Non-Operative Radiation Management of Adenocarcinoma of the Lower Rectum (NORMAL-R)

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Clinicaltrials.gov #: NCT02641691

CONFIDENTIAL

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Protocol Revision History

Initial Approval Version	01/12/2016
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Amendment #2 Version	11/28/2016
Amendment #3 Version	11/14/2017
Amendment #4 Version	06/01/2018

Non-Operative Radiation Management of Adenocarcinoma of the Lower Rectum (NORMAL-R)

Principal Investigator Signature Page

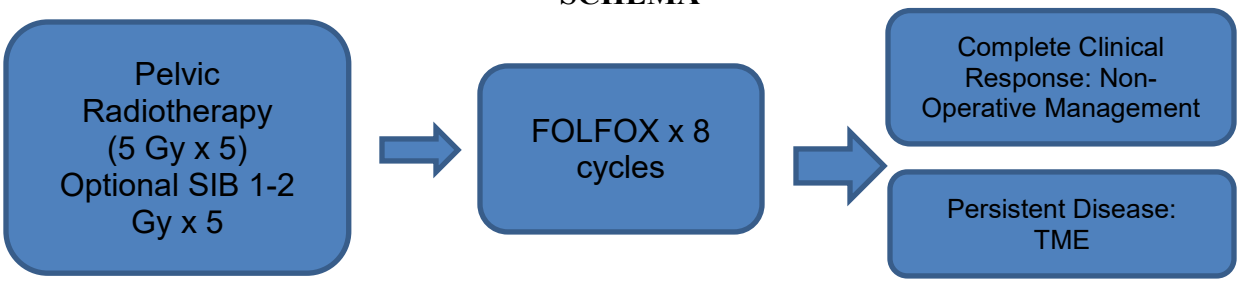
Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

SCHEMA



Primary Objective

To determine the clinical response rate of patients with Stage I-IIIB (cT1-3, N0-1, M0) rectal cancer being treated with sequential short course radiotherapy followed by 8 cycles of multi-drug chemotherapy.

Secondary Objectives:

1. To obtain prospective patient reported outcomes from an organ preservation approach towards early stage rectal cancer
2. To determine the incidence of any grade ≥ 3 toxicity during treatment
3. To determine the incidence of post chemoradiotherapy grade ≥ 3 toxicity at 1 year
4. Determine quality of anorectal function at 1 year using the FACT-C questionnaire

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1 BACKGROUND

With the exception of a small group of favorable risk stage I disease, the standard of care for stage I-III rectal cancer usually includes a total mesorectal excision (TME). TME in the form of an abdominoperineal resection (APR) results in a permanent stoma, which may significantly impact the patient's self-image and quality of life (QOL). TME in the form of a low anterior resection (LAR) obviates the need of an ostomy but is associated with poorer rectal function.

There are increasing data supporting the use of chemotherapy and radiation therapy for non-operative management of rectal cancer[1–4]. Habr-Gama et al. treated 70 distal rectal cancer (T2-4 N0-2) patients with 54 Gy in 30 fractions and concurrent 5-fluorouracil (5FU)/leucovorin and demonstrated an initial complete clinical response (cCR) in 47 (68%) patients with 39 (57%) demonstrating a sustained cCR at 56 months[4]. Appelt et al. treated 55 patients (T2-3 N0-1) with 60 Gy in 30 fractions with a 5 Gy brachytherapy boost plus oral tegafur-uracil[5]. Seventy-eight percent of patients demonstrated cCR with 16% local recurrence at 24 months[5]. Maas et al. found that patients with cCR after neoadjuvant chemoradiation therapy have similar oncologic outcomes to those with pathologic complete response (pCR)[6]. The radiation in these trials was delivered over 5-6 weeks of daily treatment.

Short course radiation therapy delivered as 25 Gy in 5 fractions is routinely used as preoperative therapy in Europe and Australia[7–9]. The first Polish rectal study demonstrated that patients with T3-4 resectable rectal cancer treated with 25 Gy in 5 fractions followed by surgery versus 50.4 Gy in 28 fractions with concurrent 5FU followed by surgery had similar local recurrence (9% vs 14%), disease free survival (58% vs 56%) and overall survival (67% vs 66%)[8]. The second Polish rectal trial demonstrated that there was no difference in R0 resection and pCR rates in patients with T3-4 rectal cancer treated with 25 Gy in 5 fractions followed by FOLFOX then surgery compared to 50.4 in 28 fractions with FOLFOX followed by surgery[9]. There was even a 3 year overall survival advantage for short course radiation (73% versus 65%), but the reason for this survival advantage in light of a non-significant difference in disease free survival is unclear. Important to note is that the dose prescribed with pre-operative short course radiation (5 Gy x 5 fractions) has a biologic effective dose (BED) of 37.5 Gy (α/β=10) in contrast to the BED of 63.7 Gy when 54 Gy is given in 30 daily fractions. Increasing the radiation dose to the tumor may further increase the clinical complete response (cCR) rate and allow for non-operative management.

