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Title: Pilot Study of Adjuvant Proton Beam Teletherapy for Post-Hysterectomy Cancers of the Uterus and Cervix with Metastases to Regional Lymph Nodes

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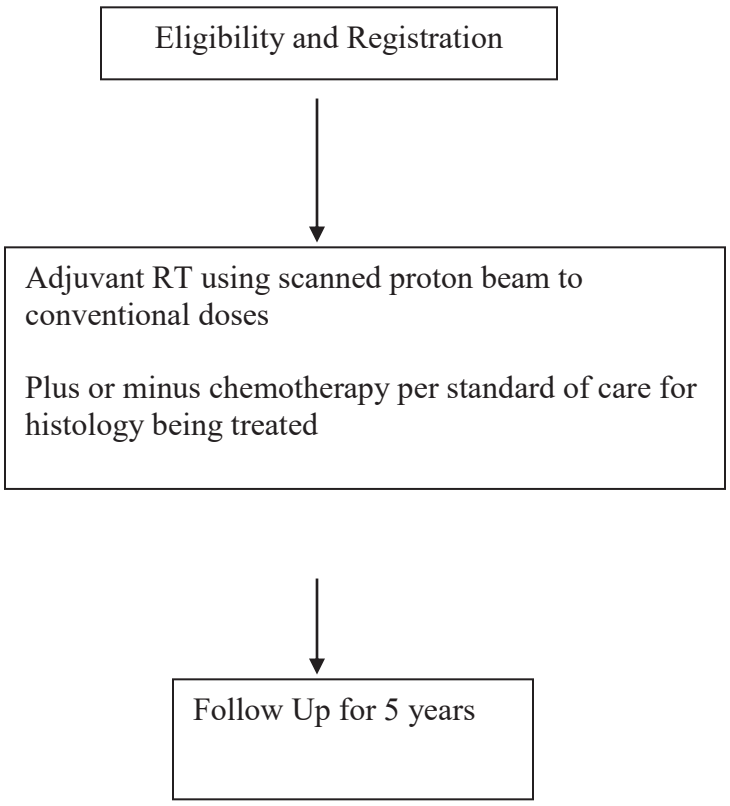

1. OBJECTIVES:

The study hypotheses are that adjuvant post-hysterectomy proton teletherapy for women with uterine and cervical cancers and histologically confirmed metastases to regional lymph nodes will be efficacious (cancer control within the irradiated volume) and reduced in both acute and delayed toxicity when compared to treatment with conventional photon teletherapy techniques. The study will quantitate the magnitude of normal tissue spared with scanning proton beam therapy compared to 3-dimensional conformal and intensity modulated photon radiation techniques, and correlate acute and late toxicity outcomes to the reduced volumes of normal tissues irradiated.

1.1 Study Design:

Patients who undergo hysterectomy for invasive cancer of the uterus or cervix who have histologically confirmed metastases to one or more regional lymph nodes (parametrial, pelvic, or para-aortic nodal groups) conventionally undergo radiation treatment as all, or a component of their adjuvant post-surgical therapy.

Such patients will be identified at the weekly Gynecologic Oncology-Pathology Multidisciplinary Tumor Board that routinely reviews all gynecologic cancer pathology in patients operated at Massachusetts General Hospital (MGH).

Potentially eligible patients operated elsewhere and referred for adjuvant treatment to MGH would be identified based on pathology review of submitted histologic sections from the referring institution.

After obtaining informed consent, eligible patients will receive conventional doses of adjuvant teletherapy conventionally scheduled (fractionated) delivered to conventional target volumes using scanning proton beam instead of photon beam.

Using data from the same treatment planning CT scans used to plan proton therapy, conventional photon plans will be generated using three dimensional conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT) for comparison purposes to quantitate the extent of normal tissue sparing through the use of dose volume histograms.

Monitoring during and after such treatment will be essentially equivalent to standard clinical practice at MGH with the exception that the schedule of post-treatment assessments will more tightly conform to the study calendar.

Assuming successful accrual and treatment of sufficient numbers of patients, a retrospective outcomes study will compare cancer control within the irradiated volume, acute side effects of teletherapy, and delayed complications of radiation treatment to a historical control population treated with photon teletherapy at MGH.

1.2 Primary Objective

1.2.1 In a population of women with cancers of the cervix or endometrium with pathologically proven spread to regional lymph nodes, to quantitate the magnitude of the normal tissue radiation dose reductions achieved by comparison of dose volume histograms achieved by scanning proton beam teletherapy with dose volume histograms of treatment plans for the same patients using 3-dimensional conformal radiation therapy (3DCRT) and intensity modulated radiation therapy (IMRT).

1.2.2 To prospectively assess acute radiation side effects and delayed complications in proton treated patients and to compare toxicity outcomes (acute side effects and delayed complications) with patients historically treated with photon teletherapy using institutional historical controls (retrospective outcomes comparison study).

1.3 Secondary Objectives

1.3.1 To prospectively collect data on quality of life (QOL) before and after adjuvant scanning proton beam therapy employing contemporary, validated instruments tailored for women treated for gynecologic cancer.

