Hypofractionated Pencil-Beam Scanning Intensity-modulated Proton Therapy (IMPT) in the Reirradiation of Locoregionally Recurrent Rectal Cancer - IMPARC

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Protocol Revision History

Initial Approval Version	**02 March 2021**
Amendment #1 Version	**09 June 2021**
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Amendment #3 Version	**23 November 2022**
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Amendment #7 Version	**16 July 2025**
Amendment #8 Version	**11 September 2025**

STATEMENT OF COMPLIANCE

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

- 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.

GLOSSARY OF ABBREVIATIONS

AC	Adenocarcinoma
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BED	Biologically Effective Dose
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CEA	Carcinoembryonic Antigen
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CTV1	Clinical Target Volume 1
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DRE	Digital Rectal Exam
ECOG	Eastern Cooperative Oncology Group
GTV	Gross Tumor Volume
IMPT	Intensity Modulated Proton Therapy
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
LRC	Locoregional Control
LRFS	Local Relapse-free Survival
MTD	Maximum Tolerated Dose
OAR	Organs at Risk
OHRP	Office of Human Research Protections
OS	Overall Survival
PFS	Progression-free Survival
PRO	Patient Reported Outcomes
PS	Performance Status
PTV	Planning Target Volumes
QOL	Quality of Life
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	Severe Adverse Event
SCCA	Squamous Cell Carcinoma Antigen
SBRT	Stereotactic Radiation
SF-12	Short Form Survey-12
TITE-CRM	Time-to-Event Continual Reassessment Method
SIB	Simultaneous Integrated Boost
UPN	Unique Patient Number

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PROTOCOL SUMMARY

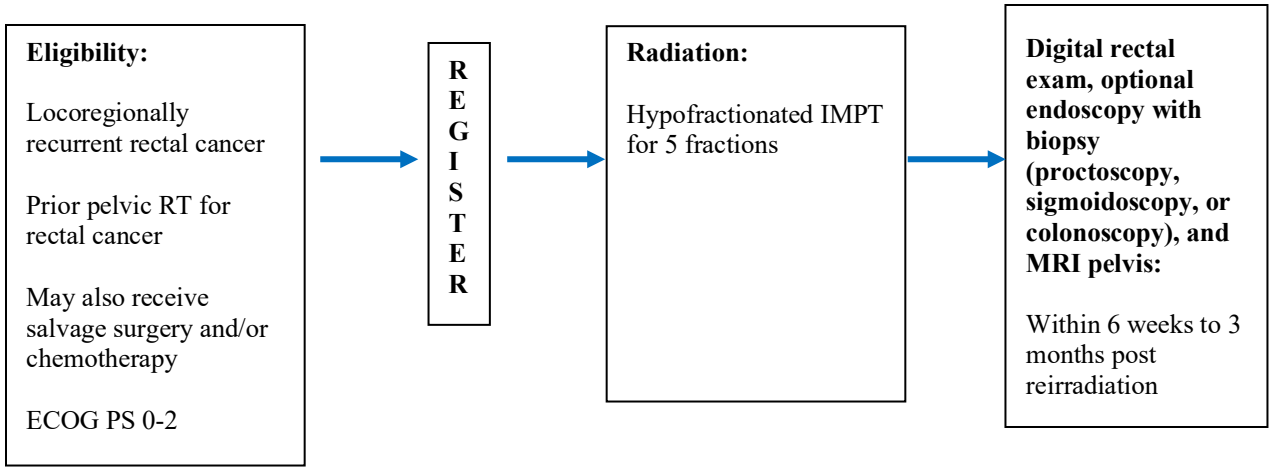
Title:	Hypofractionated Pencil-Beam Scanning Intensity-modulated Proton Therapy (IMPT) in the Reirradiation of Locoregionally Recurrent Rectal Cancer - IMPARC
Study Description:	The purpose of this trial is to determine the maximum tolerated dose (MTD) of hypofractionated IMPT for the reirradiation of locoregionally recurrent rectal cancer.
Objectives:	**Primary Objective:** To determine the MTD of reirradiation using hypofractionated IMPT. **Secondary Objectives:** 1. To determine the clinical complete response rate of patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT. 2. To estimate median freedom from locoregional progression (FFLP) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT. 3. To estimate median overall survival (OS) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT. 4. To estimate median progression-free survival (PFS) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT. 5. To evaluate patient reported outcomes (PRO) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT via QOL questionnaires. 6. To evaluate the toxicity profile of hypofractionated IMPT in patients with locoregionally recurrent rectal cancer. **Exploratory Objectives:** 1. To explore the prognostic value of serum SCCA in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT. 2. To evaluate the changes in serum inflammatory markers, CRP and LDH, in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.
Endpoints:	**Primary Endpoint:** The maximum tolerated dose (MTD) of reirradiation using hypofractionated IMPT for patients with locoregionally recurrent rectal cancer will be defined as the dose associated with a 35% probability of dose-limiting toxicity (DLT). Toxicity will be coded using CTCAE v5, and DLT will be defined as any toxicity listed below that occurs within 6 months from the start of treatment and

	is considered possibly, probably or definitely related to proton reirradiation:
	
	• Any grade 5 toxicities
	• Any grade 4-5 GI toxicities
	• Bowel obstruction
	• Grade 3-5
	  o Diarrhea
	  o Anal, colonic, or bowel ulcers
	  o Bladder perforation
	  o Any fistula formations
	  o Peripheral motor/sensatory neuropathy of the pelvis above baseline
	  o Osteonecrosis/soft tissue necrosis
	  o Radiation dermatitis
	  o Hematuria
	  o Hematochezia
	  o Bowel/pelvic hemorrhage
	  o Reproductive tract toxicity
	
	Secondary Endpoints:
	1. The clinical complete response rate as measured by DRE, endoscopy and cross-sectional imaging.
	2. Freedom from locoregional progression (FFLP), defined as time from end of RT to date of first instance of local or regional tumor progression at 12 months.
	3. Overall survival at 12 months.
	4. Progression-free survival, defined as time from end of RT to the earliest date of locoregional progression, distant progression, or death from any cause at 12 months.
	5. To determine patient reported quality of life outcomes using EORTC QLQ-C30 and QLQ-CR29.
	6. Toxicity, as measured by CTCAE v. 5.0.
	
	Exploratory Endpoints:
	1. Association of pre-treatment SCCA and post-treatment SCCA with PFS and OS at 6 months.
	2. Evaluate the effect of hypofractionated IMPT on levels of serum inflammatory markers.

