RADIATION THERAPY ONCOLOGY GROUP

RTOG 0822

A PHASE II EVALUATION OF PREOPERATIVE CHEMORADIOTHERAPY UTILIZING INTENSITY MODULATED RADIATION THERAPY (IMRT) IN COMBINATION WITH CAPECITABINE AND OXALIPLATIN FOR PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER

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INDEX

Schema

Eligibility Checklist

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations/Management

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Tissue/Specimen Submission

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Study Parameters
Appendix III - Performance Status Scoring
Appendix IV - Staging System
Appendix V - Capecitabine BSA Dose Calculation Tables
Appendix VI - Pathologic Assessment of a Rectal Cancer Specimen
Appendix VII - Blood Collection Kit Instructions

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SCHEMA

REGISTER*	**Radiation Therapy**† Pelvic IMRT: 45 Gy in 25 fx 3D-CRT boost: 5.4 Gy in 3 fx to total dose of 50.4 Gy in 28 fx *PLUS* **Concurrent Preoperative Chemotherapy**‡ Capecitabine, Oxaliplatin ↓ *(4-8 wks)* **Surgery**§ ↓ *(4-8 wks)* **Postoperative Chemotherapy**‡ FOLFOX

*** See Section 5.0 for pre-registration requirements.**
† See Section 6.0 for radiation therapy details.
‡ See Section 7.0 for drug therapy details.
§ See Section 8.0 for surgery details.

Patient Population: (See Section 3.0 for Eligibility)

- Pathologically proven diagnosis of adenocarcinoma of the rectum (located up to 12 cm from the anal verge on flexible endoscopy) within 8 weeks of registration
- Clinically determined to be T3 or T4 and N0-2, M0

Required Sample Size: 75 patients

RTOG Institution #
RTOG 0822
Case #

ELIGIBILITY CHECKLIST (4/29/08)
(page 1 of 4)

_____(Y) 1. Does the patient have pathologically confirmed adenocarcinoma of the rectum (located up to 12 cm from the anal verge on flexible endoscopy) within 56 days of registration?

_____(N) 2. Does the malignant disease extend into the anal canal?

_____(Y) 3. Is the clinical T stage 3-4, N stage 0-2, and M0?

_____(Y/N) 4. Is the clinical T stage T3?

_____(Y) If yes, was transrectal ultrasound performed within 56 days of registration?

_____(Y) 5. Has the patient had within 56 days prior to registration: (a) a colonoscopy; (b) biopsy; (c) FNA; (d) history and physical; (e) contrast-enhanced CT, MRI, or PET-CT of the abdomen and pelvis; and (f) chest x-ray or chest CT (if whole-body PET-CT not done)?

_____(Y) 6. Is the patient's Zubrod performance status 0-2?

_____(Y) 7. Is the patient ≥ 18 years of age?

_____(Y) 8. Has a CBC/differential been obtained within 14 days prior to registration that meets the requirements as specified in Section 3.1?

_____(Y) 9. Has a metabolic panel been obtained within 28 days prior to registration that meets the requirements as specified in Section 3.1?

._____(Y/NA) 10. Has a serum pregnancy test been performed within 14 days prior to registration on study (for female patients of childbearing potential)?

_____(Y/N) 11. Did the patient have a prior invasive malignancy (with the exception of non-melanomatous skin cancer?

_____(Y) If yes, has the patient been disease free for ≥ 3 years?

_____(N) 12. Has the patient had prior systemic chemotherapy for colorectal cancer?

_____(N) 13. Has the patient had prior radiation therapy to the region of the study cancer that would result in overlap of radiation therapy fields?

_____(N) 14. Does the patient have evidence of ≥ grade 2 peripheral neuropathy?

_____(N) 15. Has the patient had major surgery within 28 days of registration (other than diverting colostomy as specified in Section 9.1)?

_____(N) 16. Does the patient have synchronous primary colon carcinomas?

_____(N) 17. Does the patient have lack of physical integrity of the GI tract or malabsorption syndrome that would preclude feasibility of oral chemotherapy?

_____(N) 18. Has the patient participated in any investigational drug study within 28 days of registration?

ELIGIBILITY CHECKLIST (4/29/08)

_____(N) 19. Has the patient had a prior allergic reaction to oxaliplatin or capecitabine?

_____(N) 20. Has the patient had a transmural myocardial infarction within the last 6 months?

_____(N) 21. Does the patient have an acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?

_____(N) 22. Does the patient have chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration?

_____(N) 23. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects?

_____(N) 24. Does the patient have acquired immune deficiency syndrome (AIDS) based upon current CDC definition?

_____(N) 25. Does the patient have evidence of uncontrolled seizures, central nervous system disorder, or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance of oral drug intake?

_____(N) 26. Does the patient have known existing uncontrolled coagulopathy?

_____(Y/N) 27. Is the patient on anticoagulation medication?

_____(Y) If yes, has the patient been clinically stable for at least 2 weeks?

(Continued on the next page)

ELIGIBILITY CHECKLIST (4/29/08)

The following questions will be asked at Study Registration:

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the patient provided study-specific, signed consent prior to study entry?

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Calendar Base Date

_____ 17. Registration/randomization date: This date will be populated automatically.

(Continued on the next page)

ELIGIBILITY CHECKLIST (4/29/08)

_____ 18. Medical oncologist

_____(Y/N) 19. Tissue/Blood kept for cancer research?

_____(Y/N) 20. Tissue/Blood kept for medical research?

_____(Y/N) 21. Allow contact for future research?

_____(T3/T4)22. Clinical T stage

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background

Preoperative chemoradiotherapy is currently considered standard therapy for patients with locally advanced rectal cancer. Several important historical trials helped to establish trimodality therapy as the standard treatment for locally advanced rectal cancer almost 20 years ago.[1-3] The results of a recent large randomized trial comparing preoperative chemoradiation versus postoperative chemoradiation have clearly demonstrated that the toxicity is reduced and local control is improved with a neoadjuvant approach, thus representing the prevailing paradigm for treatment at this time.[4]

Historically, 5-fluorouracil (5-FU) has most commonly been employed concomitantly with external beam radiation as a radiosensitizer. However, in part because of patient convenience, it has become displaced in modern therapy by capecitabine, an orally active prodrug of 5-FU that has been shown to be equally efficacious in randomized studies.[5,6] Toward the improvement of results seen with capecitabine or 5-FU based chemoradiation, several institutions have explored the feasibility and efficacy of adding a second chemotherapeutic agent concurrent with capecitabine and radiation in the neoadjuvant treatment of locally advanced rectal cancer. Foremost among these have been oxaliplatin and irinotecan, owing to their proven success in the metastatic setting. Based on the early results in several pilot studies, these drugs appeared to be reasonably well tolerated when added to 5-FU and radiation therapy. These results, in part, led the Radiation Therapy Oncology Group (RTOG) to design and conduct a phase II randomized trial comparing capecitabine/oxaliplatin/radiation versus capecitabine/irinotecan/radiation in the neoadjuvant treatment of locally advanced rectal cancer (RTOG 0247).

Due to unexpectedly high grade 3-4 non-hematologic toxicity observed in both arms of the trial, accrual to RTOG 0247 was temporarily suspended. The toxicity experienced during neoadjuvant treatment was largely gastrointestinal and appeared to be consequent to excess cumulative gastrointestinal toxicity from both chemotherapy and radiation. In the irinotecan arm, 7/18 patients experienced grade 3-4 diarrhea. In the oxaliplatin arm, 5 patients had grade 3 diarrhea and 1 patient had grade 5 diarrhea. The trial was ultimately re-opened, but only after the capecitabine and oxaliplatin doses were decreased (825 mg/m^2 bid and 50 mg/m^2, respectively).

1.2 Rationale for Intensity Modulated Radiation Therapy in Rectal Cancer

Given that the dose-limiting toxicity in RTOG 0247 was gastrointestinal (not hematologic), modern highly conformal radiation therapy planning and delivery techniques could potentially reduce the radiation dose to the bowel and, consequently, reduce gastrointestinal side effects. The small bowel has been estimated to have a 5% risk of late toxicity at 5 years with doses of between 45 and 50 Gy.[7,8] The risk of grade 3 or greater bowel toxicity has been shown to increase with both total dose and with the volume of bowel irradiated to higher doses. Gallagher et al[9] have suggested that the absolute volume of small bowel irradiated to 45 Gy or higher is associated with an increased risk of late gastrointestinal toxicity. Intensity modulated radiation therapy (IMRT) has previously been demonstrated to be effective in reducing small bowel dose and resultant gastrointestinal toxicity in patients with other pelvic malignancies (cervical, endometrial, prostate).[10-12]

Research into the potential benefits of IMRT in the treatment of rectal cancer have only recently been undertaken.[13,14] In one study, Urbano et al[14] conducted a dosimetric analysis comparing three dimensional conformal radiation therapy (3D-CRT) and both forward and inverse planned IMRT with anywhere from 3 to 9 fields. They found that IMRT improved small bowel sparing when compared with 3D-CRT as much as by a 64% reduction in the amount of small bowel receiving 45 Gy. The differences in improvement between 5-, 7- and 9-field IMRT plans in sparing volume of bowel getting high doses was minimal, but they were all significantly better at sparing small bowel than the 3-field IMRT plan. The authors therefore concluded that the 5-field custom segmented IMRT plan appeared to be clinically promising.