1.3.2 To determine the progression-free survival and patterns of recurrence with this treatment.

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Proton beam radiation therapy has been employed in the clinical treatment of cancer at MGH since 1961. Initially patients were treated at the Harvard Cyclotron Laboratory in Cambridge, but since 2001 treatment has been administered on the MGH campus in the Francis H. Burr Proton Treatment Center. To date, over 10,000 patients have been treated using proton beam in MGH programs. Proton beam has equivalent biologic effects in tissue to high energy photon beams from linear accelerators employed at MGH and elsewhere. The principal clinical advantage of proton beam lies in the nature of its energy (radiation dose) deposition in tissue. In contrast to photons (X-rays), protons penetrate to a depth in tissue determined by their energy, then deposit dose over a very narrow range (Bragg peak) transmitting minimal radiation beyond that point. Exploiting this difference in physical dose deposition characteristics allows design of clinical treatments with more conformal dose distributions delivering proportionately much lower dose to normal tissues lying adjacent to the targeted malignant tissues than conventional photon techniques. [1] In general, this will result in milder acute treatment side effects, and potentially fewer and milder long-term complications of radiation treatment.

2.2 Study Disease:

2.2.1 Patients with primary cancers of the uterus conventionally undergo surgery as their initial intervention. Generally this will consist of open or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy with variable sampling or full dissection of pelvic and/or para-aortic lymph nodes. Patients in whom cancer has spread to lymph nodes (International Federation of Gynecology and Obstetrics (FIGO) Stage IIIC) routinely undergo radiation treatment to the pelvis or extended volumes (pelvis and para-aortic nodal basins) postoperatively, either as their only adjuvant treatment, or more commonly following 4-6 cycles of adjuvant systemic cytotoxic chemotherapy with carboplatin and taxol. Such treatment is endorsed by National Comprehensive Cancer Network (NCCN) guidelines.[2] Teletherapy (external radiation) is commonly supplemented by limited additional vaginal brachytherapy (internal vaginal radiation). This approach has been standard management at MGH for more than 7 years and is also endorsed by National Comprehensive Cancer Network (NCCN) guidelines.[2] Based on retrospective outcomes comparisons from M.D. Anderson Cancer Center, cancer control and overall survival statistics are substantially better in patients getting teletherapy/brachytherapy as all or a component of their treatment compared to patients getting systemic adjuvant chemotherapy/brachytherapy without teletherapy.[3] Additional data from Duke University and the University of North Carolina support this approach as well.[4]

2.2.2 Patients with primary cancer of the cervix limited to the cervix and upper vagina (FIGO stages IB and IIA) based on examination under anesthesia (EUA) supplemented by diagnostic imaging (MRI, PET/CT) will conventionally undergo modified radical or radical hysterectomy with therapeutic pelvic lymphadenectomy +/- sampling para-aortic lymphadenectomy as their initial therapeutic intervention. Patients with histologically confirmed metastasis to lymph nodes undergo adjuvant teletherapy to the pelvis or extended volumes (pelvis and para-aortic nodal basins) administered in conjunction with concurrent cisplatin-based adjuvant cytotoxic chemotherapy and limited intra-vaginal brachytherapy. This has been standard therapy at MGH for more than 7 years and is consistent with NCCN guidelines.[2]

2.3 Rationale

While combined modality therapy (surgery, radiotherapy, chemotherapy) for patients with FIGO Stage IIIC uterine cancer and American Joint Commission on Cancer (AJCC) $pT_{1,2},N_1,M_0$ cancer of the cervix is associated with prolonged cancer-free survival (“cure”) in many patients [3,4,5] acute side effects and late complications of treatment can be severe with substantial impact on quality of life (QOL) for many subsequent years. Despite chronic toxicities of treatment being recognized by both patients and the physicians involved in their longitudinal care, minimal prospective data are available documenting the impact of such treatment on quality of life, and no

quantitative data employing contemporary assessment instruments tailored for women with gynecologic malignancies.

Acute toxicities associated with radiation treatment include cramps, erratic bowel movements, diarrhea, nausea, vomiting, dehydration, electrolyte imbalance, urinary frequency, burning, and fatigue.

Late complications, which occur months to years after radiation treatment, can include leg lymphedema, radiation insufficiency fractures in pelvic bones or lumbar spine, small or large bowel obstruction which can require surgery to relieve, or chronic erratic bowel function with varying degrees of intestinal malabsorption. In some premenopausal patients with cervical cancer, ovaries will be conserved, often surgically translocated to the para-colic gutters. Teletherapy is often a contributing factor in the premature endocrine failure of such ovaries, resulting in premature menopause.

Both acute side effects and late complications of radiation treatment are mostly a function of the volume of adjacent organs at risk (OAR), the "innocent bystanders" that are unavoidably irradiated when conventional photon beam techniques are employed to target potentially cancerous tissues. Volume of normal tissue exposed, total dose, and dose per treatment fraction all correlate with the severity of both acute symptomatic side effects as well as late effects in normal tissues. Each of these parameters could be expected to be reduced by using proton beam therapy [1] rather than conventional photon beam techniques, with resultant better tolerance during treatment as well as reduced late complications. Virtually every patient undergoing pelvic or extended volume teletherapy will experience some degree of acute side effects. Only a minority will experience major symptomatic late complications. But for those patients, the effects can last a lifetime.

