UChicago Protocol #: IRB20-1390

TITLE: RT-PACE: Phase I/II Study of Adjuvant Whole Pelvic Hypofractionated Radiotherapy for Non-Metastatic Cervical and Endometrial Cancer

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Version Date: 6/24/2022

Protocol Version: 5.0

This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.
## DOCUMENT HISTORY

<table>
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<tr>
<th>Protocol Version Date</th>
<th>Summary of Changes and Rationale</th>
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<tr>
<td>6.24.2022</td>
<td>Protocol amended to add:</td>
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<td>- A phase II cohort amending the protocol from a phase I to phase I/II study with additional phase II primary and secondary endpoints, slight modifications to eligibility criteria, additional accruing sites, and updated patient accrual goals to support statistical analysis for the new primary endpoint. This amendment was written after the original phase I cohort began accrual; expansion cohort patients will be transferred to the phase II cohort. The intervention for phase II is identical to the phase I expansion cohort with the addition of additional patient-reported outcomes as secondary endpoints.</td>
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<tr>
<td></td>
<td>- Multisite/PCCC language</td>
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<td>- Investigators from University of Utah</td>
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### STUDY SUMMARY

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<th><strong>Study Duration</strong></th>
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| **Objectives**     | **Phase I**  
|                    | Hypothesis: Hypofractionated whole pelvic radiation therapy will have an acceptable toxicity profile.  
|                    | a) Primary objective: To determine the maximum tolerated dose-per-fraction (MTD) regimen of whole pelvic radiation therapy administered in the adjuvant setting for uterine or cervical cancer.  
|                    | **Phase II**  
|                    | a) Primary objective: To evaluate the change in patient-reported acute gastrointestinal toxicity after completion of hypofractionated radiation.  
|                    | b) Secondary objectives:  
|                    | 1. To estimate impact upon urinary toxicity over time  
|                    | 2. To estimate impact upon gastrointestinal toxicity over time  
|                    | 3. To assess quality of life following treatment  
|                    | 4. To quantify financial toxicity following treatment  
|                    | 5. To assess satisfaction with decision-making following treatment |
| **Number of Subjects** | Phase I: Minimum 9; maximum 36.  
|                     | Phase II: 64 patients at MTD regimen                          |
| **Diagnosis and Main Inclusion Criteria** | Uterine or cervical cancer patients recommended for standard of care adjuvant whole pelvic radiation therapy |
| **Statistical Methodology** | Phase I: Keyboard design for dose-per fraction escalation  
|                         | Phase II: Calculate change in mean bowel PRO score (using EPIC instrument) from baseline to end of treatment and compare to historic control of standard fractionation. Non-inferiority of hypofractionation will be declared if the 90% confidence interval excludes and is greater than - 18.5. |
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1. OBJECTIVES

1.1 Primary Objectives

- **Phase I**
  Primary objective: To determine the maximum tolerated dose-per-fraction (MTD) regimen of whole pelvic radiation therapy administered in the adjuvant setting for uterine or cervical cancer.

- **Phase II**
  Primary objective: To evaluate the change in patient-reported acute gastrointestinal toxicity after completion of hypofractionated radiation.

1.2 Secondary Objectives

- To estimate impact upon urinary toxicity over time
- To estimate impact upon gastrointestinal toxicity over time
- To assess quality of life following treatment
- To quantify financial toxicity following treatment
- To assess satisfaction with decision-making following treatment

2. INTRODUCTION

2.1 Background

Radiation Therapy in Endometrial Cancer

Definitive treatment of stage I-III endometrial cancer in the United States generally consists of hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic nodal dissection. Similarly, treatment of early-stage cervical cancers includes radical hysterectomy and nodal dissection. In cases where cervical or uterine cancer patients are deemed to be at high risk of recurrence post-operatively, adjuvant radiation therapy and/or chemotherapy are also recommended. Radiation therapy is an integral component of curative therapy for uterine cancers and can be administered either via brachytherapy (targeting the vaginal cuff) or external beam radiation therapy (targeting the pelvic region inclusive of the vaginal cuff and draining nodal lymphatics at risk of harboring microscopic disease). Numerous studies have demonstrated efficacy of radiation in reducing locoregional recurrence in both early and more locally advanced disease (1–3). In high-intermediate risk stage I-II disease, radiation has been shown to reduce risk of locoregional recurrence from approximately 25% to 5% (1, 3). In high-risk stage III disease, locoregional (pelvic and para-aortic nodal) recurrence risk was reduced from approximately 20% with chemotherapy to 10% with chemoradiation (2).

The question of whether brachytherapy or external beam radiation therapy (also known as whole pelvic radiation therapy, or WPRT) is the most appropriate therapy is somewhat controversial. In high-intermediate risk disease, brachytherapy is generally considered the standard therapy. This
is based on patterns of failure data noting that the vast majority of locoregional recurrences occur at the vaginal cuff in this patient population. In more high-risk or advanced disease, WPRT is preferred due to the greater risk of microscopic nodal involvement. While randomized data suggest a benefit to WPRT in stage III endometrial cancer patients, this is limited to locoregional recurrence rather than a progression-free or overall survival benefit. This has led to varying practice patterns in the United States regarding the benefit of WPRT due to the concern that the potential benefits do not outweigh the risks of therapy.

In one large, randomized study of chemotherapy with or without adjuvant WPRT, WPRT was administered prior to chemotherapy. In an effort to mitigate the potential effect of delaying chemotherapy, concurrent radiosensitizing cisplatin was given with WPRT. When reports suggested there was locoregional recurrence benefit without a progression-free survival benefit, there was some concern that the delay in systemic therapy contributed to reducing the impact of radiation therapy. Thus, some physicians delay WPRT until after adjuvant systemic therapy is completed, especially given the 5-6 weeks of treatment required, and do not administer concurrent cisplatin.

Post-operative WPRT for both cervical and uterine cancers generally consists of 25-28 daily radiation treatments (5 days per week, resulting in ~5-6 weeks of treatment) and is associated with long-term impact on quality of life, particularly in gastrointestinal domains, with 10% of patients reporting fecal leakage, 8% reporting diarrhea, and 23% reporting bowel urgency at 7 years post-treatment (4). A recently published randomized trial investigating the newer intensity-modulated radiation therapy (IMRT) technique in post-operative uterine or cervical cancer patients reported acute toxicity rates (5 weeks after start of radiation) of 26% CTCAE gr 2+ GI and 16% gr 3-4 any toxicity (5).

