the edge of the peritoneum because the bowel may lie within this space at any time throughout the course of treatment.
- 6.5.4.1** The femoral heads and the sacrum should be contoured in all slices.
- 6.5.5** Participants are strongly encouraged to remain within these limits:
- 6.5.5.1** Small bowel < 30% to receive ≥ 40 Gy, minor deviation 30% to 40 Gy
- 6.5.5.2** Rectum < 60% to receive ≥ 30 Gy, minor deviation 35% to 50 Gy
- 6.5.5.3** Bladder < 35% to receive ≥ 45 Gy, minor deviation 35% to 50 Gy
- 6.5.5.4** Femoral head $\leq 15\%$ to receive ≥ 30 Gy, minor deviation 20% to 30 Gy
- 6.5.6** I.V. contrast may be used during simulation to help better define the vessels; however, it is not required. We would not recommend oral or rectal contrast because it may interfere with the planning process and may possibly cause anatomical distortion.
- 6.5.7** All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.3 cm or smaller through the region that contains the primary target volumes and at least 4 cm above and below the target volumes. The superior limit will be at least at the L1/2 interspace and inferior limit will be below the perineum.
- 6.5.8** The ITV and CTV and normal tissues must be outlined on all CT slices in which the structures exist on the full-bladder scan. ITV contours will be modified to include the excursion of target tissues as demonstrated on the empty bladder scan (ITV). Using the full bladder scan, all normal tissues will be outlined on all CT slices in which the CTV and ITV exist and on at least 7 slices (21 mm) above and below the target. (See Section 6.5.7 for more detailed definitions.)
- 6.5.9** Lymph node groups at risk including the following:
- The lower common iliac nodes – the superior limit of the contoured common iliac will be at the top of L5 vertebral body – the PTV should be at the top of L5, therefore the CTV should be contoured up to 7 mm from the top of L5
 - Internal iliac (obturator and hypogastric) nodes
 - External iliac nodes up to the level of the top of the femoral heads
 - The presacral nodes down to the level of S3 for cervical carcinomas or patients with Stage IIB endometrial carcinoma
 - The obturator nodes – inferiorly to upper 1/3 of the obturator fossa

6.6 Documentation Requirements

- 6.6.1** Verification orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films. These films will not be collected but should be held by the institution and available for review if requested.

6.7 Compliance Criteria

- 6.7.1** The ITC will display and compare with hard copies isodose distributions through the planning target volume to verify correct digital submission and conversion.
- 6.7.2** The ITC will compare the submitted digital dose-volume histograms (DVHs) for the PTVs, the designated critical structures and unspecified tissues with DVHs calculated by the ITC.
- 6.7.3** Each treatment shall be remotely reviewed by RPC for Quality Assurance of Target Volumes and Critical Structure Volumes, which include:
- 6.7.3.1** PTV vagina 50.4
- Per protocol: The prescription criteria in Section 6.1 are fulfilled.
 - Variation acceptable: The 90% isodose surface covers between 95% and 98% of the ITV 50.4, or volumes of overdose exceed those specified in Section 6.1.1 (115%) by < 5% of the ITV 50.4 volume.
 - Deviation unacceptable: The 90% isodose surface covers < 95% of ITV 50.4 or > 5% of the ITV 50.4 receives over 115%.
- 6.7.3.2** PTV nodal
- Per protocol: The prescription criteria in section 6.4.2 are fulfilled.
 - Variation acceptable: the 90% isodose surface covers between 95% and 98% of the PTV 50.4, or volumes of overdose exceed those specified in Section 6.1.1 (115%) by < 5% of the PTV 50.4 volume.
 - Deviation unacceptable: the 90% isodose surface covers < 95% of PTV 50.4 or > 5% of the PTV 50.4 receives over 115%.

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chairs, Anuja Jhingran, M.D. and Lorraine Portelance, M.D. will remotely perform RT Quality Assurance Reviews after complete data for the first 19 cases enrolled have been received (see Section 12.0). A second remote review will be performed after receiving complete data for the next 19 cases. If early stopping does not occur (see Section 13.4.2.2), the rest of the cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received, whichever occurs first. Study chairs will not review cases from their own institutions; they will be reviewed by the other RT study chair.