The primary aim of this protocol is to test the feasibility of delivering IMRT concurrent with multiagent chemotherapy in a multi-institutional setting for the treatment of rectal cancer in the neoadjuvant setting. We hypothesize that by effectively reducing radiation to the small bowel,

there will be a consequent reduction in side effects—particularly acute gastrointestinal side effects, which have been prohibitory to higher doses of capecitabine and oxaliplatin in the recently completed RTOG 0247 study. If effective in reducing overlapping gastrointestinal toxicity through reductions in small bowel toxicity, IMRT would re-open research avenues such as dose escalation of chemotherapy and/or radiation therapy in the neoadjuvant setting, paving the way toward improving local control, pathologic complete response rates, and, ultimately, overall survival for our patients.

2.0 OBJECTIVES

2.1 Primary

2.1.1 To determine whether the incidence of acute (preoperative) grade 2-5 gastrointestinal toxicity associated with preoperative chemoradiotherapy is reduced by inverse-planned IMRT-based radiation treatment (when compared with conventionally delivered radiation treatment as was utilized in the capecitabine and oxaliplatin arm of RTOG 0247).

2.2 Secondary

2.2.1 To evaluate the feasibility of performing IMRT in a cooperative group setting for the treatment of rectal cancer.

2.2.2 To estimate the incidence of all toxicity (hematologic and non-hematologic) associated with protocol treatment in the preoperative period, the postoperative period, and overall.

2.2.3 To estimate the pathologic complete response rate following preoperative IMRT-based chemoradiotherapy.

2.2.4 To estimate the time to treatment failure and patterns of failure.

2.2.5 To correlate pre- and post-treatment levels of serum cytokines with symptoms during and pathological outcomes following preoperative chemoradiation therapy for rectal cancer.

2.2.6 To evaluate the rate of abdominoperineal resections (APR).

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically proven diagnosis of adenocarcinoma of the rectum (located up to 12 cm from the anal verge on flexible endoscopy) within 56 days of registration.
Diagnosis of rectal adenocarcinoma must be obtained by biopsy technique that does not completely excise the lesion (e.g., fine needle aspiration, core needle biopsy).

3.1.2 Clinically determined to be stage T3 or T4,N0-N2, and M0, based upon the following minimum diagnostic workup:

3.1.2.1 Colonoscopy within 56 days prior to registration

3.1.2.2 History/physical examination (including medication history screen for contraindications) within 56 days prior to registration

3.1.2.3 Contrast-enhanced imaging of the abdomen and pelvis either by CT, MRI, or PET-CT (whole body) within 56 days prior to registration. (**NOTE**: whole body PET-CT is preferred).

3.1.2.4 Chest x-ray (or CT) of the chest within 56 days prior to registration to exclude distant metastases (except for those who have had whole body PET-CT per Section 3.1.2.3).

3.1.2.5 Transrectal ultrasound (TRUS) within 56 days prior to registration is required to establish T stage, unless clinical exam, CT of the pelvis, and/or MRI demonstrates T4 lesion; in these cases TRUS is not required

3.1.3 Zubrod Performance Status 0-2

3.1.4 Age ≥ 18

3.1.5 CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:

3.1.5.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3

3.1.5.2 Platelets ≥ 100,000 cells/mm^3

3.1.5.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.6 Metabolic panel within 28 days prior to registration on study, with adequate liver and renal function defined as follows:

3.1.6.1 AST and alkaline phosphatase < 2.5 x upper limit of normal (ULN)
3.1.6.2 Bilirubin ≤ 1.5 ULN
3.1.6.3 Calculated creatinine clearance (CrCl) > 50 ml/min using Cockcroft-Gault formula as below:
CrCl male = (140 -age) x (wt. in kg) / (Serum Cr) x 72
CrCl female = 0.85 x (CrCl male)
3.1.7 Serum pregnancy test within 14 days prior to registration on study (for female patients of childbearing potential) (See also Section 4.1.2)
3.1.8 Patient must provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years
3.2.2 Prior systemic chemotherapy for colorectal cancer; note that prior chemotherapy for a different cancer is allowable. See Section 3.2.1.
3.2.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields
3.2.4 Severe, active comorbidity, defined as follows:
3.2.4.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 12 months
3.2.4.2 Transmural myocardial infarction within the last 6 months
3.2.4.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
3.2.4.4 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration.
3.2.4.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects
3.2.4.6 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
3.2.4.7 Evidence of uncontrolled seizures, central nervous system disorders, or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance of oral drug intake.
3.2.4.8 Known, existing uncontrolled coagulopathy. Patients on therapeutic anticoagulation may be enrolled provided that they have been clinically stable on anti-coagulation for at least 2 weeks.
3.2.4.9 Evidence of grade 2 or greater peripheral neuropathy
3.2.4.10 Major surgery within 28 days of study enrollment (other than diverting colostomy per Section 9.1)
3.2.5 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic
3.2.6 Prior allergic reaction to oxaliplatin or capecitabine
3.2.7 Any evidence of distant metastases (M1)
3.2.8 A synchronous primary colon carcinoma
3.2.9 Extension of malignant disease into the anal canal
3.2.10 Lack of physical integrity of the gastrointestinal tract (i.e., severe Crohn's disease that results in malabsorption; significant bowel resection that would make one concerned about the absorption of capecitabine) or malabsorption syndrome that would preclude feasibility of oral chemotherapy (capecitabine)
3.2.11 Participation in any investigational drug study within 28 days of study enrollment

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

See Appendix II; note that failure to perform these tests may result in assessment of a protocol violation:
4.1.1 Serum CEA

4.1.2 If serum pregnancy test per Section 3.1 was performed more than 14 days from the intended start of radiation therapy, another serum pregnancy test must be performed and confirmed negative within 14 days prior to radiation start.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for IMRT Treatment Approach

5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site at http://rpc.mdanderson.org/rpc/.

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this credentialing requirement on another RTOG IMRT study). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing Status Inquiry" and "RTOG."

5.1.2 The institution or investigator must complete a new IMRT facility questionnaire and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu.

Each institution must submit and successfully complete a protocol-specific Dry-Run Test (the treatment plan for the first patient to be treated at the site on this protocol), and a Rapid Review will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. The Dry–Run Test will be reviewed and the Rapid Review will be conducted by the ITC. Suggestions regarding protocol compliance will be forwarded to the participating institution by the ITC.

5.1.3 The treatment plans for subsequent patients enrolled at a site will not be required to be reviewed prior to treatment, but a review will be performed for protocol compliance at a later date. Instructions for submitting the dry run can be found on the Advanced Technology Consortium (ATC) web site, http://atc.wustl.edu.

Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. Notification will then be given to the institution from the RTOG RT Quality Assurance Department that the institution is eligible to enter patients onto this study.

5.2 Pre-Registration Requirements

5.2.1 **U.S. sites and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution's first case:

- IRB approval letter;
- IRB assurance number;
- Health Canada's TPD forms.

5.2.2 **Note: International sites** must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx .

Approved international sites fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution's first case:

- IRB approval letter;
- Federalwide Assurance (FWA) number.

5.3 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen),

and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: Intensity modulated radiation therapy (IMRT) is mandatory for all patients for the initial pelvic field encompassing the gross tumor and at-risk lymph nodes in the pelvis.

For specific questions or concerns regarding this section, please contact Dr. Michael Garofalo (see cover page for contact information).

Protocol treatment (chemotherapy and radiation therapy) should be initiated simultaneously on a Monday or Tuesday ≤ 21 days after protocol registration, with 5 days of consecutive treatment per treatment week strongly encouraged.

6.1 Dose Specifications

6.1.1 Treatment plans for patients on this protocol will consist of 2 phases: 1) the first phase will consist of inverse-planned IMRT-based treatment to the pelvis (rectum and draining lymphatics at risk) for a total of 45 Gy in 1.8 Gy daily fractions, and 2) the second phase will consist of a 3-dimensional conformal boost (a 3-field technique is suggested) to gross disease + a minimum 2 cm margin including all of the presacral space for an additional 5.4 Gy in 1.8 Gy daily fractions.

6.1.2 IMRT Dose Specifications

6.1.2.1 Inverse planning is required for the IMRT portion of treatment and planning constraints are provided in this section for both the planning target volume (PTV) as well as critical normal structures to be spared. Acceptable treatment plans will be established from a DVH-based analysis of the volumetric dose to both the PTV and critical normal structures to ensure that minimally acceptable constraints for each volume of interest have been met.

6.1.2.2 IMRT treatment to the pelvis will be planned to deliver a total of 45 Gy to the PTV in 25 fractions of 1.8 Gy over 5 consecutive weeks.

6.2 Technical Factors

6.2.1 Megavoltage equipment (minimum acceptable energy is 6 MV) capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required.

6.2.2 Inverse-planning capable software is required.

6.3 Localization, Simulation, and Immobilization

6.3.1 A custom immobilization device (such as Alpha Cradle or vac-loc bag) for supine patients is suggested to minimize setup uncertainty.

6.3.2 CT-based simulation (maximum 5 mm slice thickness) is required for this protocol and bowel exclusion techniques should be used when possible. Patients may be simulated supine or prone (if a belly board is utilized). Patients should be simulated in the "arms up" position whether prone or supine and with a full bladder.

