De-escalated Conformal Radiation Expedited Sequentially with Chemotherapy for Endometrial Cancer (DeCRESCEndo)

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Protocol Revision History

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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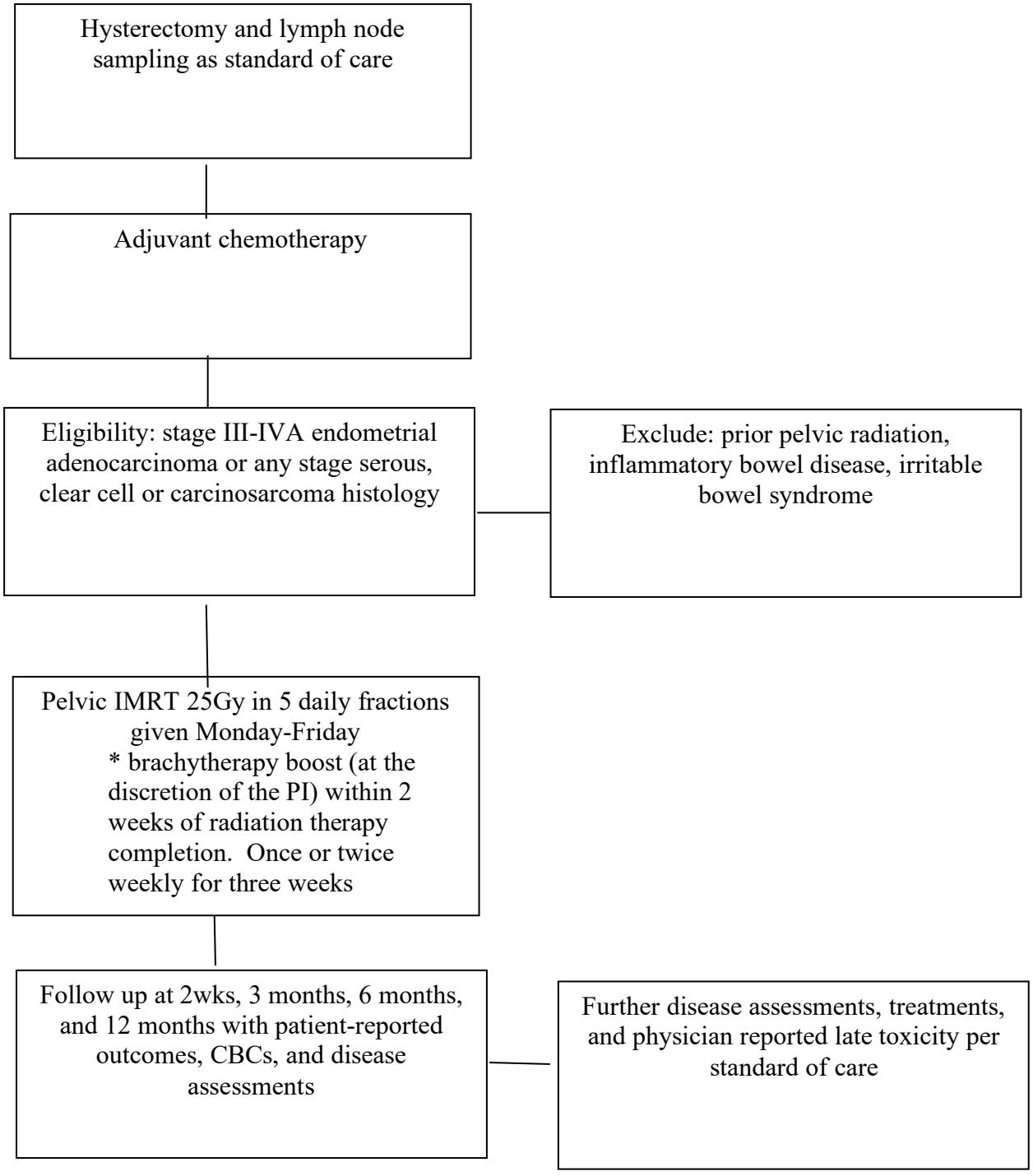
PROTOCOL SUMMARY