Current National Comprehensive Cancer Center Network guidelines suggest that for surgically staged III-IV uterine cancer patients, adjuvant treatment should include systemic therapy +/- external beam radiation +/- brachytherapy. Thus, WPRT is considered a standard treatment option for patients with uterine cancer. Although there is clear benefit to treatment based on randomized data, the clinical significance of this benefit is felt to be equivocal to many physicians and thus there is no consensus on the role of WPRT at this time. As an alternative to WPRT in these high-risk patients, some physicians prefer the use of brachytherapy as a means of garnering some local control but without the added risks of WPRT. However, brachytherapy does not address the risk of nodal recurrences, which can be significant: in one study of stage III patients, the 5-year pelvic and para-aortic recurrence rate was 20% with chemotherapy but without whole pelvic radiotherapy (2). Thus, a modified fractionation scheme for WPRT that would reduce the time on treatment as well as treatment-related toxicity may alter the perceived risk-benefit ratio in favor of treatment such that patients can benefit from the improved pelvic control associated with WPRT.

Modified Fractionation Schemes in Radiation Oncology

“Conventional” fraction sizes in radiation oncology have traditionally been 1.8-2 Gy per fraction on a daily basis. These daily small fraction sizes were believed to be essential in reducing the toxicity associated with radiation by allowing for normal tissue recovery while maintaining tumor control. Over the past 20 years, the field of radiation oncology has been moving towards
larger fraction sizes (i.e., hypofractionation) in an effort to reduce time on treatment, patient inconvenience/logistical barriers, and healthcare utilization. In some tumor histologies, it is even felt to be potentially more effective radiobiologically as well. In the meantime, advances in technology have allowed for reduction of toxicity through improved target delineation, the use of improved on-board imaging at the time of treatment, and 3-dimensional planning and/or IMRT to allow for more conformal, homogeneous dose distributions. Subsequent long-term data that has become available demonstrate no detriment to toxicity; in some studies, hypofractionation has actually resulted in reduced rates of short- and long-term toxicity (6).

Hypofractionation has now been adopted for treatment of cancers of the breast, prostate, rectum, and pancreas in both definitive and adjuvant settings as it has been deemed to be safe and efficacious. American Society of Radiation Oncology (ASTRO) guidelines for treatment of whole breast radiotherapy recommend hypofractionation, generally to 40.05-42.56 Gy in 2.66 Gy/fx, in almost all patients rather than the standard dose to approximately 50 Gy in 1.8-2 Gy/fx (7). Similar evidence-based guidelines from ASTRO recommend both “conventionally and hypofractionated RT” for localized pancreatic cancer (8). In prostate cancer, a task force guideline stated “strong consensus was reached for offering moderate hypofractionation across risk groups…” and that this provides “advantages in cost and convenience” (9). In rectal cancer, neoadjuvant radiation consists of 25-28 fractions with concurrent chemotherapy or a 5-fraction course with sequential chemotherapy without any impact on efficacy and potentially an improved toxicity profile (10, 11).

While there has been little investigation in the use of hypofractionation in gynecologic oncology, it is commonly used in the pelvis as noted above for rectal and prostate cancers. Improvements in radiation technique have allowed for the pelvic region at-risk to be targeted much more conformally compared to older 4-field box techniques, and a randomized trial of IMRT compared to the older technique demonstrated reduction in patient-reported bowel and urinary bother scores, as well as reduced rates of frequent diarrhea and use of antidiarrheals (2). IMRT has also been associated with improvement in late/chronic toxicity in a separate randomized study of post-operative pelvic radiation (12). Previously published studies of hypofractionation for intact cervical cancers have not used IMRT techniques and demonstrate potentially higher toxicity than in the post-operative setting (13, 14).

Benefits and Risks of Hypofractionation

Hypofractionation has obvious benefits to patients, mainly in the form of convenience and financial toxicity. In breast cancer, studies have also demonstrated a greater societal impact due to reduced treatment costs and improved cost-effectiveness (15). In developing countries globally, this could also expand access to radiation for many patients (16).

As noted previously, toxicity is the main concern with hypofractionation. However, in randomized studies of breast, prostate, and rectal cancers, hypofractionation has not been associated with meaningful increased toxicity. In a Cochrane meta-analysis, over 8,000 women with breast cancer enrolled in randomized studies were analyzed and hypofractionated schedules were found to have similar efficacy, toxicity, and cosmetic outcomes compared to standard schedules; in fact, there was a decrease in acute toxicity with hypofractionation (6). In prostate cancer, using higher doses of typically 2.5-3 Gy per fraction to 60-70 Gy, some studies suggest a
potential small absolute increased risk of acute and late GI grade 2+ toxicity, with likely similar rates of GU toxicity (17–20). A recently published study of prostate radiation inclusive of pelvic lymph nodes demonstrated low rates of long-term toxicity (worst grade 2-3 GI/GU <10%) after 44 Gy in 20 fractions of radiation (21). Rectal cancer hypofractionated schemes of 5 Gy/fx to 25 Gy administered pre-operatively are very well-tolerated and have demonstrated reduced acute toxicity compared to conventional fractionation with concurrent chemotherapy (10, 11).

2.2 Rationale

This study is designed to evaluate the safety of hypofractionated radiation regimens for WPRT in an effort to reduce treatment time and burden on the patient and healthcare system. Successful identification of a safe radiation regimen and subsequent expansion of the study to a larger, multi-institutional phase II cohort will allow robust evaluation of its toxicity profile in comparison to the current conventionally fractionated regimen. Potential future studies may also identify a toxicity profile that is more favorable than current regimens and improve the risk-benefit ratio of WPRT such that it is incorporated more widely into adjuvant therapy and potentially improves access to care.

3. PATIENT SELECTION

3.1 Subject Identification & Recruitment

Subjects with uterine or cervical cancer who are seen for treatment in the Departments of Radiation Oncology at all participating sites will be identified and considered for recruitment.

Patients with a diagnosis of non-metastatic uterine or cervical cancer who have undergone standard of care hysterectomy and who are eligible and recommended to receive whole pelvic radiation will be recruited for this study. Patients should have no evidence of gross residual disease post-operatively as determined by the gynecologic oncologist’s clinical judgment, intra-operative findings, any available radiographic imaging, and the final pathology report. Concurrent chemotherapy and para-aortic radiation are not allowed. Concurrent targeted therapy (i.e., trastuzumab) is allowed.