6.4 Treatment Planning/Target Volumes

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

6.4.1 *The Gross Tumor Volume (GTV)* is defined as all known gross disease as determined from a combination of physical exam, colonoscopy, ultrasound, CT (and MRI or PET-CT if performed).

6.4.2 *The Clinical Target Volume (CTV)* is defined as the GTV plus areas considered at significant risk of harboring microscopic disease. The CTV for a T3 tumor should include all gross disease (rectal and nodal) as well as the internal iliac lymph nodes and the mesorectum (perirectal fat and the presacral space). The CTV for a T4 tumor will include the same structures as for a T3 tumor but will include the external iliac lymph nodes as well.

6.4.3 *The Planning Target Volume (PTV)* will provide a margin around the CTV to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty and to potential internal organ motion. By definition, the PTV will consist of a symmetrical 5 mm expansion around the CTV. In the event that PTVs extend outside of the skin surface, the clinician should manually trim the PTV contours to be 3-5 mm inside the outer skin (unless there is direct skin involvement).

6.4.3.1 The following are guidelines for generating CTV and a unified PTV.

- Rectal GTV (+1.5 cm radially, +2.5 cm craniocaudally) = CTV
- Nodal GTV + 1.5 cm symmetrical expansion = CTV
- Uninvolved iliac vessels + 1.0 cm = CTV (include external iliac if T4)
- Presacral lymphatic CTV is generated by contouring from mid S1-S5 and 8 mm tissue anterior to the anterior border of the sacral bone
- The mesorectum and perirectal lymphatics CTV is generated by utilizing anatomic landmarks:
  - Posterior Border: anterior border of the sacrum and gluteus maximus
  - Lateral Border: ileum, piriformis and obturator muscles
  - Anterior Border: should overlap by 1 cm into the bladder, vagina or prostate

6.4.3.2 The PTV is generated by expanding all of the above structures by 0.5 cm symmetrically and unifying them into one 3-dimensional volume for planning purposes.

6.4.3.3 Examples of contoured patients are available for review on the RTOG website at http://www.rtog.org/CoreLab/ContouringAtlases/Anorectal.aspx. These examples are an excellent resource for the contouring of normal structures as well as GTV, CTV and PTV design.

6.4.3.4 PTV planning dose-volume constraints:

- ≥ 98% of the PTV receives ≥ 93% of the prescribed dose
- ≤ 10% of the PTV receives ≥ 105% of the prescribed dose
- ≤ 5% of the PTV receives ≥ 110% of the prescribed dose
- None of the PTV is to receive ≥ 115% of the prescribed dose

6.5 Critical Structures (IMRT Planning Constraints)

6.5.1 Small bowel:

- No more than 180 cc above 35 Gy
- No more than 100 cc above 40 Gy
- No more than 65 cc above 45 Gy
- No small bowel volume should receive 50 Gy

6.5.2 Femoral heads:

- No more than 40% volume above 40 Gy

- No more than 25% volume above 45 Gy
- No femoral head volume should receive 50 Gy

6.5.3 Bladder:
- No more than 40% volume above 40 Gy
- No more than 15% volume above 45 Gy
- No bladder volume should receive 50 Gy

6.5.4 Unspecified Tissue:
- No specific constraints, however a DVH will be generated for "unspecified tissue" which consists of any tissue within the skin but not contoured as a part of any of the normal structures above and/or the PTV

6.6 Documentation Requirements

Orthogonal films or images are required for isocenter verification. The length of the treatment field shall be indicated on these films.

6.7 Compliance Criteria

6.7.1 The ITC will display (and compare with hard copies) isodose distributions through the planning target volume to verify correct digital submission and conversion.

6.7.2 The ITC will compare the submitted digital dose-volume histograms (DVHs) for the PTVs, the designated critical structures, and unspecified tissues with DVHs calculated by the ITC.

6.7.3 Each treatment will be remotely reviewed for Quality Assurance of target volumes and critical structures. The following criteria will be utilized to assess compliance and/or deviation:

6.7.3.1 ***PTV***
- Per protocol if the prescription criteria in Section 6.4.3.4 are fulfilled
- Variation acceptable if you fail to meet Section 6.4.3.4 constraints but can meet the following constraints:
  - ≥ 98% of the PTV receives ≥ 90% of the prescribed dose
  - ≤ 15% of the PTV receives ≥ 105% of the prescribed dose
  - ≤ 10% of the PTV receives ≥ 110% of the prescribed dose
- Deviation unacceptable if you fail to meet any of the above criteria.

6.7.3.2 ***Small Bowel***
- Per protocol if the prescription criteria in Section 6.5.1 are fulfilled
- Variation acceptable if you fail to meet Section 6.5.1 constraints but can meet the following constraints:
  - No more than 230 cc above 35 Gy
  - No more than 130 cc above 40 Gy
  - No more than 90 cc above 45 Gy
- Deviation unacceptable if you fail to meet any of the above criteria.

6.7.3.3 ***Femoral Heads***
- Per protocol if the prescription criteria in Section 6.5.2 are fulfilled
- Variation acceptable if you fail to meet Section 6.5.2 constraints but can meet the following:
  - No more than 65% volume above 40 Gy
  - No more than 40% volume above 45 Gy
  - No femoral head volume should receive 50 Gy
- Deviation unacceptable if you fail to meet any of the above criteria.

6.7.3.4 ***Bladder***
- Per protocol if the prescription criteria in Section 6.5.3 are fulfilled
- Variation acceptable if you fail to meet Section 6.5.3 constraints but can meet the following
  - No more than 55% volume above 40 Gy
  - No more than 30% volume above 45 Gy
  - No bladder volume should receive 50 Gy
- Deviation unacceptable if you fail to meet any of the above criteria.

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Investigator, Michael Garofalo, MD, will perform a remote RT Quality Assurance Review after ITC has received complete data for the first 20 cases enrolled. Dr. Garofalo will perform the next remote review after ITC has received complete data for the next 20

cases enrolled. The final cases will be reviewed remotely within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received, whichever occurs first. These reviews will be ongoing and performed remotely.

6.9 Radiation Treatment Interruptions

6.9.1 Treatment interruptions are discouraged; however, they may be necessitated by uncontrolled diarrhea or other acute complications. The reason for and length of any such interruption must be documented. If the sum total of such interruptions exceeds 5 normally scheduled treatment days, this would constitute a major treatment violation.

A minimum of 4 daily radiation therapy treatments are required in any given week. Any missed radiation treatments will be made up at the end of the treatment schedule, such that the total number of delivered 1.8 Gy fractions remains 28.

6.9.2 If chemotherapy is held, radiation therapy will continue.

Toxicity	XRT Dose
Grade 2 thrombocytopenia	Continue at current dose
Grade 3 thrombocytopenia	Hold until recovery to grade ≤1, then resume.
Grade 4 thrombocytopenia	Hold until recovery to grade ≤1 (platelets ≥ 75 $x10^9$/L), then resume.
Grade 3 neutropenia	Hold until recovery to grade ≤1 , then resume.
Grade 4 neutropenia	Hold until recovery to grade ≤1, then resume.
Grade ≥3 febrile neutropenia	Hold until resolution of fever and neutropenia to grade ≤ 1. Hold until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume treatment.

See Section 7.3.2.1 for dose modifications for diarrhea and Section 7.3.2.2 for dose modifications for nausea/vomiting.

6.10 Radiation Adverse Events

Side effects expected from radiation therapy include fatigue, rectal frequency, diarrhea, urinary frequency, dysuria, loss of pubic hair, hyperpigmentation of the skin in the treatment field, lower blood counts. Rare but possible side effects include small bowel obstruction, fistula, small bowel ulceration, wet desquamation, infection, and urethral obstruction.

6.11 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

See Section 7.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Radiation and chemotherapy should be initiated on a Monday or Tuesday ≤ 21 days of study enrollment, with 5 days of consecutive treatment strongly encouraged. For the first week of treatment, the capecitabine should be started the evening before the first radiation dose.

7.1 Treatment

7.1.1 Concurrent **preoperative chemotherapy** will begin on the first day of radiotherapy and continue until the completion of radiation therapy. Capecitabine (825 mg/m^2) will be administered orally twice daily, and oxaliplatin (50 mg/m^2) will be administered intravenously weekly x 5 weeks. Dose calculations should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation. A summary of preoperative chemotherapy is provided in table form below:

Agent	Dose	Route	Schedule
Capecitabine	825 mg/m^2 q12 hours (1650 mg/m^2/day) **Please refer to capecitabine dosing table in Appendix V for capecitabine dosing.**	oral	5 days per week during radiotherapy. The 1st dose will begin the evening prior to day 1 of RT. Begin all subsequent weekly courses on Sunday night, and end with Friday morning dose. Final dose of capecitabine is administered on the morning of the final radiation dose. If radiotherapy is held for administrative reasons (i.e., weekday holiday), capecitabine dose for that day will also be held.
Oxaliplatin	50 mg/m^2	IV over 2 hours	Weekly x 5; days 1, 8, 15, 22, 29

If any chemotherapy dose is missed, it should be documented as such and no effort will be made to make up the missed dose.