Title:	De-escalated Conformal Radiation Expedited Sequentially with Chemotherapy for Endometrial Cancer (DeCRESCEndo)
Study Description:	The goal of this study is to evaluate short course radiation in the post-operative female pelvis after radical hysterectomy in stage III-IVA endometrial adenocarcinoma patients, or any stage patients with uterine serous, clear cell, or carcinosarcoma histology. We hypothesize that short course pelvic radiation will have an acute and late grade 3-4 toxicity rate < 10%, and patients will benefit from both convenient and effective loco-regional control comparable to the traditional 5-6 weeks of radiation.
Objectives:	Primary Objective: To prospectively evaluate hematologic, gastrointestinal (GI), and genitourinary (GU) toxicity from ultra-hypofractionated radiation to the pelvis after hysterectomy for endometrial cancer. Secondary Objectives: 1. To evaluate the effect of ultra-hypofractionated radiation to the pelvis after hysterectomy on patient-reported urinary toxicity and GI toxicity 2. To assess quality of life before and after ultra-hypofractionated radiation to the pelvis after hysterectomy 3. To determine the disease response to ultra-hypofractionated radiation to the pelvis after hysterectomy.
Endpoints:	Primary Endpoint: Acute and late GI, GU, and hematologic toxicity as defined by CTCAE v 5.0 Secondary Endpoints: 1. Change in patient-reported urinary and GI toxicity with PRO-CTCAE and bowel/bladder domains of EPIC-26 2. Quality of life measured with the FACT-En 3. Locoregional control, distant control, disease-free survival, overall survival
Study Population:	This study will enroll 25 adult women with stage III-IVA endometrial cancer or any stage uterine serous or carcinosarcoma histology who will be or have been treated with radical hysterectomy.
Phase:	N/A
Description of Sites / Facilities Enrolling:	This study will be open at the Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	Consenting and eligible patients will receive a hypofractionated course of radiation to the pelvis of 5 Gy x 5 fractions (total of 25 Gy) with elective simultaneous boost to any suspicious lymph node or residual disease to 30Gy after completion of chemotherapy.

Study Duration:	24 months for enrollment + 1 to 4 weeks of treatment + 12 months of follow-up + 12 months for analysis = 49-52 months
Participant Duration:	Approximately 12 months

SCHEMA


Hysterectomy and lymph node sampling as standard of care
Adjuvant chemotherapy
Eligibility: stage III-IVA endometrial adenocarcinoma or any stage serous, clear cell or carcinosarcoma histology
Exclude: prior pelvic radiation, inflammatory bowel disease, irritable bowel syndrome
Pelvic IMRT 25Gy in 5 daily fractions given Monday-Friday
* brachytherapy boost (at the discretion of the PI) within 2 weeks of radiation therapy completion. Once or twice weekly for three weeks
Follow up at 2wks, 3 months, 6 months, and 12 months with patient-reported outcomes, CBCs, and disease assessments
Further disease assessments, treatments, and physician reported late toxicity per standard of care

SCHEDULE OF ACTIVITIES

	Screening[1]	**Pre Treatment[1]**	**IMRT**	**Within two weeks of IMRT completion**	**2 wks post-RT[3]**	**3 mos post-RT[2]**	**6 mos post-RT[2]**	**12 mos post-RT[2]**
Informed consent	X							
Physical exam with pelvic exam		X			X	X	X	X
CBC w/diff		X			X	X	X	X
CT C/A/P	X						X	X
Hypofractionated RT			5 fractions of 5 Gy each[4]					
Brachytherapy boost[5]				x				
PRO-CTCAE		X			X	X		
FACT-En		X			X	X	X	X
EPIC bowel and urinary domains		X			X	X	X	X
AE assessment		X	X		X	X	X	X