3.2 Eligibility Criteria

- Diagnosis of primary cervical cancer or uterine cancer of any histology
- Age ≥ 18 years.
- Non-metastatic (FIGO Stage I-IIIC1 if uterine primary, FIGO Stage I-IVA if cervical primary).
- Must have been treated with definitive intent, including standard-of-care hysterectomy, without any gross residual disease post-operatively. Nodal dissection is not required.
- Recommended to undergo whole pelvic radiotherapy without concurrent chemotherapy or para-aortic radiation. Chemotherapy before or after radiotherapy is acceptable. Concurrent targeted therapy (i.e., trastuzumab, etc.) is permitted.
- Eastern Cooperative Oncology Group (ECOG) PS ≤ 2 – See Appendix C.
3.3 Exclusion Criteria

- Distant metastases as determined clinically or radiographically based upon standard-of-care work-up for endometrial cancer.
- Concurrent cytotoxic chemotherapy.
- Gross residual disease post-operatively and/or at the time of radiation based upon pre-op or post-op imaging, intra-operative findings, and gynecologic oncologists’ judgment.
- History of small bowel obstruction, inflammatory bowel disease, irritable bowel syndrome, connective tissue disorder requiring ongoing active medical management, or prior radiation therapy directed to the pelvis.
- Unresolved chemotherapy-associated diarrhea or abdominopelvic pain requiring medication prior to the initiation of radiation.
- Recommendation to undergo para-aortic nodal irradiation.

4. CONSENT

Written informed consent will be obtained by the principal investigator or other appropriate physician/research staff as authorized by the PI or Site Investigator. Written consent will be obtained after the study as well as its risks, benefits, and alternatives are thoroughly explained. The study will be fully explained to the subjects, emphasizing the potential risks and benefits of their participation, the potential loss of their confidentiality, potentially heightened risk (frequency/severity) of standard radiation-associated toxicities, and the altruistic aspect of helping future cancer patients. No monetary gain will be offered to the subjects, and they will be informed that that their decision will have no impact on the quality of care they will receive. This study will have no impact on their cancer treatment, which will be standard of care. The Principal Investigator or Site Investigator will answer any and all questions in full. Subjects will be given a copy of the consent for their own records and will be given instructions on how to withdraw from the study if they change their mind. There will be no waiver of consent/waiver of authorization.

5. RISKS AND BENEFITS

The risks associated with study participation are listed below.

Acute toxicities that are common include: fatigue, diarrhea, rectal irritation, urinary frequency and dysuria, loss of pubic hair, darkening of skin in the treatment portal, and low blood counts.

Common long-term toxicities include vaginal narrowing or shortening and dyspareunia. Uncommon long-term side effects include rectal bleeding, loose stool, rectal ulcer, dysuria, urinary frequency, hematuria, and vaginal vault necrosis. Rare long-term side effects include bowel obstruction, urethral obstruction, and vesicovaginal or rectovaginal fistula.

Interruptions in radiotherapy may be necessitated by uncontrolled diarrhea, or other acute complications. The reason for and the length of any such interruption must be documented. Radiation therapy will be continued without interruption if at all possible.

Other risks include breach of privacy. Every precaution will be taken to ensure confidentiality of patient information. Study personnel will generate anonymously-labeled specimens that will be
sent out for testing. Only the investigators and their designated staff will have access to the databases and the link between specimen code numbers and patient identifying information.

While the clinical benefit of a shortened radiation therapy treatment regimen (16-20 treatments) as compared to traditional regimens (25-28 treatments) is unknown, there is improved convenience to the patient. The investigators hope to use this information to confirm the safety of shorter radiation treatment regimens.

6. REGISTRATION PROCEDURES

6.1 General Guidelines

The University of Chicago is the lead site in the study and will handle patient registration, data oversight, and regulatory matters.

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed in Section 3. Eligible patients will be entered on study centrally by the University of Chicago study coordinator. All sites should contact the study coordinator at PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

Following registration, patients should begin protocol treatment within 28 days as noted in Study Calendar (Appendix A). Issues that would cause treatment delays should be discussed with the Study Lead Principal Investigator. If a patient does not receive protocol therapy following registration, the patient’s registration on the study will be canceled. The study coordinator/CRA should be notified of cancellations as soon as possible.

6.2 Registration Process

When a potential patient has been identified, notify the CRA via email at PhaseIICRA@medicine.bsd.uchicago.edu to ensure a reservation on the study. Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, and signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject’s scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
• Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the Study Lead PI. The Study Lead PI may clarify, but not overturn, eligibility criteria.

• Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.

• If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.

• If randomization is involved, the date the patient is randomized will be considered the patient’s “On Study Date.” If randomization is not involved, the first time the patient receives treatment will be considered the patient’s “On Study Date.” The patient’s subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go “On Study” will be recorded in the database with the date they signed consent and the reason for not going “On Study” (e.g., Ineligible, Screen Failure or Withdrawn Consent).

7. STUDY PROCEDURES

Please see Study Calendar (Schema) in Appendix A.

Should subjects have any questions or concerns between their scheduled visits, they may contact the principal investigator or appropriate research staff at any time. Subjects will be given the contact information at the time of consultation or study enrollment.

Visit Schedule

Visit 1: Screening Visit

Subject will be screened to ensure eligibility criteria are met. After receipt of informed consent, patients will be assigned to a dose-per-fraction treatment cohort for radiation therapy. Patients will be enrolled in cohorts of 3 to a dose level using the keyboard design (Yan, Mandrekar, and Yuan 2017).

Subsequent study visits

Subject will undergo weekly treatment checks by the treating radiation oncologist during the course of radiation as is standard of care. On the last day of treatment, the subject will be evaluated by the physician for treatment-associated toxicity and will also complete the Expanded Prostate Index Composite (EPIC) questionnaire.

Following the completion of daily radiation therapy, the subject will return for routine clinical follow-up approximately 1 month following radiation, then at 3 months following radiation, then every 3 months for the next 2 years following treatment. At each visit, the subject will be evaluated for clinical disease recurrence and treatment-associated toxicity by a physician. Additionally, the subject will complete the EPIC questionnaire. Further imaging or diagnostic
procedures will be performed if there is concern for disease recurrence and per the discretion of any of the subject’s treating physicians.

Study subjects may be contacted between visits for study-specific purposes to provide reminders of visits or assist with coordination of logistic concerns. If subjects are unable to visit the clinic for a scheduled follow-up visit, they may be contacted via telephone or electronically to evaluate their toxicity. Contact with study subjects following completion of the study may take place via telephone or other electronic communications to evaluate for cancer recurrence status.

8. TREATMENT PLAN

8.1 Radiation Therapy
Patients will undergo radiation therapy directed to the whole pelvis using standard target volumes described below. Intensity modulated radiation therapy (IMRT) is required. It is recommended that radiation is initiated within 8 weeks of surgery or last chemotherapy.