7.1.2 **Postoperative chemotherapy** will be administered to all patients who have a complete resection of rectal cancer with negative surgical margins and will begin no earlier than 4 and no later than 8 weeks following surgical resection. Patients with unresectable disease or involved margins will discontinue protocol therapy.

7.1.3 Postoperative chemotherapy will consist of a total of 9 cycles (each cycle = 14 days) of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). The dose, route, and schedule of FOLFOX delivery is summarized for ease of reference in table form below.

Agent	Dose	Route	Schedule
Oxaliplatin*	85 mg/m^2	IV over 2 hours	Day 1, every 14 days
Leucovorin*	400 mg/m^2	IV over 2 hours	Day 1, every 14 days
5-fluorouracil bolus*	400 mg/m^2	IV push	Day 1, every 14 days
5-fluorouracil infusion*	2400 mg/m^2	IV continuous infusion over 46 hours	Beginning day 1, every 14 days
*Administer sequentially as written, except oxaliplatin and leucovorin may be administered concurrently			

If any chemotherapy dose is missed, it should be documented as such and no effort will be made to make up the missed dose.

7.2 Study Agents

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.2.1 Capecitabine: Refer to package insert for additional information.

7.2.1.1 Other names

Xeloda

7.2.1.2 Classification

Antimetabolite, cytotoxic.

7.2.1.3 Mode of action

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) that is converted to 5-fluorouracil.

7.2.1.4 Storage and stability

Capecitabine should be stored at room temperature, excursions permitted to 15° to 30°C (59° to 86°F), with container tightly closed.

7.2.1.5 Administration

Tablets should be swallowed with water 30 minutes after the end of a meal (breakfast and dinner). If necessary, tablets can be crushed.

7.2.1.6 Availability

Capecitabine is supplied as a biconvex, oblong film-coat tablets for oral administration. Each light-peach colored tablet contains 150 mg capecitabine, and each peach colored tablet contains 500 mg capecitabine.

7.2.1.7 Supply

Commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.2.1.8 Adverse Events

- Blood: neutropenia, coagulation disorder, idiopathic thrombocytopenic purpura, pancytopenia
- Cardiac: angina pectoris, cardiomyopathy
- Constitutional Symptoms: Fatigue
- Dermatologic: Hand-foot syndrome (painful erythema and swelling of the hands and/or feet), increased sweating, photosensitivity, radiation recall syndrome, skin pigmentation changes (hyperpigmentation), alopecia, dry skin
- Gastrointestinal: Diarrhea, nausea, vomiting, anorexia, stomatitis, intestinal obstruction, rectal bleeding, GI hemorrhage, esophagitis, gastritis, colitis, duodenitis, hematemesis, necrotizing enterocolitis, taste changes
- Hepatobiliary: hepatic fibrosis, cholestatic hepatitis, hepatitis
- Infections: fever, oral candidiasis, upper respiratory tract infection, urinary tract infection, bronchitis, pneumonia, sepsis, bronchopneumonia, gastroenteritis, gastrointestinal candidiasis, laryngitis, esophageal candidiasis
- Immune System: drug hypersensitivity
- Hepatobiliary: hepatic fibrosis, cholestatic hepatitis, hepatitis
- Metabolism: cachexia, hypertriglyceridemia
- Musculoskeletal: bone pain, joint stiffness
- Neurological: ataxia, encephalopathy, depressed level of consciousness, loss of consciousness
- Ophthalmic: eye watering, eye irritation
- Psychiatric: confusion
- Renal and Urinary: nocturia
- Respiratory: dyspnea, epistaxis, bronchospasm, respiratory distress
- Vascular: hypotension, venous phlebitis and thrombophlebitis, deep venous thrombosis, lymphoedema, pulmonary embolism, cerebrovascular accident

7.2.1.9 Drug Interactions

- *Sorivudine and brivudin*: A metabolite of these investigational antiviral agents, 5-bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Patients should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine.
- *Phenytoin*: Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin, suggesting a potential interaction. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms

7.2.2 Oxaliplatin: Refer to package insert for additional information.

7.2.2.1 Other Names

Eloxatin, trans-l-diamino cyclohexane oxaliplatin, cis-[oxalato(trans-l-1,2-diamino cyclohexane)platinum(II)]/-OHP, Eloxatine , Dacplat, SR96669.

7.2.2.2 Classification

Alkylating agent. Cytotoxic.

7.2.2.3 Mode of Action

The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

7.2.2.4 Storage and Stability

Oxaliplatin vials are stored at room temperature between 20° and 25°C. Reconstituted solution in sterile water or 5% dextrose may be stored and will remain stable for 24 hours at 2°-8°C (36°-46°F).

7.2.2.5 Preparation

Reconstitute with 10 mL for 50 mg and 20 mL for 100 mg product sterile water or 5% dextrose to provide an initial concentration of 5 mg/mL. Subsequent dilution with 250-500 mL 5% Dextrose.

7.2.2.6 Administration

The diluted solution of oxaliplatin in 250 ml 5% dextrose is administered IV by an infusion pump over 2 hours.

7.2.2.7 Incompatibilities

Do not mix or administer with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride. Oxaliplatin may be administered simultaneously with leucovorin by the same infusion line, provided that they are reconstituted in D5W. Do not mix with alkaline solutions. Oxaliplatin is unstable under alkaline conditions. Do not use components containing aluminum for the preparation of oxaliplatin administration. There is a risk of drug degradation when in contact with aluminum.

7.2.2.8 Availability

Freeze-dried powder for IV infusion in vials containing 50 mg or 100 mg of oxaliplatin. The powder is a white to off-white cake or powder contained in clear glass vials, sealed with an elastomeric stopper and aluminum seal with a flip-off cover. The excipient is lactose monohydrate, 450 mg and 900 mg respectively.

7.2.2.9 Supply

Commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.2.2.10 Adverse Events

- Allergy/Immunology: Allergic/Hypersensitivity reactions (including drug fever)
- Auditory: Middle ear/hearing (ototoxicity, mild), inner ear/hearing (mild hearing loss)
- Blood/Bone Marrow: decreased hemoglobin, hemolysis (e.g. immune hemolytic anemia, drug-related hemolysis), decreased leukocytes, decreased platelets, neutropenia
- Cardiovascular (Arrhythmia): Sinus tachycardia, supraventricular arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmias (PVCs/ bigeminy/trigeminy/ventricular tachycardia)
- Cardiovascular (General): Edema, hypertension, phlebitis (superficial), thrombosis/embolism (including pulmonary embolism)
- Coagulation: DIC (Disseminated intravascular coagulation)
- Constitutional Symptoms: Fever (in the absence of neutropenia), weight loss, fatigue (lethargy, malaise, asthenia)
- Dermatology/Skin: Erythema or skin eruptions, alopecia, injection site reaction, rash/desquamation
- Endocrine: Hot flashes/flushes
- Gastrointestinal: Anorexia, constipation, dehydration, dysphagia, diarrhea, esophagitis, odynophagia (painful swallowing), gastrointestinal reflux, enteritis, ascites (NOS), intestinal obstruction, stomatitis/pharyngitis (oral/pharyngeal mucositis), taste disturbance (dysgeusia), nausea, vomiting, colitis, ileus (or neuroconstipation), typhilitis
- Hepatic: Increased alkaline phosphatase, increased bilirubin, increased GGT (gamma-glutamyl-transpeptidase), hepatic enlargement, increased AST (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase). Veno-occlusive disease of the liver has been reported with the administration of the combination of 5-FU and oxaliplatin.
- Hemorrhage: CNS hemorrhage/bleeding, hemoptysis, hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, melena/GI bleeding, rectal bleeding/hematochezia, other (hemorrhage NOS)

- Infection/Febrile Neutropenia: Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented fever (ANC < 1.0 x 10e9/L, fever > 38.5°C) infection (documented clinically or micro-biologically with grade 3 or 4 neutropenia (ANC < 1.0 x 10e9/L), infection without neutropenia
- Metabolic/Laboratory: Acidosis (metabolic or respiratory) hyperuricemia, hypokalemia, hypophosphatemia, hyponatremia, hypocalcemia, hypomagnesemia, hyponatremia
- Musculoskeletal: Involuntary muscle contractions
- Neurology: Ataxia (incoordination, including abnormal gait) insomnia, mood alteration (depression, anxiety) neuropathy cranial (ptosis), vertigo, neuropathy sensory (including acute laryngeo-pharyngeal dysesthesias, L'Hermitte's sign, paresthesia)
- Ocular/Visual: Conjunctivitis, vision abnormalities (including blindness, optic neuritis, papilledema, hemianopsia, visual field defect, transient blindness
- Pain: abdominal pain or cramping, arthralgia (joint pain), bone pain, chest pain (non-cardiac and non-pleuritic), headache (including migraine), myalgia (muscle pain including cramps and leg cramps)
- Pulmonary: Pulmonary fibrosis, cough, dyspnea (shortness of breath), hiccoughs (hiccups, singultus), pneumonitis/pulmonary infiltrates (including eosinophilic pneumonia, interstitial pneumonitis, and interstitial lung disease), laryngospasm
- Renal/Genitourinary: Increased creatinine, renal failure, urinary retention

7.2.3 5-Fluorouracil: Refer to package insert for additional information.

7.2.3.1 Other Names

5-FU, Adrucil, Efudex.