1. Enrollment must occur no more than one year after radical hysterectomy. Pre treatment procedures must occur no more than 4 weeks prior to start date of IMRT. Baseline CT scan may occur up to 3 months prior to start date of IMRT. The informed consent discussion can occur at any point during SOC adjuvant treatment regimen or follow, or at initial consult.
2. +/- 2 weeks
3. +/- 1 week
4. Over the course of 1 to 2 weeks
5. Administered at the discretion of the treating physician

1.0 INTRODUCTION

1.1 Study Rationale

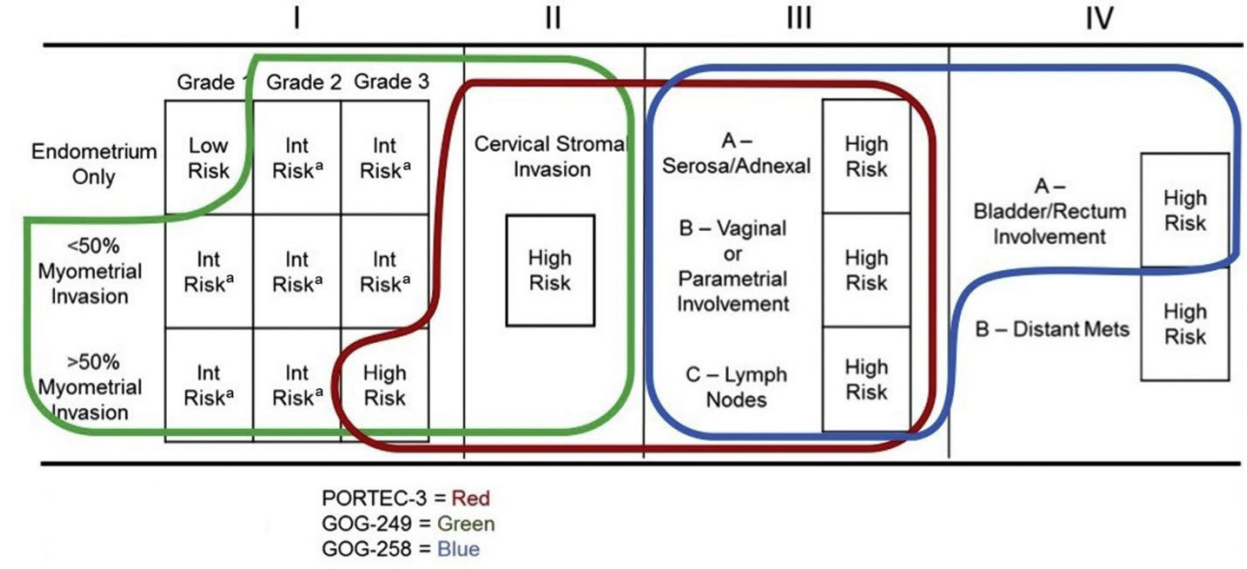
A short course of radiation to the pelvis in sequence with doublet chemotherapy for women with endometrial cancer who are status post-hysterectomy could accomplish two goals: it could reduce the risk of recurrence by sterilizing micrometastatic disease and it could reduce acute and late hematologic toxicity.

1.2 Background

1.2.1 Endometrial Cancer

Endometrial cancer is the 4th most common cancer diagnosed in women in the United States, with an estimated 62,000 new cases in 2019 [1]. Hysterectomy with lymph node sampling is the definitive surgical management. For patients with pathologic intermediate-high risk features (Figure 1), adjuvant pelvic radiation of 50Gy fractionated daily over 5-6 weeks has been shown to significantly reduce local-regional recurrence when compared to chemotherapy alone (11% vs 20%, respectively) or chemotherapy with vaginal cuff brachytherapy (4% vs. 9%, respectively) [2, 3].

Adding systemic therapy to pelvic radiation has been shown to be important in high risk patients. Chemoradiotherapy improved 5 year distant control, failure free survival, and overall survival (OS) compared to pelvic radiation alone in PORTEC-3 [4]. In GOG-258, 6 months of platinum-based chemotherapy alone had the same 5-year relapse-free survival as chemoradiation followed by 4 months of chemotherapy (58% vs 59%, respectively) [3].



Based on inclusion criteria for PORTEC-3, GOG-249and GOG-258.