DICOM files of radiation plans will be submitted for all patients for central review. The radiation plan for the first three patients from each site must be reviewed and approved prior to the start of treatment.

Contouring of Target Structures

Standard institutional protocols for delineating radiation target volumes will be followed. It is recommended that treating physicians adhere to the Radiation Therapy and Oncology Group (RTOG) contouring atlases and treatment guidelines for endometrial carcinoma (23). These can be found at [https://www.rtog.org/CoreLab/ContouringAtlases.aspx](https://www.rtog.org/CoreLab/ContouringAtlases.aspx). The following are suggested guidelines:

The nodal CTV should include lymph nodes that drain the involved site and adjacent perinodal soft tissue. This should include the internal (hypogastric and obturator), external, and common iliac lymph nodes. In patients with cervical stromal involvement, presacral lymph nodes and 1-2 cm of tissue anterior to the S1, S2 and S3 sacral segments soft tissues should be included. The nodal CTV will include the vessels, perinodal tissue and pertinent clips. Anatomic barriers such as bone, muscle, and small bowel should be excluded from the CTV. The most anterolateral external iliac lymph nodes that lie just proximal to the inguinal canal should be excluded from the CTV. The CTV of the nodes may end 7 mm from L4/L5 interspace to account for the PTV expansion or be inclusive of the common iliac LN at the treating physician’s discretion.

The vaginal CTV will include the vagina and the paravaginal soft tissue. The inferior extent of the vaginal CTV should generally be the upper symphysis pubis or just above the bottom of the obturator foramen but can be individualized based on inferior spread of tumor. The vaginal CTV should extend into the rectum if there is significant rectal distention. This will allow coverage of the vagina if the rectum is decompressed during treatment.

A vaginal internal target volume to account for organ motion of the vagina will be used only for IMRT planning. The ITV will be contoured using a fused image of the full and empty bladder.
scans obtained during CT simulation and will encompass the vagina and paravaginal soft tissues from both scans.

The Nodal Planning Target Volume (PTV) will provide a 7 mm margin around the nodal CTV. The vaginal ITV be expanded in all dimensions (anteriorly, posteriorly, laterally as well as in the superior and inferior directions) to create the vaginal PTV.

The final planning target volume may be cropped 5mm from skin to create a PTV-eval for planning purposes.

Normal Tissue Contours

Normal tissue structures will be contoured on the CT scan obtained with a full bladder since treatment will be delivered with a full bladder with the goal of reducing the volume of irradiated bowel. A description for the technique on how to contour these structures can be found at http://www.rtog.org/CoreLab/ContouringAtlases/FemaleRTOGNormalPelvisAtlas.aspx.

Bladder will be outlined on every slice, including the portion inferior to the planning target volume. Rectum will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level that it leaves the posterior pelvis around the region of the rectosigmoid. Bowel (small bowel, colon, and sigmoid) will be contoured as one structure. Bowel space will be outlined on every slice with visible bowel extending 2 cm above the planning target volume. Bowel space will include the volume surrounding loops of bowel out to the edge of the peritoneum because the bowel may lie within this space at any time throughout the course of treatment. The pelvic bone from the superior to the inferior aspect of the PTV should be contoured, inclusive of the femoral heads (but not the femoral necks).

Intensity Modulated Radiation Therapy Planning Guidelines

IMRT Dose Specifications

The prescription dose shall be according to the following specifications: The vaginal planning target volume (PTV) and nodal PTV will receive the dose per fraction and total dose as specified by the subject’s assigned dose-per-fraction cohort. Patients will be treated once a day, 5 days a week, excluding weekends and planned holidays.

The dose is prescribed to cover 97% of the vaginal PTV and nodal PTV (V95%>97% acceptable). A volume of at least 0.03 cc within any PTV should not receive > 110% of the prescribed dose. No volume within the PTV that is 0.03 cc or larger can receive a dose that is < 93% of its prescribed dose. Any contiguous volume of 0.03 cc or larger of the tissue outside the PTVs must not receive > 110% of the dose prescribed to the composite PTV. The final PTV should be named “PTV” on all submitted DICOM files for central review.

IMRT Technical Factors

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or TomoTherapy®) is required. VMAT is allowed. Six or more fields should be utilized with a minimum source-axis
distance of 100 cm. The exception is the use of the TomoTherapy unit that uses 80 cm.

**IMRT Localization, Simulation, and Immobilization**
Patients must be immobilized supine in a cradle that fixes the position of the lower body, trunk and proximal legs. Treatment planning CT scans will be required to define clinical and planning target volumes. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment.

Two separate treatment planning CT scans (full bladder and empty bladder CT scans) are required. A full bladder scan can be obtained either by instilling the bladder with 200-300cc of contrast or instructing the patient to drink 32 ounces of fluid 30-60 minutes before simulation.

The empty bladder CT scan can be obtained after the patient has voided or by draining the bladder using the foley catheter.

Intravenous, oral, and rectal contrast may be used during simulation but is not required. It is recommended that if rectal contrast is considered, the minimum volume required for visualization is used as it may possibly cause anatomical distortion.

CT scan thickness should be 3mm through the region that contains the primary target volumes and the critical structures. CT scan should extend at least 4 cm above and below the target volumes.

**IMRT treatment planning**

Full and empty bladder scans should be fused together prior to outlining target volumes. A nodal CTV and vaginal ITV will be delineated on the full bladder scan for treatment planning purposes. IMRT plan will be prescribed to the PTV on the full bladder scan. The treatment aim will be the delivery of homogeneous prescribed dose radiation to the PTVs while minimizing dose to non-involved tissues. The treatment plan used for each patient will be evaluated based on an analysis of the volumetric dose, including dose volume histogram (DVH) analyses of the PTV and critical normal structures. Full heterogeneity corrections should be utilized.

**Planning Priorities**

Dose to nodal PTV and vaginal ITV are the most important planning priorities (see “IMRT Dose Specifications” above), followed by the dose to critical structures. The critical structure constraints are listed below (Table 3). Structures should be named as listed in Table 3 for submission for central review.

