INTERNATIONAL EVALUATION OF RADIOTHERAPY TECHNOLOGY EFFECTIVENESS IN CERVICAL CANCER (INTERTECC):

PHASE II/III CLINICAL TRIAL OF INTENSITY MODULATED RADIATION THERAPY FOR CERVICAL CANCER

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Activation Date: May 1, 2011
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1.0 SCHEMA

Design: **Phase II/III Clinical Trial**

Sample Size: 91 (Phase II); 415 (Phase III)

Population / Eligibility (Section 6.0):

- **Biopsy-proven carcinoma of the cervix**
- **No Prior Radiation or Chemotherapy**
- **Medically Fit for Pelvic Chemoradiotherapy**
- **No Evidence of Distant Metastasis**
- **Does Not Require Para-aortic Radiotherapy**
- **Willing and Able to Undergo PET/CT Imaging**

Radiation Therapy (Section 9.0):

Phase III, Arm A: **Image-Guided Bone Marrow-Sparing IMRT (IG-BMS-IMRT)**

Phase III, Arm B: **Non-Bone Marrow Sparing Radiotherapy**

All Arms: **Standard Chemotherapy** (Cisplatin 40 mg/m^2 x 6 cycles)**

****Adjuvant Chemotherapy will not be given on this trial**

Stratification Factors:

-Age (≥ 60 vs. < 60)
-Stage (IB-IIA vs. IIB-IVA)

2.0 ELIGIBILITY CHECKLIST

(Y) 1. Does the patient have stage IB-IVA biopsy-proven, invasive carcinoma of the cervix?
(N) 2. Does the patient have clinical, radiographic, or pathologic evidence of para-aortic and/or distant metastasis?
(Y) 3. Will the patient receive radiation to a field including the pelvic lymph nodes, with concurrent chemotherapy (only patients undergoing concurrent chemoradiotherapy are eligible)?
(Y) 4. Can the patient undergo PET/CT or PET/CT simulation?
(Y) 5. Has the patient had a pelvic examination within 42 days prior to registration?
(Y) 6. Has the patient had an X-ray, CT scan, or PET/CT of the chest within 60 days prior to registration?
(Y) 7. Has the patient had a CT scan, MRI, or PET/CT of the pelvis within 60 days prior to registration?
(Y) 8. Is the patient's Karnofsky Performance Status ≥ 60?
(Y) 9. Is the patient ≥ 18 years of age?
(Y) 10. Has the patient met all the lab requirements as described in Section 6.1.8?
(Y) 11. If the patient is of child bearing potential, has she had a negative pregnancy test?
(Y) 12. If the patient is of child bearing potential, did she agree to practice effective birth control throughout the treatment phase of the study?
(N) 13. Is the patient pregnant or lactating?
(Y/NA)14. If clinical suspicion of AIDS, must have CD4+ T cell count > 200 per µL of blood and >14% of all lymphocytes
(Y/N) 15. Does the patient have a history of a prior different invasive malignancy (with the exception of non-melanomatous skin cancer)?
(Y) If yes, has the patient been disease free for greater than three years? (Patients with recurrences of the primary malignancy following surgery alone, with no prior history of chemotherapy or radiation, are eligible)
(N) 16. Has the patient had prior systemic chemotherapy?
(N) 17. Has the patient had prior radiation therapy to the pelvis or abdomen that would result in overlap of radiation therapy fields?
(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 myocardial infarction within the last 6 months?
(N) 20. Does the patient have an acute infection requiring antibiotics at the time of registration?
(N) 21. Does the patient have a Chronic Obstructive Pulmonary Disease 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 uncontrolled diabetes?
(N) 24. Does the patient have uncompensated heart disease or uncontrolled blood pressure per Section 6.2.6.7?
(N) 25. Does the patient have a $CD4^+$ T cell count < 200 per µL of blood or <14% of all lymphocytes?
(N) 26. Does the patient have a history of organ transplant, chronic glucocorticoid use, or any other immunocompromised status that in the opinion of the investigator would preclude the patient from receiving protocol therapy?
(Y) 27. Did the patient sign a study specific informed consent prior to study entry?

IRTOC Institution #_____

Case # _____

3.0 REGISTRATION WORKSHEET

1. Name of person registering the case
(Y) 2. Has the Eligibility Checklist been completed and the patient determined to be eligible?
(Y) 3. Has the patient signed informed consent?
4. Patient's Initials (First Middle Last)
5. Verifying Physician
6. Patient's ID Number
7. Date of Birth
8. Race
9. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
10. Patient's Country of Residence
11. Zip Code (U.S. Residents)
12. Patient's Insurance Status
13. Calendar Base Date
14. Registration date
(Y/N) 15. Does the patient consent to be contacted for future research?
16. Gynecologic Oncologist's Name
17. Radiation Oncologist's Name
18. Age
19. Stage

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

Completed by_____Date _____

***THIS FORM SHOULD BE TURNED IN AT THE TIME OF REGISTRATION**

4.0 INTRODUCTION

4.1 Background

Gynecologic malignancies are a leading cause of morbidity and mortality in women worldwide [1-2]. Many of these malignancies are attributable to human papillomavirus (HPV), the primary cause of cancers of the cervix, vagina, vulva, and anus. In North America, endometrial cancer is the most common gynecologic malignancy in women, with over 50,000 new cases annually. Often these disease present in later stages where surgical treatment alone is insufficient, and either adjuvant chemoradiotherapy (CRT) or primary CRT is required.

Locoregionally advanced gynecologic malignancies are frequently treated with primary CRT. Multiple clinical trials have established concurrent CRT as a standard treatment approach for locally advanced cervical cancer [3-8]. Increasingly, CRT has been used to treat advanced endometrial cancer as well. However, with this approach, acute and late toxicity are significant problems, while the incidence of locoregional failure, distant metastasis, and cancer mortality remain high [3-10]. Therefore, strategies to reduce toxicity and permit treatment intensification are needed.

4.2 Efficacy and Toxicity of Chemoradiation for Pelvic Cancers

Multiple studies have established that intensifying both concurrent and adjuvant CRT improves treatment outcomes for pelvic malignancies [9-12]. However, acute toxicity, particularly gastrointestinal (GI) and hematologic toxicity, are increased. Rates of high grade toxicity as high as 80% or more have been reported from multi-center trials [12]. Methods to reduce toxicity of CRT, particularly gastrointestinal and hematologic toxicity, could reduce barriers to intensifying chemotherapy and improve the therapeutic ratio of CRT.

4.3 Intensity Modulated Radiation Therapy

Conventional pelvic RT techniques often employ opposed anterior-posterior / posterior-anterior (AP/PA) and lateral fields, resulting in a box-shaped dose distribution that encompasses both targeted tissues (e.g. tumor, parametria, pelvic lymph nodes, etc.) and normal tissues (e.g., bowel, rectum, bladder, bone marrow, etc.). Field borders are frequently defined based on standard bone landmarks rather than by expressly defined targets.

Intensity modulated radiation therapy (IMRT) is a modern RT technique that differs from conventional techniques in many ways. First, patients undergo computed tomography (CT) simulation so that customized target volumes can be defined 3-dimensionally. IMRT treatment planning involves multiple beam angles and uses computerized inverse treatment planning optimization algorithms to identify dose distributions and intensity patterns that conform dose to the target, reducing radiation dose to surrounding tissues. IMRT delivery is typically accomplished with the use of multileaf collimators, which involve small motorized leaflets (collimators) that move in and out of the beam path, modulating the dose intensity.

Multiple studies in gynecologic cancer have shown that IMRT plans reduce dose to pelvic organs while maintaining acceptable target coverage [13-15]. Comparisons of IMRT to conventional treatments in patients have found reduced acute and late GI toxicity and hematologic toxicity with IMRT [16-18]. Studies have also shown that IMRT plans can be optimized to intensively reduce normal tissue dose [13-15] and have established evidence-based guidelines for dosimetric planning to reduce toxicity [19-21].

Validated predictive models indicate that optimized IMRT plans are clinically feasible and can be expected to decrease the rates of acute toxicity by approximately two-fold [21-22]. Retrospective studies have also indicated that IMRT is associated with low acute and late toxicity and favorable long-term outcomes [23-25]. Prospective clinical trials of IMRT, however, are still limited. A prospective trial of IMRT for gynecologic cancer showed that IMRT is feasible in the multi-institutional setting for post-operative patients [26], with low toxicity. A small randomized trial of IMRT in India also found that toxicity was reduced with IMRT [27].

4.4 Quality of Life and Patient-Reported Outcomes

Validated QOL measurements used in patients treated for cervical cancer have demonstrated that a considerable proportion of patients report debilitating functional compromise and psychosocial morbidity [28]. Studies have indicated that reducing pelvic radiation dose in women with endometrial cancer reduces urinary incontinence, diarrhea, and fecal leakage, leading to fewer limitations in daily activities [29-30]. However, detailed studies of the effect of IMRT on QOL in gynecologic cancer patients are lacking, particularly in the international setting. Longitudinal assessments of QOL and key functions such as activities of daily living, bowel and urinary habits, psychosocial function, and sexual function are included as secondary end points of this study.

We will explore the impact of IMRT on QOL using severalvalidated QOL instruments: the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 form and the disease site-specific module QLQ-CX24. The 30-item EORTC QOL questionnaire (QLQC30) is a psychometrically robust, cross-culturally accepted questionnaire that was designed to be applicable to a broad spectrum of cancer patients as a core questionnaire [31]. The form has been translated into many languages including English, Mandarin, Hindi, Thai, Portuguese, Czech, Dutch, Korean, Spanish, Turkish, and Vietnamese. Previous studies have shown that, despite regional variations in responses that need to be considered, the QLQ-C30 is suitable for use in a wide variety of countries and settings [32].