Figure 1: Eligibility criteria of recent clinical trials enrolling intermediate and high risk patients for adjuvant trials randomizing to vaginal brachytherapy with chemotherapy vs. pelvic radiation alone (GOG-249), cisplatin-based chemoradiation to the pelvis followed by 4 cycles of carboplatin/Taxol vs. pelvic radiation alone (PORTEC-3), and cisplatin-based chemoradiation to the pelvis followed by 4 cycles of carboplatin/Taxol vs. 6 cycles of carboplatin/Taxol alone (GOG-258). Figure from Suneja and Viswanathan [5].

In both GOG-258 and PORTEC-3, chemotherapy intensity was reduced during the 5-6 weeks of radiation to decrease the chance of toxicity. Acute grade 3 or higher toxicity occurred in about 60% of patients with chemoradiation [3, 6]. Compared to chemotherapy alone, chemoradiation had more GI toxicity but less hematologic toxicity [3]. However, only 75% of women completed all four cycles of doublet carboplatin/Taxol after chemoradiation in GOG-258, while 85% of women received all six cycles of carboplatin/Taxol in the chemotherapy alone arm [3]. Delaying and/or reducing the total amount of doublet chemotherapy could explain the increased rate of distant failure (27% vs 21%) in the chemoradiation arm.

Our institution has given 5-6 weeks of radiation concurrently with doublet chemotherapy. In a series of 51 patients treated in this manner, 34 (67%) experienced acute grade 3-4 toxicity and 16 (31%) required a chemotherapy dose reduction mainly due to hematologic toxicity; 6 (12%) experienced late grade 3-4 GI or GU toxicity [9].

Alternatively, some investigators have favored a chemotherapy-first approach, sequencing 5-6 weeks of radiation in the middle of chemotherapy ("sandwich chemo") or at the end after six cycles of platinum/Taxol. This has been done with acceptable rates of acute toxicity in selected patients, though results are limited to small retrospective series with limited follow up [7, 8]. This also lengthens the patient's overall treatment time by a couple months.

1.2.2 Hypofractionated Radiation to the Pelvis

A short or hypofractionated course of radiation to the pelvis in sequence with doublet chemotherapy could accomplish two goals. The local-regional risk of recurrence is on the order of 20% without pelvic radiation [3], but sterilization of micrometastatic disease may be possible with just 5 days radiation. Hypofractionation has also been shown to reduce acute and long-term hematologic toxicity [10, 11], which may allow more patients to complete radiation treatment without needing blood transfusions or hospitalizations.

Currently, the data to support a short course of radiation to the pelvis have come from rectal cancer studies. The Australian, Polish, and Swedish approach of treating the pelvis to 25Gy in 5 fractions prior to surgery for locally advanced rectal cancer has yielded equivalent pelvic tumor control as 50Gy in 25-28 fractions with <10% late grade 3-4 complications in three randomized studies [12–14]. Notably, the surgery for rectal cancer typically does not involve a pelvic lymph node dissection, suggesting the hypofractionated dose adequately sterilizes nodal disease in the pelvis. Washington University in Saint Louis was an early adopter of the short

course rectal treatment paradigm in the United States [15], and also has conducted a phase 2 trial sequencing chemotherapy after radiation for total neoadjuvant therapy [16]. Earlier delivery of chemotherapy was shown to improve distant-metastasis free survival in a matched-pair analysis comparing total neoadjuvant therapy with the more popular standard of care in the US (5-6 weeks of preoperative chemoradiation followed by surgery and further multi-agent chemotherapy) [17].

Post-operative short course radiation has also been attempted in prostate cancer patients. In a recently published phase 1 trial, 12 patients received 35Gy in 5 fractions to the prostate fossa after radical prostatectomy with no acute grade 3 or higher gastrointestinal (GI) or genitourinary (GU) toxicity [18]. The median follow up of 14 months was not long enough to evaluate for late toxicities. In another phase 1 trial, 15 patients received dose escalated radiation up to 45Gy in 5 fractions to the prostate fossa [19]. There were no late grade 3 or higher GI toxicities and 2/15 (13%) late grade 3 GU toxicities. Dose constraints for the rectum and bladder in DeCRESCEndo will be derived from these two studies.