<table>
<thead>
<tr>
<th>Structure</th>
<th>SOC/Dose Level 0</th>
<th>Dose Level 1</th>
<th>Dose Level 2</th>
<th>Dose Level 3</th>
<th>All Cohorts</th>
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<tr>
<td>$\alpha/\beta=3$</td>
<td>45 Gy in 25 fx</td>
<td>44 Gy in 20 fx</td>
<td>43.2 Gy in 18 fx</td>
<td>42.56 Gy in 16 fx</td>
<td></td>
</tr>
<tr>
<td>Bowel space</td>
<td>V40Gy&lt;30%</td>
<td>V36Gy&lt;30%</td>
<td>V36Gy&lt;30%</td>
<td>V35Gy≤30% Variation</td>
<td>Max (0.03cc) ≤105% of Rx</td>
</tr>
</tbody>
</table>
### Treatment and Image Verification

Patients should be treated in the simulation position and with a full bladder. Image guidance using orthogonal films should be performed daily for verification of the treatment position. The use of cone-beam CT is highly recommended to evaluate for bladder filling and target motion. These films should be available for review if requested.

### Brachytherapy

Patients may be treated with HDR vaginal brachytherapy boost at the discretion of the treating radiation oncologist. Iridium sources are to be used for intracavitary application with vaginal dome and cylinders with an afterloader applicator system. Dose fractionation regimens are at the discretion of the treating physician but the following are recommended treatment schedules as per the American Brachytherapy Society (ABS) guidelines for brachytherapy after 45 Gy of external beam radiation: 5-6 Gy/fraction x3 fractions, prescribed to the vaginal surface (24). The largest possible vaginal dome cylinder diameter should be selected that fits into the vaginal apex. The length of vagina treated is at the discretion of the treating physician, but the introitus should not be included within the target. In general, brachytherapy should be completed as soon as possible following completion of external beam radiation, ideally within 2 weeks. A report on the source specifications, strengths, spacing relative to the applicators, size of applicator, dwell times and dwell positions should be made for each treatment plan.

Vaginal surface dose may be calculated at the vaginal surface lateral to the midpoint of the surface of the ovoid or cylinder. The dose at the apex of the cylinder should be calculated to be

<table>
<thead>
<tr>
<th>Region</th>
<th>V10Gy&lt;90%</th>
<th>V10Gy&lt;90%</th>
<th>V10Gy&lt;90%</th>
<th>V10Gy&lt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(optional)</td>
<td>V10Gy&lt;90%</td>
<td>V10Gy&lt;90%</td>
<td>V10Gy&lt;90%</td>
<td>V10Gy&lt;90%</td>
</tr>
<tr>
<td></td>
<td>Max (0.03cc)</td>
<td>≤105% of Rx dose</td>
<td>Variation Acceptable:</td>
<td>≤107% of Rx dose</td>
</tr>
<tr>
<td></td>
<td>Max (0.03cc)</td>
<td>≤105% of Rx dose</td>
<td>Variation Acceptable:</td>
<td>≤107% of Rx dose</td>
</tr>
</tbody>
</table>

**fx= fractions**

---

**Table:**

<table>
<thead>
<tr>
<th>Region</th>
<th>V40Gy&lt;80%</th>
<th>V36Gy&lt;80%</th>
<th>V36Gy&lt;80%</th>
<th>V35Gy≤80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>V40Gy&lt;80%</td>
<td>V36Gy&lt;80%</td>
<td>V36Gy&lt;80%</td>
<td>V35Gy≤80%</td>
</tr>
<tr>
<td></td>
<td>≤105% of Rx dose</td>
<td>≤107% of Rx dose</td>
<td>V35Gy&lt;100%</td>
<td>Variation acceptable:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>V45Gy&lt;70%</th>
<th>V42Gy&lt;70%</th>
<th>V40Gy&lt;70%</th>
<th>V40Gy≤35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>V45Gy&lt;70%</td>
<td>V42Gy&lt;70%</td>
<td>V40Gy&lt;70%</td>
<td>V40Gy≤35%</td>
</tr>
<tr>
<td></td>
<td>≤105% of Rx dose</td>
<td>≤107% of Rx dose</td>
<td>V40Gy&lt;70%</td>
<td>Variation acceptable:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>V10Gy&lt;90%</th>
<th>V10Gy&lt;90%</th>
<th>V10Gy&lt;90%</th>
<th>V10Gy&lt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow (optional)</td>
<td>V10Gy&lt;90%</td>
<td>V10Gy&lt;90%</td>
<td>V10Gy&lt;90%</td>
<td>V10Gy≤90%</td>
</tr>
<tr>
<td></td>
<td>Max (0.03cc)</td>
<td>≤105% of Rx dose</td>
<td>≤107% of Rx dose</td>
<td>Variation acceptable:</td>
</tr>
</tbody>
</table>

---

16
as close as possible (within +/- 25%) to the lateral vaginal surface dose. Dose points 0.5 cm posterior and anterior to the cylinder should be calculated.

8.2 Duration of External Beam Radiation Treatment

In the absence of treatment delays due to adverse events, external beam radiation treatment may continue for 3-5 weeks or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating investigator.
- Patient refusal
- Lost to follow-up/Non-compliance
- Study termination

8.3 Duration of Follow Up

Patients will be followed up to 2 years after completion of external beam radiation treatment on study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Subjects will be followed for AEs/SAEs for 30 days after their last day of radiation (See Appendix A – Study Calendar for follow-up schedule).

8.4 Subject Withdrawal and Criteria for Removal from Study

Subjects will not be remunerated for their participation in this study. Subjects will be withdrawn from the study for any of the following reasons: the subject wishes to withdraw, or death. The investigator will maintain previously collected data.

8.4.1 Method of Withdrawing Subjects

- Method of withdrawing subjects following completion of study: Subjects will be considered withdrawn from the study upon verbal/written notification to the principal investigator of their wish to withdraw from the study.
- Method of withdrawing subjects before completion: Subjects may terminate their participation in the study at any time, for any reason, by informing the principal investigator through verbal or written means.
9. ADVERSE EVENTS:

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The characteristics of an observed AE (Section 9.1) will determine whether the event requires expedited reporting in addition to routine reporting.

9.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 5. A copy of the CTCAE Version 5 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite (5) – The AE is clearly related to the study treatment.
  - Probable (4) – The AE is likely related to the study treatment.
  - Possible (3) – The AE may be related to the study treatment.
  - Unlikely (2) – The AE is doubtfully related to the study treatment.
  - Unrelated (1) – The AE is clearly NOT related to the study treatment.

9.2 Adverse Event Definitions

9.2.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient’s physical examination, laboratory results, and/or signs and symptoms, and review of the patient’s own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from the study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 30 days after last day of radiation (See Study Calendar – Appendix A).
9.2.2 Serious Adverse Events

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) Life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred at greater severity)
3) Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.3 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol, informed consent, investigator brochure, or FDA-approved package insert. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug’s pharmacological properties but has not been previously observed with this specific investigational agent.