The hypothesis of this study is that use of proton beam teletherapy in-lieu of conventional photon techniques will result in reduced radiation exposure to normal tissues and reduced side effects and complications of treatment. Use specifically of the "pencil-beam" scanning (PBS) proton capability at the FHBPTC makes the treatment of these protocol patients practically feasible by reducing the complexity of treatment planning and delivery compared to scattered proton fields. Due to limitations on field size and deep range of scattered proton fields, treatment of large, deep-seated target volumes becomes complex, time consuming, and expensive. PBS reduces costs incurred in the construction of field-specific hardware and provides more conformal dose distributions.[6,7]

3. PARTICIPANT SELECTION

Patients will be identified at the weekly Gynecologic Oncology-Pathology Multidisciplinary Tumor Board that routinely reviews all gynecologic cancer pathology in patients operated at

Massachusetts General Hospital (MGH). Potentially eligible patients operated elsewhere and referred for adjuvant treatment to MGH would be identified based on pathology review of submitted histologic sections from the referring institution.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically confirmed primary cancer of the uterus or cervix with histologically confirmed metastasis to one or more parametrial, pelvic, or para-aortic nodes prior to enrollment. Participants diagnosed at other institutions must have pathology reviewed and confirmed at MGH or another DF/HCC institution.

3.1.1.a Uterine cancer participants will be FIGO stage IIIC and may have endometrioid cancer, clear cell cancer, uterine papillary serous cancer, carcinosarcoma, or endometrial stromal sarcoma.

3.1.1.b Cervical cancer participants will be AJCC stages $pT_{1,2},N_1,M_0$ with squamous carcinoma, adenocarcinoma, adenosquamous carcinoma, or glassy cell carcinoma histology.

3.1.2 Participants must have undergone simple, modified radical, or radical abdominal hysterectomy or vaginal hysterectomy and lymphadenectomy (pelvic nodes, para-aortic nodes, or both nodal basins) by open or laparoscopic assisted technique.

3.1.3 Participants may have undergone prior chemotherapy for their uterine malignancy or may undergo chemotherapy in conjunction with adjuvant proton therapy per discretion of treating physicians. The agents, doses, routes and schedule of administration will be determined by their attending Gynecologic Oncologist or Medical Oncologist. For participants who have undergone prior chemotherapy, protocol radiation may commence no sooner than 21 days after the last chemotherapy treatment.

3.1.4 Participants with cervical cancer may undergo chemotherapy in conjunction with adjuvant proton therapy. The agents, doses, routes and schedule of administration will be determined by their attending Gynecologic Oncologist or Medical Oncologist.

3.1.5 Prior therapeutic radiation exposure to tissues for which protocol irradiation is anticipated is an exclusion criterion.

3.1.6 There will be no upper age limit for eligibility. Elderly patients will be eligible for participation provided they are competent to provide informed consent, or written consent can be provided by their duly appointed healthcare proxy.

3.1.7 Life expectancy of greater than 18 months.

3.1.8 ECOG performance status $\leq$2 (Karnofsky $\geq$60%, see Appendix A).

3.1.9 Baseline hematology laboratories will be performed prior to registration, the patient can be enrolled in the trial if laboratory values are deemed clinically acceptable by treating physician.

3.1.10 Participants must have no clinical, radiographic, or laboratory evidence of cancer dissemination to the peritoneal cavity, chest cavity, or spread via hematogenous dissemination. CT or PET/CT of the chest, abdomen and pelvis must have been obtained within 10 weeks of study entry. There must be no measurable (macroscopic) disease within the radiation target volume following hysterectomy and lymphadenectomy.

3.1.11 Participants must have the ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Inability to sign informed consent document.

3.2.2 Evidence of extra-abdominal cancer dissemination or hematogenous cancer dissemination.

3.2.3 Evidence of measurable (macroscopic) residual disease following hysterectomy and lymphadenectomy.

3.2.4 Prior therapeutic radiation to target tissues for protocol radiation.

3.2.5 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years or are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.2.6 Age less than 18.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

All participants are women. Eligibility criteria otherwise do not limit or impede participation or retention of minorities or underrepresented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the ODQ in the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for proton beam teletherapy are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Pre-treatment Criteria

5.1.1 Day 1 proton beam teletherapy: Provided all laboratory determinations and imaging findings specified in section 3.1 are within the protocol eligibility requirements, no further pre-treatment criteria are established.

5.1.2 Subsequent proton beam teletherapy treatments 2-30: Maintenance of platelet count $\geq$ 35,000/mcL and absolute neutrophil count $\geq$800/mcL.

5.1.3 Uterine cancer patients who have received chemotherapy prior to proton therapy may have twice-weekly complete circulating blood counts commencing on or before treatment fraction 8. These labs will be ordered and monitored at the discretion of the treating physician.

5.1.4 Cervix cancer patients may have weekly complete blood counts commencing on or before treatment fraction 8. Cervix patients receiving concurrent chemotherapy will have weekly determination of serum electrolytes, renal function, Ca++, and Mg++. These labs will be ordered and monitored at the discretion of the treating physician.