1.2.3 Correlative Studies Background

Patient reported outcomes (PROs) and quality of life assessments will be done to supplement physician-assessed treatment toxicity. The assessments will mirror those used and validated in RTOG 1203, a randomized phase 3 trial comparing IMRT to large field pelvic radiation. The change in patient-reported GI and urinary toxicity from baseline will be measured with the bowel and urinary domain of the Expanded Prostate Cancer Index Composite (EPIC). Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) and quality of life measured with the Functional Outcome of Cancer Therapy- Endometrial cancer (FACT-EN) instruments will also be used.

1.3 Study Design

In this study, women with stage III-IVA endometrial adenocarcinoma who are post-hysterectomy will receive ultra-hypofractionated radiation therapy of five fractions (5 Gy each) and elective simultaneous boost to any suspicious lymph node or residual disease to 30 Gy if needed. Patient-reported outcomes, quality of life assessments, and complete blood counts will be done at baseline and 2 weeks, 3 months, 6 months, and 12 months post-completion of radiation.

1.4 Risk/Benefit Assessment

1.4.1 Known Potential Risks

Pelvic radiation is associated with diarrhea, bladder irritation (burning on urination), rectal irritation and discomfort, fatigue, and decreased blood counts. Late reactions to radiation may include scar tissue in pelvic tissues which may lead to bowel obstruction, abnormal opening between vagina

and/or bladder and/or rectum requiring artificial bladder or colostomy, possibility of decreased ovarian function, possible decreased sexual desire and function, damage to the nerves in the pelvic area which could cause decreased motor or sensory function or decreased control of anal sphincter, and possibility of damage to hips and other bones in the pelvis leading to fracture. Some reports suggest that there is a small risk for development of a second malignant tumor in/or outside the tissues being irradiated.

1.4.2 Known Potential Benefits

Pelvic radiation is expected to reduce the loco-regional cancer recurrence rate by about 50%, which may lead to increased survival. In GOG 258, the locoregional recurrence rate was 20% vs. 11% ($p < 0.05$) for chemotherapy alone vs. chemoradiotherapy, respectively.

1.4.3 Assessment of Potential Risks and Benefits

Pelvic radiation has been well tolerated in multiple prospective clinical trials when given over 5-6 weeks after hysterectomy and lymph node dissection. This is especially true when delivered with IMRT. Shortening the radiation course to 5 days has been shown to be safe in multiple studies of pre-operative pelvic radiation for rectal cancer. We expect the acute and long-term complication of ultra-fractionated radiation to be tolerable with less than 5% late grade 3 or higher complications requiring surgical correction. Assuming a 10% absolute reduction of pelvic recurrence with pelvic radiation over chemotherapy alone, 10 patients would need to be treated and exposed to risk of additional toxicity to prevent one recurrence. This is acceptable in the opinion of the investigators.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
To prospectively evaluate hematologic, gastrointestinal (GI), and genitourinary (GU) toxicity from ultra-hypofractionated radiation to the pelvis after hysterectomy for endometrial cancer.	Acute (through Day 90) and late (Day 91 through Month 12) GI, GU, and hematologic toxicity as defined by CTCAE v 5.0	Physician-assessed toxicity of treatment will be used to assess safety
Secondary		
1. To evaluate the effect of ultra-hypofractionated radiation to the pelvis after	1. Change in patient-reported urinary toxicity and GI toxicity measured with PRO-	Patient reported toxicity and quality of life will be collected and reported as secondary outcomes.

hysterectomy on urinary toxicity and GI toxicity 2. To assess quality of life before and after ultra-hypofractionated radiation to the pelvis after hysterectomy 3. To determine the disease response to ultra-hypofractionated radiation to the pelvis after hysterectomy.	CTCAE and bowel/bladder domains of EPIC-26 2. Quality of life measured with the FACT-En 3. Locoregional control, distant control, disease-free survival, overall survival	This is a pilot study to determine the expected disease control after ultra-hypofractionated radiation to the pelvis.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed stage IIIA-IVA endometrial cancer, or any stage I-IVA where any proportion of the tumor is uterine serous, clear cell, de-differentiated, or carcinosarcoma histology

2. Must have already undergone radical hysterectomy. Hysterectomy may have occurred no more than one year prior to enrollment.