There are increasing data to support increasing the interval from radiation to surgery. The pCR rate of standard short course radiation followed by surgery 1 week later is approximately 1%[7,8]. Increasing the interval to surgery from 2 to 6-8 weeks may increase the pCR rate without compromising oncologic outcomes[10–12]. The Lyon R90-01 trial demonstrated that patients with T2 rectal adenocarcinoma treated with 39 Gy in 13 fractions had increased pCR if surgery is delayed to 6-8 weeks post-radiation versus 2 weeks post-radiation (26% vs 10%)[10]. In the non-inferiority Stockholm III, which evaluated short course radiation followed by surgery at 1 versus 4-8 weeks versus long course radiation therapy, there were no differences in long term cancer outcomes between the three treatment groups[13]. Thus increasing the interval from radiation completion to surgery may improve treatment outcomes.

In a phase II trial for patients with cT3-4, any N, any M rectal cancer recently completed at Washington University (HRPO# 09-0696) evaluating short-course radiotherapy followed by 4 cycles of FOLFOX chemotherapy (5FU, oxaliplatin, and leucovorin), a complete tumor response was seen in 28% of patients, with a complete pathologic response rate of 42% and downstaging rate of 87% for patients with lower risk tumors (3). QOL data was prospectively evaluated using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire. Mean FACT-C scores for all five categories were not significantly different for pre-treatment (20.6 +/- 5.6), pre-surgery (20.2 +/- 5.4), or post-surgery time points (20.0 +/- 5.4) ($p = 0.8$), confirming clinically observed absence of treatment related toxicity. Improved patient-reported functional outcomes were observed for patients undergoing sphincter sparing surgery, compared to those requiring an abdominoperineal resection with ostomy, In patients with an ostomy, FACT-C scores for functional well-being 1-year post-surgery were significantly reduced (lower QOL) compared to patients without ostomy (13.2 vs 19.2, $p = 0.01$) (2). Given the negative quality of life impact of abdominoperineal resection with ostomy, it is plausible that the side effect profile of radiation therapy and chemotherapy may allow improved overall quality of life in the context of an organ preservation strategy.

To date, short course radiation therapy has not been evaluated in the setting of non-operative management. Given the highly favorable response rates reported in higher risk stage II-III patients and patient-reported outcomes data which confirm a benefit to sphincter sparing approaches, we propose a pilot study of organ preservation treatment for rectal cancer which would otherwise require total mesorectal excision (TME).

2 OBJECTIVES

Our principal objectives in this trial will be to determine if short course radiotherapy followed by 8 cycles of chemotherapy results in cCR , to permit an organ preservation strategy for patients with stage I-IIIB (cT1-3, N0-2, M0) rectal cancer. We do not anticipate being able to prove this in the present single arm pilot study; that would be the principal objective of a successor, multi-institution phase II/III protocol.

2.1 Primary Objective

To determine the cCR response rate of patients with stage I-IIIB (cT1-3, N0-2, M0) rectal cancer being treated with sequential short course radiotherapy followed by 8 cycles of multi-drug chemotherapy.

2.2 Secondary Objectives

1. To obtain prospective patient reported outcomes from an organ preservation approach for early stage rectal cancer.
2. To determine the incidence of any grade ≥ 3 toxicity during treatment.
3. To determine the incidence of post chemoradiotherapy grade ≥ 3 toxicity at 1 year
4. To determine quality of anorectal function at 1 year using the FACT-C questionnaire.

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Diagnosis of biopsy proven stage I-IIIB (cT1-3, N0-2, M0) adenocarcinoma of the rectum; staging must also be based on multidisciplinary evaluation including MRI and/or endorectal ultrasound
2. Tumor ≤ 12 cm from anal verge as determined by MRI or endoscopy
3. ECOG performance status 0-2
4. At least 18 years of age
5. Adequate bone marrow function defined as:
   a. ANC > 1,500 cells/mm^3
   b. Hgb > 8 g/dl
   c. platelets >100,000 cells/mm^3
6. 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.
7. Able to understand and willing to sign an IRB-approved written informed consent document.