5.2 Agent Administration

5.2.1 Proton beam therapy will be planned based on patient supine CT simulation with custom immobilization per standard practice in the Department of Radiation Oncology, Massachusetts General Hospital.

5.2.2 Full contours will be obtained for all abdominal organs at risk including: stomach, duodenum, bowel (small bowel will be contoured separately if patient requires boost with teletherapy), rectum, liver, kidneys, spinal cord, thoraco-lumbar spine T12-L5, pelvic bone girdle, and proximal femurs from the femoral heads to below the lesser trochanters.
5.2.3 Comparative treatments plans for IMRT and 3DCRT will be generated for each participant from the same CT-simulation data set for comparison purposes and for actual treatment of participants in the event of the proton beam being unavailable for any reason longer than 2 working days.

5.2.4 Standard immobilization-stabilization procedures and treatment verification procedures will be employed as customarily performed for patients at the FHBPTC.

5.2.5 For participants undergoing proton beam therapy to the pelvis, the superior extent of the target volume will be at the interspace of the fifth lumbar vertebra and the first sacral segment (L5-S1).

5.2.6 For participants undergoing proton beam therapy to an extended volume (pelvic and para-aortic nodal basins) the superior border will be at the interspace of the twelfth thoracic and the first lumbar vertebrae (T12-L1).

5.2.7 For participants treated for cervical cancer the inferior extent of the target volume will encompass the proximal 2 cm of the vagina.

5.2.8 For participants treated for uterine cancer, the inferior extent of the target volume will encompass the full extent of the vagina from the apex to the introitus defined as the external urethral meatus.

5.2.9 All proton beam teletherapy treatments will be administered at a daily dose of 1.8 Gy (RBE). The RBE for proton radiation is set at 1.1. The dose unit Gy (RBE) is defined as the proton dose in Gy x RBE 1.1.

5.2.10 All proton beam teletherapy treatments will be administered no more than 5 treatment days per week.

5.2.11 Total absorbed teletherapy dose will be 45 Gy (RBE) in 25 daily fractions of 1.8 Gy (RBE) over 6 weeks for all participants except as noted in 5.2.12.

5.2.12 For patients with extra-nodal extension and cancer extension to adjacent structures (bone, artery, vein, muscle, nerve, bladder serosa, rectal serosa) reduced volume(s) may be treated with proton beam to 54 Gy (RBE) in 30 fractions of 1.8 Gy (RBE) over 7 weeks.

5.2.13 Participants with cervical cancer who have more than two positive pelvic lymph nodes or

extranodal involvement may be treated with a pelvic and para-aortic radiation field.

5.2.14 Target coverage requirements

- $V_{90} \geq 90\%$ (40.5 Gy (RBE))
- D_{97}(43.65 Gy (RBE)) $\geq 97\%$
- D_{99}(44.55 Gy (RBE)) $\geq 90\%$
- D_{110}(49.5 Gy (RBE)) $\leq 10\%$
- D_{115}(51.75 Gy (RBE)) $\leq 1\%$
- Dose maximum should occur within the PTV

For patients not receiving reduced volume "boost" therapy:

Organs at risk (OAR) hard constraints:

- Bowel (including duodenum, large bowel): $V_{45} \leq 250$ cc; $D_{max} \leq 50$ Gy (RBE)
- Rectum: $D_{max} \leq 50$ Gy (RBE)
- Bone Marrow: $V_{10} \leq 90\%$; $V_{20} \leq 75\%$
- Bladder: $D_{max} \leq 50$ Gy (RBE)
- Femoral Head: $D_{max} \leq 50$ Gy (RBE)
- Spinal cord: $D_{max} \leq 36$ Gy (RBE)
- Cauda: $D_{max} \leq 50$ Gy (RBE)
- Stomach: $D_{max} \leq 42$ Gy (RBE)
- Kidneys: $V_{18} \leq 30\%$ and $V_{10} \leq 50\%$ (for each kidney)

OAR soft constraints:

- Bowel: $V_{45} \leq 200$ cc; $V_{40} \leq 30\%$; $D_{max} \leq 45$ Gy (RBE)

- Rectum: $V_{45} \leq 50\%$; $V_{30} \leq 60\%$; $D_{max} \leq 50$ Gy (RBE)
- Bone Marrow: $V_{10} \leq 80\%$; $V_{20} \leq 66\%$
- Bladder: $V_{45} \leq 50\%$; $D_{max} \leq 50$ Gy (RBE)
- Femoral Head: $V_{30} \leq 15\%$; $D_{max} \leq 50$ Gy (RBE)
- Cauda Equina: $D_{max} \leq 42$ Gy (RBE)
- Kidneys: $V_{14} \leq 30\%$ (for each kidney)

For patients receiving reduced volume supplementary "boost" radiation:

- Small Bowel: $D_{max} \leq 52$ Gy (RBE)
- Large Bowel: $D_{max} \leq 56$ Gy (RBE)
- Cauda Equina: $D_{max} \leq 56$ Gy (RBE)
- Rectum: $D_{max} \leq 56$ Gy (RBE)
- Bladder: $D_{max} \leq 56$ Gy (RBE)
- Femoral Head: $D_{max} \leq 56$ Gy (RBE)

The deviations in dose constraints described are considered planning deviations only and will not constitute protocol deviations. Treatment plans that include minor planning deviations may be delivered as part of this protocol.