9.3 Adverse Event Reporting Requirements

9.3.1 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported using the MedWatch Form discussed below must also be reported in routine study data submissions.**

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Study Lead Principal Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5 and their causal relationship.

9.3.2 MedWatch

This study will use MedWatch for SAE reporting.

MedWatch forms and information: [http://www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

The minimum information required for SAE reporting includes identity of investigator, site number, patient number, an event description, SAE term(s), onset date, the reason why the event
is considered to be serious (ie the seriousness criteria) and the investigator’s assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE.

When reporting serious adverse events, the following additional points should be noted:

• When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.

• Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then Death may be used as an event term and should be reported as “death, cause unknown”. If an autopsy was performed, the autopsy report should be provided.

• While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
  • Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair.
  • Procedures for pre-existing conditions that have not worsened after initiation of treatment.
  • Pre-specified study hospitalizations for observation.
  • Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics.
  • SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
  • All serious unexpected adverse drug reactions (unexpected, related SAEs) must be reported to the FDA by the investigator as required by 21 CFR 312.32.
  • These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form).

9.3.3 Reporting Requirements for Participating Sites

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined in Section 9.2.2) and all adverse events that have been specified to require expedited reporting occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Principal Investigator, the University of Chicago CRA and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be
reported to the CCTO by 12 p.m. (noon) the next business day. Reports should be made using the MedWatch Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhasellICRA@medicinebsd.uchicago.edu
Phone: 773-834-1746
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

- The following information is required when calling in the event:
  - Caller’s Name and Telephone Number
  - Patient Initials
  - Patient Medical Record Number
  - IRB Protocol Number
  - PI of Study
  - Attending Physician
  - Date of Event
  - Description of Event (including grade of the event and attribution of the event and if the event required hospitalization)

Participating sites should also report all serious adverse events to their own IRB according to their institution’s policies and procedures.

9.3.4 Reporting Requirements for University of Chicago Comprehensive Cancer Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed MedWatch Form 3500A will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.
10. DATA SUBMISSION

10.1 REDCap for Data Reporting

Data reporting will be performed utilizing the REDCap electronic data capture system. The University of Chicago PCCC Team will provide you with the applicable user registration information.

All required data must be recorded in the REDCap database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the MedWatch Form within 24 hours of the site’s knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseICRA@medicine.bsd.uchicago.edu and qaccto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel.

Each screened (consented) patient is to be entered into REDCap within 48 hours of patient registration. The site will prepare and maintain adequate and accurate source documents. Source records are original documents, data, and records (e.g. medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

10.2 Data Sharing and PHI

Each site will register the patient with an assigned study ID. Any data shared (as authorized by Dr. Son or the Site PI) with participating sites will be labeled with an identification number. Apart from dates of diagnosis, treatments, and recurrences, no PHI will be shared in data. Data analysis will be conducted by University of Chicago and University of Utah.

11. STATISTICAL CONSIDERATIONS

11.1 Phase I

The maximum tolerated dose schedule (MTD) is defined in this study as the dose-per-fraction regimen that is associated with an CTCAE gr 3+ GI/GU toxicity rate of <=10%. This is based on results from the TIME-C randomized trial in which the non-hematologic grade 3+ toxicity rate was 7-8% (5).

CTCAE GI toxicity will be determined using the v5.0 domains of diarrhea and proctitis (whichever is maximum). CTCAE GU toxicity will be determined using the domains of urinary frequency, urinary incontinence, and urinary urgency (whichever is maximum). Time point of evaluation is on the last day of radiation.

We will employ the keyboard design to find the MTD (Yan, Mandrekar, and Yuan 2017). The
keyboard design is a novel Bayesian interval design that can be implemented in a simple way similar to the traditional 3+3 design but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM). The keyboard design provides an upgrade to the modified toxicity probability interval (mTPI) design, with a substantially lower risk of overdosing and a better precision to identify the MTD.

The target toxicity rate for the MTD is $\phi = 0.1$, with the acceptable toxicity probability interval of $(0.05, 0.15)$. The maximum sample size is 36. We will enroll and treat patients in cohorts of size 3. The keyboard design is described as follows:

a) Patients in the first cohort are treated at dose level 1.

b) To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 4. “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

c) These steps will be repeated until the maximum sample size of 9 patients per dose-level is reached.

Table 4. Dose escalation/de-escalation rule for the keyboard design

<table>
<thead>
<tr>
<th>Number of Patients treated</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalate if # of DLT &lt;=</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deescalate if # of DLT &gt;=</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Eliminate if # of DLT &gt;=</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

After the trial is completed, the MTD will be selected based on isotonic regression as specified in Yan, Mandrekar and Yuan (2017). This computation is implemented by the shiny app “Keyboard” available at [http://www.trialdesign.org](http://www.trialdesign.org). Specifically, we will select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, we will select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

**Operating Characteristics:**

Table 5 shows the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app “Keyboard” available at [http://www.trialdesign.org](http://www.trialdesign.org). The operating characteristics show that the design selects the true MTD, if any, with high probability and
allocates more patients to the dose levels with the DLT rate closest to the target of 0.1.

Table 5. Operating characteristics of the keyboard design

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
<th>Number of Patients</th>
<th>% Early Stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td>True DLT rate</td>
<td>0.1</td>
<td>0.27</td>
<td>0.35</td>
<td>0.44</td>
<td>67.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Selection %</td>
<td>7.08</td>
<td>6.4</td>
<td>1.9</td>
<td>0.43</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td># Pts treated</td>
<td>0.04</td>
<td>0.1</td>
<td>0.25</td>
<td>0.47</td>
<td>18.9</td>
<td>61.3</td>
</tr>
<tr>
<td>True DLT rate</td>
<td>3.13</td>
<td>8.35</td>
<td>4.85</td>
<td>1.18</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>Selection %</td>
<td>0.01</td>
<td>0.05</td>
<td>0.1</td>
<td>0.27</td>
<td>4.9</td>
<td>29.3</td>
</tr>
<tr>
<td># Pts treated</td>
<td>1.27</td>
<td>6.2</td>
<td>7.04</td>
<td>4.06</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>True DLT rate</td>
<td>0.02</td>
<td>0.04</td>
<td>0.06</td>
<td>0.1</td>
<td>3.5</td>
<td>15.4</td>
</tr>
<tr>
<td>Selection %</td>
<td>0.9</td>
<td>4.76</td>
<td>5.33</td>
<td>6.39</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td># Pts treated</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11.2 Phase II

Once the MTD is determined, the study will proceed to the phase II portion, where additional patients will be enrolled to the MTD cohort (goal 64 patients total including patients treated at the MTD from the phase I portion).