6.9 Radiation Treatment Interruptions

- 6.9.1** Interruptions in radiotherapy may be necessitated by uncontrolled diarrhea, or other acute complications. The reason for and the length of any such interruption must be documented. If the sum total of such interruptions exceeds five normally scheduled treatment days, the treatment may be considered in major violation of protocol. Radiation therapy will be continued without interruption if at all possible.
- 6.9.2** If radiation therapy is held, then chemotherapy will also be held. (If chemotherapy is held for toxicity the missed treatments are not completed after RT ends. Chemotherapy stops at the completion of RT.)
- 6.9.2.1** 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.)

6.10 Radiation Adverse Events

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

All toxicities will be recorded on data collection forms.

6.11 Radiation Adverse Event Reporting

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

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

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days
Note:						
<ul style="list-style-type: none"> All grade 4 and 5 adverse events (AEs) that occur during or within 30 days after the completion of radiation therapy (RT), regardless of causation, must be reported within 5 days; Grade 4 and 5 AEs that occur in follow up (beyond 30 days after the completion of RT but still within the timeframe of follow up of the patient on study) and that are thought to be probably or definitely related to RT (e.g., radiation-induced spinal cord myelopathy) must be reported within 5 days. 						

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.

Only cervical cancer patients will receive drug therapy on this study.

7.1 Cisplatin (Platinol®) (9/20/06, 5/15/07)

See package insert for further information.

7.1.1 **Formulation:** Cisplatin is available 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.

7.1.2 **Preparation:** 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 (as recommended) results in a clear, colorless solution.

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.

7.1.3 **Storage:** 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. Unopened containers should not be refrigerated; and should be stored at 15-20°C; and should be protected from light.

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

7.1.4 **Adverse Effects:** 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:

7.1.4.1 **Nephrotoxicity:** Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of cisplatin. Renal toxicity has 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 toxicity becomes more prolonged and severe with repeated courses of cisplatin, renal function must return to normal before another dose can be given. Severe renal toxicity can be avoided by induction of diuresis before, during and after treatment.

7.1.4.2 **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 rarely reported.

7.1.4.3 **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.

7.1.4.4 **Gastrointestinal Toxicity:** Marked nausea and vomiting occur in almost all patients treated with cisplatin. Diarrhea and anorexia have also been reported.

7.1.4.5 **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.

7.1.5 Supplier: Commercially available.

7.1.6 Administration: Only patients with cervical cancer will receive Cisplatin 40 mg/m² IV starting on a Monday or a Tuesday for 5 weeks concurrently with IMRT. Patients will be prehydrated per institutional guidelines/policy. Cisplatin is given over 30-60 minutes in 500 ml of NS followed by 1 L of NS. Modification of the fluid regimen for specific reasons and the anti-emetic regimen for this combination is to be determined by the treating physician, and documented in patients' treatment record. The maximum total does of cisplatin is 70 mg. Close attention should be paid to potassium and magnesium levels and substitution given when necessary.

7.1.7 Treatment:

Cervical Cancer patients:

Agent	Dose	Route	Schedule
Cisplatin	40 mg/m ² (max total weekly dose = 70 mg)	IV	Weekly (on Monday or Tuesday) X 5 weeks

7.2 Dose Modifications (3/20/06, 9/20/06, 5/15/07)

7.2.1 Based on blood work performed prior to each cycle

Toxicity	Parameters	Modification
Serum creatinine and creatinine clearance**	> 2.0 mg/dl and/or creatinine clearance \leq 50 cc/min	Hold chemotherapy, repeat blood chemistry in one week; if within parameters resume at 40 mg/m ² ; if not hold for 1 more week, if still not within parameters stop chemotherapy completely.
ANC	< 1500 mm ³	Hold for that week and use neupogen x3, repeat CBC diff. next week, if above parameter treat with 40 mg/m ² , otherwise hold, use neupogen x3 and repeat CBC diff. next week, if still not within parameters discontinue chemotherapy.
Platelets	< 100,000 mm ³	Hold for that week, repeat CBC diff. next week; if above parameter treat 40 mg/m ² , otherwise hold and repeat CBC diff. and platelets next week, if still not within parameters discontinue chemotherapy.
Bilirubin	\geq 2 mg/dl	Hold for that week and repeat blood chemistry next week; treat 40 mg/m ² only if within parameters; if more than 2 treatments missed discontinue chemotherapy
AST	\geq 3 \times ULN	Hold for that week and repeat blood chemistry next week; treat 40 mg/m ² only if within parameters, if more than 2 treatments missed discontinue chemotherapy.
Platinum-related neuropathy	\geq grade 2	Discontinue chemotherapy
Ototoxicity	\geq grade 2	Discontinue chemotherapy