3.2 Exclusion Criteria

1. No clinically detectable (MR, endoscopy or DRE) tumor present.
2. Prior radiation therapy, chemotherapy or extirpative surgery for rectal cancer.
3. Any evidence of disease from another malignancy or history of other malignancy ≤ 3 years previous (with the exception of basal cell or squamous cell carcinoma of the skin which 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.
4. Currently receiving any investigational agents.
5. A history of allergic reaction attributed to compounds of similar chemical or biologic composition to 5FU, oxaliplatin, or leucovorin.
6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
7. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test within 14 days of study entry.
8. Known HIV-positivity and on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with the study drugs. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive

therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

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 Patient Registration

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

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

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

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by

the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

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

5 EVALUATION STUDIES

5.1 Pre-treatment

Within 12 weeks of day of simulation for RT but no later than the first radiation treatment:

- Staging study to evaluate extent of disease in the abdomen and pelvis: CT with IV contrast or MRI w/ IV contrast.
- Staging study to evaluate the lungs: CT scan of the chest
- CBC, CMP, CEA
- Pregnancy test (for women of childbearing potential) – within 14 days of first treatment
- Colonoscopy
- Examination by treating surgeon, medical oncologist, and radiation oncologist

  If feasible it is strongly recommended that the following physical findings should be scored:
  - Tumor location (distance in cm from the anal verge to the distal tumor margin)
  - Circumferential lesion Y/N

- Imaging study to assess the local extent of the primary tumor, including T stage. A pelvic MRI is the preferred method for doing this; but depending on the lesion this could be endorectal ultrasound, or CT scan.
- FACT-C quality of life questionnaire

5.2 During Radiotherapy and Chemotherapy

Routine standard of care examinations and blood work will be done. This consists of a CMP and a CBC with differential prior to each cycle of chemotherapy and examination by the radiation oncologist during the week of radiation therapy and by a medical oncology physician or nurse with each cycle of chemotherapy. Please see Section 6 for radiation therapy guidelines and Section 7 for chemotherapy guidelines.

5.3 Completion of Chemotherapy/Post-Treatment Evaluation

Two to four weeks after completion of chemotherapy, patients will have the following assessments:

- FACT-C questionnaire.
- Surgical assessment w/ endoscopy (sigmoidoscopy preferred, rigid proctoscopy acceptable) to evaluate the extent of residual tumor
- MRI (when feasible) to evaluate ycT stage
- DRE (when feasible) to evaluate ycT stage

For patients with a cCR, non-operative management will be pursued. Patients will be assessed for sustained cCR by pelvic MR, endoscopy (sigmoidoscopy preferred, rigid proctoscopy accepted) and DRE every three months (not necessarily on the same day / appointment) for 1 year. Follow-up after 1 year will be left to the discretion of the treating physician, although DRE, pelvic MR and endoscopy every 3-4 months is recommended for the second year. CT chest/abdomen/pelvis every 6 months is recommended for at least the first 2 years. For patients with residual disease who do not meet criteria for cCR by 4 weeks after completion of the 8th cycle of FOLFOX, further therapy is mandated and at the discretion of the treating physicians. Patients whose disease is amenable to transanal endoscopic microexcision (TEM) or local excision (LE) may undergo TEM/LE to evaluate degree of residual disease. For those with pT1 disease without LVSI present, non-operative management may continue with evaluation noted above. For those with residual T2-3 disease or T1 with LVSI, extirpative surgery including TME is recommended with treatment at investigators discretion proceeding off-study.

Post-treatment lymph nodes are to be evaluated by imaging and reviewed in muldisciplinary tumor board with a radiologist and classified as progressive, persistent disease, indeterminate or benign. Patients with progressive or persistent lymph node disease will not be eligible for non-operative management and will undergo additional therapy. Patients with indeterminate or benign lymph nodes AND cCR of primary will undergo non-operative management.

5.4 Follow-up

The FACT-C questionnaire and follow-up visit will be done 10-14 months from treatment (radiotherapy) start date. Long-term follow-up will be done per routine policies of the treating physicians. It is recommended that there be follow up visits every 6 months with clinical exam until 5 years from study enrollment.

6 RADIATION THERAPY GUIDELINES

6.1 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.

Radiotherapy will consist of five fractions, delivered once daily, to a total dose of 25 Gy at 5 Gy per fraction (PTV2500). Daily imaging to verify accurate setup is mandatory. It is required that at least 95% of the PTVs receive at least 95% of the prescription dose and that the maximum dose be $\leq$ 115% of the prescription dose. Every effort should be made for 100% of the PTV to be covered by 95% of the prescription dose. The maximum allowed dose to small bowel is 25 Gy.

An optional concomitant boost may be delivered to the primary tumor of 1-2 Gy per day (30-35 Gy to tumor total). If a boost is given then the maximum allowed dose to small bowel is 25 Gy. Lymph nodes that are outside of the mesorectum may be boosted up to 35 Gy in 5 fractions also, as long as this small bowel constraint is met.

The following constraints are recommended when boosting lymph node or primary:
Bladder V20Gy < 15 cc. Dmax < 38 Gy.
Penile bulb V30Gy < 3 cc.
Femoral heads V30Gy < 10 cc.
Skin V36.5Gy < 10 cc. Dmax < 38.5 Gy.