A. PRIMARY OBJECTIVE:

To be considered evaluable for primary analysis, an eligible patient must have completed radiation treatment and completed EPIC bowel domain questionnaire at baseline and at the completion of treatment.

EPIC was originally created to evaluate patient-reported outcomes in men with prostate cancer but has since been validated in gynecologic cancer patients undergoing radiation (25). The EPIC score will be calculated for each domain at each study time point specified in the schema. Higher scores indicate greater functioning (i.e., less symptoms). Changes in these scores over time will be analyzed in relation to baseline, pre-radiation scores.

The primary endpoint is change in acute GI toxicity from baseline to end-of-treatment as
measured by the EPIC bowel domain. We will administer the same version of EPIC as administered in the RTOG 1203/TIME-C trial. It focuses on quality-of-life experience in the past 7 days (as compared to the past 4 weeks) on the bowel and urinary domains. The overall feasibility endpoint will be the percent of eligible patients who begin treatment that meet evaluability criteria for the primary analysis.

**Sample size determination**

This trial will enroll 64 patients with the end goal of enrolling at least 57 evaluable patients. We anticipate that 90% of patients will be considered evaluable. If at the end of enrolling 64 patients we have not achieved 57 evaluable patients, and if the study is deemed feasible (i.e. achieving at least 80% of eligible patients who receive at least one treatment that are considered evaluable), we will submit an amendment for an increased sample size to achieve 57 evaluable patients.

The trial will be successful if at least 80% of eligible patients who begin treatment are evaluable (criteria for feasibility) and if we can establish hypofractionated radiotherapy to be non-inferior to standard IMRT in terms of historical acute toxicity (as measured by EPIC Bowel score at 3 weeks). In the RTOG 1203/TIME-C trial, patients of the same patient population who received IMRT had an end of RT week EPIC Bowel decrease of -14 (95% Confidence Interval extracted from Figure 2A: -11.5, -16.5; this corresponds to a standard deviation of 13. We have set the non-inferiority margin at -18.5 which is 1/3 of a standard deviation below -14, and it is superior to the average end of RT Bowel Score observed in the RTOG 1203/TIME-C study (-18.6).

Based on a single sample, one-sided t-test with alpha of 0.05 and a change in EPIC Bowel score equivalent to IMRT, the trial is 80% powered to establish hypofractionation as non-inferior to standard IMRT within 1/3 of a standard deviation. We are still 77% powered if, in our study, the EPIC bowel standard deviation is 5% greater than observed in the RTOG 1203/TIME-C trial. Power will further increase by adjusting for baseline EPIC bowel score, site, stage, and ECOG status (or other covariates of interest).

The benchmark of 80% evaluable patients for establishing feasibility was set based upon RTOG 1203/TIME-C which increased the anticipated sample size by 20% in a conservative anticipation of 80% completion rate. They observed an 88.1% completion rate at 3 weeks among patients receiving IMRT or standard treatment.

**Statistical Analyses**

Primary endpoint: We will calculate a 90% Confidence Interval for change in RT EPIC Bowel Score from an ordinary least squares regression, adjusting for baseline EPIC bowel score, stage, and ECOG status (or other covariates of interest). All evaluable patients will be included. Non-inferiority will be declared if the interval excludes and is greater than -18.5.

Feasibility will be established if at least 80% of eligible patients who begin treatment are deemed evaluable. This will be assessed on the initially enrolled 64 patients even though additional patients may be enrolled.
B. SECONDARY OBJECTIVES

For acute change (from baseline to end of treatment), 1 year change from baseline, and change over time:

1. To estimate impact upon urinary toxicity
2. To estimate impact upon gastrointestinal toxicity
3. To assess quality of life following treatment
4. To quantify financial toxicity following treatment
5. To assess satisfaction with decision-making following treatment

All secondary analyses will be assessed upon patients considered evaluable for the primary analysis.

We will use the EPIC urinary domain and CTCAE GU toxicity as the outcome to assess urinary toxicity; Patient Reported Outcomes (PRO-CTCAE), CTCAE GI toxicity, and EPIC Composite outcomes to assess gastrointestinal toxicity; Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) to assess quality of life. Financial toxicity will be evaluated by FACIT-COST and satisfaction with decision-making will be evaluated by the Decision Regret Scale. Information on FACIT-COST can be found at: https://www.facit.org/measures/FACIT-COST

For consistency with the primary analysis, we will report 90% confidence intervals for each secondary endpoint following an ordinary least square regression adjusting for baseline toxicity (for toxicity outcomes), site, stage, and ECOG status. We will assess change in endpoints over time using a linear mixed effects model with time fit non-linearly using restricted cubic splines, including afore mentioned clinical covariates, and a patient random effect.

CTCAE GI toxicity will be determined using the v5.0 domains of diarrhea and proctitis (whichever is maximum). CTCAE GU toxicity will be determined using the domains of urinary frequency, urinary incontinence, and urinary urgency (whichever is maximum). Each follow-up time period will be evaluated for CTCAE GI and GU maximum toxicity and tabulated by grade of toxicity. Acute toxicity is defined as the time period during and within 1-month post-radiation.

The PRO-CTCAE was developed to characterize the frequency and severity of treatment toxicities and the extent to which these toxicities interfere with daily activities. Responses are provided on a 5-point Likert scale, and the recall period is the past 7 days. For this study, 5 items related to pain in the abdomen (severity and interference), diarrhea (frequency), and fecal incontinence (frequency and interference) are used. We will tabulate the frequency of each response for each item.

The FACT-General is a validated, 27-item measure of QOL in patients with cancer using a 7-day recall period (26). The 27 items on the FACT-General are divided into 4 subscales, for physical, functional, social, and emotional well-being. A total QOL score and scores for each of the 4 subscales can be calculated. The cervix additional concerns subscale is a 15-item assessment that was developed for patients with cervix cancer but is also relevant to patients with endometrial...
cancer. For the FACT-Cx, which consists of the FACT-General questions plus the cervix additional concerns subscale, a higher score indicates better QOL. All items in a subscale are added to obtain subscale totals, with certain items requiring reverse scoring. The Trial Outcome Index is a composite score of the 3 subscales of FACT-Cx that are directly impacted by disease and treatment: physical well-being, functional well-being, and additional concerns. The FACT-Cx requires at least 50% of the items to be completed to obtain subscale scores while the overall response rate of the FACT-Cx including the FACT-G must be greater than 80%. Since patients with cervical and endometrial cancer are treated the same way post-operatively and no differences in sexual functioning due to treatment were expected, it was felt that the FACT-Cx would provide valuable information not only for patients with cervical cancer but also for patients with endometrial cancer.