3. At least 18 years of age.

4. ECOG performance status ≤ 2 (see Appendix A)

5. Minimal bone marrow and organ function as defined below:
   a. Leukocytes ≥ 1,000 /cumm
   b. Absolute neutrophil count ≥ 500 /cumm
   c. Platelets ≥ 50,000 /cumm
   d. Hemoglobin ≥ 7g/dL

6. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Prior radiation to the pelvis.

2. Currently receiving any investigational agents.

3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, inflammatory bowel disease, or irritable bowel disease.

4. Patients with HIV are eligible unless their CD4+ T-cell counts are < 350 cells/mcL or they have a history of AIDS-defining opportunistic infection within the 12 months prior to registration. Concurrent treatment with effective ART according to DHHS treatment guidelines is recommended.

3.3 Inclusion of Women and Minorities

Women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Strategies for Recruitment and Retention

All patients eligible for trial will be referred upon near completion of their adjuvant chemotherapy for evaluation by a radiation oncologist for pelvic radiation. Our current institutional practice is to recommend pelvic IMRT over 5-6 weeks in this patient population. This trial will be offered as a shorter more convenient alternative. Based on our experience with treating rectal cancer patients with five fraction pelvis radiation, minimal side effects are experienced during radiation, so retention on trial is not expected to be difficult.

5.0 TREATMENT PLAN

5.1 Study Intervention Description

Consenting and eligible patients will receive 5 fractions of IMRT.

5.2 Study Intervention Administration

Five 5-Gy fractions of IMRT will be given to the pelvis with elective simultaneous boost to any suspicious lymph node or residual disease to 30 Gy. Patients will have fiducial markers placed at the vaginal cuff, and simulated with a vaginal dilator and no specific instruction on bladder filling. The clinical treatment volume will be contoured per our institutional standard protocol. Vessels will be contoured from the bifurcation of the aorta to the internal and external iliac vessels and end inferiorly where the circumflex vessels branch off the external iliac vessels. The obturator vessels will be included with at least a 1cm diameter brush. A 7mm expansion from the vessels excluding bone will be the nodal clinical treatment volume. The proximal 4cm of the vaginal dilator will be contoured and expanded 1cm in all directions except 0.5cm inferiorly for the vaginal cuff clinical treatment volume. A 5mm planning treatment volume expansion off both the nodal and vaginal cuff clinical treatment volume will be used. If a simultaneous boost is planned to gross residual disease, a 5mm planning treatment volume will be used to expand the gross residual disease contours. Planning goals are 95% of the planning treatment volume should receive at least 95% of the prescription dose. Organs at risk in the pelvis will have dose constraints as outlined in the table below. Daily image guided radiation with CBCT will be used to visualize the markers inside the planning treatment volume. Radiation should be delivered over the course of 1-2 weeks (allowing for weekends/holidays).

Dose Constraints for IMRT planning

Structure	Parameter	Constraint	References
Bladder	V25	< 50% (goal <25%)	Short course rectal data
	Dmax to 0.5cc	< 35Gy	Timmerman, Sampath[19], Ballas [18]
Rectum	V25	< 50% (goal <25%)	Ballas [18]
	Dmax to 0.5cc	< 35Gy	Sampath [19], Ballas[18]
Bowel (bag)	V25	< 200cc (goal <100cc)	
	Dmax to 0.5cc	< 30Gy	Oar [22], Ballas [18], Timmerman
Femoral heads	Dose to 10cc	< 30Gy	Timmerman

Patients will have a brachytherapy boost at the discretion of the treating physician. Factors considered for a brachytherapy boost include but are not limited to cervical stromal invasion, deeply invasive disease, lymph-vascular space invasion, or vaginal disease extension.