6.2 Treatment Planning Procedures

Image-based treatment planning and intensity modulated radiotherapy (IMRT) is permitted. Proton therapy is not permitted. Dose volume histogram (DVH) information for the target volumes, small bowel, and uninvolved colon (defined to be large bowel outside the clinical target volumes) is mandatory. This is to assist in interpreting outcome, including morbidity.

6.3 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.

6.4 Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions

CTV2500 should include rectum and associated mesentery extending caudad at least to two cm below the distal edge of palpable disease. Superiorly it should include the rectum and its mesentery to the level of the rectosigmoid or two cm proximal to macroscopic disease, whichever is more cephalad. In addition, the internal iliac, internal obturator, and pre-sacral lymph node regions should be included. Contouring should be as per the RTOG

anorectal contouring atlas (www.rtog.org).

If the concomitant boost is prescribed then the GTV3500 is defined by radiographic findings and clinical exam, as per treating physician judgment. Pelvic MRI is required for patients to receive boost.

PTV2500 is generated by a uniform 0.7 cm expansion about CTV2500. PTV expansion for boost is 1-1.5 cm expansion off of the GTV (including mesorectum at the axial level of the GTV is at physician's discretion). 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.

6.5 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 CTV2500.

7 CHEMOTHERAPY GUIDELINES

7.1 Chemotherapy Schedule and Doses

Chemotherapy should begin 2 to 4 weeks after completion of radiotherapy and will consist of 5FU/leucovorin/oxaliplatin every other week for 8 courses (16 weeks). Alternatively, capecitabine/oxaliplatin (CAPE PO 1000 mg/m2 BID days 1-14 Q21 days, oxaliplatin IV 130 mg/m2 IV Q21 days on day 1) x 5 cycles over 15 weeks may be administered instead of FOLFOX. A maximum (total) delay of treatment of 4 weeks is allowed per protocol due to factors/AEs listed in this section. Cumulative delays in excess of 4 weeks will need to be discussed with the Principal Investigator. Such cases will need to be individualized depending on the clinical scenario.

7.2 Agent Administration

Folfox	**Dose**	**Route**	**Schedule**
Oxaliplatin*	85 mg/m^2	IV over 2 hours	On Day 1, Q 14 days
Leucovorin*	400 mg/m^2	IV over 2 hours	On Day 1, Q 14 days
5-FU Bolus*	400 mg/m^2	IV push	On Day 1, Q 14 days
5-FU Infusion*	2400 mg/m^2	IV CIIV	On Day 1, Q 14 days over 46 hours

*Administer sequentially as written, except oxaliplatin and leucovorin may be administered concurrently

CapeOx	Dose	Route	Schedule
Oxaliplatin	130 mg/m^2	IV	On Day 1, Q 21 days
Capecitabine	1000mg/m^2	PO BID	On Days 1-14, Q 21 days

Dose calculations should be based on actual weight and not corrected for obesity.

7.3 Supportive Care Recommendations

Veno-occlusive disease is a very rare AE associated with the administration of the combination of 5-FU and oxaliplatin. VOD disease is characterized by hepatomegaly, ascites, and jaundice. These signs and symptoms should prompt consideration of VOD. A Doppler ultrasound showing reversal of portal blood flow or other evidence of portal hypertension is suggestive of this diagnosis. In addition, standard clinical practice for evaluation of VOD should include observation of liver and spleen size, history of or gastrointestinal bleeding, development of esophageal varices, ascites, bleeding, or jaundice. All patients on and off therapy who develop signs and symptoms suggestive of VOD should be thoroughly evaluated and closely monitored and supported as clinically dictated.

Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, has been observed with oxaliplatin. These allergic reactions, which can be fatal, can occur within minutes of administration, and can occur during any cycle. There were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. These reactions are usually managed with standard epinephrine, corticosteroid, and antihistamine therapy, and require discontinuation of therapy.

Ice should be avoided during the infusion of oxaliplatin because cold temperatures can exacerbate acute neurological symptoms.

8 DOSE DELAYS/DOSE MODIFICATIONS

Radiotherapy for this trial may take place over a maximum of 10 business days before it is considered a protocol deviation. There are no dose adjustments (reductions, omissions) associated with radiotherapy.

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose modifications are based upon dose level administered at last treatment day. If the dose level has been reduced due to toxicity, re-escalation is not permitted. If dose reduction is required after dose level -3, patient will discontinue protocol therapy.

8.1 Dose Levels

Folfox	Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	40 mg/m^2
Bolus 5-FU	400 mg/m^2	300 mg/m^2	200 mg/m^2	100 mg/m^2
Infusion 5-FU	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2	1360 mg/m^2
Leucovorin	400 mg/m^2	400 mg/m^2	400 mg/m^2	400 mg/m^2

CapeOx	Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
Capecitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2	540 mg/m^2
Oxaliplatin	130 mg/m^2	104 mg/m^2	78 mg/m^2	70 mg/m^2

*Rounding capecitabine to nearest full tablet dose is acceptable (i.e. Dose 1900 mg rounded to 2000 mg (4x 500 mg tablets) daily).