**If the serum creatinine is > 2.0, a creatinine clearance must be obtained as per the Cockcroft-Gault formula: (140-age)(kg ideal wt) / 72 x (serum creatinine) x 0.85 or nomogram calculation (valid only if serum creatinine is not changing rapidly), and the dose modified as indicated. Chemotherapy can be held up to 2 weeks, if longer, then chemotherapy should be stopped.

7.2.2 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.)

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

7.3 Criteria for Removal From Protocol Treatment

- Progression of disease;
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;
- A delay in chemotherapy > 2 weeks; discontinue chemotherapy.
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.

7.4 Modality Review

“The Medical Oncology Co-Chair, Brigitte E. Miller, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **per protocol; variation acceptable; deviation unacceptable; not evaluable for chemotherapy review**, or, **incomplete chemotherapy**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.5 Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined 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](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

Serious adverse events (SAEs) as defined below will be reported using either the FDA MedWatch Report or AdEERS. The RTOG Data Manager will tell the site which type of report to use for each study. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

7.5.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 Hours/Day)

Definition of an AE: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment (21 CFR & ICH Guidelines. *GCP Reference Guide*. Media, PA; 2004: 330)

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 and attributed to the protocol treatment (**definitely, probably, or possibly related**) should be reported via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also **must be reported on the AE case report form** (see Section 12.1).

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

7.5.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, 800-227-5463 ext. 4189; available 24 hours/day) within 24 hours of discovery of the event.

Definition of an SAE: Any adverse drug experience occurring at any dose 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.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller's contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS **within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call.** SAEs reported using AdEERS also **must be reported on the AE case report form** (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to 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. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must 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 print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6 Phase 2 and 3 Trials Utilizing a Commercially Available Agent Under a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days¹ of the Last Dose of the Cisplatin (Platinol®) in this Study

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days
¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows: AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via email to [Group] AE Coordinator for agents in non-CTEP IND studies) followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> • Grade 4 and Grade 5 unexpected events AdEERS 10 calendar day report: <ul style="list-style-type: none"> • 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. ³ Please see exceptions below under section entitled “Additional Instructions or Exceptions.” March 2005									

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

All patients will undergo surgery for their cancer prior to enrolling in this protocol.

9.0 OTHER THERAPY

9.1 Growth Factors

- 9.1.1 Patients will NOT receive growth factors (filgrastim [G-CSF], sargramostim [GM-CSF], pegfilgrastim [Neulasta]) UNLESS they experience neutropenic complications.
- 9.1.2 Patients will NOT receive prophylactic thrombopoietic agents. If they experience thrombocytopenia, treatment should be initiated following the judgment of the treating physician.
- 9.1.3 Patients may receive erythropoietin (Aranesp® [darbepoetin alfa], Procrit® [epoetin alfa]) for management of anemia AFTER documentation of hemoglobin less than 10 g/dl (CTCAE v3.0 grade 2).

- 9.2 Patients may NOT receive amifostine or other protective reagents.
- 9.3 Aminoglycoside antibiotics such as neomycin, paromomycin, capreomycin, amikacin, kanamycin, gentamycin, tobramycin and streptomycin should be avoided if possible.

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 Tissue/Specimen Submission (9/20/06)

The RTOG Tissue Bank at LDS Hospital in Utah acquires and maintains high-quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Tissue Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Tissue Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the RTOG tissue bank for the purpose of tissue banking and translational research (recommended). For patients who have consented to participate in the tissue/blood component of the study see Appendix I for consent forms.