7.2.3.2 Classification

Antimetabolite.

7.2.3.3 Mode of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

7.2.3.4 Storage and Stability

Stable for prolonged periods of time at room temperature, if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

7.2.3.5 Administration

5-FU will be administered as an IV bolus and as a 46-hour infusion.

7.2.3.6 Availability

Available in 500 mg/10 ml ampules and vials, and 1 gm/20 ml, 2.5 gm/50 ml, and 5 gm/100 ml vials.

7.2.3.7 Supply

Commercially available.

7.2.3.8 Adverse Events

- Cardiac: Angina, noted with continuous infusion
- Constitutional: Fatigue
- Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia
- Gastrointestinal: Nausea, vomiting, anorexia, diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin; taste changes
- Hematologic: Leukopenia, thrombocytopenia, anemia, can be dose limiting; less common with continuous infusion
- Hepatic: Hepatitis with hepatic infusion
  Veno-occlusive disease of the liver has been reported with the administration of the combination of 5-FU and oxaliplatin.
- Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia)
- Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision

7.2.3.9 Drug Interactions

- *Allopurinol*: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.
- *Cimetidine*: Because cimetidine can decrease the clearance of 5-FU, patients should not enter on this study until the cimetidine is discontinued. Ranitidine or a drug from another anti-ulcer class can be substituted for cimetidine, as necessary.

7.2.4 Leucovorin Calcium: Refer to package insert for additional information.

7.2.4.1 Other Names

Leucovorin, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

7.2.4.2 Classification

Tetrahydrofolic acid derivative.

7.2.4.3 Mode of Action

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

7.2.4.4 Storage and Stability

All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/ml, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/ml the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light.

7.2.4.5 Preparation

The 50 and 100 mg vials for injection are reconstituted with 5 and 10 ml of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/ml solution. The 350 mg vial is reconstituted with 17 ml of sterile water resulting in a 20 mg/ml solution.

7.2.2.6 Compatibilities

Leucovorin (0.5-0.9 mg/ml) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin is also compatible with fluorouracil and oxaliplatin.

7.2.4.7 Availability

Available in parenteral formulations (3 and 5 mg ampule; 50 mg, 100 mg and 350 mg vial).

7.2.4.8 Supply

Commercially available.

7.2.4.9 Adverse Events

- Allergy/Immunology: Allergic/hypersensitivity reaction, urticaria

7.2.4.10 Drug Interactions: Leucovorin may potentiate the toxic effects of fluoropyrimidine therapy, resulting, for example, in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

7.3 PREOPERATIVE Dose Modifications

7.3.1 Hematologic Toxicity (Preoperative)

7.3.1.1 All adverse events should be graded according to the Common Terminology Criteria for Adverse Events (Version 3.0). The final dose modification according to the following tables should be based upon the worst grade of adverse event experienced.

7.3.1.2 If any of the treatment agents is held or discontinued for toxicity or intolerance, patients may continue on study with the remaining agents unless otherwise specified.

7.3.1.3 Held doses of capecitabine and/or oxaliplatin will not be made up at a later date. If more than one dose reduction applies, then use the most stringent (i.e., the greatest dose reduction). Doses that are reduced at any point during a cycle will not be re-escalated.

7.3.1.4 Grade 1 toxicities will not result in dose modifications

7.3.1.5 Preoperative dose levels are as follows:

	Capecitabine*	**Oxaliplatin**
Start Level	1650 mg/m^2/day	50 mg/m^2/week
Level -1	1237 mg/m^2/day	40 mg/m^2/week
Level -2	825 mg/m^2/day	32 mg/m^2/week

***Refer to capecitabine dosing table in Appendix V for capecitabine reduction doses.**

If the patient requires dose reductions lower than level -2 protocol therapy should be discontinued.

7.3.1.6 For hematologic toxicities listed below, in the case where there are concurrent toxicities, dose modification should follow the most stringent management (dose levels as defined earlier in this section). Patients who have capecitabine held should have oxaliplatin held until capecitabine is restarted. Patients may continue on radiation treatment as clinically indicated. (See Section 6.9 for XRT Dose Modifications)

Toxicity	**Capecitabine Dose Modification**	**Oxaliplatin Dose Modification**
Grade 2 thrombocytopenia	Continue at current dose	Continue at current dose
Grade 3 thrombocytopenia)	Hold until recovery to grade ≤1, then resume one dose level lower.	Hold until recovery to grade ≤1, then resume one dose level lower.
Grade 4 thrombocytopenia	Hold until recovery to grade ≤1, then resume one dose level lower.	Hold until recovery to grade ≤1, then resume one dose level lower.
Grade 3 neutropenia	Hold until recovery to grade ≤1, then resume one dose level lower.	Hold until recovery to grade ≤1, then resume one dose level lower.
Grade 4 neutropenia	Hold until recovery to grade ≤ 1, then resume one dose level lower.	Hold until recovery to grade ≤ 1, then resume one dose level lower.
Grade ≥ 3 febrile neutropenia	Hold until resolution of fever and neutropenia to grade ≤ 1. Hold until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume at the next lower dose level.	Hold until resolution of fever and neutropenia to grade ≤ 1. Hold until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume at the next lower dose level.

7.3.1.7 Capecitabine-Induced Hyperbilirubinemia (Preoperative)

Capecitabine is known to cause hyperbilirubinemia. Please follow the table below for instructions regarding management of hyperbilirubinemia. Patients with > grade 2 hyperbilirubinemia should

be evaluated with radiologic study for biliary obstruction. Patients who have capecitabine held for hyperbilirubinemia may continue on radiation therapy and oxaliplatin as clinically indicated.

Hyperbilirubinemia Grade	Capecitabine Adjustment
Grade 1	Continue capecitabine
Grade 2	Hold capecitabine until grade ≤1, then restart capecitabine at current dose
Grade 3	Hold capecitabine until grade ≤1, then restart capecitabine at current dose
Grade 4	Hold capecitabine until grade ≤1, then restart capecitabine at current dose

7.3.2 Nonhematologic Toxicity (Preoperative)

7.3.2.1 Diarrhea (Preoperative)

7.3.2.1.1 Capecitabine can cause diarrhea and must be stopped if diarrhea is ≥ grade 3. Diarrhea must be managed symptomatically. IV hydration and use of loperamide, as well as close observation, are recommended for diarrhea. For loperamide dosage recommendation and treatment start, see below. If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment, and possible investigation of DPD deficiency should be considered. Capecitabine cannot be re-started until diarrhea has resolved to grade < 2 with the last loperamide dose given at least 24 hours beforehand. The recommended dosage regimen for loperamide: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended.

7.3.2.1.2 The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

7.3.2.1.3 Patients with grade 3 diarrhea should also be evaluated for C. difficile colitis.

7.3.2.1.4 Patients with neutropenia and diarrhea should be considered for empiric use of prophylactic antibiotics such as oral quinolones.

7.7.2.1.5 Dose modifications for diarrhea are summarized in table form below:

Grade Diarrhea (stool number is over pretreatment number of stools)	Capecitabine	Oxaliplatin	XRT
Grade 1	Maintain dose, institute supportive care for diarrhea	Maintain dose	Maintain dose
Grade 2	Maintain dose, institute supportive care for diarrhea if not already instituted	Maintain dose	Maintain dose

Grade 3	Hold until Grade ≤ 1, then restart capecitabine one dose level lower.	Hold until Grade ≤ 1, then restart oxaliplatin one dose level lower	If grade 3 diarrhea for > 4 days, hold until Grade ≤ 1, then restart.
Grade 4	Hold until Grade ≤ 1, then restart capecitabine one dose level lower.	Hold until Grade ≤ 1, then restart oxaliplatin one dose level lower. .	Hold until Grade ≤ 1, then restart.

7.3.2.2 Nausea and/or Vomiting (Preoperative)

The prophylactic administration of 5-HT3 antagonists (granisetron, ondansetron or variants) with corticosteroids (e.g. dexamethasone) is highly recommended for primary prevention and treatment of oxaliplatin-induced emesis. The dose of each agent is left to the discretion of each investigator.

Secondary treatment and prophylaxis: Patients must be supplied with antiemetics at the initiation of study treatment. The choice and dose of anti-emetics will be determined by the treating physician. Anti-emetics should be initiated at the onset of symptoms and continued as directed by the treating physician until resolution of symptoms to grade 0-1. Additional supportive care measures, e.g. oral or intravenous rehydration, etc., should be instituted as required by the patient's clinical condition. Additional medical evaluation is recommended for those patients with continued nausea/vomiting > grade 2, lasting > 48 hours despite institution of optimal supportive care measures. Secondary prophylaxis must be initiated once nausea or vomiting has occurred if initial primary prophylaxis was not initially employed. Dose modification is not required if primary prophylaxis was not initiated as recommended in the protocol. Recurrent episodes of > grade 2 nausea/vomiting despite institution of optimal supportive care and prophylaxis should receive dose reductions as outlined below.