The QLQ-CX24 is a validated and reliable psychometric module consisting of 3 multi-item scales and 5 single-item scales. It is characterized by high internal consistency, good compliance and fast completion with no or minimal assistance [33]. Cross-cultural studies in Asian samples, for example, have found the module to be a reliable and valid measure of QOL [34-35]. The module has been translated into many languages including English, Mandarin, Hindi, Portuguese, Czech, Dutch, Korean, and Spanish.

4.5 Image-Guided Bone Marrow-Sparing IMRT

Hematologic toxicity (HT) is a key barrier to intensifying chemoradiotherapy in patients with pelvic malignancies. It is well-known that both radiation and chemotherapy are myelosuppressive, but the extent to which pelvic radiation contributes to HT in patients undergoing CRT is unknown. Radiation causes apoptosis of bone marrow (BM) and peripheral blood stem cells and BM stromal damage, resulting in myelosuppression and characteristic pathologic and radiographic BM changes [36-38]. BM stem cells are exquisitely sensitive to low doses of radiation [39]. Older clinical studies have shown that radiation BM injury depends on both radiation dose and volume of BM irradiated [40-42]. CT-based IMRT plans can be optimized to reduce BM irradiation [14-15], but the large avoidance volume constrains IMRT plan optimization. Refining IMRT plans to focus on sparing BM subregions may therefore be a more effective strategy. Previous studies have shown that functional imaging can help optimize IMRT plans to spare active BM

[43-47]. However, the locations of BM subregions most important for sparing remain unknown, and studies investigating functional BM imaging are needed to optimally design BM-sparing IMRT plans.

We have implemented functional imaging to identify "active" BM subregions for avoidance. It is known from pathology and imaging studies that BM is comprised of subregions of hematopoeitically active, fat-poor, "red" BM and inactive, fat-rich, "yellow" marrow [48-52]. Red BM contains approximately 40% fat, 40% water, and 20% protein; yellow BM contains approximately 80% fat, 15% water, and 5% protein [48]. Up to 50% of the body's red BM may be located in the pelvis and lumbar spine [53] and thus contained within conventional RT ports. These active and inactive regions cannot be distinguished on computed tomography (CT) [54-55], which is the principal imaging modality used for RT planning. Functional imaging studies indicate that active BM tends to be concentrated particularly in vertebral and ilial subregions [44-46,49]. These regions co-localize with regions which, by MRI studies, show longer T1 relaxation times and longer T2 indicative of red vs. yellow BM [48]. Reducing dose specifically to active subregions of pelvic BM may be beneficial, but the precise location of active BM subregions, variation in active BM distribution between individuals, and relationship between toxicity and radiation dose to these active BM regions are all unknown.

[18F]-deoxyfluorothymidine (^{18}F-FLT) is an effective PET imaging tracer for proliferating BM. FLT is a DNA precursor that is phosphorylated and sequestered intracellularly by the enzyme thymidine kinase 1 [56], which is active during DNA synthesis, leading to specific tracer uptake in proliferating tissues [57]. Hayman et al. showed was useful for *in vivo* measurements of proliferating BM [58]. Several studies have noted decreased tracer uptake in BM after irradiation with doses as low as 2 Gy, and complete absence of uptake after 10-20 Gy [57,59-61]. ^{18}F-FLT appears superior to ^{18}F-FDG for BM imaging, due to the inability of ^{18}F-FDG to discriminate between proliferating cells and metabolically active non-proliferating cells [58,62-63]. Recently a study found that increased radiation to BM sub-regions with higher ^{18}F-FDG-PET activity was associated with increased HT [64], supporting the hypothesis that reducing dose to active subregions could mitigate HT. In this protocol, we will test the hypothesis that BM-sparing IMRT plans designed to avoid active subregions identified by PET can reduce HT. This technique could improve patients' tolerance to chemotherapy and increase the therapeutic ratio of CRT for pelvic malignancies in general.

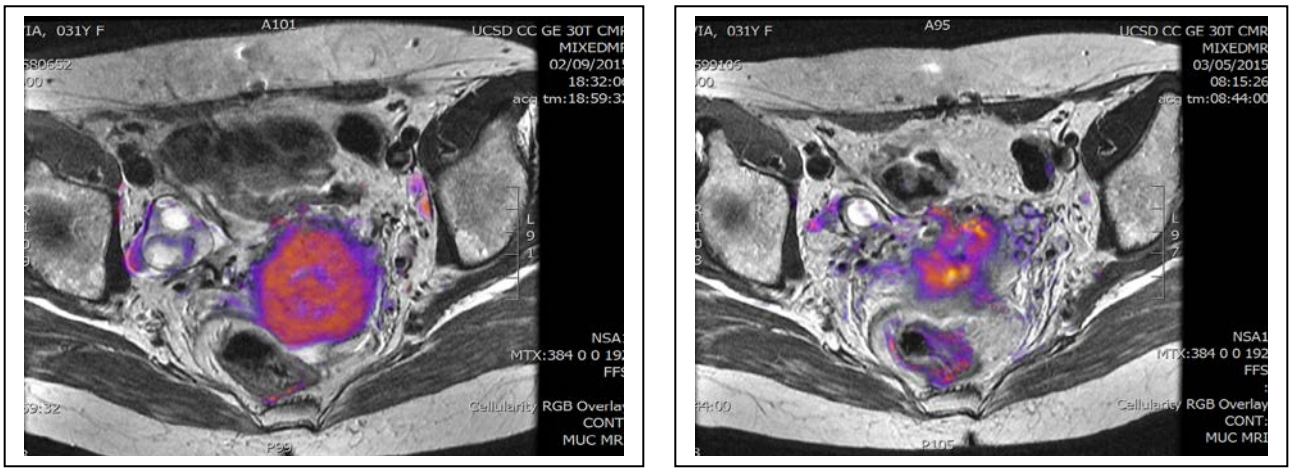
4.6 Restriction Spectrum Imaging

Diffusion-weighted MRI (DW-MRI) has been intensively studied in cervical cancer for both diagnostic and prognostic utility. DW-MRI quantifies water diffusion within tissues, highlighting differences between normal tissue and tumors. Tumors generally have higher cellular density and higher N/C ratio, which restricts water diffusion more than in normal tissue. A measure called the apparent diffusion coefficient (ADC) is a commonly used indicator of water diffusion detected with DW-MRI, and the ADC is often lower in tumors than surrounding normal tissue. Multiple studies have shown the utility of DW-MRI for diagnosis, prognosis, and evaluation of response to therapy. For example, Lin et al. showed that change in ADC was associated with reduced tumor size in response to therapy, showing the promise of DW-MRI as an imaging biomarker. An important limitation of standard DW-MRI, however, is its inability to distinguish tumor hypercellularity from other causes of altered water diffusion, such as inflammation or hemorrhage. Moreover, standard diffusion imaging can have poor contrast resolution, and all MR diffusion imaging is susceptible to large anatomic distortion from ever-present inhomogeneity (or non-uniformity) in the MRI system's magnetic field. As a

result, image quality is too poor to make DW-MRI useful for radiation therapy planning or for assessing response to therapy.

In contrast, Restriction Spectrum Imaging (RSI) is a highly novel MRI technique developed at UCSD for cancer imaging (Figure). The chief advantage of RSI over DW-MRI is that it provides better functional information about tumors, particularly cellularity, with superior image contrast. Additionally, the anatomic distortion is removed from the RSI images by accounting for the magnetic field inhomogeneity, a critical step for accurately locating tumors. Unlike PET, the RSI technique delivers no ionizing radiation to patients, and may improve resolution over PET. Certain refractory tumors retain high cellularity after treatment. RSI is likely to be a useful technique to determine response to therapy, and to identify patients who are not responding well earlier in the course of treatment than can be done with standard imaging methods. The use of RSI in cervical cancer is completely novel, and there are no published studies of it in this context.

Figure 4.1. RSI of a poorly differentiated squamous cell carcinoma of the cervix before treatment (LEFT) and mid-treatment (RIGHT) showing the reduction in tumor (orange/red colorwash) in response to therapy. Note these are the first ever RSI images in a patient with cervical cancer.



4.7 Knowledge-Based Planning

Our research group has developed mathematical models to detect sub-optimal IMRT plans with high sensitivity and specificity, using a process termed Knowledge-Based Planning (KBP) [43]. This system is built to identify optimal plans amongst prior training cohorts, and use the resulting model to develop predictive dose-volume histograms (pDVH) for organs-at-risk (OARs) that give precise quantitative information on plan quality deficiencies. This approach will allow us to identify, quantify, and ultimately correct sub-optimal treatment plans, a process that is ideally suited for application to quality control in the multi-center clinical trial setting, particularly when new technologies or implementations are being introduced.

4.8 Primary Hypothesis

Compared to standard radiotherapy, IG-BMS-IMRT will improve progression-free survival for cervical cancer patients treated with concurrent chemotherapy.

5.0 OBJECTIVES

5.1 Primary

5.1.1 To test whether IG-BMS-IMRT improves progression-free survival (PFS) for cervical cancer patients treated with concurrent chemotherapy.