The vaginal brachytherapy boost should commence after the completion of IMRT and within two weeks ofIMRT completion. A high dose rate (HDR) vaginal boost will be delivered with a cylinder or vaginal ovoids. An active treatment length of 3-4 cm will be treated to a total dose of 18 Gy in 3 fractions of 6 Gy per fraction prescribed to the surface of the applicator. Treatments will be given at a minimum of once per week for three weeks and at most twice weekly, with 48 hours between treatments

5.3 Definitions of Evaluability

Endpoint	To be evaluable for this endpoint, a patient must have…
Acute GI, GU, and hematologic toxicities	Received at least one fraction of RT
Late GI, GU, and hematologic toxicities	Received at least one fraction of RT and been evaluated for AEs after Day 91
Change in patient-reported urinary toxicity and GI toxicity	Received at least one fraction of RT and completed both a baseline and at least one post-treatment PRO-CTCAE and/or EPIC-26 assessment
Quality of life	Received at least one fraction of RT and completed both a baseline and at least one post-treatment FACT-En questionnaire
Locoregional control	Received at least one fraction of RT and undergone at least one post-treatment disease assessment
Distant control	
Disease-free survival	
Overall survival	Received at least one fraction of RT

Patients who do not complete their IMRT within 2 weeks will be removed from the treatment and will be replaced for all endpoints.

5.4 Concomitant Therapy and Supportive Care Guidelines

Patients should be counseled about the possibility of diarrhea the week following radiation treatment and educated on how to use anti-diarrhea medications.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 5 fractions of IMRT or until one of the following criteria applies:

- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of radiation
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed at 2 weeks, 3 months, 6 months, and 12 months post-end of RT 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.

5.7 Lost to Follow-Up

A participant will be considered lost to follow-up if she fails to return for 3 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

No dose modifications are permitted.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 12 months after end of treatment. Acute toxicities are followed from start of IMRT through 90 days. Late toxicities are followed from Day 91 through 12 months after end of IMRT. All adverse events (including AEs related to adjuvant chemotherapy or surgical complications) must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Non-hematologic lab values < grade 2

Refer to the data submission schedule in Section 9 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 WU PI Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PATIENT-REPORTED OUTCOMES / QUALITY OF LIFE

The EPIC bowel and urinary domain surveys as well as the FACT-En will be completed at baseline and at 2 weeks, 3 months, 6 months, and 12 months post-completion of radiation. PRO-CTCAE relating to GI, GU, and sexual toxicity will be completed at baseline and at 2 weeks and 3 months post-completion of radiation to reduce the burden of questionnaires on patients.

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment

Follow Up Form	2 weeks, 3 months, 6 months, 12 months
QOLs	Baseline, 2 weeks, 3 months, 6 months, 12 months
Disease Assessment Form	Baseline, 6 months, 12 months
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

10.0 MEASUREMENT OF EFFECT

Locoregional recurrence is defined as histologic or radiographic evidence of cancer in the previously resected site or regional lymph nodes included in the radiated field.

Distant recurrence is defined as histologic or radiographic evidence of cancer outside of the radiated field.

Disease-free survival is defined as survival with no evidence of disease recurrence or death.

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Hypotheses

12.1.1 Primary Objective and Endpoints

Short course pelvic radiation will have an acute and late grade 3-4 toxicity rate less than 10%, and patients will benefit from both convenient and effective loco-regional control comparable to the traditional 5-6 weeks of radiation. Hematologic, gastrointestinal and genitourinary toxicity from ultra-hypofractionated radiation to the pelvis after hysterectomy for endometrial cancer will be prospectively evaluated. The acute and late gastrointestinal, genitourinary and hematologic toxicity will be defined by CTCAE v5.0. Acute toxicity timeframe is defined as 90 days from start of IMRT. Late toxicity timeframe is defined as Day 91 from start of IMRT through 12 months after end of IMRT.