FACIT-COST is a validated patient-reported outcome measure that describes the financial distress experienced by cancer patients (27). Responses are tabulated based on a 5-point Likert type scale with a recall period of 7 days. A higher score represents greater financial well-being. We will describe the financial distress of patients, including change over time.

The Decision Regret Scale is a validated measure of “distress or remorse after a [healthcare] decision” (28). Responses are tabulated based on a 5-point Likert type scale. A score of 100 represents high regret, while a score of 0 represents no regret. We will characterize the measure of regret experienced in the study patients over time.

C. EXPLORATORY OBJECTIVES:

1. To determine rate of pelvic control at 2 years post-radiation

Crude rates and cumulative incidence of first failure and any failure (pelvic failure, para-aortic, or distant) will be calculated. Pelvic failure is defined as clinical or radiographic evidence of recurrent disease within the irradiated pelvis (pelvic lymph nodes, vaginal cuff/parametria) as determined by the treating physician(s). Peritoneal metastases will not be considered a pelvic failure.

12. STUDY MANAGEMENT AND REGULATORY AFFAIRS

12.1 Multicenter Guidelines

The specific responsibilities of the Study Lead Principal Investigator and the Coordinating Center are presented in Appendix B. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

The Study Lead PI/Coordinating Center is responsible for distributing all official protocols, amendments, and IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

12.2 Institutional Review Board (IRB) Approval and Consent
Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the treating investigator should comply with the applicable regulatory requirements and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the treating investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient’s participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

12.3 Required Documentation

Prior to the selection of a study site that is not a full member of the Personalized Cancer Care Consortium, the audit and trial oversight processes for the site must be reviewed and approved by the UC CCC Clinical Research Advisory Committee.

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center. All documents must be sent to CCTO prior to study activation.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the Study Lead Principal Investigator and any sub-investigators who will be involved in the study.
- The Site Investigator’s signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance. In the latter case, an investigator signature page should be added to the protocol.
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

12.4 Data and Safety Monitoring

This study will be remotely monitored by the University of Chicago PCCC Monitoring Staff in accordance with the University of Chicago, Section of Hematology/Oncology standard operating
procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site’s Study Lead Principal Investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhasellCRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects’ willingness to participate in the study must be reported within 7 days. Please contact the University of Chicago CRA (PhasellCRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

12.5 Auditing

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan. For institutions
who are formal members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

12.6 Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the UCCCC regulatory contact or their designee will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically.

For external sites utilizing a local IRB:

- Upon receipt of the amendment documents the affiliate institution is expected to submit the amendment documents to their local IRB for approval as soon as possible.

- A copy of the IRB approval letter and approved consent document(s) should be sent to the UCCCC regulatory contract as soon as possible.
  - IRB approval should be obtained within 90 calendar days of the document distribution date. If approval cannot be obtained within this window, the reason for the delay should be provided to the designated UCCCC regulatory contact.

For external sites utilizing the BSD IRB as the IRB of record:

- Upon receipt of the amendment documents the affiliate institution is expected to implement the revised documents as soon as possible and no later than 30 calendar days from the document distribution date.
  - The date of local implementation should be documented in the local study records and provided upon request at time of monitoring and/or auditing.

- No changes to the provided documents may be made at the local site without prior approval from the BSD IRB.
12.7 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions’ IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution’s IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

12.8 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Study Lead Principal Investigator/treating Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.9 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

12.10 Financial Considerations

There will be no financial renumeration or cost to the subject for participation in the study.

12.11 Conflict of Interests

The investigators state that they have no conflicts of interest with regard to the conduct of this research.
12.12 Publication

Results of this research will be published by the principal investigator and/or co-investigators. Results are expected to be submitted approximately 5 years after initiation of the study. The investigators and study personnel will be involved in compiling and analyzing results for publication.

REFERENCES


## APPENDIX A  STUDY CALENDAR (SCHEMA)

<table>
<thead>
<tr>
<th>Baseline*</th>
<th>External Beam Radiation Therapy**</th>
<th>Post-Treatment Follow Up***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk1 Wk2 Wk3 (Wk4) (Wk5)</td>
<td>Last day EBRT**</td>
</tr>
<tr>
<td>**</td>
<td>1m 3m 6m 12m 18m 24m</td>
<td></td>
</tr>
</tbody>
</table>

| Informed Consent | X |
| Radiation Therapy | X X X (X) (X) |
| Clinical Assessment§ | X X X X (X) (X) X |
| Physician Toxicity Assessment* | X |
| Patient questionnaire^ | X |

"Wk" = week. "1m" = 1 month post-treatment, etc. EBRT=external beam radiation

§Clinical Assessment as is considered standard of care.

*CTCAE

^EPIC, PRO-CTCAE, FACT,FACIT-COST, Decision Regret Scale. Decision Regret Scale will not be administered at baseline.

** +/- 2 days

† Baseline clinical and toxicity assessments should be performed within 28 days prior to the start of radiation.

***External beam radiation will be 3-5 weeks as determined by patient’s dose-fraction level.

+++Time from last day of EBRT. Study evaluations at 1m follow up should occur within +/-15 days. Evaluation for subsequent follow-ups should occur within +/- 30 days. Clinical assessments can be from any clinical oncology provider.
APPENDIX B  MULTICENTER GUIDELINES

The Protocol Chair, Dr. Christina Son, is responsible for performing the following tasks:
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments. **There will be only one version of the protocol, and each participating institution will use that document.** The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- Assuring that all participating institutions are using the correct version of the protocol.
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs).
- Reviewing data from all sites.
- Acting as the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies.
- All reporting requirements are the responsibility of the Protocol Chair.
- The timely review of Adverse Events (AE) to assure safety of the patients.
- The review of and timely submission of data for study analysis.

The Lead Center, University of Chicago, is responsible for performing the following tasks:
- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site.
- Maintaining copies of IRB approvals from each site.
- Implementing central patient registration.
- Prepare appropriate data as required for review by the Protocol Chair.
- Establishing procedures for documentation, reporting and submitting of AEs and SAEs to the Protocol Chair and all other applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating sites are responsible for performing the following tasks:
- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP)
- Submitting data to the Lead Center.
- Registering all patients with the Lead Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Lead Center.
- Collecting and submitting data according to the schedule specified by the protocol.
### APPENDIX C  ECOG PERFORMANCE STATUS CRITERIA

<table>
<thead>
<tr>
<th>ECOG Performance Status Scale</th>
<th>Karnofsky Performance Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
<td><strong>Descriptions</strong></td>
</tr>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;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.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>