5.2 Secondary

5.2.1 To compare acute and long-term QOL in the study arms
5.2.2 To compare acute and late hematologic and gastrointestinal (GI) toxicity in the study arms
5.2.3 To compare total chemotherapy dose delivered in the study arms
5.2.4 To compare locoregional (pelvic) failure, distant metastasis, and overall survival in the study arms
5.2.5. To evaluate the quality of IMRT planning in the international cooperative group setting
5.2.6 To quantify changes in tumor cellularity using Restriction Spectrum Imaging (RSI substudy)
5.2.7 To compare hematologic toxicity of FLT-PET-based IG-BMS-IMRT vs. other treatment approaches (FDG-PET-based IG-BMS-IMRT and standard radiotherapy)

6.0 POPULATION AND ELIGIBILITY CRITERIA

6.1 Conditions for Patient Eligibility

6.1.1 Biopsy-proven, unresected stage IB-IVA invasive carcinoma of the cervix.
6.1.2 Candidate for pelvic or pelvic-inguinal radiotherapy and concurrent chemotherapy. Patients undergoing preoperative chemoradiotherapy are excluded.
6.1.3 Able to undergo diagnostic PET/CT or PET/CT simulation
6.1.4 History/physical examination within 42 days prior to registration to document cervical tumor size and stage
6.1.5 CT, MRI, or PET/CT imaging of the chest, abdomen, and pelvic regions within 60 days prior to registration (for stage I patients, PA and lateral chest x-ray is sufficient for chest imaging)
6.1.6 Karnofsky Performance Status 60-100
6.1.7 Age ≥ 18
6.1.8 Laboratory data obtained ≤ 42 days prior to registration on study, with adequate bone marrow, hepatic and renal function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
- Creatinine clearance ≥ 50 mg/dl OR Serum Creatinine ≤ 1.5 x ULN
- Bilirubin < 1.5 mg/dl
- WBC ≥ 3,000/µl
- ALT/AST < 3 x ULN
- Negative pregnancy test for women of child-bearing potential

6.1.9 Women of childbearing potential must agree to practice effective birth control throughout their participation in the treatment phase of the study.
6.1.10 If there is clinical suspicion of AIDS, an HIV test must be done within 60 days prior to registration. Note: HIV positive patients with a $CD4^+$ T cell count > 200 per µL of blood and >14% of all lymphocytes are eligible for this trial.
6.1.11 Patients must sign informed consent prior to study entry.

6.2 Conditions for Patient Ineligibility

6.2.1 Prior invasive malignancy (except non-melanomatous skin cancer), unless disease free for a minimum of 3 years.)

6.2.2 Prior systemic chemotherapy
6.2.3 Prior radiotherapy to the pelvis or abdomen that would result in overlap of radiation therapy fields.
6.2.4 Para-aortic or inguinal metastasis.
6.2.5 Distant metastasis
6.2.6 Severe, active co-morbidity, defined as follows:

6.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization within the past 6 months;
6.2.6.2 Transmural myocardial infarction within the last 6 months;
6.2.6.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
6.2.6.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
6.2.6.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
6.2.6.6 Uncontrolled diabetes, defined as diabetes mellitus, which in the opinion of any of the patient's physicians requires an immediate change in management; a patient may be considered eligible for the study if the physician managing the patient's diabetes considers that the appropriate changes in management have resulted in adequate control.
6.2.6.7 Uncompensated heart disease or uncontrolled high blood pressure, which in the opinion of any of patient's physicians, requires immediate change in management; a patient may be considered eligible for the study if the physician managing the patient's heart disease or blood pressure considers that the appropriate changes in management have resulted in adequate control.
6.2.6.8 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; patients with AIDS will be ineligible for this protocol because the treatments involved may be significantly immunosuppressive. Patients with clinical suspicion of AIDS and who are unwilling to have an HIV test are not eligible for this trial.
6.2.6.9 Uncontrolled infection
6.2.6.10 Other immunocompromised status (e.g., a history of organ transplant, chronic glucocorticoid use, or any other immunocompromised status that in the opinion of the investigator would preclude the patient from receiving protocol therapy).

6.2.7 Women who are pregnant or lactating are ineligible due to teratogenic effects on developing fetuses. Women who are of child-bearing potential need to practice effective methods of contraception including oral contraceptives, intrauterine device, diaphragm with spermicides, and/or abstinence.
6.2.8 Prior history of hip, pelvic, or lumbosacral prosthesis or other implanted device.
6.2.9 Patients undergoing preoperative chemoradiotherapy

7.0 PRE-TREATMENT EVALUATIONS / MANAGEMENT

7.1 History and physical examination including assessment of tumor size, height, weight and body surface area and performance status.
7.2 Assessment of smoking and alcohol history (past and current) within 42 days prior to study entry.
7.3 Assessment of race and ethnicity and comorbidity index within 42 days prior to study entry

7.4 Patients must not be allergic to iodinated contrast if undergoing a contrast enhanced CT scan of the pelvis.
7.5 Pre-treatment MRI is not required but is encouraged to aid staging evaluation and target delineation.
7.6 PET/CT and Study-Related Functional Imaging
At baseline, all patients will undergo PET/CT or PET/CT simulation with a slice thickness of 3 mm and large field-of-view pelvic protocol. Subjects imaged with FDG-PET will undergo intravenous administration of 200-400 MBq of ^{18}F-FDG 60 minutes prior to imaging. Subjects imaged with FLT-PET will undergo intravenous administration of 4.5 MBq/kg of ^{18}F-FLT 60 minutes prior to imaging. These doses can be repeated for patients undergoing serial imaging.

Patients on the functional MRI (RSI) and/or ^{18}F-FLT will undergo serial imaging as described in section 14.2

8.0 REGISTRATION PROCEDURES

8.1 Pre-Registration Requirements

8.1.1 Pre-Registration Requirements for IMRT
In order to register patients on this study, the institution must provide baseline physics information and an anonymized case study, including all contours and a sample treatment plan ("Dry Run"). For instructions on pre-registration requirements, contact the study PI (lmell@ucsd.edu) or the Physics Chair (kevinmoore@ucsd.edu).
An IMRT phantom study may be required to be eligible to register patients. Institutions will be notified with further instructions if they are required to submit a phantom study. Instructions for requesting and irradiating the phantom will be available at the Radiological Physics Center (RPC) at MD Anderson Cancer Center website (http://rpc.mdanderson.org/rpc)

8.1.2 Central Review
All external beam treatment plans will be centrally reviewed at UC San Diego to determine protocol compliance (**section 9.9**).

8.2 Registration

8.2.1 Screening Procedures
Diagnostic or laboratory studies will be performed to determine eligibility. Studies or procedures that were performed for clinical indications or as standard of care (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained, provided they occur within the proper window.

8.2.2 Informed Consent
Written informed consent will be obtained prior to any study procedures. Each institution should customize the consent form according to their institutional requirements. The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent (e.g. scanned record) will be transmitted to UC San Diego via the secure FTP server.

8.2.3 Recruitment
Subjects will be recruited at participating centers by local investigators.

8.2.4 Registration Procedures
Patients will be registered through UC San Diego's Velos system. Each participating site will be given a Velos account username and password. Eligible patients will be assigned a case number and study arm through this system. Velos will contain the data submission calendar including all data forms, images, and reports and the dates on which they are due.

9.0 RADIATION THERAPY

9.1 General

- Patients will be randomized to one of two arms:

A. Image-guided bone marrow sparing IMRT (IG-IMRT)
B. Non-Bone Marrow-Sparing Radiation Therapy

- The total duration of concurrent chemoradiotherapy should be ≤ 60 days.

- The patient's baseline PET/CT, CT simulation, and external beam treatment plan(s) should be submitted within 45 days of completing treatment.

Delivery Compliance Criteria

	Per Protocol	Acceptable Variation	Unacceptable Variation
Overall Treatment time	≤ 60 days	≤ 66 days	> 66 days

9.2 Simulation

All patients should be simulated according to the criteria below for this protocol.

9.2.1 Bladder and Bowel Preparation
The degree of bladder and rectal fullness should be made to duplicate that which is anticipated for daily treatment, i.e., if the patient is instructed to maintain a full bladder for treatment, she should be simulated as such. It is recommended to use a consistent bladder filling state (e.g. always full or always empty) for simulation and treatment. It is recommended for patients not to be simulated or treated with a full rectum as this may result in irreproducible setup. Bowel preparatory agents (enema, stool softeners, etc.) may be applied at the discretion of the physician. If a full rectum is noted on the simulation study it is recommended that the patient undergo a new simulation scan.

9.2.2 Contrast and Markers
Intravenous contrast is recommended unless medically contraindicated. Oral contrast is optional. A radio-opaque cervical marker may be placed in the apex of the vagina to assist with target delineation and is optional. Implanted fiducials are optional.

9.2.3 Position
Simulation will be done in the supine position.

9.2.4 Immobilization
All subjects will have a customized immobilization device (e.g., Alpha Cradle or Vac-Lok) fabricated at the time of simulation.

9.2.5 Imaging
All subjects should undergo a CT (or PET/CT) simulation scan using a slice thickness of 2.5-3.0 mm and large field-of-view pelvic protocol. CT scans should be obtained from the T12 vertebral body to 5 cm below the ischial tuberosities.

9.2.6 Isocenter placement
Isocenter placement is left to discretion of treating physician, however, it is recommended to place the isocenter along the patient's midline 1.5 cm caudal to the inferior border of the sacroiliac joint.

9.3 Normal Tissue Delineation

9.3.1 General
Normal tissues will be contoured on the simulation scan. The tissue within the skin surface and outside all other critical normal structures and the PTV is designated as unspecified tissue.