5.2.15 Vaginal brachytherapy will be administered on an outpatient basis employing standard techniques with high dose rate (HDR) remote afterloading equipment.

5.2.16 Cervix cancer patients will receive 3 brachytherapy fractions of 5 Gy each (15 Gy total) administered to the proximal 2 cm of the residual vagina with dose specified at the vaginal mucosa (surface of the intra-vaginal applicator).

5.2.17 Uterine cancer patients will receive 3 brachytherapy fractions of 5 Gy each (15 Gy total) to the proximal vagina with dose specified at the vaginal mucosa (surface of the intra-

vaginal applicator). The full length of the vagina will be treated employing a gradient dose distribution such that the distal anterior sub-urethral vagina receives 3 Gy with each brachytherapy treatment.

5.2.18 For patients with cystocoele or rectocoele or vaginal introital diameter <2.5 cm, vaginal brachytherapy will be administered in 5 fractions of 3 Gy mucosal dose to the proximal vagina using techniques and dose distributions as specified in 5.2.13-5.2.15. Uterine cancer patients will have the distal vaginal dose administered in 5 fractions of 1.8 Gy.

5.2.19 Maximum point dose to the bladder and rectum from brachytherapy will be calculated and recorded from CT dosimetry from one insertion with applicator in the vagina. These dose contributions will not be applied to dose constraints in sections 5.2.13.

5.2.20 Other Modalities or Procedures:

5.2.20a Uterine cancer patients may receive conventional chemotherapy prior to proton radiation, with the drugs, doses and routes of administration to be selected by their attending Gynecologic Oncologist or Medical Oncologist. Uterine cancer patients will not receive concurrent chemotherapy with protocol teletherapy. All pre-radiation chemotherapy will be with commercially available agents approved for use with uterine cancer patients.

5.2.20b Cervical cancer patients may receive concurrent adjuvant cytotoxic chemotherapy with the drugs, doses and routes of administration to be selected by their attending Gynecologic Oncologist or Medical Oncologist. All chemotherapy will be with commercially available agents approved for use with cervical cancer patients.

5.2.20c Experimental or non-standard chemotherapy regimens will not be administered to study participants. All chemotherapy agents administered prior to or during study participation will be FDA approved agents commercially available.

5.2.20d For patients developing cancer recurrence after protocol therapy, investigational agents will not be precluded from their subsequent care.

5.3 Definition of Dose-Limiting Toxicity N/A

5.4 General Concomitant Medication and Supportive Care Guidelines:

5.4.1 Standard supportive therapies currently employed for radiation side effects will be administered in conventional dose, including anti-diarrheal medication (Imodium, Lomotil) anti-

emetic medication (Ativan, Zofran, Reglan, Compazine, etc.), colony stimulating factors, transfusions, etc. as required to provide optimal medical symptom management and support of study participants. No experimental medications or off-label medications will be employed.

Transfusion of red blood cells to maintain hemoglobin >10 g/dl will be employed at discretion of treating physician and medical team in the case of hemoglobin <10 g/dl at study entry and in the eventuality that hemoglobin declines during the course of protocol therapy.

5.5 Duration of Therapy

Duration of therapy will depend on evidence of disease progression and tolerance. In the event of a treatment break for circulating blood counts (neutrophils, platelets) to recover, treatment will resume when counts have recovered per section 5.1.2. The treatment break will be documented in the data set; any length of break to allow blood counts to recover is allowed. In the absence of treatment delays due to adverse events, treatment may continue until completed or until one of the following criteria applies:

- Disease progression outside of the radiation target volume,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), including grade 4 thrombocytopenia or neutropenia; grade 3 hemoglobin, diarrhea, urinary frequency, or fatigue; or grade 2 weight loss.
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.6 Duration of Follow Up

Participants will be followed for 60 months after completion of protocol therapy or removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Participants who experience a recurrence of their disease will be followed for survival only after the recurrence.

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator:

Dr. Andrea Russo at 617-219-1200 or

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.02 from 9/15/2009) which is available at http://ctep.cancer.gov/reporting//ctc.html).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

Acute toxicities expected from conventional photon therapy administered alone, or with concurrent chemotherapy, to the pelvis or extended volume (pelvic and para-aortic nodal basins) are listed below. Because radiation will be administered to a smaller volume using proton beam, acute toxicities are expected to be delayed in onset and/or milder in severity. Recovery from acute side effects is expected over a 3-6 week period after the last treatment has been administered.

Acute (temporary) effects include:

Likely (more than 50% chance this will happen):

- Fatigue
- Cramps
- Frequent bowel movement
- Diarrhea
- Nausea
- Urinary frequency and urgency
- Burning with urination
- Vaginal irritation with itching and discharge
- Skin reaction (radiation dermatitis)
- Rectal irritation

Frequent (10-50% chance this will occur):

- Nausea (mild) and vomiting (rare) that is treatable with medications.
- Reduction in circulating blood counts including red cells which are important for carrying oxygen, platelets which are important for normal blood coagulation, and white cells which are important in fighting infection. If severe, changes in circulating blood counts may require blood transfusion, hospitalization, and medication intended to bring blood counts to normal levels.