10.2 Specimen Collection for Tissue Banking (9/20/06)

The following specimens are required and must be provided in order for the case to be evaluable for the Tissue Bank:

- 10.2.1 One H&E stained slide of the primary tumor.
- 10.2.2 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 Tissue Bank. If sites are unfamiliar or are uncomfortable obtaining a punch from the tissue block, the block may be submitted to the tissue bank where the tissue bank will obtain the punch and return the block to the submitting institution for storage. If such a procedure is required, please include a note with the specimen transmittal form requesting a punch be taken and block returned.
- 10.2.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- 10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.
- 10.2.5 Submit materials to:

**LDS Hospital
RTOG Tissue Bank, 1st Floor North
8th Avenue and C Street
Salt Lake City, UT 84143
(801) 408-5626; (801) 408-2035
FAX (801) 408-5020
RTOG@intermountainmail.org**

10.3 Reimbursement

RTOG will reimburse submitting institutions \$200 per case for a block or core of material. After confirmation from the RTOG Tissue Bank 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.

10.4 Confidentiality/Storage

(For further details see the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/tissuebank/tissuefaq.html>.)

- 10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Tissue Bank 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.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution from where it was submitted.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (3/20/06, 9/20/06, 5/15/07)

Assessments	Pre-Study Entry	Weekly During RT (Endometrial Patients)	CTX/RT (cervix cancer pts only)	Follow-up
History/physical	X ^b			X ^c
Disease Documentation	X			X ^c
Chest x-ray or chest CT	X ^a			X ^d
CT scan (or MRI or PET-CT) of abdomen and pelvis	X ^h			Xi
Hemoglobin	X ^{b,k}			
CBC/Platelets	X ^{b,l}	week 3	X ^e	
AST, bilirubin, alkaline phosphatase, serum creatinine	X ^{b,l}	week 3	X ^e	
creatinine clearance	X ^{b,l}		X ^g	
BUN, Lytes, Mg	X ^{b,l}	week 3	X ^e	
Weight, Zubrod	X ^b	X	X ^e	X ^c
Pap smear				X ^j
Toxicity Evaluation		X	X ^e	X ^c
Audiogram	X ⁱ		X ⁱ	

- a. Studies must be completed ≤ 8 weeks (56 days) prior to study entry.
- b. ≤ 14 days prior to study entry.
- c. Follow-up will be performed four weeks post completion of IMRT and then every 3 months during the first two years; every 6 months during years 3-5; then annually.
- d. 3 month scan post CTX/RT; then every 6 months for 2 years; then annually for 5 years.
- e. Prior to each cycle.
- f. At the discretion of the individual investigator.
- g. Prior to each cycle, if serum creatinine > 1.5 mg mg/dl.
- h. Pre- or post-surgical procedure (Cervix patients only).
- i. 3 month scan post CTX/RT (Cervix patients only).
- j. Every 3-6 months during the first two years; every 6 months during years 3-5; then annually.
- k. Endometrial and cervix patients.
- l. Cervix patients only.

12.0 DATA COLLECTION

12.1 Data Submission to ITC

12.1.1 *Digital Data Submission* may be accomplished using media or the Internet.
For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:
itc@castor.wustl.edu

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

**Image-Guided Therapy Center (ITC)
4511 Forest Park, Suite 200
St. Louis, MO 63110
314-747-5415
FAX 314-747-5423**

12.1.2 Data Submission to ITC for Patient Treatment

<u>Item</u>	<u>Due</u>
Initial Dosimetry Information:	Within 1 week of RT start
Digital Data Submission Information Form (DDSI)	
Digital treatment planning data (Digital patient data CT scans, critical normal structures, all CTV/ITV/PTV contours, doses for all fraction groups, DVHs for total dose plan).	
Color Isodose Distribution (T6)	Within 1 week of RT end
Final Dosimetry Information:	
Radiotherapy Form (T1)*	
Complete Daily Treatment Record (T5)	

* Send copy to RTOG Headquarters

Please see the ATC web site (<http://atc.wustl.edu>) for detailed information regarding digital data submission requirements; and if applicable, including optional brachy boost data submission.

12.2 Summary of Data Submission to RTOG (3/20/06)

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.

Item	Due
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	Within 2 weeks of study entry
Treatment Form (TF) (cervix cancer patients only)	within 1 week of chemo/RT completion
Radiotherapy Form (T1)	Within 1 week of RT completion
Adverse Event Form(AE)	Within 1 week of chemo/RT completion
Follow-up Form (F1)	6 weeks post IMRT completion then every 3 months post IMRT completion for the first 2 years; then every six months years 3-5; then for at least 3 years annually. Also at progression/relapse and at death.
Adverse Event Form(AE)	With each follow-up form as applicable.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints: All study endpoints will be evaluated separately for two groups based on the patient's primary disease site: cervical or endometrial.