8.2 Dose Modifications for Toxicity Related to FOLFOX and CapeOx

The provided dose modifications are strongly recommended. However, out of consideration of unforeseen clinical scenarios, dose modifications during FOLFOX chemotherapy are ultimately at the discretion of the primary treating provider. The use of 5-FU bolus is at the discretion of the treating physician. Modifications should be reported to the research coordinator. Refer to table 8.2 and 8.3 for guidance regarding suggested dose reductions and treatment delays, consistent with best oncologic practices.

Toxicity NCI Grade (Value)	Worst interval toxicity	Day of treatment
Neutropenia (ANC)		
Grade 1 (ANC < LLN – 1500/mm³)	Maintain dose level	If ANC < 1000 on day of treatment, hold and check weekly until ≥ 1000 mm³. Then treat based on interval toxicity. If ANC < 1000 after 4 weeks, discontinue therapy.
Grade 2 (ANC <1499 – 1000/mm³)		
Grade 3 (ANC <999 – 500/mm³)	Reduce 1 dose level	
Grade 4 (ANC < 500/mm³)		
Thrombocytopenia		
Grade 1 (PLT < LLN – 75,000/mm³)	Maintain dose level	If PLT < 75,000 on day of treatment, hold and check weekly until ≥ 75,000 mm³. Then treat based on interval toxicity. If PLT < 75,000 after 4 weeks, discontinue therapy.
Grade 2 (PLT 74,999 – 50,000/mm³)		
Grade 3 (PLT 49,999 – 25,000/mm³)	Reduce 1 dose level	
Grade 4 (PLT< 25,000/mm³)		
Diarrhea		
Grade 1	Maintain dose level	Hold chemotherapy if any grade of diarrhea above grade 1 is present with the patient not taking antidiarrheal agents within 24 hours of treatment. Reduce 5-FU and oxaliplatin 1 dose level upon resolution of diarrhea. If diarrhea has not resolved within 4 weeks of scheduled treatment day, discontinue therapy.
Grade 2	Reduce 5-FU and oxaliplatin 1 dose level	
Grade 3		
Grade 4		
Other nonhematologic toxicities (except neurologic, alopecia, anorexia, nausea/vomiting if can be controlled by antiemetics)		
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
Grade 3	Reduce 1 dose level	Hold until resolved to grade ≤1. Reduce 5-FU and oxaliplatin 1 dose level
Grade 4		

8.3 Dose Modifications for Neurologic Toxicity (Paresthesia or Dysesthesia) Related to Oxaliplatin

Grade	Duration of Toxicity		
	1 – 7 Days	> 7 Days	Persistent Between Doses
Grade 1 Short duration that resolves and does not interfere with function	No change	No change	No change
Grade 2 Interfering with function, but not activities of daily living (ADL)	No change	No change	Reduce oxaliplatin 1 dose level
Grade 3 With pain or with functional impairment that also interferes with ADL	1st time: reduce oxaliplatin 1 dose level 2nd time: reduce oxaliplatin another dose level	1st time: reduce oxaliplatin 1 dose level 2nd time: reduce oxaliplatin another dose level	Discontinue oxaliplatin
Grade 4 Persistent symptoms that are disabling or life-threatening	Discontinue oxaliplatin	Discontinue oxaliplatin	Discontinue oxaliplatin

9 ADVERSE EVENT REPORTING

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 9.2.

9.1 Definitions

9.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 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

9.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

9.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

9.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm

(including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

9.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

9.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

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

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.

- Noncompliance with federal regulations or the requirements or determinations of the IRB.

- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the

event or notification to the PI of the event.

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

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (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 a QASMC auditor.

9.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 9.2) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

9.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

9.6 Timeframe for Reporting Required Events

All Grade 3 and above adverse events should be collected until 1 year post start of radiation therapy on case report forms and reported to the QASMC as part of the DSM Report as applicable.

10 PHARMACEUTICAL INFORMATION

FOLFOX is a standard of care, FDA-approved regimen for the treatment of rectal cancer, and treatment will be provided and administered according to standard of care guidelines. More detailed information can be found in the products' package inserts.

10.1 Leucovorin

10.1.1 Mechanism of action

Leucovorin is a tetrahydrofolate acid derivative that acts as a biochemical cofactor for carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase for conversion to tetrahydrofolic acid. Leucovorin potentiates the effects of fluorinated pyrimidines like 5-FU. Leucovorin increases the folate pool, increasing the biding of folate cofactor and active metabolites of 5-FU.