Occasional (Between 1-10% chance this will occur):

- Dehydration and Electrolyte imbalances (changes in body salts) may occur in patients experiencing nausea, vomiting and diarrhea. This may not cause symptoms but sometimes causes fatigue, muscle weakness, muscle cramps, irregular heart beat or seizures. This can be severe and possibly life threatening, and may require hospitalization and intravenous treatment.

Delayed effects which may develop after completion of Proton beam radiation treatment include:

Frequent (10-50% chance this will occur):

- Leg lymphedema (swelling of legs due to a block in lymphatic flow)

Occasional (Between 1-10% chance this will occur):

- Bowel obstruction requiring surgery to repair.
- Bowel injury
- Premature menopause: probable if ovaries have not been conserved surgically and removed to locations remote from the radiation target volumes.
- Bone fractures in the pelvis or spine
- Weight loss is slow and progressive and rarely exceeds 10% of pre-protocol treatment weight.

Rare (Less than a 1% chance this will occur):

- Appearance of radiation caused cancer in or next to the radiation site: very rare and usually observed 20 or more years after radiation treatment.
- Reduced bladder capacity with urinary frequency and urgency
- Potential injury to any/all normal tissues unavoidably irradiated
- Possible injury to liver and/or kidneys

6.1.2 Toxicity Management

Standard supportive therapies currently employed for radiation side effects will be administered in conventional dose, including anti-diarrheal medication (Imodium, Lomotil) anti-emetic medication (Ativan, Zofran, Reglan, Compazine, etc.) as required. No experimental medications or off-label medications will be employed. All supportive medications will be commercially available.

Outpatient intravenous hydration will be instituted for symptomatic dehydration or electrolyte imbalance induced by diarrhea (hypokalemia, hyponatremia).

6.2 Dose Modifications/Delays

6.2.1 Dose per proton teletherapy fraction will be 1.8 Gy (RBE) and will not be modified.

6.2.2 Treatment for uterine cancer patients will be suspended for thrombocytopenia with platelets <35,000 mcL or neutropenia with absolute neutrophil count <800/mcL or for abnormal bleeding or febrile neutropenia.

6.2.3 Treatment will resume at the same daily dose and fractionation schedule when circulating blood counts rise above these levels. Differential blood counts may be obtained twice weekly for uterine cancer patients, once weekly for cervix cancer patients commencing on or before fraction 8 of teletherapy.

6.2.4 Treatment will be suspended for symptomatic dehydration and/or hyponatremia or hypokalemia requiring intravenous fluids. Treatment will resume as soon as parameters have normalized.

6.2.5 For cervical cancer patients getting chemotherapy concurrently with proton teletherapy, chemotherapy will be suspended for grade 3 neutropenia or grade 2 thrombocytopenia and resume when circulating counts have recovered above these levels. Daily radiation will not be suspended unless platelets fall below 35,000/mcL or absolute neutrophils fall less than 800/mcL.

7. DRUG FORMULATION AND ADMINISTRATION: N/A

8. CORRELATIVE/SPECIAL STUDIES: N/A

9. STUDY CALENDAR

9.1 Baseline hematologic evaluations are to be conducted within 2-weeks prior to study entry. Scans must be done ≤10 weeks prior to study entry.

9.2 Patients will be interviewed and examined weekly during treatment.

9.3 Routine surveillance follow-up will be: 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36, 42, 48, 54 and 60 months (+/- 4 weeks) following adjuvant radiation treatment.

9.4 Study Calendar/Required Data

Tests and Observations	At Study Entry	During Treatment	At Follow Up (1)
Informed Consent	x		
History	x		x
Concurrent Meds	x	x	x
Physical Exam (2)	x	x	x
Pelvic Exam (3)	x	x	x
CBC with diff, PLT (4)	x	x	
Serum Chemistries (5)	x	x	
Toxicity and AE evaluation	x	x	x
Radiological imaging (6)	x		x
Quality of Life (7)	x		x

Notes:

(1) Follow up schedule (+/- 4 weeks for each time point): every 3 months for 2 years; every 4 months to year 3; every 6 months until year 5.
(2) Physical includes, weight, vitals, performance status required at baseline. For weekly on-treatment and follow up visits, physical exam will be performed as pertinent at the discretion of the treating physician, and includes weight. .
(3) Pelvic Exam pre-study, during vaginal brachytherapy (typically week 6 of treatment) and at each follow up visit
(4) Study entry labs for pre-treatment must be done within14 days of study entry. Labs may be repeated twice weekly for uterine cancer patients, once weekly for cervix cancer patients during treatment to ensure maintenance of platelets >35,000mcL and ANC >800mcL. These labs are ordered and monitored at the discretion of the treating physician.
(5) Required chemistries are: Albumin, Alk Phos, T bili, BUN, bicarbonate, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT, SGPT, sodium, calcium, magnesium. These will be ordered and monitored at the discretion of the treating physician.
(6) Contrast enhanced CT scan of the chest, abdomen and pelvis pre-study (≤10 weeks of study entry) and in post treatment, twice per year to year 3.
(7) Quality of Life will be assessed using the FACT-En Version 4 (Appendix 2) instrument for uterine patients and the FACT-Cx Version 4 (Appendix 3) instrument for cervix patients. QOL will be assessed at study entry, and at 6, 12, 24, 36, 48, and 60 months (+/- 4 weeks) after protocol therapy.