12.1.2 Secondary Objectives and Endpoints

1. Evaluate the effect of ultra-hypofractionated radiation to the pelvis after hysterectomy on urinary toxicity. The change in patient urinary toxicity will be reported.
2. Evaluate the effect of ultra-hypofractionated radiation to the pelvis after hysterectomy to the pelvis after hysterectomy on gastrointestinal toxicity. The

change in gastrointestinal toxicity will be measured with PRO CTCAE and bowel/bladder domains of EPIC-26.

3. Assess quality of life before and after ultra-hypofractionated radiation to the pelvis after hysterectomy. The quality of life will be measured with the FACT-En.
4. Determine the disease response to ultra-hypofractionated radiation to the pelvis after hysterectomy. The locoregional control, distant control, disease-free survival and overall survival (the survival probability of all the enrolled patients from the beginning of the treatment to the end of the follow-up) will be computed.

12.2 Sample Size Determination

A sample size of 24 achieves 83.52% power to detect a superiority proportion (P0) of 0.3 using a one-sided exact test with a target significance level of 0.05. The actual difference to generate this power is 0.21.

12.3 Statistical Analyses

Descriptive statistics will be calculated on all variables. Frequencies will be computed for all binary/categorical variables, and continuous variables will be summarized using medians, quartiles, and ranges. Next all variables will be compared with the historical data using Chi-square tests for binary/categorical variables and t-tests for continuous variables.

ANCOVA will be used to estimate the effect of ultra-hypofractionated radiation and may include dosing regimen and baseline measurements as covariate. The effect of other covariates such as age and race will also be examined.

For repeated measures such as clinical outcomes, the generalized estimating equation (GEE) approach will be used for assessing the change over time. The GEE model will include time as the categorical variable. To model the covariance structure, the exchangeable covariance matrix will be selected initially. If the exchangeable covariance structure leads to non-convergence, Quasi-Likelihood Information Criterion (QIC) will be used to select the best covariance structure. Model based estimates of the changes from baseline and corresponding 95% confidence intervals will also be provided along with p-values for assessing statistical significance. As exploratory analyses, covariates such as baseline measures, race and age will also be considered for adjustment within GEE model.

Kaplan-Meier curves will be created to show the disease-free survival (DFS) and overall survival (OS) after applying ultra-hypofractionated radiation to the pelvis after hysterectomy. Cox Proportional Hazard model will also be generated to explain the effect of explanatory variables on the survival times.

12.4 Early Stopping Rule

The trial will stop if > 5 patients are admitted for inpatient care for GI or GU side effects

determined to be related to IMRT as determined by the PI.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Serious AND unexpected suspected adverse reaction		
Unexpected fatal or life-threatening suspected adverse reaction		
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to	Adverse events will be reported in the toxicity table in the DSM report

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
	participants or others, report summary information at the time of continuing review	which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

APPENDIX D: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
To prospectively evaluate hematologic, gastrointestinal (GI), and genitourinary (GU) toxicity from ultra-hypofractionated radiation to the pelvis after hysterectomy for endometrial cancer.	Acute = Late =
Secondary	
1. To evaluate the effect of ultra-hypofractionated radiation to the pelvis after hysterectomy on urinary toxicity and GI toxicity	
2. To assess quality of life before and after ultra-hypofractionated radiation to the pelvis after hysterectomy	
3. To determine the disease response to ultra-hypofractionated radiation to the pelvis after hysterectomy	Locoregional = Distant = DFS = OS =

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? No
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? Yes
If yes, please insert text describing early stopping rules from the protocol: The trial will stop if > 5 patients are admitted for inpatient care for GI or GU side effects determined to be related to IMRT as determined by the PI.
If yes, please provide data describing whether the stopping rules have been met:

Response							
UPN	**On tx date**	**# fx received**	**Locoregional recurrence? (Y/N/NA)**	**Date of locoregional recurrence**	**Distant recurrence? (Y/N/NA)**	**Date of distant recurrence**	**Pt replaced? (Y/N)**

Treatment Discontinuation and Survival				
UPN	**Off tx date**	**Reason off tx**	**Vital status**	**If dead, cause**