All patients will have the following normal tissues delineated for this trial:

9.3.2 Bowel
The bowel will be contoured beginning from the axial slice situated 1 cm superior to the superior-most slice containing PTV (if bowel is not present at this level, the bowel contour will start from its most superior extent), and will continue to its most inferior extent in the pelvis. The outermost extent of the bowel loops will be outlined on each axial CT slice, as described in the literature [22]. Individual loops of bowel should not be contoured separately. Rectum should be contoured separately from bowel. An instructional video can be viewed at https://healthsciences.ucsd.edu/som/radiation-medicine/research/clinical-translational/clinical-trials/intertecc/protocol/Pages/Videos.aspx.

9.3.3 Rectum
The outer rectal wall will be contoured and filled in, treating the organ as a solid continuous structure, and will be defined from the level of the sigmoid flexure to the anus.

9.3.4 Bladder
The outer bladder wall will be contoured and filled in, treating the organ as a solid continuous structure.

9.3.5 Pelvic Bone Marrow (PBM)
The outer bone contour will be delineated and filled in, treating the bone marrow as a solid continuous structure. The regions contoured will include the os coxae, L4 and L5 vertebral bodies, entire sacrum, acetabulae, and proximal femora. The superior extent of

the bone marrow contour should be at the level of the superior border of L4 or the iliac crest, whichever is more superior. The caudal-most extent of the bone marrow contour should be at the level of the ischial tuberosities. For examples see Mell et al. [20], Figure 3. An instructional video can be viewed at https://healthsciences.ucsd.edu/som/radiation-medicine/research/clinical-translational/clinical-trials/intertecc/protocol/Pages/Videos.aspx.

9.3.6 Femoral Heads
The outer contours of the femoral heads will be delineated and filled in, treating each as a solid continuous structure. Do not include the femoral neck.

9.3.7 Active Bone Marrow (ABM)
Active BM (ABM) will be a subset of the entire Pelvic BM (PBM) volume (delineated in 9.2.3.5). ABM will be defined as the subregion with a standardized uptake value (SUV) greater than the mean value over the BM volume. Automatic segmentation using commercially available software can be used to define ABM. The functional imaging technique will be either FDG-PET or FLT-PET depending on availability of funding for FLT-PET. This volume can be generated locally or (for patients on Arm A) the ABM can be generated centrally at UCSD and supplied to the treating site after the DICOM data has been transmitted.

9.4 Target Delineation

9.4.1 General
For patients treated with conventional techniques, 3-D planning with target delineation according to the criteria below is suggested, but not required. If target delineation is not performed, follow the guidelines for blocking outlined in section 9.5.3.

9.4.2 Image fusion
Pelvic MRI and/or PET fusion is encouraged to aid clinical target volume delineation. Fusion should be optimized to match the MRI / PET scan to the treatment position. The Gross Tumor Volume (GTV) and Clinical Target Volume (CTV) and normal tissues will be contoured on all CT slices in which the structures exist. The definition of all volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy (http://www.icru.org/index.php?option=com_content&task=view&id=72).

9.4.3 Definition of Target Volumes and Margins

It is strongly recommended that investigators read guidelines for contouring target volumes [66-69]. A visual demonstration of target delineation procedure can also be viewed or downloaded from https://healthsciences.ucsd.edu/som/radiation-medicine/research/clinical-translational/clinical-trials/intertecc/protocol/Pages/Videos.aspx

Standard Name	**Description**	**Detailed Specification**
CTV_4500	CTV to receive 45 Gy **Required**	It is recommended to divide the CTV into 3 sub regions: CTV1, CTV2, CTV3. CTV1 will consist of the gross tumor, cervix, and uterus. CTV2 will consist of the parametria

		and superior third of the vagina (or half of the vagina, if the vagina is clinically involved). CTV3 will include the common, external, and internal iliac and presacral lymph nodes. It is acceptable for CTV1, CTV2, and/or CTV3 to overlap each other. The upper border of the CTV3 should not extend above the confluence of the common iliac arteries with the aorta (i.e., aortic bifurcation), and should begin no lower than superior border of L5. The nodal CTV (CTV3) will be obtained by ensuring an approximately 7 mm margin around the vessels, plus extension to include any adjacent visible lymph nodes, lymphoceles, or pertinent surgical clips. The presacral nodes should be contoured until the superior border of the S3 vertebral body is reached; below this point the nodal volume can be separated into two structures. The external iliac nodes should be contoured to the superior aspect of the femoral head. CTV3 should be modified to exclude bone, muscle, and bowel. The CTV should not extend inferior to the ischial tuberosities.
CTV_4760 (for SIB schemes only)	CTV to receive 47.6 Gy **Required**	Same as description of CTV_4500 above
CTV_Boost (for SIB schemes only)	CTV to receive 54.0-59.4 Gy **Required**	Gross pelvic lymph nodes
ITV_4500	ITV to receive 45 Gy **Contouring is required only when ITV approach is used.**	Patients should be simulated with both a full and empty bladder (i.e., 2 simulation scans). CTV1-CTV3 and PTV1-PTV3 should be delineated as described above on the plan used for treatment (either the full or empty bladder scan), and CTV1 should be delineated on both scans. The CTV1 from both scans should be fused together to generate ITV_4500. A 7 mm margin should be applied to generate PTV4.
PTV_4500	PTV to receive 45 Gy **Required**	Around CTV1, a 15 mm uniform expansion should be used. Around CTV2, a 10 mm uniform expansion should be used. Around CTV3 (and CTV_boost, if applicable), a 5 mm uniform expansion should be used. These expansions will generate PTV1, PTV2, and PTV3, respectively. PTV1-3 will

		be fused to generate the PTV. If the ITV approach is used, PTV4 should be fused with PTV1-PTV3 to generate PTV_4500.
PTV_4760 (for SIB schemes only)	PTV to receive 47.6 Gy **Required**	Same as description of PTV_4500 above
PTV_Boost (for SIB schemes only)	PTV to receive 54.0-59.4 Gy **Required**	5 mm uniform expansion around CTV_Boost

9.5 Treatment Planning and Delivery

9.5.0 General

The experimental arm (Arm A) will be treated with image-guided bone marrow sparing IMRT (section 9.5.4.4.2). Standard radiation therapy (Arm B) will consist either of a conventional 4-field box technique (section 9.5.3) or non-bone marrow sparing IMRT (section 9.5.4.4.1). **Bone marrow will not be used as an avoidance structure in treatment planning for patients assigned to Arm B.**

9.5.1 Photon Energy

All treatment plans must use 6-18 MV photons. Heterogeneity corrections should be applied.

9.5.2 Setup Verification

For patients treated with conventional techniques, MV portal verification is required at least weekly. For patients treated with IMRT, skeletal imaging (e.g., kV imaging and/or CBCT) must be performed daily to verify setup accuracy.

For patients undergoing CBCT with each fraction, at the time of simulation, the isocenter should be placed along the patient's midline 1.5 cm caudal to the inferior border of the sacroiliac joint. Patients will undergo CBCT acquisition prior to each fraction, for a total of 25 scans. CBCTs should be obtained in half-fan mode, using 125kV, 80mA, and 25ms/frame. If a marked discrepancy is observed between the patient's imaged anatomy on the day of treatment versus the day of simulation, at the treating physician's discretion, the patient may be taken down off the machine (e.g., to void the bladder or rectum) and may be treated later that same day. If the anatomical discrepancy is still present, the treating physician may elect to postpone treatment, and re-simulation

should be considered.

9.5.3 Conventional Radiation Therapy (**Arm B only**)

9.5.3.1 Field Arrangement

Conventional RT consisting of a 4-field "box" arrangement using opposed AP/PA and lateral fields is allowed for patients randomized to Arm B. For conventional RT, it is permissible to use bone landmarks to draw field borders or to use 3-D planning with explicit targeting as outlined above, using customized blocking to encompass the PTV. If explicit targeting is used, follow the target coverage requirements in 9.5.3.4. If bone landmarks are used, use the following portals:

- Superior border: L4-5
- Lateral border: 1-2 cm lateral to the border of the true pelvis
- Inferior border: Obturator foramen or 4 cm inferior to vaginal cuff, whichever is lower
- Anterior border: line from pubic symphysis to 1 cm anterior to common iliac nodes at L4-5
- Posterior border: draw border posterior to or splitting the sacrum from S1-S4
- Custom blocking to shield femoral heads. Do not block the obturator foramen or within 1 cm of the common iliac nodes

9.5.3.2 Prescription Dose

The initial prescription dose will be 45.0 Gy in 1.8 Gy fractions to the PTV. PTV_boost (if defined) may receive an additional 9.0-14.4 Gy, either with conventional techniques or IMRT, at the discretion of the treating physician.

9.5.3.3 Normal Tissue Constraints and Compliance Criteria

No criteria for normal structure doses are applied for Conventional RT.

9.5.3.4 Target Volume Constraints and Compliance Criteria

If 3-D planning is used, create the volume CTV_4500 as the union of CTV1, CTV2, and CTV3, and use the following guidelines:

Name of Structure	Dosimetric parameter	Per Protocol	Acceptable Variation	Unacceptable Variation
CTV_4500	D_{Min} (Gy)	≥ 41.85	≥ 40.5	< 40.5
	D_{Max} (Gy)	≤ 48.15	≤ 51.75	> 51.75

9.5.4 General Intensity Modulated Radiation Therapy Criteria (**Arm A or B**)

9.5.4.1 Beam arrangement

IMRT plans may include static field arrangements (e.g. 5-9 fields), modulated arc therapy, or Tomotherapy. Pseudo-step wedge techniques are also permitted.

9.5.4.2 Prescription dose

For sequential boost plans or plans with no nodal boost, the initial prescription dose will be 45.0 Gy in 1.8 Gy fractions to the PTV. PTV_boost (if defined) may receive an additional 9.0-14.4 Gy, with IMRT, at the discretion of the treating

physician.