13.1.1 Primary Endpoint

Reproducibility of Radiation Technique

Reproducibility is the primary endpoint because whether or not the technique is widely applicable in a multi-center setting must be demonstrated prior to undertaking a Phase III trial. Specific tools to measure the quality of the radiation technique have been developed in Section 6. The ability of various clinical sites to perform IMRT within the guidelines delineated in this protocol will provide a measure of feasibility for this technique. Since patient treatments at M.D. Anderson and McGill University Health Center (the study chairs' institutions) are most likely to be scored acceptable, the accrual from each of these centers will be capped at approximately 12.5% (see Section 13.2).

13.1.2 Secondary Endpoints

13.1.2.1 Adverse Events (AEs)

13.1.2.1.1 To determine if there is a reduction in grade 2 or higher short-term bowel AEs occurring within 90 days of treatment start as compared to standard treatment.^{10,11} For purposes of this study, "bowel AEs" are defined as the following: **diarrhea, enteritis, fistula, ileus:GI, incontinence:anal, necrosis:GI, obstruction:GI, perforation:GI, proctitis and stricture/stenosis (including anastomotic):GI as graded by CTCAE v. 3.0**

13.1.2.1.2 To evaluate adverse events associated with this treatment regimen.

13.1.2.2 To evaluate chemotherapy compliance with this regimen for the cervical carcinoma patients.

13.1.2.3 Local-regional failure

Estimate the rate of local-regional failure. Local-regional failure will be considered any failure in the treatment field, which will be the pelvis only.

13.1.2.4 Distant Metastases

Estimate the rate of distant metastases. For distant metastases, distant disease is considered a failure. Para-aortic nodal disease is considered to be distant disease for a cervical primary, but not for an endometrial primary.

13.1.2.5 Disease-Free Survival

Estimate the rate of disease-free survival. All disease recurrences will be recorded. In disease-free survival, any tumor recurrence, development of distant metastases or death is considered a failure.

13.1.2.6 Overall Survival

Estimate the overall survival rate. Death from any cause is considered a failure.

13.2 Study Design

13.2.1 Sample Size Derivation

The sample size will be the same for each primary disease site group (cervical and endometrial) and will be determined by the primary endpoint (Section 13.1.1), namely, the reproducibility of the radiation technique. There will be a central review by the radiation oncology study chairs after the treatment is delivered. The radiation therapy will be scored by the study chairs as acceptable, marginally acceptable, or unacceptable, using the criteria in Section 6.7. Study chairs will not review cases from their own institutions, they will be reviewed by the other RT study chair. All eligible patients will be included in the analysis. The optimal two-stage design by Simon¹⁰ will be used. Let p be the true probability that the final review is acceptable or marginally acceptable. A p close to 1 implies that the radiation therapy is reproducible in a multi-center setting. If p is less than or equal to 80%, the goal is to have at most a 5% probability of concluding that the technique is reproducible. On the other hand, if p is greater than or equal to 95%, the desired level, the goal is to have at most a 10% probability of concluding that the technique is not reproducible. With these specifications, 19 eligible patients will be required in the first stage. It is required that M.D. Anderson Cancer Center and McGill University Health Center each enter no more than 3 eligible patients for this stage. If 3 or more of the 19 treatments are scored unacceptable, then early stopping will be recommended to the study chair. Otherwise, the trial will continue until a total of 42 eligible patients are accrued. The maximum number that M.D. Anderson Cancer Center and McGill University Health Center can each enter is 6 eligible patients. If 5 or more of the 42 treatments are scored unacceptable, the technique will be considered not reproducible, and a Phase III study will not be pursued. Otherwise, we will consider a further randomized Phase III study using this regimen. Under the null hypothesis of an 80% reproducibility rate, this two-stage design has an expected sample size of 24.4. When p is 80%, this design minimizes the expected sample size among all designs satisfying the same specifications. To allow for an 8% ineligible/lost rate, the sample size for each primary disease site (cervical and endometrial) will be 46 patients, making **the total sample size for the study 92 patients**.