10. MEASUREMENT OF EFFECT: Participants are excluded if they have measurable disease following hysterectomy. (3.2.2, 3.2.3)

10.1 **Progression-Free Survival**

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression at any site as detected by symptomatic recurrence or routine surveillance follow-up physical examination or imaging as described in the Study Calendar (Section 9) .

10.1.1 Following protocol therapy, patients will be seen in routine surveillance follow- up at 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, 36, 42, 48, 54 and 60 months

10.1.2 At each follow-up interval history, weight and vital signs will be obtained, and general physical examination including pelvic examination will be performed.

10.1.3 CT scans of the chest, abdomen, and pelvis will be obtained twice per year post treatment to year 3.

10.1.4 For this protocol, routine blood work will not be obtained in asymptomatic patients except as required for imaging contrast administration.

10.2 Pattern of Recurrence

Local recurrence is defined as cancer detected at any time after initiation of treatment that lies within the volume of target tissue undergoing adjuvant proton beam teletherapy.

Marginal Recurrence is defined as cancer detected at any time following initiation of adjuvant proton beam teletherapy that lies within 1 cm of tissue that receives 90% of the daily prescribed radiation dose.

Distant Recurrence is defined as cancer which has spread by hematogenous dissemination or peritoneal dissemination to sites spatially remote from the irradiated target volume.

10.3 Quality of Life

Quality of life will be assessed at 6, 12, 24, 36, 48, 60 months following protocol therapy.

QOL will be assessed using the FACT-En Version 4 instrument for uterine patients and the FACT-Cx Version 4 for cervix patients.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.02 9/15/2009 that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study treatment, throughout the study, and within 60 months of the last dose of study medication. Participants who experience an ongoing adverse event or related to a study procedures and/or study medication beyond 60 months will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Definitions

11.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.2.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.2.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of adjuvant radiation treatment. For the purposes of this study, an adverse event is considered expected when it is included in the informed consent document as a potential risk.

Refer to Section 6.1 (Anticipated Toxicities) for a listing of expected adverse events associated with the study treatment.

11.2.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the informed consent document or when it is not included in the informed consent documentation as a potential risk.

11.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.3 Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

11.4 Reporting Adverse Events

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator (or Protocol Chair), IRB, and others of all serious adverse events as required in the protocol.

The Principal Investigator (or Protocol Chair) will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available.

11.4.1 Serious Adverse Event Reporting Requirements

All events meeting the criteria for Serious Adverse Event (see Section 11.2.2) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported as serious adverse events.

The participating investigator must report each serious adverse event, regardless attribution, to the Principal Investigator (or Protocol Chair) within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone and facsimile to:

Andrea Russo, MD Tel: 617-219-1200 FAX: 617-726-3603

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events will be reported to the Principal Investigator (or Protocol Chair) on the toxicity Case Report Forms.

11.5 Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (or Protocol Chair) and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

11.6 Hospital Risk Management Notification by Investigator

The participating investigator will report to the Principal Investigator (or Protocol Chair) and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with ODQ
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the treatment
Toxicity Form	Weekly during treatment; within 14 days of protocol defined follow-up visit
Lab Form	With Baseline assessment form and weekly during treatment
Adverse Event Report Form	Immediately upon detection of adverse event

	during treatment. Within 14 days of adverse event detected during surveillance follow-up.
Off Treatment/Off Study Form	Within 14 days of being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet as needed to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual;; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6)
  www.fda.gov/cder/guidance/iche6.htm
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
- Title 21 Part 11 – Electronic Records; Electronic Signatures
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
- Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines: N/A

14. STATISTICAL CONSIDERATIONS

The primary objective of this protocol is to determine whether the substitution of scanning pencil beam proton teletherapy for conventional photon teletherapy will administer less radiation dose to the normal tissues of organs at risk compared to conventional techniques (IMRT or 3-D conformal teletherapy). Additional endpoints are to determine whether scanning pencil beam proton teletherapy is associated with cancer control rates within the irradiated volumes comparable to those reported in existing literature and to determine the rates of acute radiation side effects and delayed radiation complications.

14.1 Study Design/Endpoints:

The primary endpoint is the comparison of dose volume histograms (DVH) from proton teletherapy and conventional photon teletherapy. Structure sets contoured for proton beam treatment will be used to plan alternative IMRT and 3DCRT plans by the same medical physics team and attending physician, and DVH will be generated for each plan. It is hypothesized that the area under the DVH curve will be at least 25% smaller in the bowel, in favor of the proton plan, for virtually all patients. With a sample size of 22 patients, we will have 91% power to accept that the proton plan is superior for 95% of patients if at least 20 of them have a proton plan with an area under the DVH curve at least 25% smaller in the bowel. The decision rule is associated with type 1 error of 15% if only 80% of patients truly have a superior proton plan for the bowel. This magnitude of radiation dose difference is expected to be clinically significant with respect to acute GI side effects, thus GI toxicities will be a major focus of the data analysis to explore the correlation between DVH and radiation effects.