For simultaneous integrated boost technique, the primary PTV should be treated to 47.6 Gy in 1.7 Gy fractions (28 fractions) and PTV_boost should be treated to 59.4 Gy in 2.12 Gy fractions (28 fractions). At the discretion of the treating radiation oncologist, the fraction size to PTV_boost may be reduced as low as 1.93 Gy (i.e., total dose 54.0 Gy), in order not to overdose adjacent bowel or other critical normal structures.

If a pseudo-step wedge technique is used, the central pelvis (i.e., PTV1) should receive 20 Gy, with the remainder of dose to the central pelvis delivered via brachytherapy. Cervical cancer primaries should be boosted using intracavitary brachytherapy (see section 9.6), unless the patient refuses or is otherwise unable to undergo brachytherapy or is treated at a center without access to brachytherapy (see section 9.8).

9.5.4.3 Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Acceptable Variation	Unacceptable Variation
PTV_4500	$D_{95\%}$ (Gy)	≥ 45	≥ 43.65	< 43.65
	$D_{97\%}$ (Gy)	≥ 43.65	≥ 40.5	< 40.5
	$D_{99\%}$ (Gy)	≥ 40.5	≥ 39.6	< 39.6
	D_{Max} (Gy)	≤ 51.75	≤ 54	> 54
PTV_4760	$D_{95\%}$ (Gy)	≥ 47.6	≥ 45	< 45
	$D_{97\%}$ (Gy)	≥ 46.17	≥ 41.85	< 41.85
	$D_{99\%}$ (Gy)	≥ 42.84	≥ 40.5	< 40.5
	D_{Max} (Gy)	≤ 68.31	-	> 68.31
CTV_Boost*	D_{Min} (Gy)	≥ 50.22	≥ 43.65	< 43.65
	D_{Max} (Gy)	≤ 63.56	≤ 68.31	> 68.31
PTV_Boost*	$D_{95\%}$ (Gy)	≥ 54	≥ 51.75	< 51.75
	$D_{97\%}$ (Gy)	≥ 52.38	≥ 47.6	< 47.6
	$D_{99\%}$ (Gy)	≥ 48.6	≥ 45	< 45
	D_{Max} (Gy)	≤ 68.31	-	> 68.31
Dose maximum should occur within the PTV.				

*Minimum dose

*Minimum dose is applied to a 54 Gy prescription and maximum dose to a 59.4 Gy prescription.

9.5.4.4 Normal Tissue Volume Constraints and Compliance Criteria

9.5.4.4.1 Non-Bone Marrow-Sparing IMRT (**Arm B only**)*

***Note that Bone Marrow should not be used as an avoidance structure for patients treated on Arm B**

Name of Structure	Dosimetric parameter	Per Protocol	Acceptable Variation	Unacceptable Variation
Bladder	$D_{50\%}$ (Gy)	≤ 45	≤ 55	> 55
	D_{Max} (Gy)	≤ 50	≤ 57.5	> 57.5
Rectum	$D_{50\%}$ (Gy)	≤ 45	≤ 54	> 54
	$D_{60\%}$ (Gy)	≤ 30	≤ 50	> 50
	D_{Max} (Gy)	≤ 50	≤ 55	> 55
Bowel	$D_{30\%}$ (Gy)	≤ 40	≤ 50	> 50
	D_{Max} (Gy)	≤ 59.4	≤ 62.1	> 62.1
	V_{45} (cc)	≤ 200 cc	≤ 250 cc	> 250 cc
Femurs	$D_{15\%}$ (Gy)	≤ 30	≤ 50	> 50
	D_{Max} (Gy)	≤ 50	≤ 55	> 55

9.5.4.4.2 Image-Guided Bone Marrow-Sparing IMRT (**Arm A only**)

Name of Structure	Dosimetric parameter	Per Protocol	Acceptable Variation	Unacceptable Variation
Bladder	$D_{50\%}$ (Gy)	≤ 45	≤ 55	> 55
	D_{Max} (Gy)	≤ 50	≤ 57.5	> 57.5
Rectum	$D_{50\%}$ (Gy)	≤ 45	≤ 54	> 54
	$D_{60\%}$ (Gy)	≤ 30	≤ 50	> 50
	D_{Max} (Gy)	≤ 50	≤ 55	> 55
Bowel	$D_{30\%}$ (Gy)	≤ 40	≤ 50	> 50
	D_{Max} (Gy)	≤ 59.4	≤ 62.1	> 62.1
	V_{45} (cc)	≤ 200 cc	≤ 250 cc	> 250 cc
Pelvic Bone Marrow	D_{Mean} (Gy)	≤ 27	≤ 29	> 29
	V_{10} (%)	≤ 85.5%	≤ 90%	> 90%
	V_{20} (%)	≤ 66%	≤ 75%	> 75%
Active Bone Marrow	D_{Mean} (Gy)	≤ 28.5	≤ 30	> 30
	V_{10} (%)	≤ 90%	≤ 90%	> 90%
	V_{20} (%)	≤ 70%	≤ 75%	> 75%
Femurs	$D_{15\%}$ (Gy)	≤ 30	≤ 50	> 50
	D_{Max} (Gy)	≤ 50	≤ 55	> 55

9.5.5 Parametrial Boost

Parametrial boost is optional according to the discretion of the treating physician. In this case either brachytherapy or external beam radiotherapy (e.g., opposed anterior-posterior field arrangements with appropriate blocking, to a total dose of 8.0-14.4 Gy in 4-8 daily fractions) is acceptable.

9.5.6 Re-planning

Re-planning (such as to account for changes in tumor volume) is allowed. If re-planning is necessary, the new treatment plan should meet the same criteria as the initial plan, as if the new plan were delivered for the entire treatment course (i.e., 25 or 28 fractions). The new treatment plan should be submitted for central review according to the same process as the initial plan.

9.6 Brachytherapy

9.6.1 General

Either low dose rate (LDR) or high dose rate (HDR) brachytherapy is permitted according to each institution's standard. Either standard (point-directed) or volume-directed brachytherapy techniques are permitted according to each institution's standard. For institutions wishing to implement pulse dose rate (PDR), please contact the study P.I. Interstitial brachytherapy may be used to treat disease that cannot be adequately treated with intracavitary treatment. External beam radiation and brachytherapy may not be administered on the same day. It is recommended to start brachytherapy after delivery of at least 39.6 Gy of external beam RT.

Iridium-192 should be used for HDR brachytherapy and Cs-137 should be used for LDR brachytherapy.

In general, HDR insertions should be separated by a minimum of 24 hours and no more than 3 insertions should be performed per week.

For volume-directed brachytherapy, a pelvic MRI (≤ 5 mm slice thickness) should be acquired with either the first or second insertion.

9.6.2 Target and Normal Tissue Delineation (for volume-directed brachytherapy)

The following targets and organs at risk (OAR) will be contoured at each insertion, according to the GEC ESTRO Recommendations [81-82]. The MRI based target delineation can be reused by superimposition in the process of contouring on CT, if for subsequent fractions of brachytherapy only CT can be used with the applicator in place. No planning margins will be added to the CTV.

- GTVB: Macroscopic tumor (if present) at time of brachytherapy
- High risk target (HR-CTV): GTVB + whole cervix + presumed extra cervical tumor extension
- Point-A (left and right) - Measure 2 cm along the intrauterine tandem from the cervical os or flange of the tandem and 2 cm laterally in the plane of the intracavitary system.
- Bladder (the outer bladder wall is contoured)
- Rectum (the outer rectal wall is contoured from above the anal sphincter to the level of transition into the sigmoid)
- Sigmoid (the outer sigmoid wall is to be contoured from the recto-sigmoid flexure to 2 cm superior to the parametria and the uterus
- ICRU bladder point
- ICRU rectal point

9.6.3 Prescription Dose and Fractionation

For HDR, permissible dose/fractionation schemes are:

- 5.5 Gy x 6 fractions
- 5.5 Gy x 5 fractions
- 6.0 Gy x 5 fractions
- 6.0 Gy x 6 fractions
- 7.0 Gy x 3 fractions
- 7.0 Gy x 4 fractions
- 7.0 Gy x 5 fractions
- 7.5 Gy x 3 fractions

For LDR, 35-40 Gy (80-85 Gy total in EQD2, $\alpha/\beta=3$, $T_{1/2}$ = 1.5 hours) will be delivered to point A in 1-2 insertions. If 2 insertions are used they should be separated by a minimum of 7 and maximum of 21 days.

For volume-directed brachytherapy, the following dose-volume criteria for HR-CTV should be met:

EBRT + Volume-directed Brachytherapy

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
HR-CTV	$D90_{Min}$ (Gy)	≥ 75	-	< 75
	$D90_{Max}$ (Gy)	≤ 90	-	> 90

Note: Dose to HR-CTV is cumulative EQD2 ($\alpha/\beta=3$, $T_{1/2}$ = 1.5 hours).

9.6.4 Normal Tissue Dosimetric Criteria

EBRT+ Brachytherapy

Name of Structure	Dosimetric parameter	Per Protocol	Acceptable Variation	Unacceptable Variation
LDR point-directed/HDR Volume-directed				
Bladder (ICRU reference point)	D_{Max} (Gy)	≤ 85	≤ 90	> 90
Rectum (ICRU reference point)	D_{Max} (Gy)	≤ 80	≤ 85	> 85
Vaginal_Surface* (reference point)	D_{Max} (Gy)	≤ 150	≤ 175	> 175
Sigmoid**	D_{Max} (Gy)	≤ 75	≤ 80	> 80
HDR Point-directed				
Bladder (ICRU reference point)	D_{Max} (Gy)	≤ 80	≤ 85	> 85
Rectum (ICRU reference point)	D_{Max} (Gy)	≤ 75	≤ 80	> 80
Vaginal_Surface (reference point)	D_{Max} (Gy)	≤ 150	≤ 175	> 175

*For point-directed

**For volume-directed

Note: Doses to critical structures are cumulative EQD2 (α/β=3, $T_{1/2}$ = 1.5 hours). If CT is used for planning it is recommended to keep the maximum bowel dose < 25% of the brachytherapy prescription dose.