13.2.2 Short-Term Bowel Adverse Events (AEs)

A secondary objective of this study is to determine, within each primary disease site group, if there is a reduction in the short-term grade 2 or higher bowel AEs (as specified in Section 13.1.2). The sample size of 42 patients, for each primary disease site group, provides 64%, 88% and 98% power to detect a reduction in short-term grade 2 or higher bowel AEs (as specified in 13.1.2.1) from 40%^{11,12} to 25%, 20% and 15% respectively.

13.3 Patient Accrual

For each primary disease site group, after the accrual of the first stage of 19 eligible patients is completed, the two-stage design calls for suspension of patient accrual until the results of the first stage are known. However, after the initial reviews of treatment plans and partial reviews of final treatments, if it appears that the early stopping boundary will not be crossed, then no suspension of accrual will occur. Based on RTOG 9708,¹³ the projected monthly accrual for the patients with a primary disease site of endometrial will be three patients. Based on trials from SWOG¹⁴ and GOG¹⁵ for post-op cervical patients, the projected monthly accrual for this group will be four patients. It will take approximately 19 months to complete the accrual to this study, assuming there will be very little accrual during the first 4 months after activation while institutions become credentialed and obtain IRB approval.

13.4 Schedule of Analyses

13.4.1 Interim Reports

Interim reports will be prepared every six months until the primary endpoint has been presented. In general, these reports include:

- the patient accrual rate with projected completion date
- institutional accrual
- pretreatment characteristics
- the frequency and severity of toxicities due to protocol therapy
- compliance rates of treatment delivery with respect to the protocol prescription

13.4.2 Analyses for Reporting Treatment Results

For each primary disease site group, after 19 eligible patients have finished their treatment, the study chairs will review the dosimetry together with other data.

13.4.2.1 Analyses with Early Stopping

If three or more radiation treatments are unacceptable, early stopping will be recommended. If this occurs, the primary endpoint of feasibility, preliminary adverse event data and chemotherapy compliance (cervix patients only) will be analyzed after each patient has been

followed for at least 90 days. (Endpoints 13.1.1, 13.1.2.1.1, 13.1.2.2) Two years after the early stopping, long-term AEs and efficacy analyses will be done.

13.4.2.2 Analyses without Early Stopping

Without early stopping, the first analysis will be made after each patient has been followed for at least 90 days. This first analysis will focus on feasibility, preliminary adverse event data and chemotherapy compliance (cervix patients only). The results will be used to determine whether a further Phase III study is appropriate. Analyses on long-term AEs and efficacy endpoints will be done two years after completion of accrual.

13.4.2.3 Analysis Components

The usual components of the above-mentioned analyses are:

- tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion
- institutional accrual
- patient accrual rate
- distribution of important pretreatment characteristics
- **Compliance rate for treatment delivery with respect to the protocol prescription**
- observed results with respect to the appropriate endpoints described in Section 13.1.

13.4.2.4 Adverse Event Analyses

13.4.2.4.1 Fisher's exact test will be used to determine if there is an association in these data between the type of hysterectomy and the presence of grade 2 or higher bowel AE's as defined in Section 13.1.2.1.1. If the data shows such an association, then the hypothesis of decreased AE's will be analyzed with binomial tests separately within each type of hysterectomy. Otherwise the binomial test will be done for all hysterectomy types combined.

13.4.2.4.2 Tables showing (1) adverse events occurring more than 90 days from start of treatment and (2) adverse events at any time will be constructed.

13.4.2.5 Estimation of secondary endpoints related to efficacy:

The cumulative incidence approach¹⁶ will be used to estimate the failure rates for local-regional and distant failures. The Kaplan-Meier method¹⁷ will be used to estimate the overall survival and disease-free survival rates.

13.5 Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, the possible difference in any of the above endpoints among the racial groups will be investigated. Summary statistics such as percentage of minorities entered, estimates of the endpoints by the racial groups will be reported. Based on RTOG endometrial study 9708¹³ and SWOG¹⁴ it is projected that 76% of the women will be Hispanic or Latino and 24% will not. It is also projected that 78% of women in the study will be white, 16% will be black or African American, 2% will be Asian and 2% will be Native Hawaiian or other Pacific Islander. With the proposed 42 evaluable patients within each primary disease site, there will not be enough statistical power to detect the difference in the primary endpoint between race groups. Nonetheless, the descriptive statistics for each of these groups will be reported.