Study Population:	Twenty patients with locoregionally recurrent rectal cancer who have had prior pelvic RT for rectal cancer will be enrolled.
Phase:	N/A
Description of Sites / Facilities Enrolling:	Washington University School of Medicine
Description of Study Intervention:	Reirradiation will consist of hypofractionated IMPT for 5 fractions. Assessments include digital rectal exam (DRE) and MRI

	pelvis within 6 weeks to 3 months post-completion of reirradiation. QOL assessments will be performed pre-treatment and at several time points after the end of treatment.
Study Duration:	61 months
Participant Duration:	36 months (recruitment) + 13 months (participation and follow-up) + 12 months (analysis)

SCHEMA



Dose-painted hypofractionated intensity-modulated proton therapy dose levels:

Dose Level	Number of fractions of IMPT	PTV Dose/fx (Gy)	PTV Total Dose (Gy)	PTV Standard BED (Gy_{10})	PTV EQD2
-1	5	5	25	37.50	31.25
1 Starting Level	**5**	**6**	**30**	**48.00**	**40.00**
2	5	7	35	59.50	49.58
3	5	8	40	72.00	60.00

Note – the first 6 evaluable patients enrolled will be treated at Dose Level 1
Please refer to section 10.0

SCHEDULE OF ACTIVITIES

	Screening	Pre-treatment[8]	Radiation	1-2 Weeks post RT	6-8 Weeks post RT	3 Mo post RT[1]	6 Mo post RT[1]	9 Mo post RT[1]	12 Mo post RT[1]	
Informed consent	X[2]									
H&P / PS / weight / DRE[13]	X[2]		X[3]	X	X	X	X	X	X	
MRI pelvis[4]	X[2]				X[5]		X	X	X	
CT chest / abdomen / pelvis with contrast[6]	X[2]				X[6]		X	X	X	
Endoscopy[7]	X[2]				X[15]					
OPTIONAL biopsy	X[2, 15]				X					
CBC w/diff	X[2]	X[2]			X[9]		X			
CMP	X[2]	X[2]			X[9]		X			
CEA		X			X[9]		X			
SCCA		X			X[9]		X			
CRP		X			X[9]		X			
LDH		X			X[9]		X			
Pregnancy test	X[10,11]									
Radiation therapy			X[12]							
EORTC QLQ-C30		X		X		X	X	X	X	
EORTC QLQ-C29		X		X		X	X	X	X	
Adverse events		X	X[3]	X	X	X	X	X	X	

1. +/- 2 weeks
2. No more than 60 days prior to registration. Screening and baseline labs can be the same draw provided the timing aligns.
3. Performed once during radiation therapy.
4. Cross-sectional imaging with either MRI or CT is acceptable.
5. MRI pelvis and CT chest/abdomen with contrast may be obtained 6 weeks to 3 months after radiation completion with a RECIST read at 3 months only.
6. If PET/CT scan is done, then CT chest/abdomen/pelvis not required.
7. Endoscopy with colonoscopy, sigmoidoscopy, or proctoscopy will be performed if feasible after screening.
8. Baseline labs and QOL assessments should be performed within 30 days of radiation therapy.
9. Labs should be drawn once 6 weeks to 3 months after radiation completion but should be drawn before surgery if the patient undergoes salvage surgery.
10. Mandatory for women of childbearing potential.
11. Within 14 days of registration.
12. 5 fractions over 1 week.
13. DRE only to be done if feasible.15. OPTIONAL endoscopy with biopsy performed 6 weeks to 3 months after completion of RT; for research purposes only.
15. OPTIONAL screening biopsy to be performed at time of baseline SOC endoscopy.

1 BACKGROUND

1.1 Recurrent Rectal Cancer

Advances in the management of locally advanced rectal cancer in the recent decades, such preoperative chemotherapy (CRT) (1, 2) in conjunction with total mesorectal excision (TME) (3, 4), have led to marked improvements in patient outcomes, with a 10-year overall survival of approximately 40%-60% (4, 5). The improvement in overall survival is in large part due to reductions in local-regional recurrences (LRF), which have decreased from 10-25% (6, 7) to 4-8% (4, 8–10).

While the clinical outcomes of locally advanced rectal cancer have improved as a whole, select patients, such as patients with advanced pathologic T and N stages (11, 12), lymphovascular or perineural invasion (11), low-lying rectal primaries (11), and involved or "threatened" circumferential margins (CRM) (13), remain at increased risks for locoregional failures (LRFs). Patients with locoregionally recurrent rectal cancer (LRRC) carry significant disease morbidity and have a poor prognosis (14). They may experience intractable pelvic or sciatic pain, bleeding, fistulas, intestinal obstruction, fecal discharge, dysuria, urinary tract dysfunction, and chronic pelvic sepsis (15), which compromise quality of life (16).

The management of patients with LRRC poses a clinical dilemma. Since the majority of these patients have been previously treated with multimodality therapy, which causes fibrosis in the treatment field, salvage therapy options are limited. Complete surgical resection confers the best chances for long-term survival (6, 17, 18), but R0 resections can only be achieved in approximately 50-66% of the patients (14, 18) since recurrences near critical neuro-vascular structures and/or occupying large volumes are often unresectable.

While LRFs mostly occur in the central pelvis after incomplete TMEs, LRFs after preoperative chemoradiation and TME occur more in the lateral pelvis, such as in the iliac, obturator, paraaortic, and retroperitoneal lymph nodes (19–21). Surgical salvage of lateral pelvic failures may require extensive resections such as pelvic exenteration and extravascular lateral pelvic sidewall resections (14), which cause significant perioperative and postoperative morbidity and mortality (16) while only achieving modest improvements in overall survival (OS) (6, 17, 18).

1.2 Reirradiation

Given the clinical challenges and limitations with salvage surgery, investigators have explored pelvic reirradiation with and without salvage surgery and chemotherapy in the setting of LRRC (22–24). Reirradiation of the pelvis poses significant risks due to the cumulative effects on the organs at risk (OARs), such as the residual rectum, bladder, small, and large bowel, and the maximum lifetime dose to OARs for which toxicities outweigh the benefits of local-regional control remain undefined (25). Studies have reported reirradiation using conventional fractionation (1.8-2.0 Gy/fraction daily) (26–32) and hyperfractionation (1.2-1.5 Gy/fraction twice a day) (26, 33–37).

Metanalyses of these reirradiation studies showed pooled 1-, 2-, and 3-year OS rates for patients who received reirradiation and surgery were 86%, 72%, and 52%, respectively (24). The pooled grade ≥3 acute and late complication rate was 12% in patients who underwent reirradiation alone and was 26% in patients who underwent reirradiation and surgery (24). However, the 3-year OS was merely 24% in patients who received reirradiation alone (24). Since the low doses of 30-45 Gy delivered via conventional or accelerated hyperfractionation with photon therapy are generally insufficient to eradicate gross disease and are considered to the be palliative without salvage surgery (24).

1.3 Hypofractionated Radiation Therapy

Technologic advances have improved patient immobilization, tumor tracking, and radiation delivery, allowing for larger doses to be given to tumors safely with reduced margins and steep gradients outside the target volume. Hypofractionated radiation therapy, or radiation treatments with greater than 2 Gy per fraction, delivers a higher biologically effective dose (BED). Hypofractionated radiation techniques such as stereotactic body radiotherapy (SBRT) have been shown to increase local control in primary lung (38, 39), pancreatic (40–43), and liver (44–46) cancers, as well as in brain metastases (47).

In primary rectal cancer, the use of hypofractionated short-course preoperative radiation therapy to 25 Gy in 5 once daily fractions has been shown to have similar disease control and toxicities compared to conventionally fractionated long-course preoperative chemoradiation in the Polish rectal trial (48, 49) and the Australian Trans-Tasman Radiation Oncology Group Trial (9), and has been adopted as the standard of care at our institution. Reirradiation of recurrent rectal cancers with conventionally fractionated or hyperfractionated regimens has resulted in poor local control outcomes (30, 33, 35, 36). We aim to improve local control of recurrent rectal cancer by using a hypofractionated regimen.