Grade Nausea and/or Vomiting (despite adequate prophylaxis)	Capecitabine	Oxaliplatin	XRT
Grade 1	Maintain dose	Maintain dose	Maintain dose
Grade 2	Maintain dose	Maintain dose	Maintain dose
Grade 3	Hold until grade ≤ 1, then restart one dose level lower	Hold until grade ≤ 1, then restart one dose level lower	Maintain dose
Grade 4	Hold until grade ≤ 1, then restart two dose levels lower	Hold until grade ≤ 1, then restart two dose levels lower	Maintain dose

7.3.2.3 Capecitabine-Induced Hand Foot Skin Reaction (Preoperative)

Capecitabine dose adjustments for hand-foot skin reaction are listed below

Toxicity Grade	Capecitabine Dose Adjustment
1	Maintain dose
2	Interrupt until ≤ grade 1. May then restart capecitabine at full dose. For second occurrence, hold capecitabine until ≤ grade 1, then restart capecitabine one dose level lower.
3	Interrupt until ≤ grade 1. Then restart capecitabine one dose level lower.

7.3.2.4 Oxaliplatin-Induced Neuropathy (Sensory) [Preoperative]

The table below summarizes the assessment, classification and dose modifications to be made for oxaliplatin induced neuropathy.

Neurological Toxicity Scale for Oxaliplatin Dose Adjustments

Grade	Duration of Toxicity	
	1-7 Days	**> 7 Days**
Grade 1	Maintain dose	Maintain dose
Grade 2	Maintain dose	Maintain dose
Grade 3	Maintain dose	Hold until ≤ grade 1, then reduce one dose level.
Grade 4	Hold until ≤ grade 1, then reduce one dose level.	Hold until ≤ grade 1, then reduce one dose level.

7.3.2.4.1 *Acute Oxaliplatin-Induced Laryngopharyngeal Dysesthesia*

An unusual laryngopharyngeal dysesthesia (LPD), a loss of sensation of breathing without any objective evidence of respiratory distress (laryngospasm, bronchospasm or hypoxia), has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold and should be distinguished from a hypersensitivity reaction. If a patient develops LPD, the patient's oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance that the LPD will resolve itself, a benzodiazepine or other anxiolytic agent should be considered and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at a reduced rate, 33% of the original rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions. To minimize the risk of LPD, patients will be instructed to avoid ice and cold drinks the day of treatment

7.3.2.5 Oxaliplatin-Induced Hypersensitivity Reactions (Preoperative)

Oxaliplatin, as is the case with all platinum-containing compounds, is associated with a measurable (approximately 11%) incidence of hypersensitivity reactions, usually after multiple doses of treatment. This may present as bronchospasm, hypotension, and even hemolytic anemia. Pretreatment with glucocorticoids and antihistamines may be useful for some patients but may not always prevent the development of anaphylactoid reactions, especially in patients with a prior history of hypersensitivity to this agent. For patients who have experienced a Grade 1 or 2 acute hypersensitivity reaction that is assessed as related to oxaliplatin administration, the following premedication is recommended prior to each subsequent dose of oxaliplatin (patients who have grade 3 or 4 acute hypersensitivity reactions should discontinue oxaliplatin therapy):

- Dexamethasone 20 mg PO or IV, 12 and 6 hours prior to the oxaliplatin dose;
- Dexamethasone 20 mg PO or IV, as well as diphenhydramine 50 mg IV, and one of the following: ranitidine 50 mg IV, or famotidine 20 mg IV 30-60 minutes prior to oxaliplatin administration.

If these prophylactic measures fail to prevent oxaliplatin-related hypersensitivity, therapy with oxaliplatin should be discontinued. Patients may continue on capecitabine and XRT as clinically indicated. Patients who have oxaliplatin held for uncontrollable hypersensitivity may not restart oxaliplatin at any time.

7.3.2.6 Oxaliplatin-Induced Pulmonary Fibrosis (Preoperative)

Oxaliplatin can be associated with a low risk of pulmonary fibrosis. If pulmonary fibrosis is suspected, hold oxaliplatin. If pulmonary fibrosis is ruled out, oxaliplatin may be restarted. If pulmonary fibrosis is diagnosed, discontinue oxaliplatin indefinitely.

7.4 POSTOPERATIVE Dose Modifications

7.4.1 Hematologic Toxicity (Postoperative)

7.4.1.1 Grade 1 toxicities will not result in dose modifications.

7.4.1.2 Postoperative dose levels are as follows:

	Oxaliplatin	**Leucovorin**	**Bolus 5-FU**	**Infusion 5-FU**
Start Level	85 mg/m^2	400 mg/m^2	400 mg/m^2	2400 mg/m^2
Level -1	65 mg/m^2	400 mg/m^2	300 mg/m^2	1800 mg/m^2
Level -2	45 mg/m^2	400 mg/m^2	200 mg/m^2	1200 mg/m^2

If the patient requires dose reductions lower than level -2 protocol therapy should be discontinued.

7.4.1.3 Dose modifications are provided below; in the case where there are concurrent toxicities, dose modification should follow the most stringent management.

Toxicity	**5-FU/Leucovorin Dose Modification**	**Oxaliplatin Dose Modification**
Grade 2 Thrombocytopenia	Continue at current dose	Continue at current dose
Grade 3 Thrombocytopenia	Hold until recovery to grade ≤1, then resume one dose level lower.	Hold until recovery to grade ≤1, then resume one dose level lower.
Grade 4 Thrombocytopenia)	Hold until recovery to grade ≤1, then resume one dose level lower.	Hold until recovery to grade ≤1, then resume one dose level lower.
Grade 3 Neutropenia	Hold until recovery to grade ≤1, then resume one dose level lower.	Hold until recovery to grade ≤1, then resume one dose level lower.
Grade 4 Neutropenia	Hold until recovery to grade ≤ 1, then resume one dose level lower.	Hold until recovery to grade ≤ 1, then resume one dose level lower.
Grade 3/4 febrile neutropenia	Hold until resolution of fever and neutropenia to grade ≤ 1. Hold until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume at the next lower dose level. At third recurrence of febrile neutropenia, discontinue 5-FU/leucovorin.	Hold until resolution of fever and neutropenia to grade ≤ 1. Hold until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume at the next lower dose level. At third recurrence of febrile neutropenia, discontinue oxaliplatin.

7.4.2 Nonhematologic Toxicity (Postoperative)

7.4.2.1 Diarrhea (Postoperative)

7.4.2.1.1 5-FU can cause diarrhea and must be stopped if diarrhea is ≥ grade 3. Diarrhea must be managed symptomatically. IV hydration and use of loperamide, as well as close observation, is recommended for diarrhea For loperamide dosage recommendation and treatment start, see below. If control takes longer than 2 days, medical evaluation including relevant diagnostic procedures, alternative treatment, and possible investigation of DPD deficiency should be

considered. 5-FU cannot be re-started until diarrhea has resolved to grade < 2 with the last loperamide dose given at least 24 hours beforehand.

7.4.2.1.2 The recommended dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended.

7.4.2.1.3 The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

7.4.2.1.4 Patients with grade 3 diarrhea should also be evaluated for C. difficile colitis

7.4.2.1.5 Patients with neutropenia and diarrhea should be considered for empiric use of prophylactic antibiotics such as oral quinolones.

7.4.2.1.6 Dose modifications of 5-FU/leucovorin and oxaliplatin for diarrhea are listed below:

Grade Diarrhea (stool number is over pretreatment number of stools)	**5-FU/Leucovorin**	**Oxaliplatin**
Grade 1	Maintain dose, institute supportive care for diarrhea	Maintain dose
Grade 2	Maintain dose, institute supportive care for diarrhea	Maintain dose
Grade 3	Hold until Grade ≤ 1, then restart 5-FU/leucovorin one dose level lower. .	Hold until Grade ≤ 1, then restart oxaliplatin one dose level lower.
Grade 4	Hold until Grade ≤ 1, then restart 5-FU/leucovorin one dose level lower.	Hold until Grade ≤ 1, then restart oxaliplatin one dose level lower.

7.4.2.2 Nausea and/or Vomiting (Postoperative)

The prophylactic administration of 5-HT3 antagonists (granisetron, ondansetron or variants) with corticosteroids (e.g., dexamethasone) is highly recommended for primary prevention and treatment of oxaliplatin-induced emesis. The dose of each agent is left to the discretion of each investigator.

Secondary treatment and prophylaxis: Patients must be supplied with antiemetics at the initiation of study treatment. The choice and dose of antiemetics will be determined by the treating physician. Anti-emetics should be initiated at the onset of symptoms and continued as directed by the treating physician until resolution of symptoms to grade 0-1. Additional supportive care measures (e.g., oral or intravenous rehydration, etc.) should be instituted as required by the patient's clinical condition. Additional medical evaluation is recommended for those patients with continued nausea/vomiting > grade 2, lasting > 48 hours despite institution of optimal supportive care measures. Secondary prophylaxis must be initiated once nausea or vomiting has occurred if initial primary prophylaxis was not initially employed. Dose modification is not required if primary prophylaxis was not initiated as recommended in the protocol. Patients with recurrent episodes of > grade 2 nausea/vomiting despite institution of optimal supportive care and prophylaxis should receive dose reductions as outlined below.

Grade Nausea and/or Vomiting (despite adequate prophylaxis)	5-FU/Leucovorin	Oxaliplatin
Grade 1	Maintain dose	Maintain dose
Grade 2	Maintain dose	Maintain dose
Grade 3	Hold until grade ≤ 1, then restart one dose level lower	Hold until grade ≤ 1, then restart one dose level lower
Grade 4	Hold until grade ≤ 1, then restart two dose levels lower	Hold until grade ≤ 1, then restart two dose levels lower

7.4.2.3 Oxaliplatin-Induced Neuropathy (Sensory) [Postoperative]

The table below summarizes the assessment, classification, and dose modifications to be made for oxaliplatin-induced neuropathy during postoperative FOLFOX.