Planned Gender and Minority Inclusion

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	11	n/a	11
Not Hispanic or Latino	81	n/a	81
Ethnic Category: Total of all subjects	92	n/a	92
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	n/a	0
Asian	2	n/a	2
Black or African American	16	n/a	16
Native Hawaiian or other Pacific Islander	2	n/a	2
White	72	n/a	72
Racial Category: Total of all subjects	92	n/a	92

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APPENDIX I (3/20/06, 9/20/06)
RTOG 0418

Informed Consent for Cancer Treatment Trials

**A Phase II Study of Intensity Modulated Radiation Therapy (IMRT) to the Pelvis +/-
Chemotherapy for Post-operative Patients with either Endometrial or Cervical
Carcinoma**

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

You are being asked to take part in this study because you have endometrial or cervical cancer that has a high risk for coming back as pelvic or endometrial cancer.

Why is this study being done? (9/20/06)

The purpose of this study is to test whether the use of an advanced radiation therapy delivery technique called intensity-modulated radiation therapy (IMRT – see definition below) can spare your normal tissue, including small bowel and large bowel, from radiation.

Definition of IMRT: Many normal tissues, including small bowel and large bowel, are very close to areas at high risk of cancer coming back, such as nodes and vagina. Standard radiation techniques cannot avoid delivering radiation to these normal tissues that do not need to get radiation. IMRT tries to lower the amount of radiation that normal tissues receive, while still delivering the desired amount of radiation to your cancer and to areas that the study doctor thinks may have cancer cells, such as lymph nodes in the pelvis. IMRT does this by using multiple, complicated computer-controlled radiation beams aimed at your cancer.

This research is being done to try to reduce radiation side effects (especially diarrhea) that occur with the standard radiation methods. With the new radiation techniques that are being used in this study (IMRT), special credentialing is required of all institutions prior to treating patients with IMRT.

How many people will take part in the study?

About 92 people will take part in this study. About half the patients will have endometrial cancer and the rest will have cervical cancer.

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

Patients with endometrial and cervix cancer will receive the following treatment:

Radiation therapy will be given once a day, five days a week, for 28 days. This will be given to you as an outpatient. IMRT treatment usually takes longer each day than a “standard” radiation treatment (a “standard” radiation treatment takes 5-15 minutes, and an IMRT treatment may take 20-30 minutes) even though the radiation dose to the cancer is the same.

If you have cervix cancer, you will also get the chemotherapy drug cisplatin during your radiation treatments. You will get five doses of cisplatin in your vein. Starting at the time of radiation, the drug will be given every Monday or Tuesday. The cisplatin will take 20-30 minutes to go into your vein. You will also be given additional fluids into your vein. The additional fluids will be given before and after

cisplatin is given. The total time you will be getting fluids and the drug cisplatin into your vein will be 3-4 hours.

If you take part in this study, you will have the following tests and procedures:

Prior to study entry:

History and physical examination
Surgery (Hysterectomy)
Chest x-ray/CT of chest
CT/MRI/ PET-CT scan of the abdomen and pelvis (Cervix cancer patients only)
Blood tests
Audiogram (at the study doctor's request)

Every week during treatment:

Weekly visits with the radiation oncologist
Blood tests

During follow-up: (3/20/06, 9/20/06)

Physical examination 4 weeks after treatment, then every 3 months during years 1 and 2, every 6 months during years 3 through 5, and then yearly until data collection is no longer required.
Pap smear every 3-6 months during years 1 and 2; every 6 months during years 3 through 5; then yearly until data collection is no longer required.
Laboratory studies as needed
Chest x-ray/Chest CT 3 months following completion of chemotherapy and radiation therapy treatments and then every 6 months for 2 years, and then once a year for 5 years.
CT/PET/PET-CT of abdomen and pelvis 3 months following completion of chemotherapy and radiation therapy treatments (cervix patients only)

How long will I be in the study?

The study treatment will take 6 weeks to complete. Follow-up visits will be scheduled 4 weeks after completion of the treatment and then every 3 months during years 1 and 2; every 6 months during years 3 through 5; and then once every year for at least 3 years.

The study doctor may take you off study treatment if:

- it is in your best medical interest, or
- your condition worsens, or
- new information becomes available that suggests that the treatment is not working or is unsafe for you.

It is unlikely, but the study may be dropped due to lack of funding or participation.