1.4 Proton Therapy

To improve clinical outcomes for LRRC, proton therapy may be considered for reirradiation to reduce dose to previously irradiated OARs and allow for dose escalation (50). Compared to x-ray photon therapy, proton therapy has decreased proximal dose deposition (51) and virtually no exit dose distal to the target volume (52), resulting in reduced integral dose and clinical toxicities. Reirradiation with proton therapy has been reported in various disease sites, such as glioma (53), head and neck (54–57), esophageal (58), NSCLC (59–61), sarcoma (62), chordoma (63), pancreatic (64), and liver cancers (65). In rectal cancer, dosimetric studies have illustrated the ability of proton therapy to reduce radiation dose to the bone marrow, small bowel, and urinary bladder while maintaining clinical efficacy (66–71).

Preliminary studies have reported the feasibility of proton therapy for reirradiation of LRRC (30, 72). At the University of Pennsylvania, seven patients with LRRC who previously received 50.4 Gy of RT underwent double-scatter proton beam therapy to a

mean dose of 61.2 Gy (range, 45–64.8 Gy), with a maximum total dose sum of 109.8 Gy (range, 95.4–151.2 Gy) (30). At a median follow-up of 19 months, 57% of patients had a durable partial or complete radiographic response and four were still alive (30). Dosimetric comparison to VMAT showed that the bowel exposure at the V10Gy and V20Gy levels was significantly reduced by 85% and 55%, respectively, and doses to 200 and 150 cm^3 of bowel were also reduced (30). Grade 3 acute toxicity was observed in 3 patients (1 abdominal pain and 3 diarrhea) and small bowel obstruction developed in 2 patients (30). A Japan case report series also reported the use of carbon ion RT and proton therapy in three patients with LRRC (72).

Given the paucity of prospective data on reirradiation with proton therapy for rectal cancer, we propose to conduct a study to evaluate the safety and efficacy of reirradiating patients with LRRC using pencil beam scanning proton beam therapy (PBSPT). PBSPT delivers intensity-modulated proton therapy (IMPT), which is achieved by narrow beam spots that are delivered to the patient in a scanning pattern. Compared to double-scatter proton therapy, IMPT allows improved dose-conformity not only at the distal region of the target, but also to the proximal region of the target from a given field and allows further sparing of the OARs located proximal to the target (73–75). We propose reirradiation with hypofractionation to improve local tumor control (23, 28, 76–78).

1.5 Patient-Reported Outcomes (PROs)

Patient-reported outcomes will be assessed using the quality of life (QOL) questionnaires European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Quality of Life of Cancer Patients (79, 80) (Appendix B) and EORTC QLQ-CR29 Colorectal QOL (81) (Appendix C). The QOL questionnaires will be answered by the patients prior to the start of proton reirradiation, 1-2 weeks after RT, 3 months, 6 months, 9 months, and 12 months post completion of RT.

1.5.1 EORTC QLQ-C30 Quality of Life of Cancer Patients

The EORTC QLQ-C30 Quality of Life of Cancer Patients is a validated, widely utilized QOL questionnaire in general oncology for adult patients (79, 80). The EORTC QLQ-C30 consists of a 30-question questionnaire, which assesses patient well-being with five functional scales (the physical, role, emotional, cognitive, social, and global). It also includes three symptom scales (fatigue, pain, nausea/vomiting) and six single items (dyspnea, sleep disturbance, appetite loss, diarrhea, constipation, and financial impact) (79, 80). Single-item QL scores for overall physical condition (question 29), overall quality of life (question 30), and the global and social functioning scales have been shown to be prognostic for overall survival in adult patients with advanced malignancies (82)

1.5.2 EORTC QLQ-CR29 Colorectal QOL

Developed in 2007 (83) as an update to QLQ-CR38 (84), the EORTC QLQ-CR29 questionnaire is a supplemental module designed to be delivered alongside the core

QLQ-C30 to assess QOL for patients with colorectal cancer.

The QLQ-CR29 contains 29 questions, including items in 4 scales (urinary frequency, blood/mucus in stools, stool frequency, body image) and 19 single items (urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, anxiety, weight, flatulence, fecal incontinence, sore skin, embarrassment, stoma care problems, sexual interest for men, sexual interest for women, impotence, dyspareunia) (83). There are 11 items allocated for specific sub-populations, including males, females, and stoma patients. Scores of the QLQ-CR29 can be linearly transformed to provide a score from 0 to 100, with higher scores representing higher levels of functioning on the functional scales, greater degrees of symptomatology on the symptom scales and improved QOL on the global QOL scale (83).

1.6 Squamous cell carcinoma antigen and inflammatory markers

Squamous cell carcinoma antigen (SCCA) is a serine protease inhibitor that belongs to the clade B subset of serpins and includes 2 isoforms, SCCA1-1 and SCCA1-2. SCCA isoforms are commonly detected in the serum of patients with solid organ squamous- or adenocarcinomas, such as breast cancer (85), cervical cancer (86), ovarian cancer (87), and hepatocellular carcinoma (88). SCCA is also upregulated in human colorectal cancer (89). Recent research demonstrated that SerpinB3, together with COX-2 and β-Catenin, are positively correlated and associated with more advanced tumor stage in colorectal cancer (90). Therefore, we intend to explore the prognostic value of SCCA prospectively in patients with locoregionally recurrent rectal cancer receiving hypofractionated radiation therapy.

Additionally, epidemiological studies revealed that chronic inflammation predispose individuals to different cancers (91). Accordingly, non-steroidal anti-inflammatory drugs (NSAIDs) decreases the incidence of colorectal cancer (92, 93). Studies have also shown the prognostic significance of serum inflammatory markers, such as C-reactive protein (94) and lactate dehydrogenase (LDH) (95, 96), in association with treatment response and survival. Therefore, we also propose to evaluate the changes in CRP and LDH following reirradiation with IMPT and assess their prognostic value for clinical endpoints.

1.7 Study Design

1.7.1 Overall Design

Patients will be enrolled on a prospective dose escalation protocol whereby they will receive hypofractionated IMPT. Radiotherapy dose escalation in this study will be defined as intensification of dose through increasing dose per fraction while maintaining the total same total number of fractions.

Dose Level	Number of fractions of IMPT	PTV Dose/fx (Gy)	PTV Total Dose (Gy)	PTV Standard BED (Gy_{10})	PTV EQD2
-1	5	5	25	37.50	31.25
1 Starting Level	**5**	**6**	**30**	**48.00**	**40.00**
2	5	7	35	59.50	49.58
3	5	8	40	72.00	60.00

IMPT = intensity-modulated proton radiotherapy, fx = fractions, RBE = Relative Biological Effectiveness, BED10 = Biologically effective dose using an α/β=10 and the formula BED=nd(1+(d/[α/β])) where n=# of fx and d=dose/fx, EQD2 = Equivalent dose at 2 Gy/fx.

1.7.2 Scientific Rationale for Study Design

The standard phase I 3+3 dose-escalation design is poorly suited for trials of radiotherapy, for which toxicities may occur up to several months after treatment. In this case, the 3+3 design, or any design that requires all patients to have completed observation for toxicity, is subject to openings and closings as patients present after a dose level potentially has filled, but before sufficient time has elapsed to be certain that treatment has not produced dose-limiting toxicities (DLT).