For point-directed brachytherapy, the dose to points A and B, the rectal reference point dose, bladder reference point dose, and vaginal surface reference point dose, and central axis isodose curve must be calculated and reported. Please follow the definitions in ICRB 38.

For volume-directed brachytherapy, uniform dose volume reporting according to the GEC ESTRO guidelines is required. For each fraction the following parameters should be recorded:
• TRAK
• D100 for GTV, CTV
• D90 for GTV, CTV
• D50 for CTV
• V100 for CTV
• D2cc of the bladder, rectum and sigmoid, (converted to EQD2 doses per formula EQD2= D X [(d + α/β)/ (2 + α/β)]); use α/β=3.
• ICRU bladder and ICRU rectal points

9.7 Radical IMRT for boost therapy

Use of fractionated IMRT in place of brachytherapy to boost gross cervical cancer is considered a protocol deviation and is strongly discouraged. If deemed necessary or essential for the patient's care (e.g., if a patient refuses brachytherapy), please notify the study PI.

9.8 Stereotactic Boost Radiotherapy

Patients treated at centers without access to brachytherapy or who otherwise are poor candidates for brachytherapy (e.g., refusal, medical comorbidities, etc.) should undergo SBRT with 5 fractions of 6 Gy prescribed to the high-risk CTV, with dose constraints identical to those for high dose rate, volume-directed brachytherapy (see section 9.6.3). In this case it is recommended that the patient undergo arc therapy with a minimum of two arcs, and that on-line kV CBCT be used to verify the isocenter prior to each arc delivery. Patients should be resimulated for SBRT boost planning.

9.9 Protocol Compliance and Quality Assurance Review

Quality assurance to verify protocol compliance will be performed by the protocol review committee at the UC San Diego. For instructions on data transfer, contact the study PI (lmell@ucsd.edu) or the Physics Chair (kevinmoore@ucsd.edu).

External beam treatment plans should be submitted no later than 45 days following completion of treatment. Criteria for IG-BMS-IMRT protocol compliance are listed below.

9.9.1 Simulation

9.9.1.1 Position

- Per Protocol: supine
- Deviation: not supine

9.9.1.2 CT Slice Thickness

- Per Protocol: ≤ 3.0 mm
- Variation Acceptable: > 3.0 mm and ≤ 5.0 mm

- Deviation: > 5.0 mm

9.9.1.3 CT Range
- Per Protocol: T12 – 5.0 cm inferior to ischial tuberosity
- Variation Acceptable: ≤ 2 cm deviation from protocol
- Deviation: > 2 cm deviation from protocol

9.9.2 Target Delineation (IMRT or 3-D planning)

9.9.2.1 CTV_4500 / CTV_4760
- Per Protocol: includes gross tumor, cervix, and uterus as described in section 9.4.3
- Variation Acceptable: ≤ 1 cm deviation from volumes as described in section 9.4.3
- Deviation: fails to include gross tumor, cervix, or uterus and/or any other deviation > 1 cm from volumes as stated in section 9.4.3

9.9.2.2 PTV_4500 / PTV_4760
- Per Protocol: Minimum 15 mm margin around tumor/cervix/uterus, 10 mm margin around upper vagina/parametria, 5 mm margin around nodal CTV
- Deviation: Margins less than described above

9.10 Treatment Modifications

Modification of the radiotherapy protocol is admissible if necessary in the opinion of the treating physician in order to ensure patient safety, but the rationale should be documented and communicated to the study P.I. Physicians may consider holding treatment for ANC <500/mm^3, platelets < 20,000 mm^3, febrile neutropenia, or uncontrolled bleeding. No radiation dose reductions are allowed, however. Treatment may be resumed upon resolution of neutropenia (ANC ≥500/mm3), thrombocytopenia (platelets ≥ 20,000 mm3), and febrile neutropenia (temperature<38.0º C).

9.11 Radiation Adverse Events

Risks and side effects related to radiation therapy include:

Likely (more than 10%)
- Redness and skin irritation in the treatment area that may result in bleeding and/or infection, which may require hospitalization
- Loss of pubic hair in the treated area, usually temporary
- Tiredness
- Nausea and/or vomiting
- Sterility (inability to bear children) in fertile women
- Sterility (inability to produce children) in men

Less Likely (3-9%)
- Diarrhea
- Sores and bleeding from the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Narrowing and dryness of the vagina (birth canal) and genital area with painful or difficult intercourse and possibly bleeding

- Development of extra tissue (fibrosis) in the anal canal, which may result in decreased function
- Long-term dryness of the skin
- Hip, pelvic, or sacral fracture
- Build up of fluid in ankles, feet, and/or legs

Rare, but serious (less than 2%)

- Narrowing or blockage of the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Blockage of the urinary tubes
- Development of an abnormal path or connection between organs (fistulae)
- Skin damage (tissue death), which may result in surgery
- Narrowing of or persistent bleeding in the vagina (birth canal), which may result in surgery

10.0 DRUG THERAPY

10.1 Concurrent chemotherapy will be cisplatin 40 mg/m^2 weekly x 6 cycles

10.2 Source and Formulation: per institutional standard

10.3 Administration: Patients will be prehydrated per institutional guidelines. Drug preparation is per institutional standard. Supportive treatment will be given according to institutional policy.

10.4 Storage and Stability: per institutional standard

10.1.4 Adverse Events: Incidence rates of adverse events are provided in the product package insert.

10.1.5 Supply: Drugs used in this protocol are commercially available.

10.1.6 Timing of administration: It is recommended to start chemotherapy on day 1 of external beam RT but it is acceptable to begin on days 1, 2, or 3 of external beam RT.

10.5 Dose Modification

10.5.1 Chemotherapy will be held for:

- ANC < 500 /mm^3.
- Platelets < 50,000/mm^3.
- Febrile neutropenia or bleeding.
- Persistent (>24 hours) grade 3 or 4 nausea and vomiting.
- Renal Failure (creatinine > 2.0 mg% or creatinine clearance < 50 ml/min).

10.5.2 Criteria for resumption of chemotherapy or holding for other toxicities is per institutional policy.

10.5.3 For persistent renal insufficiency, neurotoxicity, or ototoxicity, it is acceptable to replace cisplatin with carboplatin per institutional policy. Otherwise, cisplatin should be discontinued.

10.5.4 Modifications from the chemotherapy protocol are admissible if necessary in the opinion of the treating physician in order to ensure patient safety, but the rationale for treatment modification should be documented and communicated to the study P.I.

11.0 SURGERY

Patients who have undergone hysterectomy are ineligible for the study. Planned radical surgery following preoperative chemoradiotherapy is not allowed.

12.0 OTHER THERAPY

12.1 Permitted Supportive Therapy/Procedures:

12.1.1 Antiemetics
12.1.2 Antidiarrheals
12.1.3 Analgesics
12.1.4 Nutritional and fluid supplementation
12.1.5 Myeloid growth factors
12.1.5 Packed red blood cell transfusions

12.2 Non-permitted Supportive Therapy

12.2.1 Erythropoieitic growth factors (e.g. epoetin alfa, epoetin beta, darbepoetin alfa, etc.

13.0 PATHOLOGY AND TISSUE / SPECIMEN SUBMISSION

13.1 Histologic Confirmation of Diagnosis

All patients must have pathologically confirmed carcinoma by biopsy or surgical pathology.

13.1 Specimen Submission

No specimen submission is required for this protocol

14.0 PATIENT ASSESSMENTS, FOLLOW-UP, AND DATA COLLECTION PROCEDURES

14.1 General

Data will be submitted electronically via secure FTP server using the Velos system and stored centrally at UC San Diego. For instructions for data transfer, contact the study PI (lmell@ucsd.edu). A case report form packet will be provided to participating sites including a demographic and health information form (DHIF), disease evaluation form (DEF), treatment information form (TIF), symptom and toxicity evaluation form (STEF), outcomes evaluation form (OEF), and quality of life (QOL assessments; EORTC QLQ-C30 and CX24 forms).

14.2 Time Schedule for Assessment, Follow-Up and Data Collection

Study Procedures	Pre-CRT	Weekly During CRT	Mid-Treat-ment (Week 3)	1 & 2 wks post-External Beam RT	1 mo. post-CRT[c]	Months post-CRT[d]
Informed Consent	X					
History and Physical	X				X	6, 12, 24, 36
CBC with Differential[a]	X	X		X	X	
Comprehensive Metabolic Panel[b]	X					
Cervical / vaginal cytology	X					6, 12, 24, 36
Diagnostic chest x-ray, chest CT, or PET/CT	X					6, 12, 24, 36
Diagnostic pelvic CT, MRI, or PET/CT	X					3-4[e], 12, 24, 36
CT or PET/CT Simulation	X					
Baseline Data (DHIF, DEF, TIF)	X					
Evaluation for Toxicity (STEF)	X	X		X	X	6, 12, 24, 36
Outcomes Form (OEF)					X	6, 12, 24, 36
QLQ-C30 form	X				X	6, 12, 24, 36
CX24 form	X				X	6, 12, 24, 36
RSI (MRI) (Substudy only)	X		X		X	3-4
FLT-PET/CT (Substudy only)	X		X[f]		X[f]	3-4[f]

[a] CBC with differential should be collected weekly during treatment (patient is considered on treatment until all radiation is complete). CBC with differential must be collected in weeks 1 and 2 following completion of external beam radiotherapy.
[b] Electrolytes including Mg and Ca, Creatinine, Bilirubin, SGOT, and SGPT
[c] Visit should occur 1 month post completion of all radiation +/- 14 days
[d] +/- 2 months (for initial post-treatment imaging, no earlier than 2 months)
[e] Post-treatment PET/CT at 3-4 months is strongly encouraged to assess for recurrence
[f] If FLT-PET/CT is done at 3-4 months post-treatment, FDG-PET/CT should not be done at this time point. Serial FLT-PET/CT scans will be acquired conditional on funding.