10.1.2 Pharmacodynamics

Leucovorin is well absorbed after oral administration and is readily converted to 5-methyltetrahydrofolate after administration. Peak serum concentrations occur 1.7 to 2.5 hours after an oral dose. Leucovorin is excreted in the urine as metabolites and has a half-life of approximately 2-6 hours.

10.1.3 Availability

Leucovorin calcium is commercially available in: 50 mg, 100 mg, 350 mg vials for reconstitution.

10.1.4 Supplier(s)

Leucovorin is commercially available and will not be provided by this study.

10.1.5 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with Bacteriostatic Water for Injection (BWI) are stable for at least 7 days at room temperature.

10.1.6 Administration

Leucovorin may be reconstituted with BWI or with sterile water. Solutions should be further diluted in D5W, 0.9% NaCl or Ringers solution for infusion over two hours.

Leucovorin will be administered as a 400 mg/m^2 IV infusion over 2 hours. It may

be given either concurrent with (via a separate infusion line) or following oxaliplatin and immediately before fluorouracil.

10.2 5-Fluorouracil (5-FU)

10.2.1 Mechanism of Action

Fluorouracil, $C_4H_3FN_2O_2$, a pyrimidine antagonist, is an antimetabolite antineoplastic agent. Although the precise mechanisms of action of fluorouracil have not been fully elucidated, the main mechanism is thought to be the binding of the deoxyribonucleotide of the drug (FdUMP) and the folate cofactor, N5-10-methylenetetrahydrofolate, to thymidylate synthase (TS) to form a covalently bound ternary complex, which inhibits the formation of thymidylate from uracil, thereby interfering with DNA synthesis. In addition, FUTP can be incorporated into RNA in place of uridine triphosphate (UTP), producing a fraudulent RNA and interfering with RNA processing and protein synthesis.

10.2.2 Pharmacodynamics/kinetics

Absorption: Following IV administration of fluorouracil, no intact drug is detected in plasma after 3 hours.

Distribution: Fluorouracil is distributed into tumors, intestinal mucosa, bone marrow, liver, and other tissues. Despite its limited lipid solubility, the drug readily crosses the blood-brain barrier and distributes into CSF and brain tissue. Distribution studies in humans and animals have usually shown a higher concentration of the drug or its metabolites in the tumor than in surrounding tissue or in corresponding normal tissue. It has also been shown that there is a longer persistence of fluorouracil in some tumors than in the normal tissues of the host, perhaps due to impaired uracil catabolism. From these data, it has been suggested that the drug may possibly have some specificity against certain tumors in comparison with normal tissues.

Elimination: Following IV administration, the plasma elimination half-life averages about 16 minutes (range: 8-20 minutes) and is dose dependent. A small portion of fluorouracil is anabolized in the tissues to 5-fluoro-2-deoxyuridine and then to 5-fluoro-2-deoxyuridine-5-monophosphate, the active metabolite of the drug. The major portion of the drug is degraded in the liver. The metabolites are excreted as respiratory carbon dioxide and as urea, α-fluoro-β-alanine, α-fluoro-β-guanidopropionic acid, and α-fluoro- β-ureidopropionic acid in urine. Following a single IV dose of fluorouracil, approximately 15% of the dose is excreted in urine as intact drug within 6 hours; over 90% of this is excreted in the first hour.

10.2.3 Availability

Fluorouracil is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials.

10.2.4 Supplier(s)

5-FU is commercially available and will not be provided by this study.

10.2.5 Solution Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath. Bolus injections are prepared using undiluted drug. Continuous infusions of fluorouracil should be prepared for administration via ambulatory infusion pump according to the individual institution's standards. These solutions may be prepared in D5W or 0.9% NaCl.

10.2.6 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Slight yellow discoloration does not usually indicate decomposition. 5-FU is stable in syringes for up to 72 hours. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and dilution. Please refer to appropriate reference sources for additional information.

10.2.7 Administration

Fluorouracil will be given as a 400 mg/m^2 IV bolus injection followed by 2400 mg/m^2 continuous IV infusion over 46 hours.

10.3 Oxaliplatin

10.3.1 Mechanism of action

Oxaliplatin is a new platinum derivative with an oxalo ligand group. Although the exact mechanism of oxaliplatin's action remains unclear, the cytotoxicity of platinum compounds is thought to result from inhibition of DNA synthesis. Intrastrand platinum DNA adducts, the main cytotoxic lesions, are formed by cross-linking activated platinum species and specific base sequences, notably 2 adjacent guanine residues or 2 adjacent guanine-adenine bases.