As such, dose escalation for this trial will be guided by the Time-to-Event Continual Reassessment Method (TITE-CRM). TITE-CRM seeks to determine the target dose, defined as the dose most closely identified with the target rate, which is the largest acceptable probability of toxicity, determined a priori by the investigators based on the relative costs and benefits of the treatment (typically between 5% and 25%). As the trial progresses and patients do or do not experience toxicities at different doses, the estimates of probability of toxicity are recalculated using a Bayesian expectation, and subsequent patients are assigned to doses under the principle to always treat at the target dose.

In a Monte Carlo simulation of 60,000 phase I trials comparing 3+3 design to TITE-CRM in studies with delayed toxicity, the TITE-CRM trials were significantly shorter when toxicity observation times are long, treated more patients at or above the maximum-tolerated dose, identified the MTD more accurately, but did not expose patients to significant additional risk (97). Additionally, given that TITE-CRM concentrates most of the accrual around the target dose, early estimates of efficacy are possible.

1.7.3 Justification for Dose

In order to minimize toxicity, elective lymph nodes will not be treated. Only the dose to the gross tumor volume (GTV) will be escalated. This will minimize the

volume of tissue receiving the escalated dose. The starting dose to planned tumor volume (PTV) will be 30 Gy in 5 fx of 6 Gy/fx. Dose per fraction will be escalated in 1 Gy/fx increments. Such increments translate into approximately 11 Gy_{10} increments of BED up to a target dose of 40 Gy(RBE) in 5 fx of 8 Gy/fx for a PTV2 BED of 72 Gy_{10}.

Given the potential for significant toxicity with hypofractionated radiation at these doses, suggested dose limits to organs at risk (OARs) will be defined using BED-adjusted conversions of published limits for both conventionally fractionated and hypofractionated regimens scaled appropriately for 5 fractions.

Such dose limits are being employed as a means to minimize the likelihood of toxicity, but true tolerance to OARs are not yet known for such hypofractionated schemes. Therefore, prioritization will be employed for planning purposes taking into account the balance between tumor coverage and relative consequences of toxicity to specific OARs. A simultaneous integrated protection method using a planning organ at risk volume around luminal structures such as uninvolved bowel will be utilized to reduce the dose of radiation to nearby luminal organs to safe levels (97).

2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
To determine the MTD of reirradiation using hypofractionated IMPT.	The maximum tolerated dose (MTD) of reirradiation using hypofractionated IMPT for patients with locoregionally recurrent rectal cancer will be defined as the dose associated with a 35% probability of dose-limiting toxicity (DLT). Toxicity will be coded using CTCAE v5, and DLT will be defined as any toxicity listed below that occurs within 6 months from the start of treatment and is considered possibly, probably or definitely related to proton reirradiation: • Any grade 5 toxicities • Any grade 4-5 GI toxicities • Bowel obstruction	Given the paucity of prospective data on reirradiation with proton therapy for locoregionally recurrent rectal cancer, this is a study aimed to evaluate the safety and efficacy of reirradiation using pencil beam scanning proton intensity-modulated proton therapy (IMPT). Hypofractionated radiation therapy may increase in the risk of treatment-related toxicities to spinal cord, intestines, kidneys, bowel, or skin. We aim to determine the maximally tolerated dose of hypofractionated radiation therapy by increasing the boost dose up to a potential

	• Grade 3-5 o Diarrhea o Anal, colonic, or bowel ulcers o Bladder perforation o Any fistula formations o Peripheral motor/sensatory neuropathy of the pelvis above baseline o Osteonecrosis/soft tissue necrosis o Radiation dermatitis o Hematuria o Hematochezia o Bowel/pelvic hemorrhage o Reproductive tract toxicity	maximum of 40 Gy in 5 fractions. We will monitor patients for toxicity. A dose limiting toxicity is defined as a high-grade toxicity occurring up to 6 months from the start of therapy in any of the organs above.
Secondary		
1. To determine the clinical complete response rate of patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	1. The clinical complete response rate as measured by DRE, endoscopy, and cross-sectional imaging.	We will report the preliminary estimate of the local-relapse free survival, progression-free survival, and overall survival rate. If a phase II study is eventually performed. The survival rates of the patients in the phase I study and phase II study will be combined for efficacy assessments. Tolerability of the treatment regimen (phase I endpoint) will determine if further trials testing this regimen will be performed. Little data exist on patient-reported quality of life for patients with locoregionally recurrent rectal cancer treated with proton therapy. We aim to report the patients' results
2. To estimate median freedom from locoregional progression (FFLP) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	2. Freedom from locoregional progression (FFLP), defined as time from end of RT to date of first instance of local or regional tumor progression at 12 months.	
3. To estimate median overall survival (OS) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	3. Overall survival at 12 months.	

4. To estimate median progression-free survival (PFS) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	4. Progression-free survival, defined as time from end of RT to the earliest date of locoregional progression, distant progression, or death from any cause, at 12 months.	and compare results as a part of this proton dose-escalation trial. The toxicity profile of this radiation therapy regimen for reirradiation of locoregionally recurrent rectal cancer is unknown.
5. To evaluate patient reported outcomes (PRO) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT via QOL questionnaires.	5. To determine patient reported quality of life outcomes using EORTC QLQ-C30 and QLQ-CR29.	
6. To evaluate the toxicity profile of hypofractionated IMPT in patients with locoregionally recurrent rectal cancer.	6. Toxicity, as measured by CTCAE v 5.0.	
Exploratory Objectives		
1. To explore the prognostic value of serum SCCA in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	1. Association of pre-treatment SCCA and post-treatment SCCA with PFS and OS at 6 months.	To our knowledge there is no prospective data on SCCA and serum inflammatory markers in patients with recurrent rectal cancer.
2. To evaluate the changes in serum inflammatory markers, CRP and LDH, in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	2. Evaluate the effect of hypofractionated IMPT on levels of serum inflammatory markers.	

3 STUDY POPULATION

3.1 Inclusion Criteria

In order to participate in this study, a patient must meet all of the criteria listed in this section:

1. History of biopsy-proven adenocarcinoma of the rectum, anus or rectosigmoid junction of any stage now with recurrent disease in the pelvis.
2. One prior course of radiation therapy to the pelvis for rectal cancer.
3. ECOG performance status 0-2.
4. At least 18 years of age.
5. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.
6. Able to understand and willing to sign an IRB-approved written informed consent document.

3.2 Exclusion Criteria

In order to participate in this study, a patient must not meet any of the criteria listed in this section:

1. Patients with pre-existing radiosensitizing conditions, such as connective tissue disorders (i.e. lupus, scleroderma) and genetic mutations (i.e. ataxia-telangiectasia).
2. A history of other malignancy with the exception of malignancies for which all treatment was completed at least 2 years before registration and the patient has no evidence of disease, basal cell or squamous cell carcinoma of the skin that were treated with local resection only, or carcinoma *in situ* of the cervix. Patients with history of prostate cancer treated without radiotherapy and no evidence of disease are eligible.
3. More than one prior course of radiation to the pelvis for rectal cancer.
4. Prior radiation to the pelvis for disease other than rectal cancer.
5. Tumor in the rectum/colon requiring radiation therapy to the full circumference of the rectum/colon.
6. Current treatment with any investigational agents.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or unstable angina pectoris.
8. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative urine or serum pregnancy test within 14 days of study entry.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION AND ENROLLMENT PROCEDURES

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

1. Registration of consented patient in the Siteman Cancer Center OnCore database

2. Assignment of unique patient number (UPN)
Confirmation of patient eligibility**Patients must not start any protocol intervention or procedures prior to signing of informed consent.**

4.1 Registration in OnCore Database

Patient registration to the Siteman Cancer Center OnCore database must occur within one business day of the patient signing consent.