Neurological Toxicity Scale for Oxaliplatin Dose Adjustments

Grade	Duration of Toxicity		Persistent Between Cycles[a]
	1-7 Days	> 7 Days	
Grade 1	Maintain dose	Maintain dose	Maintain dose
Grade 2	Maintain dose	Maintain dose	Hold until grade 0-1, then reduce one dose level.
Grade 3	Maintain dose	Hold until grade 0-1, then reduce one dose level.	Hold until grade 0-1, then reduce one dose level.
Grade 4	Hold until grade 0-1, then reduce one dose level.	Hold until grade 0-1, then reduce one dose level.	Hold until grade 0-1, then reduce one dose level.

[a] Not resolved by the beginning of the next cycle.

7.4.2.3.1 *Acute Oxaliplatin-Induced Laryngopharyngeal Dysesthesia*

An unusual laryngopharyngeal dysesthesia (LPD), a loss of sensation of breathing without any objective evidence of respiratory distress (laryngospasm, bronchospasm or hypoxia), has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold and should be distinguished from a hypersensitivity reaction. If a patient develops LPD, the patient's oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance that the LPD will resolve itself, a benzodiazepine or other anxiolytic agent should be considered and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at a reduced rate, 33% of the original rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions. To minimize the risk of LPD, patients will be instructed to avoid ice and cold drinks the day of treatment.

7.4.2.4 Oxaliplatin-Induced Hypersensitivity Reactions (Postoperative)

Oxaliplatin, as is the case with all platinum-containing compounds, is associated with a measurable (approximately 11%) incidence of hypersensitivity reactions, usually after multiple doses of treatment. This may present as bronchospasm, hypotension, and even hemolytic anemia. Pretreatment with glucocorticoids and antihistamines may be useful for some patients but may not always prevent the development of anaphylactoid reactions, especially in patients with a prior history of hypersensitivity to this agent. For patients who have experienced a grade 1 or 2 acute hypersensitivity reaction that is assessed as related to oxaliplatin administration, the following premedication is recommended prior to each subsequent dose of oxaliplatin (patients who have grade 3 or 4 acute hypersensitivity reactions should discontinue oxaliplatin therapy):

- Dexamethasone 20 mg PO or IV, 12 and 6 hours prior to the oxaliplatin dose;
- Dexamethasone 20 mg PO or IV, as well as diphenhydramine 50 mg IV, and one of the following: ranitidine 50 mg IV, or famotidine 20 mg IV 30-60 minutes prior to oxaliplatin administration.

If these prophylactic measures fail to prevent oxaliplatin-related hypersensitivity, therapy with oxaliplatin should be discontinued. Patients may continue on capecitabine and XRT as clinically indicated. Patients who have oxaliplatin held for uncontrollable hypersensitivity may not restart oxaliplatin at any time.

7.4.2.5 Veno-Occlusive Disease (VOD) [Postoperative]

Veno-occlusive disease is a very rare adverse event associated with the administration of the combination of 5-FU and oxaliplatin. VOD disease is characterized by hepatomegaly, ascites, and jaundice. Especially in patients without liver metastases, 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 or presence of gastrointestinal bleeding; and 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/supported. If clinically warranted, 5-FU and oxaliplatin should be discontinued.

7.4.2.6 Oxaliplatin-Induced Pulmonary Fibrosis (Postoperative)

Oxaliplatin can be associated with a low risk of pulmonary fibrosis. If pulmonary fibrosis is suspected, hold oxaliplatin. If pulmonary fibrosis is ruled out, oxaliplatin may be restarted. If pulmonary fibrosis is diagnosed, discontinue oxaliplatin indefinitely.

7.4.2.7 Other Nonhematologic Toxicities Not Mentioned Above (Postoperative)

If a toxicity is believed to be attributable to only one agent, then follow dose modifications below for only that agent. If toxicity is thought to be attributable to more than one agent, then follow dose modifications for all responsible agents as below. A dose modification chart is provided below.

Nonhematologic Toxicity*	5-FU/Leucovorin Dose Modification	Oxaliplatin Dose Modification
Grade 0-1	No change	No change
Grade 2	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, hold 5-FU/leucovorin until recovery to grade ≤1, then reintroduce at current dose. If event returns to grade 2, hold 5-FU/leucovorin until recovery to grade ≤1. Then restart 5-FU/leucovorin at the next lower dose level.	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, hold oxaliplatin until recovery to grade ≤1, then reintroduce at current dose. If event returns to grade 2, hold oxaliplatin until recovery to grade ≤1. Then restart oxaliplatin at the next lower dose level.
Grade 3	Hold until recovery to grade ≤1. Then reintroduce 5-FU/leucovorin at the next lower dose level.	Hold until recovery to grade ≤1. Then reintroduce oxaliplatin at the next lower dose level.
Grade 4	Hold until recovery to grade ≤1. Then reintroduce 5-FU/leucovorin at the two dose levels lower.	Hold until recovery to grade ≤1. Then reintroduce oxaliplatin at the two dose levels lower. Can consider discontinuation of oxaliplatin.

*Excluding alopecia, anorexia, and fatigue.

7.5 Modality Review

The Medical Oncology Co-Chair, Johanna Bendell, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Bendell will perform a Quality Assurance Review after complete data for 20 cases have been received at RTOG Headquarters. Dr. Bendell will perform the next review after complete data for the next 20 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received at RTOG Headquarters, whichever occurs first.

7.6 Adverse Events (8/17/2011)

Beginning October 1, 2011 this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP web site
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTCAE v4.0. **All AE reporting on the study case report forms will continue to use CTCAE version 3.0.**

All adverse events (AEs) as defined in the tables below will be reported via the AdEERs (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERs. Sites also can access the RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERs reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERs submissions.

7.6.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.7 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.6.2 Serious Adverse Events (SAEs)

All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

Definition of an SAE: 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;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) **submitted to RTOG Headquarters must include the RTOG study/ case numbers;** non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system. If you are reporting in CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or, 3) Treatment related secondary malignancy.

7.7 AdEERS Expedited Reporting Requirements

Phase 2 and 3 Trials Utilizing an Agent a Commercially Available Agent: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agents in this Study

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days

Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercially available agent require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled "Additional Instructions or Exceptions."

March 2005

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a non-CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions: None

8.0 SURGERY

8.1 Surgical Quality Assurance Reviews

A full surgical quality assurance review is required for this study. The review will be performed by The Surgical Oncology Co-Chair, Adam Berger, M.D., after complete data for 20 cases have been received at RTOG Headquarters. Dr. Berger will perform the next review after complete data for the next 20 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received at RTOG Headquarters, whichever occurs first.

8.2 General Operative Evaluation

8.2.1 All patients will undergo surgery 4 to 8 weeks following the completion of radiation therapy. The use and method of bowel preparation is at the discretion of the surgeon.

8.2.2 The surgeon will perform a thorough examination of the abdomen to detect for metastatic disease, specifically in the liver, ovaries and peritoneal surfaces. Negative as well as positive findings should be recorded in the operative report.

8.2.3 The finding at surgery of unexpected unresectable hepatic metastases or peritoneal seeding will preclude radical resection of the primary unless at the discretion of the surgeon it is indicated for local control and palliation.

8.2.4 If a patient has a solitary, unexpected liver metastasis that can be removed with a minimal resection (i.e., wedge resection), this can be done at the surgeon's discretion. Major hepatectomy at the time of rectal resection is discouraged but not absolutely contraindicated.

8.3 Operative Procedure

8.3.1 The choice of procedure (abdominoperineal resection (APR), low anterior resection (LAR), or LAR/coloanal anastomosis) is at the discretion of the surgeon. Total mesorectal excision (TME) is strongly recommended and should be documented. En bloc hysterectomy, vaginectomy, and/or multivisceral resection should be performed if felt to be indicated without violation of primary tumor mass. The ureters should be identified bilaterally and preserved.

8.3.2 Techniques for anastomosis are at the discretion of the surgeon, as are use, placement, and removal of pelvic drains.

8.3.3 APR will involve resection of the rectum and mesorectum from the perineum to the sacral promontory. The distal left colon is divided with a linear stapler to prevent spillage of intraluminal contents at a minimum of 5 cm proximal to the tumor mass in vivo (not required to be documented ex vivo due to potential retraction). Closure of the perineum and use of pelvic drain(s) is recommended.

8.3.4 For an LAR, the left colon is mobilized, with ligation of the inferior mesenteric artery and vein. The distal left colon is divided with a linear stapler to prevent spillage of intraluminal contents at a minimum of 5 cm proximal to the tumor mass in vivo (not required to be documented ex vivo due to potential retraction). The rectum and mesorectum will be removed with a distal rectal margin of at least 2 cm in vivo for sphincter preservation. Unirradiated colon from outside the pelvis should be used for the anastomosis. If necessary, takedown of the splenocolic ligament should be performed to ensure adequate length to reach the planned anastomosis without tension. Diversion of fecal stream via ileostomy or colostomy in these patients will be left to the discretion of the investigator.