10.3.2 Pharmacodynamics/kinetics

Time to peak concentration with a single 2-hour infusion of oxaliplatin 85 milligrams/square meter yielded a peak plasma concentration (Cmax) of 0.814 micrograms/milliliter. The area under the curve for total plasma platinum was 207-

290 mg/L x hr; ultrafilterable plasma platinum was 11.9-13.6 mg/L x hr. Oxaliplatin has 70 to 95% platinum-protein binding while 37% represents total platinum taken up by red blood cells (addition of oxaliplatin to whole blood). The volume of distribution is 440 liters after a single 2-hour infusion of 85 milligrams/square meter oxaliplatin. Oxaliplatin undergoes rapid and extensive (30%) nonenzymatic biotransformation. In vitro studies indicate no cytochrome P450-mediated metabolism. Oxaliplatin metabolites include approximately 17 different platinum containing derivatives with some being cytotoxic (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum). Breast milk – It is not known whether oxaliplatin is excreted into breast milk. Renal clearance is 9.3-17 liters/hour. Elimination half life: intravenous, total plasma platinum, alpha half-life (0.2-0.43 hours), beta half-life (15-16.8 hours), gamma half-life (252-391 hours). The decline of ultrafilterable platinum levels is triexponential with a relatively short alpha and beta half-life (0.43 hours and 16.8 hours) and a long terminal gamma half-life (391 hours).

10.3.3 Formulation

Molecular formula: $C_8H_{14}N_2O_4Pt$ with the chemical name of cis-[(1R, 2R)-1,2 cyclohexanediamine-N, N'][oxaloto (2-)-o, o'] platinum. Molecular weight is 397.3.

10.3.4 Availability

Oxaliplatin is formulated as a white freeze-dried powder in amber glass vials containing 50 mg and 100 mg of oxaliplatin in lactose monohydrate. Each vial is sealed with a stopper with a crimped aluminum cap. Drug will be ordered from commercial supply.

10.3.5 Supplier(s)

Oxaliplatin is commercially available and will not be provided by this study.

10.3.6 Solution Preparation

The freeze-dried powder is reconstituted by adding 10 to 20 ml (for the 50-mg vial) or 20 to 40 ml (for the 100-mg vials) of sterile water for Injection or 5% dextrose solution and then by diluting in an infusion solution of 250 ml or 500 ml of 5% dextrose solution. Avoid performing these manipulations with aluminum needles. The reconstitution or final dilution must never be performed with a sodium chloride solution.

10.3.7 Storage and Stability

Oxaliplatin freeze-dried powder may be stored at room temperature protected from light. Do not combine with alkaline medications or media, which cause oxaliplatin

to degrade. Do not use needles or intravenous infusion sets containing aluminum items (risk of degradation of oxaliplatin upon contact with aluminum) for the preparation or administration of oxaliplatin. Do not mix oxaliplatin with sodium chloride or other chloride containing solutions. Freeze-dried powder: The compound may be stored for 3 years at room temperature protected from light. Reconstituted solution: In 5% dextrose solution or sterile Water for Injection in the original vial, the solution may be stored for 24 to 48 hours at 2-80° C. Infusion solution: after dilution in 5% dextrose solution, the shelf-life is 24 hours at room temperature.

10.3.8 Administration

Antiemetic premedication (5-HT3 blocker with or without dexamethasone) is recommended. Cold temperatures can precipitate/exacerbate neurological symptoms-avoid during the infusion of oxaliplatin. Never reconstitute/dilute with a chloride-containing solution; avoid aluminum parts when preparing/mixing oxaliplatin. Incompatible with alkaline media (i.e., solutions of 5-fluorouracil). Prepare oxaliplatin in 250-500 mL D5W.

11 STUDY CALENDAR

	Screening[4]	During Radiotherapy	Day 1 of Each Cycle of Chemotherapy[8]	Completion of Chemotherapy[10]	10 to 14 Months after Radiotherapy	Long-term Follow-up[9]
Informed consent	X					
H&P	X	X (once)	X	X	X	
CBC diff, plts	X	X (once)	X			
CMP	X		X			
Pregnancy test[5]	X[6]					
Colonoscopy or barium enema or Hypaque enema	X[11]					
Surgical assessment with proctoscopy or sigmoidoscopy				X		
Digital rectal exam	X			X		
Staging study to evaluate disease in abdomen and pelvis[1]	X					
Staging study to evaluate disease in lungs[2]	X					
Imaging study to assess local extent of primary tumor[3]	X			X		
Radiotherapy		X[7]				
FOLFOX / CAPEOX			X			
FACT-C	X			X	X	