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 cisplatin and radiation therapy can be evaluated by the study doctor. Another reason to tell the study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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

What side effects or risks can I expect from being in the study?

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 the radiation therapy and chemotherapy. 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 and side effects related to Radiation Therapy (including IMRT) to the pelvis include those that are:

Likely

- Decrease in blood counts, which can lead to a risk of infection and bleeding
- Fatigue
- Diarrhea
- Rectal irritation
- Urinary frequency and painful urination
- Loss of pubic hair
- Darkening of skin
- Vaginal narrowing and shortening
- Painful intercourse

Less Likely, but Serious (9/20/06)

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

Young women will go through the change of life. Medication may be given to help with their symptoms.

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 spasms
- Loss of coordination
- Involuntary movements or shaking

Less Likely, But Serious

- Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet

- Facial swelling
- Decreasing ability of the kidneys to handle the body's waste, which may be permanent
- Allergic reactions, which can cause difficulty in breathing, fast heartbeat, and sweating
- Decrease in liver function causing temporary elevation in blood tests
- Another cancer called Acute Leukemia

Risks Associated with Blood Drawing

- You may experience some discomfort, bruising and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. Doctors hope *IMRT* will have less side effects, and be more useful than the usual treatment, but there is no proof of this yet. We do know that the information from this study will help doctors learn more about *IMRT* as a treatment for cancer. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting standard radiation therapy

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

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:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?

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

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

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

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Consent Form for Use of Tissue for Research

About Using Tissue for Research

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Is Tissue Used for Research" to learn more about tissue research.

This information sheet is available to all at the following web site:

<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>

Your tissue may be helpful for research whether you do or do not have cancer. 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 effect on your care.

Things to Think About

The choice to let us keep the leftover tissue 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 can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research, and will be returned.

In the future, people who do research may need to know more about your health. While reports may be given about your health, your name, address, phone number, or any other personal information will not be given, so the researchers will not know who you are.

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

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

Benefits

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

Risks

The greatest risk to you is the release of information from your health records. 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.

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 your doctor or nurse, or call our research review board at _____ [IRB's phone number].

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

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

Yes No

2. 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

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

Yes No

Where can I get more information?

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

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

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

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

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

Signature

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

Participant _____

Date _____

APPENDIX II

ZUBROD PERFORMANCE SCALE

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

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III (9/20/06, 5/15/07)

STAGING SYSTEM

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

Primary Tumor (T) (Surgical-Pathologic findings)

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

STAGE GROUPING

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

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

Primary Tumor (T)

<u>TNM</u>	<u>FIGO</u>	
<u>Categories</u>	<u>Stages</u>	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	0	Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are Stage IB/T1b
T1a1	IA1	Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	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 IA2/T1a2
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	Tumor invades beyond the uterus but not to pelvic wall or to lower third of the vagina
T2a	IIA	Without parametrial invasion
T2b	IIB	With parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumor involves lower third of vagina no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumor invades <i>mucosa</i> of bladder or rectum and/or extends beyond true pelvis*
M1		Distant metastasis

**Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.*

**Note: The presence of bullous edema is not sufficient to classify a tumor as T4.*

Regional Lymph Nodes (N)

- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Regional lymph node metastasis

Distant Metastasis (M)

- MX – Distant metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis

(Continued on Next Page)

STAGE GROUPING

FIGO Stage	UICC		
	T	N	M
0	Tis	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
IIIB	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
IVA	T4	Any N	M0

**APPENDIX IV
TISSUE COLLECTION KIT/SHIPPING PROCEDURE**

Summary Table

Specimens Strongly Encouraged for Tissue Bank Submission		
Specimens taken from patient:	Submitted as:	Shipped:
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	Paraffin-embedded tissue block or punch biopsy	Block or punch sent ambient

Paraffin Blocks: All specimens should be fixed in 10% buffered formalin. The method of fixation is dependent on feasibility at the local institution. Immersion of the serially sliced sections in formalin is acceptable provided that slices are no more than 1 cm in thickness. Specimens are to be placed in adequate-sized containers with a 10-fold excess of fresh (non-bloody formalin). Whatever method is chosen, good penetration of tissue by fixative is essential. After overnight fixation, the specimen is to be carefully dissected, and the tissue blocks are to be removed from the specimen for embedding in paraffin, orienting the specimen **on edge**.