14.2 Sample Size/Accrual Rate:

As of October 2016, 9 node positive uterine cancer patients and 5 node positive cervical cancer patients have been enrolled and treated with proton beam teletherapy. We project another 8 patients will be enrolled and treated by the end of 2018 for a total accrual of 22 patients. Based on the tumor distribution to date, we expect the final accrual will consist of approximately 14 uterine cancer patients and 8 cervical cancer patients. Patients who do not start protocol treatment will be replaced.

All patients will be followed for a minimum of 60 months following completion of protocol therapy.

14.3 Stratification Factors: N/A

14.4 Analysis of Secondary Endpoints:

Secondary endpoints are QOL, progression-free survival and patterns of recurrence. QOL outcomes will be analyzed using mixed models for longitudinal data. Progression-free survival will be analyzed using standard methods for failure time data, primarily the Kaplan-Meier estimate. Progression-free survival is defined as the duration from the start of protocol treatment to the time of objective disease progression at any site or death in the absence of documented progression, while patients who have not progressed or died will be censored at the time of last follow-up. Differences between patient subgroups may be explored by the log-rank test, using exact methods as the event numbers will be modest. Patterns of recurrence will be reported descriptively.

14.5 Reporting and Exclusions;

All patients starting protocol therapy will be analyzed and reported for all study endpoints, whether or not treatment is completed.

14.5.1 **Evaluation of toxicity.**

All participants will be evaluable for toxicity from the time of their first treatment.

14.5.2 **Evaluation of response.** N/A. Patients with measurable disease are ineligible.

14.5.3 **Evaluation of cancer control.** At or before each scheduled follow-up surveillance visit patients will be categorized as clinically cancer-free, alive with cancer, dead from cancer, dead from complications of therapy, or dead from inter-current illness, or cause of death unknown.

14.5.4 **Pattern of cancer recurrence**: In patients developing cancer recurrence, the pattern of recurrence will be recorded according to the criteria in 10.2 for local, regional and distant sites. As a patient may recur at multiple sites and at different times, the dates of recurrence will be recorded for each site. Progression-free survival will be based on the date of the earliest date of documented recurrence.

15. PUBLICATION PLAN

15.1.1 The intent of the investigators is to publish results in peer-reviewed journals.

15.1.2 A preliminary publication will compare DVH results from proton, IMRT, and 3DCRT plans after accrual has been completed.

15.1.3 A second preliminary publication is anticipated when all surviving participants have been followed a minimum of 24 months following completion of protocol therapy, as the large majority of symptomatic late radiation complications will be manifest within this time window.

15.1.4 A final publication is anticipated when all patients have been followed a minimum of 5 years or until death.

15.1.5 Primary responsibility for publication will reside with the Principal Investigator (Study Chair) and may be delegated to the Division of Medical Physics for preliminary publication of comparative dosimetric results (endpoint 1.3.1).

16. REFERENCES

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4) Alvarez-Secord A, Havrilesky LJ, Bae-Jump V, Chin J, et al. The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. Gynecol Oncol (2007) 107, 285-291.

5) Peters WA 3rd, Liu RJ, Stock RJ, Monk BJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early stage cancer of the cervix. J. Clin Oncol (2000) 18,1606-1613.

6) Kooy HM, Clasie BM, Lu H-M, Madden TM et al. A case study in proton pencil-beam scanning delivery. Int J Radiat Oncol Biol Phys (2010) 76, 624-30.

7) Rutz HP, Weber DC, Goitein G, Ares C, et al. Postoperative spot-scanning proton radiation therapy for chordoma and chondrosarcoma in children and adolescents. Initial experience at Paul Scherrer Institute. Int J Radiat Oncol Biol Phys (2008) 71, 220-225.

17. APPENDICES

Appendix 1. Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix 2: FACT-En Version 4 Quality of Life Instrument for uterine cancer patients.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					

GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
O1	I have swelling in my stomach area	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4
ES6	I have vaginal bleeding or spotting	0	1	2	3	4
ES4	I have vaginal discharge	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
ES1	I have hot flashes	0	1	2	3	4
ES2	I have cold sweats	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
ES8	I have pain or discomfort with intercourse	0	1	2	3	4
En1	I have trouble digesting food	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
En2	I have discomfort or pain in my pelvic area	0	1	2	3	4

Appendix 3: FACT-Cx Version 4 Quality of Life instrument for cervix cancer patients.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					

GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Cx1	I am bothered by discharge or bleeding from my vagina	0	1	2	3	4
Cx2	I am bothered by odor coming from my vagina	0	1	2	3	4
Cx3	I am afraid to have sex	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
Cx4	My vagina feels too narrow or short	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
Cx5	I am afraid the treatment may harm my body	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
BL1	I have trouble controlling my urine	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
Cx7	I have discomfort when I urinate	0	1	2	3	4
HN1	I am able to eat the foods that I like	0	1	2	3	4