15.0 PATIENT SAFETY AND ETHICAL CONSIDERATIONS

15.1 Informed Consent

Written informed consent will be obtained prior to any study procedures.

15.2 Adverse Event Reporting

All expected adverse events will be documented on the Symptom and Toxicity Evaluation Form (STEF). Any unsuspected or confirmed unanticipated adverse event should be reported immediately (within 24 hours) to the study principal investigator (lmell@ucsd.edu) and Data Safety Monitoring Committee via the INTERTECC main email (irtoc@ucsd.edu). This study will utilize the Common Terminology Criteria for adverse events (CTCAE) of the National Cancer Institute for reporting of unanticipated serious adverse events (SAE). A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). Unanticipated SAE information will be collected, documented, and reported comprehensively starting with entry into the study and continuing through 1 month post treatment. SAEs will be reported to the study principal investigator, the patient's institution's IRB, and the Data Safety and Monitoring Committee. This reporting will include a description of the event, the subject's study identification number, severity of the event, and its suspected cause. This form will include timing, severity and perceived causation of the events and followed until they either stabilize or resolve.

15.3 Steps to Determine If an Adverse Event is Reported in an Expedited Manner

Step 1: Identify the type of adverse event using the CTCAE v4. The CTCAE v4 provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE v4 can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). Additionally, if assistance is needed, the NCI has an Index to the CTCAE v4 that provides help for classifying and locating terms.

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
Unrelated, Unlikely Related, Possibly Related, Probably Related, and Definitely Related.
Note: This includes all events that occur within 30 days of the last day of protocol treatment. Any event that occurs more than 30 days after the last day of treatment and is attributed (possibly, probably, or definitely) to the treatment must also be reported according to the instructions above.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the STEF of this protocol ;
- the investigator's brochure or the drug package insert

Step 5: Review Section 15.2 to determine if:

- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

15.4 Reporting Requirements for Serious Adverse Events

The investigator will report all unexpected SAEs that are determined to be possibly, probably or definitely related to the research within 10 working days of learning of the event to both the principal investigator (lmell@ucsd.edu) and the Data and Safety Monitoring Committee via the INTERTECC main email (irtoc@ucsd.edu).

Toxicities from Experimental Treatment

- Death on Study - regardless of cause: Written Report
- Grade 4 anaphylaxis: Written report
- All other expected toxicities, grades 1-4: Report in Continuing Review.

15.5 Criteria for Removal from Protocol Therapy

a) Unacceptable toxicity requiring removal from study.
b) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
c) Physician determines it is in the subject's best interest.
d) Patient refusal of protocol therapy

15.6 Criteria for Removal from Study

a) Loss to follow-up.
b) Withdrawal of consent for any further data submission.

15.7 Data and Safety Monitoring Plan

The INTERTECC Data and Safety Monitoring Board will assume the responsibility for the data and safety monitoring. Monitoring will be conducted remotely by review of electronically submitted eligibility forms, consents, primary endpoint data, and treatment plans. On-site audits by members of the DSMB will also be conducted at least once for each collaborating site, to review sample charts for registered subjects. All adverse events will be reported to the IRB in accordance with regulations. Confidentiality of data will be maintained through subject de-identified numbers, the use of locked cabinets to store paper records, and a secure database which is maintained at the Moores UC San Diego Cancer Center.

Study data will be collected and managed using Velos electronic data capture tools hosted at the Clinical and Translational Research Institute at UC San Diego. Velos is a secure, web-based application designed exclusively to support data capture for research studies. Velos provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; 5) tools for on-the-fly generation of plots, descriptive statistics, and reports for study monitoring and quality assurance; and 6) advanced features, such as branching logic and calculated fields. Creation of the forms via Velos web interface will be conducted by Dr. Mell in conjunction with the Clinical and Translational Research Institute (CTRI) Biostatistics team at UC San Diego.

15.8 Confidentiality Procedures

All acquired data will be stored at UC San Diego on a secure password-protected server with access limited to the principal investigator, co-investigators, clinical trial coordinator, and authorized personnel (e.g., post-doctoral researchers, etc.). The database will be de-identified by removing subjects' names and only maintaining the subjects' medical record numbers as a unique identifier. Similarly, data acquired locally at each participating institution will be stored on a secure password-protected server with access limited to the site principal investigator, co-investigators, and authorized personnel. Deliberations and recommendations of the Data and Safety Monitoring Committee are strictly confidential. Each member of the Data and Safety Monitoring Committee must sign a statement of confidentiality.

15.9 Oversight of Other Centers and Dissemination of Information

Whenever there is an adverse event reported or a protocol amendment or change in the consent form or interim results or other information that may impact the risks to subjects or others, the study PI and/or coordinator at UC San Diego will notify all the institution's PI's and study coordinators via email.

16.0 STATISTICAL CONSIDERATIONS

16.1 Definition of Primary Endpoint

The primary endpoint of this study is progression-free survival (PFS). Patients will be randomized in a 3:2 ratio favoring the experimental arm. Unequal randomization is justified based on the "learning curve" argument as described by Dumville et al. [76]. Event time is calculated as the time from randomization to the date of first evidence of disease progression or death due to any cause. Event times will be censored for surviving patients if there is no evidence of disease progression at the latest follow-up assessment or if the patient is lost to follow-up. If a new therapeutic course for cervical cancer is initiated after completing protocol therapy without documented evidence of progression, a progression event will be considered to have occurred at the time the therapeutic course is initiated.

Prior data indicate that the median time to progression or death on the control treatment is 3.2 years, and that with better chemotherapy delivery, this may be extended to 5 years or more [12,75]. If the true median PFS times on the control and experimental treatments are 3.2 and 5 years, respectively, we will need to study 275 experimental subjects and 137 control subjects to be able to reject the null hypothesis that the experimental and control survival curves are equal with 80% power and alpha=0.05.

16.2 Sample Size and Study Duration

16.2.1 The primary aim of the study is to test whether treatment with IG-BMS-IMRT improves progression-free survival compared to treatment with standard of care. For this aim we consider a 2-arm group sequential design with progression-free survival as the primary endpoint. The sample size is based on testing the hazard ratio (HR) for Treatment A vs B. We test the two-sided hypothesis:

$$H_0 : HR = 1 \qquad \text{vs} \qquad H_1 : HR \neq 1$$

Based on past data [12] we assume that median survival in the standard care group is 3.2 years, and we power against the alternative that median survival in the IG-BMS-IMRT group is 5 years, i.e. that the hazard ratio is as small as 0.64. The total sample

size is 415 patients and a total of 163 events is required for the final analysis. Planned recruitment duration is 5 years and the minimum follow-up planned is 1 year. Thus, the total expected study duration is 6 years. Enrollment is assumed to be constant at a rate of 83.0 patients per month. The assumed dropout rate is 5% per year. There is a single interim analysis planned after 82 events have accrued which is expected to occur after approximately 3.9 years.

Timing, number of events, sample size, and boundaries (Z-values, nominal p-values, approximate hazard ratios) are shown in Table 16.1, as well as the probability of crossing study boundaries under the null and alternative hypotheses. Following are plots of the Z-values (Figure 16.1) and approximate hazard ratios (Figure 16.2) at the design bounds. Table 16.2 shows the effect of the drop-out rate and randomization ratio on the design.

Table 16.1 Progression-free survival trial design with HR=0.64, 80% power and 2.5% one-sided Type 1 error. P{Cross} is the probability of crossing the given bound (efficacy or futility) at or before the given analysis under the assumed hazard ratio (HR).