AE assessment	AEs should be collected through 1 year following the start of RT	

1. CT with contrast or MRI or PET/CT or PET/MRI
2. Chest x-ray or CT of the chest or PET/CT
3. Pelvic MRI (preferred), endorectal ultrasound, MRI, CT scan
4. Within 8 weeks of day of simulation for RT but no later than the first radiation treatment
5. Women of childbearing potential only
6. No more than 14 days prior to the first day of treatment
7. 5 fractions delivered over the course of 5 days (preferably starting on a Monday). Optional concomitant boost may be delivered to the primary tumor of 1-2 Gy per day (30-35 Gy to tumor total). If a boost is given then the maximum allowed dose to small bowel is 25 Gy.
8. Chemotherapy should start 2 to 4 weeks after the end of RT. Each cycle is 14 days; a total of 8 cycles of chemotherapy will be given
9. Long-term follow-up will be done per routine policies of the treating physicians. It is recommended that there be follow up visits every 6 months with clinical exam until 5 years from study enrollment. Data will be collected from the medical record every 6 months on progression/recurrence and survival.
10. 3-8 weeks after the end of chemotherapy
11. Within 12 weeks of day of simulation for RT but no later than the first radiation treatment

12 DATA SUBMISSION SCHEDULE

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

Form	Completion Schedule
On-Study Form	Time of registration
Radiation Therapy Form	Completion of RT
Chemotherapy Form	At the end of each cycle of chemotherapy
RECIST Form	Baseline Completion of chemoradiation
Follow-Up Form	1 year after the start of RT
FACT-C	Baseline Completion of chemoradiation 10-14 months after chemoradiation
Long-Term Follow-Up Form	Every 6 months for 5 years after the start of RT
Adverse Events Form	Ongoing

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

13 MEASUREMENT OF EFFECT

Criteria for complete clinical response:

- No residual gross tumor at procto/sigmoidoscopy, or only erythematous scar or ulcer
- No palpable tumor on DRE
- No radiographic evidence of tumor on MRI
- No suspicious mesorectal lymph nodes on MRI
- Negative biopsy from scar, ulcer, or former tumor site (if necessary according to surgeon's judgment)

Criteria for no significant clinical response:

- Residual disease by DRE, endoscopy or MR.
- Increase in primary tumor size upon clinical exam or imaging
- Any new lesions

14 DATA AND SAFETY MONITORING PLAN

Outcome, including response rates and patient morbidity, will be reviewed by the principal investigator with the medical oncology and surgery co-investigators (Drs. Singh and Hunt) every six months.

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

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

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

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

15 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

16 STATISTICAL CONSIDERATIONS

16.1 Study Objectives and Endpoints

Primary Objective:
Demonstrate that sequential short course radiotherapy followed by 8 cycles of multi-drug chemotherapy will elicit a rate of significant clinical response to allow an organ preservation approach for at least 30% (6/20) patients at 1 year.

Secondary Objectives

1. Obtain prospective patient reported outcomes from an organ preservation approach for early stage rectal cancer.
2. Determine the incidence of any grade ≥ 3 toxicity during treatment.
3. Determine the incidence of post chemoradiotherapy grade ≥ 3 toxicity at 1 year
4. Determine quality of anorectal function at 1 year by FACT-C

16.2 Study Design and Sample Size Justification

This pilot study is designed to demonstrate proof of concept for an organ preservation strategy applied to a low risk rectal cancer cohort. As such, the sample size is not determined by traditional power calculations, but rather by clinical judgment – if organ preservation is not possible in 30% of this initial cohort (6/20 patients), then the strategy will be abandoned. If at least 30% of patients at 1 year may be treated with organ preservation, then the concept may proceed to a separate phase II approach.

16.3 Interim Analyses and Stopping Rules

An interim analysis will be performed on the primary endpoint once 10 subjects have been enrolled and have completed the evaluation after chemotherapy. There will be possible early stopping if less than 2/10 of the initial patients enrolled who complete radiotherapy and chemotherapy remain potential candidates for organ preservation.

16.4 Definition of Evaluability

Patients who have completed all radiotherapy and chemotherapy will be considered evaluable for analysis. Patients who are inevaluable for the primary endpoint will be replaced.

16.5 Data Analysis

Demographic and clinical characteristics of the sample, as well as response, toxicity by grade and loss to follow up will be summarized using descriptive statistics. Incidence of grade 3 or higher acute toxicities (overall and gastrointestinal), incidence of organ preservation will be calculated. Descriptive statistics from the FACT-C questionnaire will be generated for evaluation of anorectal function at 1 year. The incidence of post radiotherapy grade 3 or higher toxicities at 1 year will also be provided.

16.6 Accrual

Assuming 10% inevaluable cases, the overall accrual will be 22 patients. The rate of accrual for the study is expected to be about 8 patients per year. It is expected that the accrual period of the study will be completed in about 3 years.

17 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.

- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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Appendix A: FACT-C Questionnaire

Patient ID#: _____ Date of Completion: _____

FACT-C (Version 4)

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

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

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient ID#: _____ Date of Completion: _____

FACT-C (Version 4)

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

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

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

Patient ID#: _____ Date of Completion: _____

FACT-C (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Q2	Do you have an ostomy appliance? (Mark one box)	☐ No		or	☐ Yes	
	If yes, please answer the next two items:					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4