4.2 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. The UPN must not include patient initials or other identifying information. All data will be recorded with this identification number on the appropriate CRFs.

4.3 Confirmation of Patient Eligibility

Patient eligibility will be confirmed using the information listed below:

1. Completed eligibility checklist, signed and dated by a member of the study team
2. Copy of appropriate source documentation confirming patient eligibility

4.4 OnCore Subject Status Definitions

Note: subject status should not be updated in OnCore until the subject is actively in that status; future dates are not allowed.

Subject Status	Definition
Consented	Patient has signed an IRB approved consent for the trial.
Eligible	Patient eligibility has been confirmed by Washington University PI or delegate.
Not Eligible	Patient did not meet eligibility criteria for the trial. Note that if a patient is determined to be eligible but never initiates study participation, they are not considered a screen fail.
On Study	Patient is confirmed eligible for the study and enrolled.
On Treatment	Patient is receiving study therapy. On Treatment date should be the date of the first study treatment.
Off Treatment	Patient has discontinued study therapy. Off Treatment date should be the last day any study treatment was administered.
On Follow Up	One day post RT to one year post RT
Off Study	Patient has fully discontinued all study procedures (including any follow-up procedures and/or review of medical record for outcomes data).

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently enrolled in the study (status of On 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).

4.6 Strategies for Recruitment and Retention

The radiation therapy technology necessary to deliver this treatment regimen is only available at the main campus facility at the Center for Advanced Medicine. Follow-up can be done at the center nearest to the patient's home at our community practice sites, such as Barnes-Jewish West County Hospital, Siteman Cancer Center South County, Barnes Jewish St Peters Hospital and potentially others. This approach reduces travel and expense and improves compliance. There will be no additional expense for the patient for participating in the clinical trial.

5 TREATMENT PLAN

5.1 Hypofractionated IMPT

5.1.1 Dose, Fractionation, and Constraints

When feasible it is strongly recommended that radiotherapy begin on a Monday. It is accepted that occasional logistical delays may occur during radiotherapy treatment due to machine downtime or other issues. Radiotherapy as administered during this study may take up to 10 business days without being considered a protocol deviation. The use of Intensity Modulated Radiation Therapy (IMRT) with photon beam therapy is permitted at the discretion of the treating investigator in order to avoid extended treatment delays due to logistical reasons (e.g. machine downtime).

Radiotherapy will consist of five fractions, delivered once daily, with pencil beam scanning proton beam therapy. Treatment with passive-scatter proton beam therapy is not allowed. Single Field Optimization (Single Field Uniform Dose) plans are preferred over Multi-Field Optimization plans. Beam angles should be selected that minimize traversing bowel gas. The use of rectal balloons filled with water is optional.

The dose to the PTV will be escalated, starting from 30 Gy in 5 fx of 6 Gy/fx. Dose per fraction will be escalated in 1 Gy/fx increments. Such increments translate into

approximately 11 Gy_{10} increments of BED up to a target dose of 40 Gy(RBE) in 5 fx of 8 Gy/fx for a = BED of 72 Gy_{10}.

Daily imaging with cone beam CT to verify accurate setup is mandatory. The target coverage goal is that 95% of the PTV receives at least 95% of the prescription dose while not violating OAR dose constraints and the maximum dose should be $\leq$115% of the prescription dose.

5.1.2 Treatment Planning Procedures

Treatment planning will be performed on a non-contrast CT scans. CT scans with small bowel contrast and/or IV contrast are allowed, but the contrast CT scans will have to be fused to the planning non-contrast scans. Fusion of the diagnostic MRI pelvis with the simulation CT is encouraged, but not required. Diagnostic PET/CT scans are optional. Dose volume histogram (DVH) information for the target volumes, small bowel, and uninvolved colon and uninvolved rectum (defined to be large bowel outside the clinical target volumes) is mandatory. This is to assist in interpreting outcome, including morbidity. LET optimization will be encouraged in the inverse planning of IMPT when the technology becomes available.

5.1.3 Simulation Procedures/Patient Positioning

The prone position with a bowel displacement device incorporated into the immobilization cast is generally recommended as the best way to exclude small bowel from the pelvis. The exceptions would be patients unable to lay prone or morbidly obese patients whose diagnostic supine CT scans demonstrate little or no small bowel in the pelvis. Those patients with good bladder control should be treated with a full bladder to further exclude small bowel. All patients should be simulated with oral small bowel contrast.

5.1.4 Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV) Definitions

GTV should include all gross recurrent disease including lymph node metastases as determined by CT, PET/CT, MRI or biopsy.

The creation of a CTV is at the discretion of the treating radiation oncologist, but generally should be minimized to only gross disease and a margin 2-5 mm to account for microscopic spread. Elective lymph nodes should not be treated.

PTV is generated by a uniform 0.5 cm expansion about CTV or GTV if no CTV was created. In order for this tight PTV margin to be used, it is required that a physician review daily setup images for each of the five fractions.

5.1.5 Normal Tissue Contours

Small bowel and uninvolved colon should be contoured tightly. Uninvolved colon is defined to be large bowel that lies outside the CTV. Colon that lies within the CTV (rectum and parts of the sigmoid) is a target structure, not an avoidance structure, hence its exclusion from "uninvolved colon." The CTV is NOT to be extracted from small bowel. If small bowel lies within a CTV, that WILL contribute to the small bowel dose. Since absolute rather than relative bowel volumes are to be tracked, it is not necessary to contour the entire large and small bowel, only those loops caudal to 1 cm above the most cephalad extent of PTV.

These dose constraints are a general guideline. They are soft constraints that assume that the patient's prior DICOM data is unavailable and that each listed organ received an EQD2 of 50 Gy previously. If prior DICOM data is available, then the modeled dose to the organs from the prior treatment plan would take precedence.

Tissue	Contouring Instructions	Vol (cc)	Vol Max (Gy)	Max** Point Dose (Gy)
Spinal Cord	Entire bony canal including at least 1 cm superior and inferior to PTV.	<0.35 cc	10	11.5
Cauda Equina	Based on the bony limits of the spinal canal starting superiorly at the bottom of the spinal cord (typically around L2) and ending at the inferior extent of the thecal sac (typically S3).	< 5 cc	12	14
Skin	The outer 0.5 cm of the body surface anywhere within the whole-body contour.	<10 cc	22.5	28.5
Small bowel* + 5 mm	Any and all loops of small bowel as one structure within 1 cm of the PTV in any direction.	<30 cc	20	32
Uninvolved Colon* + 5 mm	One structure including wall and contents of lumen starting 1 cm superior to PTV and ending 10 cm below PTV.	<20 cc	28.5	40
Uninvolved Rectum + 5 mm	One structure including wall and contents of lumen subtracting out the GTV or CTV (if CTV is created).	<3.5 cc <20 cc <62.7%	50 32.5 16	55
Bladder wall	Contour the bladder wall and all urine ending inferiorly at the base of the prostate.	<15 cc	20	25
Ureter	Entire organ.	n/a	n/a	30 Gy
Femoral heads	Entire femoral head and proximal femur.	<10 cc	15	n/a
Penile bulb	Contour starting superiorly at the inferior aspect of the pelvic diaphragm (urethral sphincter) and extending inferiorly and anteriorly up to 3 cm	<3 cc	15	n/a

Sacral Plexus	Outlining the space defined medially by the sacral foramina from S1-S3 including contouring within the sacral foramina, posteriorly along the limits of the true pelvis, laterally to 2-3 cm lateral to the sacral foramina, and anteriorly about 3-5 mm from the posterior limits of the contour.	< 5 cc	12	14
Prostate	Entire organ	n/a	n/a	25

*Avoid circumferential irradiation
** "point" defined as 0.035cc or less

5.2 Dose Escalation Schema and MTD Definition

Refer to Section 10 for a description of the TITE-CRM design and dose escalation rules as well as for the protocol definition of MTD.