Analysis	Value	Futility	Efficacy
IA 1: 50%	Z-value	-2.8	2.8
N: 324	HR	1.88	0.53
Events: 82	p (1-sided)	0.9974	0.0026
3.9 years	P{Cross} if HR=1	0.0026	0.0026
	P{Cross} if HR=0.64	< 0.0001	0.2096
Final analysis	Z-value	-1.98	1.98
N: 415	HR	1.37	0.73
Events: 163	p (1-sided)	0.976	0.024
6 years	P{Cross} if HR=1	0.025	0.025
	P{Cross} if HR=0.64	< 0.0001	0.8

Figure 16.1. Z-value Bound Plot

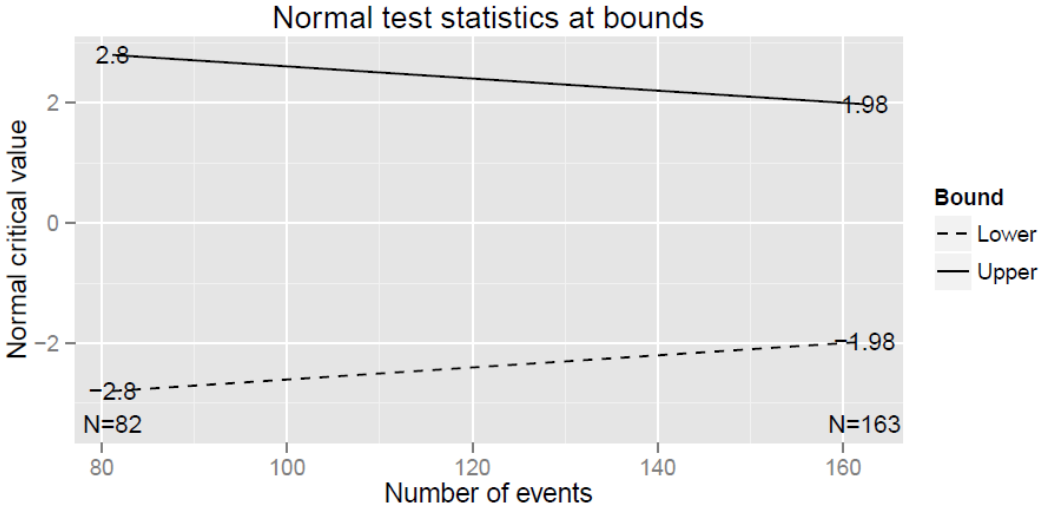


Figure 16.2. Hazard Ratio Bound Plot

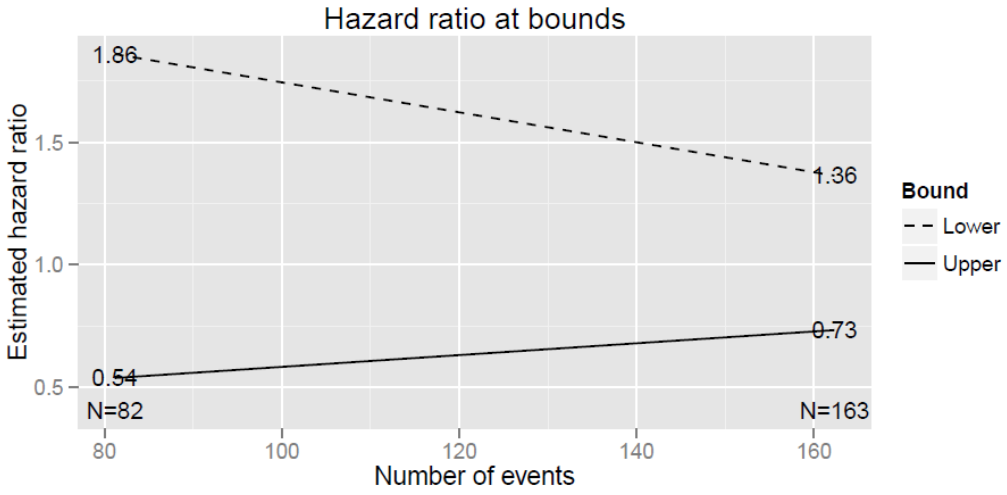


Table 16.2

Randomization Ratio	Drop-out rate per year			
	1%	2.5%	5%	10%
1:1	368	378	394	430
3:2	388	398	415	454
2:1	423	434	453	494

Secondary aims

In secondary analyses, we will further test the effect of treatment on hematologic and gastrointestinal toxicities. Hematologic toxicity is typically measured with numeric biomarkers such as neutrophil count. Also of particular interest in this study are patient-reported outcomes pertaining to health and quality of life. The EORTC QLQ-C30 and QLQ-CX24 instruments will be used to measure gastrointestinal toxicity as experienced by patients.

Specifically, a composite of QLQ-C30 item Q17 and CX-24 item Q32, which deal with diarrhea and bowel control, will be considered. Responses to each item are numeric with integer values from one to four. Both the hematologic biomarkers and the quality of life instruments yield quantitative outcomes. The mean response between treatment groups will be tested using two-sided, two-sample t-tests. Table 16.3 below gives the power of the tests based on the sample size from the primary outcome, correcting for multiple testing.

Table 16.3: Power for the secondary analyses. The table shows the power for the two-sample, two-sided t-test based on a sample size of 102 patients per group. The calculations assume that two tests are performed; a Bonferroni correction is used to maintain a family-wise type-1 error rate of 0.05. Since some outcomes are patient-reported and subject to missing-ness, the columns index the effective sample size in

terms of the compliance rate. Rows index the effect size under the alternative hypothesis.

	Compliance rate			
	100%	90%	80%	70%
Effect size				
0.4	72.5	66.9	61.2	54.8
0.5	90.4	86.6	82.0	76.1
0.6	97.8	96.2	93.9	90.3
0.7	99.7	99.3	98.5	97.1

FLT/RSI Imaging Substudy Aims

Patients treated on the FLT/RSI substudy must have access to FLT-PET and RSI (i.e., be treated at UCSD or participating institutions with access to this technology). The primary aim of the imaging substudy is to compare the rate of acute grade ≥ 3 hematologic toxicity with FLT-PET-guided BMS-IMRT vs. the other 2 arms. Based on prior institutional and published data [12,74] the probability of acute hematologic toxicity with multiagent concurrent chemoradiotherapy (institutional standard) is 45% or more. If the relative risk (RR) of toxicity for patients receiving experimental therapy (FLT-PET-guided BMS-IMRT) is 0.5, we will be able to reject the null hypothesis that RR=1 with 80% power, with a 1-sided Type I error of 15%, with 60 subjects (30 experimental, 30 control). Based on prior accrual at our institution this is a feasible accrual goal, and based on prior published data this effect size is plausible. We will use an uncorrected chi-squared statistic to test the null hypothesis. At the conclusion of the trial, we will also compare hematologic toxicity for all patients treated with FLT-PET-guided BMS-IMRT vs. FDG-PET-guided BMS-IMRT vs. usual care.

All 60 patients will undergo serial RSI imaging before (<4 weeks before treatment), during (at 3-4 weeks), immediately following (2-4 weeks after), and 3-4 months after chemoradiotherapy at the UCSD Multimodal Imaging Lab (MMIL). Regions of interest (ROIs) will be delineated on both MRI and PET/CT, and both cellularity indices (z-scores) and standardized uptake values (SUV) will be collected, respectively, for each subject before and after treatment. ROIs will be defined and z-scores and SUVs calculated using commercially available software. We will compare the changes in mid-treatment and post-treatment cellularity indices within the tumor on RSI to the change from baseline to 3-4-months using PET/CT. We expect to see inter-patient variation in the degree of response measured by change in cellularity and change in SUV. At the end of the study we will plot the distribution of observed changes in cellularity indices and the change in z-score vs. change in SUV for patients undergoing both FDG-PET/CT and FLT-PET/CT. Statistical tests will be performed using a rank correlation test (z-score versus SUV).

16.2.2 The study duration will be 5 years (3 years for the imaging sub-study). The accrual period will be 4-5 years and the expected accrual rate is 3-4 patients per month. Subjects will be followed for long-term outcomes and toxicity for up to three years.

16.2.3 Patients will be randomized at the time of registration. Randomization will be done at UCSD with stratification on age and stage using randomized blocks of size 4.

16.3 Plan for Data Analysis

16.3.1 Time to recurrence will be defined as the time from study enrollment to the time of recurrence of disease, determined by biopsy or imaging. If biopsy is not obtained to confirm diagnosis of recurrence, treatment failure will be determined to have occurred only if the patient undergoes a change in management on the basis of the imaging results (e.g., salvage or palliative therapy or hospice referral). Local recurrence will be defined as persistence or recurrence of tumor at the cervix or vaginal cuff. Regional recurrence will be defined as recurrence of tumor elsewhere in the pelvis or para-aortic nodal region (if treated). Distant recurrence will be defined as recurrence of tumor outside of the treatment field, including the para-aortic nodal region. Time to locoregional recurrence will be defined as the shortest time to local or regional recurrence, whichever occurs first. Time to recurrence will be defined as the shortest time to locoregional or distant recurrence, whichever occurs first. The cumulative probability of recurrence will be estimated using cumulative incidence functions, considering other first events (such as deaths) as competing events.

16.3.2 Disease-free survival will be defined as freedom from recurrence or death. Disease-specific survival will be defined as freedom from death due to cervical cancer. Overall survival will be defined as freedom from death due to any cause. These outcomes will be estimated using Kaplan-Meier survival curves with 95% confidence bands. Final outcomes will be assessed at the conclusion of the study, three years after enrollment of the last patient.

16.3.3 Analysis of the phase III data will be according to intention to treat. If significant site-to-site variability is observed, we will plan to model this in phase III using frailty or mixed-effects models.

16.3.4 Analysis of the phase III longitudinal QOL data will use linear random effects modeling, adjusting for important covariates such as the baseline QOL in addition to the treatment assignment. Nested random effects can also be used to model site-to-site variation. Non-informative missingness in the data is naturally accommodated by the random effects models. The QOL data at 1 month post treatment will be correlated with peak toxicities which occur during that month.

16.3.5 Primary and secondary endpoints will be analyzed according to several factors, as listed in the schema (section 1.0). Differences in proportions will be tested using the chi square or t test. Differences in time to events will be analyzed using the log rank test or Gray's test and/or inclusion as covariates in multi-variable Cox proportional hazards models. We will use Forest plots to analyze treatment effects within subgroups.

16.3.6 Missing data

Differences in baseline characteristics between those lost to follow-up and those completing the protocol will be assessed using chi-square or t-test. A worst-case sensitivity analysis will be conducted to assess whether findings are robust to the missing data.

16.3.7 Site effects

We will use logistic and proportional hazards mixed-effects regression models to test for and, as necessary, model site effects on safety and efficacy outcomes [72-73].

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