5.2.1 Dose-Limiting Toxicities (DLTs)

Dose-limiting toxicities (DLTs) are defined as any toxicity listed below that occurs within 6 months from the start of treatment and is considered possibly, probably, or definitely related to proton reirradiation:

- Any grade 5 toxicities
- Any grade 4-5 GI toxicities
- Bowel obstruction
- Grade 3-5
    - Diarrhea
    - Anal, colonic, or bowel ulcers
    - Bladder perforation
    - Any fistula formation
    - Peripheral/motor sensatory neuropathy of the pelvis above baseline
    - Osteonecrosis/soft tissue necrosis
    - Radiation dermatitis
    - Hematuria
    - Hematochezia
    - Bowel/pelvic hemorrhage
    - Reproductive tract toxicity

5.3 Study Procedures

5.3.1 Screening Evaluations

The following procedures must occur during screening:

1. Complete history and physical including assessment of ECOG performance status, weight, and digital rectal exam within 60 days prior to registration (Appendix A).

2. CBC with differential and complete metabolic panel within 60 days prior to registration.
3. Urine or serum pregnancy test for female patients that are of childbearing potential within 14 days prior to registration.
4. CT chest/abdomen/pelvis or staging within 60 days prior to registration. If PET/CT scan is done, then CT chest/abdomen/pelvis not required.
5. MRI of the pelvis within 60 days prior to registration.
6. Endoscopy with colonoscopy, sigmoidoscopy, or endoscopy of the locoregionally recurrent tumor within 60 days of registration (recommended if feasible)
7. OPTIONAL biopsy at time of SOC endoscopy.
8. Charlson Comorbidity Index score will be calculated based on patient comorbidities and age.

5.3.2 Pre-RT Evaluations

No more than 30 days before the start of radiation treatment, the following procedures must occur:

3. CBC with differential and CMP
4. Study labs (CEA, SCCA, CRP, LDH)
5. QOL questionnaires (Appendices B, C)
6. Assessment of baseline symptoms

5.3.3 On Therapy Evaluations

The following evaluations will occur while the patient is receiving radiation therapy:

- One on-treatment visit during the 5 fractions of RT including a physical exam, vital signs, assessment of ECOG performance status, and digital rectal exam.
- Physician-reported assessment of patient symptoms will be done using CTCAE version 5.0 once during radiation therapy (preferably during fraction 4 or 5).

5.3.4 Post-Radiation Evaluations

All patients will be followed from time of enrollment until 1 year post radiation Mandatory follow-up time points are as below. In the event that an in-person evaluation is not possible, or if not indicated by the treating investigator, a telehealth visit may be performed in its place.

- 1-2 weeks post-RT
- 6-8 weeks post-RT
- 3 months post-RT (+-/- 2 weeks)
- 6 months post-RT (+/- 2 weeks)
- 9 months post-RT (+/- 2 weeks)
- 12 months post-RT (+/- 2 weeks)

5.3.4.1 Treatment Response Assessment

The following assessments should be performed 6 weeks to 3 months after radiation (but should be completed before surgery if the patient will be undergoing salvage surgery) and again 6 months after radiation:

- MRI pelvis
- CT chest/abdomen with contrast (if a PET is performed, a CT is not required)
- CBC with differential and CMP
- Study labs (CEA, SCCA, CRP, LDH)

In addition, MRI pelvis and CT chest/abdomen with contrast should be performed at 9 and 12 months after radiation. Endoscopies are optional after radiation therapy.

5.3.4.2 Adverse Events and PRO QOL

Patients will be clinically evaluated after completion of radiation therapy at the time points listed above. Physician reported assessment of patient symptoms will be done using the NCI-CTCAE v5.0 at each time point. Patient evaluation by a physician should occur sooner for any symptoms concerning for treatment-related toxicity or disease recurrence/progression. PROs will be assessed at all time points (except the 6-8 weeks post-RT time point) using the QOL questionnaires (Appendices B, C).

5.4 Definitions of Evaluability

Endpoint	**In order to be evaluable for this endpoint, a patient must…**
Maximum tolerated dose	Have received at least one fraction of study radiation. Patients will be evaluated for DLTs from the start of treatment through 6 months after the start of treatment. DLT is defined in Section 5.2.1.
Clinical complete response rate.	Have received at least one fraction of study radiation and undergone response assessment by DRE, endoscopy, and/or cross-sectional imaging.
Freedom from locoregional progression (FFLP) at 12 months.	Have received at least one fraction of study radiation and undergone response assessment.
Overall survival at 12 months.	Have received at least one fraction of study radiation
Progression-free survival at 12 months.	Have received at least one fraction of study radiation and undergone response assessment.

Patient reported quality of life.	Have completed the EORTC QLQ-C30 and/or QLQ-CR29 QOLs at pre-treatment and a minimum of one post-treatment time point
Toxicity	Have received at least one fraction of study radiation. Patients are evaluated from first receiving study radiation until 12 months after the conclusion of radiation.
Association of pre-treatment SCCA and post-treatment SCCA with PFS and OS at 6 months.	Have had blood drawn for SCCA at screening and after completion of study radiation
Levels of serum inflammatory markers.	Have had blood drawn for CRP and LDH after completion of study radiation

5.5 Supportive Care Guidelines

Standard antiemetics, anti-diarrheals, and pain medications may be provided at the discretion of the treating radiation oncologist(s) and physicians who evaluate the patients for follow up. Grade 3-5 adverse events may require hospitalization and inpatient management.

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative urine or serum pregnancy test within 14 days prior to the first fraction of radiation therapy.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and 30 days following the fraction of radiation therapy.

If a patient is suspected to be pregnant, radiation therapy should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 30 days after the last fraction of radiation, the investigator must be notified in order to facilitate outcome follow-up.

5.7 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 or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- 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.

5.8 Duration of Follow-up

Patients will be followed for 12 months following the completion of IMPT 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. Follow-up is described in Section 5.3.4. Patients will be followed by office visits, phone calls, and review of medical record. Any additional follow-up and imaging will be obtained off-study as per routine clinical policies of the treating physician.

5.9 Lost to Follow-Up

A participant will be considered lost to follow-up if he or 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 5 business days 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, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix D for definitions and Appendix E for a grid of reporting timelines. All investigators treating patients on this study are responsible for ensuring that serious adverse events (as defined in Appendix B) are reported to the Sponsor-Investigator within an adequate timeframe for the event to be assessed by the Sponsor-Investigator for reporting to HRPO, QASMC, and/or FDA. **Note that for investigator-initiated studies, the term "Sponsor-Investigator" refers to the investigator holding the IND.**

Adverse events will be tracked from start of treatment through 12 months after completion of radiation therapy. All adverse events 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
- Toxicities that are definitely or highly likely related to salvage surgery and/or salvage chemotherapy

Refer to the data submission schedule in Section 7 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 6.1.

6.1 WU PI Reporting Requirements

6.1.1 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.

6.1.2 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.

6.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 6.1 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.

7 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
On-Study Form Medical History Form	Prior to starting treatment
Treatment Summary Form	End of treatment
DLT Form	6 months post-treatment
PRO Form	Prior to starting treatment, 1-2 weeks post-treatment, 3 months post-treatment, 6 months post-treatment, 9 months post-treatment, 12 months post-treatment
Toxicity Form	Continuous
Follow Up Form	1-2 weeks post-treatment, 6-8 weeks post-treatment, 3 months post-treatment, 6 months post-treatment, 9 months post-treatment, 12 months post-treatment
Tumor Measurement Form	Baseline, 6-8 weeks post-treatment OR 3 months post-treatment
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 6.0 for reporting requirements

7.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 6.0) 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.

8 MEASUREMENT OF EFFECT

8.1 Antitumor Effect – RECIST 1.1

For the purposes of this study, patients should be re-evaluated for response at the specified times in section 5.3.4.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.1.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in clinical complete response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

8.1.3 Response Criteria

8.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in clinical complete response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and

the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.1.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD

Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

8.1.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

9 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.
. The first report is required either 30 days after the enrollment of the 5th participant (if sooner than 6 months after study activation) or 6 months after study activation (provided at least one patient has been enrolled; if zero patients have been enrolled at the 6-month mark, the first report will be required one year after accrual opens provided at least one patient has been enrolled).

The Principal Investigator will review all patient data at least monthly and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- Study demographic information (local protocol number, protocol title, list of primary study team members, study sites, primary and secondary sponsors, IND/IDE status, date of most recent QA audit, and study status and history (including activation and suspension dates)
- Accrual information, including study-wide target accrual and actual accrual, anticipated and/or actual accrual end date, and accrual by year by site (if applicable)
- Subject status information presented in both cumulative format (total number of subjects who consented, enrolled, screen failed, started intervention, discontinued

intervention, went off study, expired) and current format (number of subjects in screening, on intervention, in follow-up, or off study at time of report)
- Protocol objectives and the number of participants who are evaluable for each objective
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Summary of exceptions, noncompliance reports, and unanticipated problems reported to the IRB
- Early stopping rules and data describing whether the stopping rules have been met (if applicable)
- Interim analysis plans and the results of the interim analysis (if applicable)
- Separate SAE and worst grade toxicity tables, each separated by site (if applicable) and arm/cohort/dose level (if applicable)
- Participant-level response and survival data by arm/cohort/dose level (if applicable)
- Summary of specimen collection (percentage of participants who have had specimens collected at each required time point)
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety of participants or the 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.

10 STASTISTICAL CONSIDERATIONS

10.1 Phase I Methodology for Primary Endpoint

10.1.1 Background of TITE-CRM and trial rules

The Time-to-Event Continual Reassessment Method (TITE-CRM) proposed by Cheung and Chappell is an adaptive Phase I design (98). In a TITE-CRM clinical trial, patients enroll as they become available to be studied. Each participant is assigned to a dose level from a set of dose levels pre-defined by investigators and is monitored for DLTs over time. The design is adaptive in that the dose level assigned to a newly enrolled patient depends on the dose level assignments and dose limiting toxicity outcomes of the patients already in the study. A patient's observation period ends at the occurrence of a DLT or, if a DLT does not occur, after a fixed time T of follow-up. The trial ends when a fixed number of patients, n, have been observed. Once the final patient has been observed, the MTD can be estimated using the available data.

The TITE-CRM differs from the traditional CRM in that the estimation process is weighted to account for the proportion of the observation period that each currently enrolled patient has been observed. By not requiring complete observation before the enrollment of the next patient, new participants can be assigned a dose and begin evaluation as they become available, subsequently shortening the overall duration of the study.

The Biostatistics Unit at the University of Michigan Comprehensive Cancer Center has developed a program titecrm.sas for SAS 9 (SAS Institute, Inc.; Cary, NC) that makes all of the calculations necessary to determine dose allocation of a trial in real-time. They have also developed simulation programs that allow the user to determine the efficacy of the trial based on *a priori* estimates of the probabilities of toxicity and necessary sample sizes.

In order to properly utilize this type of trial, a few assumptions and many rules must be determined before the start of the trial. The main assumption that must be determined is how many different dose levels will be included in the trial and *a priori* estimates of the probability of a DLT at each of those dose levels. For this trial, we have 5 dose levels listed below (d_1,…, d_5), with initial toxicity probability estimates (p_1,…, p_5) ranging from 0.05 to 0.25, respectively. The following table shows the dose design with associated estimated probabilities of toxicity.

Dose Level	Number of fractions of IMPT	PTV Dose/fx (Gy)	PTV Total Dose (Gy)	PTV Standard BED (Gy_{10})	PTV EQD2
-1	5	5	25	37.50	31.25
1 Starting Level	**5**	**6**	**30**	**48.00**	**40.00**
2	5	7	35	59.50	49.58
3	5	8	40	72.00	60.00

10.1.2 TITE-CRM design

The starting dose can have a large impact on the properties of the design. After the trial is completed, most information about the MTD will be obtained if many patients are treated at or near the MTD. Thus, the sooner the choice of dose can converge on the MTD the more effective the trial will be. However, due to the uncertainty of the MTD in the reirradiation of locoregionally recurrent rectal cancer, we will start at the two dose levels lower than the expected MTD to prioritize safety. Therefore, our starting dose for this trial will be PTV total dose of 30 Gy.

The next thing to be considered is the dose escalation rules. For this trial, we will only allow a single dose level escalation per new patient enrolled on the trial.

Therefore, if the previous patient was treated at dose level, d_k, then a new patient can only be treated at dose levels d_{k+1} or lower. In order to determine at which level to treat the new patient, we will use a weighted, cumulative time of exposure approach.

The total length of follow-up for DLT for any patient is 6 months from the start of radiation therapy. In order to efficiently and effectively determine the MTD, we allow for a dose change when the cumulative time of exposure is 6 months. Additionally, since previously published data shows that most toxic events occur within the first 6 months from start of treatment, we also implement a linear weighting function wherein the first 6 months accounts for 75% of the follow-up where the last 3 months attributes 25% of the follow-up information. The dose for the next patient is selected so that the estimated probability at that dose is close to the target level.

A feature of the dose escalation part of the TITE-CRM program is the flexibility in specifying the margin for the dose selection. This allows the selection of the dose level for the next patient that may have an estimated probability of toxicity larger than the target level but less than the target level plus the margin. It finds the dose closest to the target probability even if it has a higher estimated probability. For this trial we set the admissible margin to be 5%, therefore, the MTD will be chosen as the dose that yields a posterior toxicity estimate closest to 35% while being between 30% and 40%. The admissible margin is also used to help determine stopping rules for the trial.

In order to account for the possibility of poor initial outcomes we will employ a run-in of 6 patients, meaning that the minimum number of treated patients will be 6. If after these 6 patients, or any other time during the trial, the lowest dose level has a posterior probability higher than 40% then the trial will stop.

10.2 Simulation and Sample Size Calculations

The TITE-CRM manual details methods for utilizing trial simulation in order to obtain estimated posterior probabilities on toxicity estimates. We utilized the simulation program to determine the efficacy of our trial and obtain estimates for needed sample size. While there is no exact power calculation for this type of trial, the effectiveness of the trial's sample size can be determined by looking at the stability of the posterior probability under different prior probabilities.

We ran 1000 simulations under various increasing and decreasing prior probability estimates utilizing the previously described rules and assumptions for this trial and saw sufficient stability in posterior probability estimates with a sample size of 20 patients with a run-in of 6 patients. Simulations showed that approximately 95% of the time the trial will come to completion and the MTD will fall between the 3rd and 5th dose level 89% of the time. Therefore, we will use a fixed sample size of 20 patients for this trial. The posterior probability distribution of these 1000 simulations follow in the next table.

Dose Level	Estimated initial toxicity	Mean Posterior toxicity (SD)
d-1	0.25	0.328 (0.434)
1 (Starting Dose)	0.30	0.38 (0.453)
2	0.35	0.43 (0.463)
3	0.40	0.479 (0.464)

Summary of simulation with estimated posterior probabilities. SD, Standard Deviation

10.2.1 Workflow

The first patient will be enrolled on the trial and treated at PTV total dose 30 Gy, which is one dose level below the hypothesized MTD. That patient will be entered into the titecrm.sas program and follow-up will begin from start of treatment.

For the purposes of this trial, the patient will be followed from start of treatment until the patient completes 12months of follow-up, has a DLT, or is lost to follow-up. If any of these endpoints occur, the statistician will be notified and the date corresponding to the event will be entered into the program. While there is a maximum follow-up of 6 months for observation of possible toxicities, sometimes patients have a delay in their treatment resulting in the need for a prolonged observation period. This delay will be accounted for, as needed, for this study to ensure a complete 6-month follow-up.

When a new patient is enrolled on the trial, the statistician will be notified of the date of enrollment. At that time the statistician will update the follow-up for all patients currently on the trial and determine the dose that will be administered for the new patient. We will utilize the cumulative time of exposure method, which will allow the contribution of patients with no DLT at this time to be partially weighted consistent with their time observed. We will also utilize the weight function to place more emphasis on the first 6 months follow-up (75% weight) compared to the last 3 months of follow-up (25% weight). At this point, the program provides a summary of the number of patients treated at each dose so far, along with the number of DLTs that have occurred. The posterior probability and 95% credible intervals of dose limiting toxicity for each dose level is calculated. At this point, the model determines the dose level that has an estimated toxicity rate closest to 35% within the 5% admissible margin.

The newly enrolled patient will be enrolled in the corresponding dose level if that dose level is within one dose level from the dose level the most current patient is enrolled on. If the suggested dose level is more than one dose level from the current dose level the next patient will be enrolled on the dose level that is closest to the current level in the direction of the dose level determined from the estimated

posterior probability. This continues until the trial has accrued all 20 patients or, if after 6 patients are enrolled, the estimated posterior.

10.2.2 Recommended Phase 2 Dose

The MTD will be estimated using the proposed TITE-CRM model. After the phase I study, the MTD will be chosen as the dose that yields a posterior toxicity estimate closest to 35% while being between 30% and 40%.

10.2.3 Replacement of Subjects that are not Evaluable

Patients who withdraw from the dose escalation component of the trial for any other reason than toxicity and who have not already developed a dose-limiting toxicity (DLT) at that point will be replaced by recruiting another patient at the same dose level.

10.2.4 Stratification Factors

There is no stratification in this trial.

10.2.5 Analysis Plan

The primary endpoint of the study is to determine the maximum tolerated dose (MTD) of reirradiation using hypofractionated IMPT for patients with locoregionally recurrent rectal cancer. The MTD will be defined as the dose associated with a 35% probability of dose-limiting toxicity (DLT) as described above.

The secondary endpoints are clinical complete response rate, freedom from locoregional progression (FFLP), overall survival (OS), progression-free survival (PFS), PRO QOL, and adverse events as defined by CTCAE version 5.

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.

All the survival events will be measured from the end of radiation therapy and subjects who do not develop events will be censored at the last follow-up. Patients with distant metastasis will be continued to be followed for locoregional tumor recurrence until the last follow-up or time of death whether. Death will be analyzed as a competing cause in FFLP. Kaplan-Meier curves will be performed to compare the freedom from locoregional progression (FFLP), progression-free survival (PFS) and overall survival (OS). Cox proportional hazard model with log-rank test will be used to explain the correlation between explanatory variables and survival times.

Adjusted hazard ratios (HR) and the corresponding 95% confidence intervals (CI) will be reported.

PRO QOL questionnaires (Appendix B and C) will be tabulated for each domain and summed to generate a composite global QOL score. Repeated measures ANOVA will be used to compare QOL scores collected at baseline and at 1-2 weeks, 3 months, 6 months, 9 months, and 12 months after RT.

Adverse events or treatment-related toxicities will be classified as acute (<3 months after RT completion) toxicities and late (3-12 months after RT completion) toxicities. Adverse events, along with their maximum grade and relationship to study treatment, will be tabulated and assessed descriptively for patterns of occurrence. Frequency tables will include frequencies and percentages at the patient level as well as at the AE level. Point estimates for proportions will be reported, along with small sample confidence interval estimates.

All analyses will be performed in R (RFoundation for Statistical Computing) or in SAS (SAS Institute, Inc.; Cary, NC).

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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: EORTC QLQ-C30 Quality of Life of Cancer Patients

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX C: EORTC QLQ-CR29 Colorectal QOL

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

APPENDIX D: 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 E: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
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	
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 participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report 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 F: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
To determine the MTD of reirradiation using hypofractionated IMPT.	
Secondary	
To determine the clinical complete response rate of patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	
To estimate median freedom from locoregional progression (FFLP) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	
To estimate median overall survival (OS) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	
To estimate median progression-free survival (PFS) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	
To evaluate patient reported outcomes (PRO) in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT via QOL questionnaires.	
To evaluate the toxicity profile of hypofractionated IMPT in patients with locoregionally recurrent rectal cancer.	
Exploratory	
To explore the prognostic value of serum SCCA in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT.	
To evaluate the changes in serum inflammatory markers, CRP and LDH, in patients with locoregionally recurrent rectal cancer who receive hypofractionated IMPT	

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, describe.

In order to account for the possibility of poor initial outcomes we will employ a run-in of 6 patients, meaning that the minimum number of treated patients will be 6. If after these 6 patients, or any other time during the trial, the lowest dose level has a posterior toxicity probability higher than 40% then the trial will stop.

Please complete the table below.

Have any patients experienced a DLT?	**If yes, provide UPN(s).**	**If yes, specify AE.**

Treatment Response							
UPN	**Dose Level**	**On tx date**	**# fx received**	**DLT?**	**Best response**	**Replaced?**	**Date of progression**

Survival				
UPN	**Off tx date**	**Reason off tx**	**Date of death**	**Cause of death**