8.3.5 If a LAR/coloanal anastomosis is performed, the entire left colon is mobilized, with ligation of the inferior mesenteric artery and vein. The distal left colon is divided with a linear stapler to prevent spillage of intraluminal contents at a minimum of 5 cm proximal to the tumor mass in vivo (not required to be documented ex vivo due to potential retraction). A radical resection of the rectum and mesorectum to the levators (distal rectal margin of at least 2 cm in vivo) is performed from the abdominal incision. At the level of the anorectal ring, the muscular rectal wall is divided by cautery and the specimen removed. The colon is brought into the anal canal and an anastomosis performed to the dentate line with interrupted full-thickness sutures. Unirradiated colon from outside the pelvis should be used for the anastomosis. If necessary, takedown of the splenocolic ligament should be performed to avoid undue tension on the anastomosis. Use of pelvic drain(s) is recommended. Temporary diversion of the fecal stream (through the formation of either an ileostomy or transverse colostomy) should be performed. The temporary ostomy should not be closed until at least 6-8 weeks after the completion of all cycles of postoperative chemotherapy.

8.3.6 Adequacy of bowel preparation (poor or adequate), presence or absence of liver/peritoneal metastases, estimated proximal and distal in vivo surgical margins, use of TME, anastomotic method, location of drains, need to takedown splenocolic ligament, and concomitant procedures should be clearly documented in the operative report.

8.3.7 Laparoscopic rectal resection is allowed as long as all of the above mentioned criteria are met and properly documented.

8.4 Surgical Pathology

8.4.1 The resected specimen is oriented for pathologic examination by placing a suture on the distal anterior rectal wall. The pathologist should ink the specimen, prior to fixation, for radial margin determination. See Appendix IV for specific details.

8.4.2 Separate biopsies of unresected tissue at the closest tumor margins may be taken to rule out histologically residual tumor and submit in a separate bottle.

8.4.3 Biopsy of suspicious areas on the peritoneum, liver, or any other sites is recommended.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.1 A diverting colostomy without tumor resection is permitted prior to study entry when clinically indicated.

9.1.2 All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented n each site's source documents as concomitant medication.

Suggested supportive therapies are listed when appropriate in Sections 7 and 8.

9.2 Non-Permitted Supportive Therapy

9.2.1 The use of cimetidine, amifostine and/or depot Sandostatin is not allowed on this protocol.

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at University of California at San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking (highly recommended).

10.2 Specimen Collection for Tissue Banking

For patients who have consented to participate in this component of the study (See Appendix I).

The following must be provided in order for the case to be evaluable for the Tissue Bank:

10.2.1 Tissue

10.2.1.1 One H&E stained slide

10.2.1.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.1.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.1.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource.; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.2.1.5 Specimens should be taken from the original diagnostic biopsy (≤ 8 weeks prior to study entry) and from surgical resection tissue

10.2.2 Blood

10.2.2.5 Peripheral blood will be collected at two time points: pre-treatment (≤ 28 days prior to study entry) and on the last week of treatment and shipped using RTOG collection kits. Sites will collect 5-10 mL of whole blood in a red-top tube and 5-10 mL of whole blood in EDTA tubes. Red top tube is spun down for serum. EDTA tubes are spun for plasma and lymphocytes/buffy coat cells. (See Appendix VII for detailed collection and shipping instructions). Collection kits are available by contacting the RTOG Biospecimen Resource.(see contact information below).

Specimens should be sent with a Specimen Transmittal Form documenting the date of collection of the serum; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included. Questions regarding blood collection or shipment should be directed to the RTOG Biospecimen Resource(see contact information below). Ship by express overnight service, Monday through Thursday; avoid a weekend or holiday arrival date, and DO NOT ship on Friday. Fedex labels will be supplied for sending frozen materials.

10.2.3 Summary of Specimens for Tissue Banking

Specimens taken from patient:	Collection Schedule:	Submitted as:	Shipped:
One H&E stained slide of the primary tumor	From the original diagnostic biopsy (≤ 8 weeks prior to study entry) and from surgical resection tissue	H&E stained slide	Slide sent ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a skin punch	From the original diagnostic biopsy (≤ 8 weeks prior to study entry) and from surgical resection tissue	Paraffin-embedded tissue block or punch biopsy	Block or punch sent ambient
5-10 mL of whole blood (red-top) centrifuge for serum	≤ 28 days prior to study entry and during the last week of treatment	Serum samples into four (4) 1 mL cryovials	Frozen overnight
5-10 mL of anticoagulated blood (EDTA) centrifuge for plasma and buffy coat	≤ 28 days prior to study entry and during the last week of treatment	Plasma samples into three (3) 1 mL cryovials Buffy coat samples into three (3) 1 mL cryovials	Frozen overnight

10.2.4 Submit materials to:

USPS mailing address ***(all non-frozen specimens only)***
RTOG Biospecimen Bank
University of California San Francisco
Campus Box 1800
San Francisco, CA 94143-1800

FedX/Courier address ***(all frozen samples)***
RTOG Biospecimen Bank
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Tel: 415-476-RTOG (7864)
Fax: 415-476-5271
Email: RTOG@ucsf.edu

10.3 Reimbursement

RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue, serum or plasma, and buffy coat cells; and $200 per case for a block or core of material. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II for a summary of assessments and time frames.

11.2 Criteria for Evaluation and Endpoint Definitions

11.2.1 Measurement of the incidence of preoperative toxicity

11.2.1.1 Preoperative toxicity will be assessed based on CTCAE v3.0 criteria on a weekly basis during preoperative chemoradiation and within 14 days prior to surgical resection (for patients undergoing surgery) or 6-8 weeks from radiotherapy completion (for patients not undergoing surgery).

11.2.2 Measurement of the incidence of postoperative toxicity

Postoperative toxicity will be assessed based on CTCAE v3.0 criteria in the postoperative period following preoperative chemoradiation and surgical resection. Assessments will be made as per the study schedule found in Appendix II.

11.2.3 Documentation of Tumor Response and Incidence and Patterns of Relapse

11.2.3.1 Pathologic complete response: No evidence of residual cancer histologically in the resection specimen.

11.2.3.2 Local failure: recurrence or persistence of disease within radiation treatment volumes. Persistent disease is defined as either: (1) micro- or macroscopic margins following surgery, or (2) radiographically or intra-operatively unresectable at time of surgery as defined in Section 8.2.

11.2.3.3 Regional failure: failure outside the treatment field on basis of direct and/or lymphatic spread to include aortic nodes.

11.2.3.4 Distant failure: includes both peritoneal seeding and distant metastases to sites beyond those described as locoregional per Sections 11.2.3.2 and 11.2.3.3.

11.2.3.5 Disease relapse: will be documented by biopsy whenever possible. When biopsy is impossible or poses significant risk, clinical and radiographic evidence will be used to document recurrence

11.3 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment > 4 weeks;
- Positive margin at time of surgery;
- Unresectable disease at time of surgery.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)**	Within 2 weeks of study entry
Radiotherapy Form **(T1) [Copy to ITC]** Daily Treatment Record **(T5) [Copy to ITC]**	Within 1 week of RT end
Preoperative Chemo/RT Treatment Form **(TF)**	At the end of concurrent preoperative therapy
Postoperative Chemo/RT Treatment Form **(SF)**	**3 times** during postoperative chemotherapy (once every 3 cycles)
Surgical Form **(S1)** Operative Report **(S2)** Surgical Pathology Report **(S5)**	Submit for all patients either 2 weeks after surgery or at the time that surgery is ruled out. In addition, complete this form for all subsequent surgical procedures. Submit with copies of an operative (S2) note and pathology (S5) report.
Follow-up Form **(F1)**	Every 3 mos from the start of treatment x 2 yrs; every 6 mos for yrs 3-5; then annually

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) (3/30/10)

Item	Due
Preliminary Dosimetry Information (DD) Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist. Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan **(DV)**	Within 1 week of RT start
Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/ddsi/ddsi.html)	
Hard copy isodose distributions for total dose plan (T6)	

NOTE: Sites must notify ITC via e-mail (itc@castor.wustl.edu) after digital data IS submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".	
Final Dosimetry Information	Within 1 week of RT end
Radiotherapy Form **(T1) [copy to HQ and ITC]** Daily Treatment Record **(T5) [copy to HQ and ITC]** Modified digital patient data as required through consultation with Image Guided Therapy QA Center	

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@castor.wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

13.1.1.1 ≥ Grade 2 treatment-related gastrointestinal adverse events per CTCAE v. 3.0, occurring preoperatively

13.1.2 Secondary Endpoints

13.1.2.1 IMRT feasibility (per criteria in Section 6.7)

13.1.2.2 pCR rate

13.1.2.3 All treatment-related adverse events for the following time periods:

13.1.2.3.1 The preoperative period

13.1.2.3.2 The postoperative period, up to 3 months after the completion of postoperative chemotherapy

13.1.2.3.3 Overall

13.1.2.4 Patterns of failure (per Section 11.2.3), including overall survival (failure is death due to any cause)

13.1.2.5 Correlation of pre- and post-treatment serum cytokines with adverse events and efficacy

13.1.2.6 Abdominoperineal Resections (APR) rate

13.2 Study Design

13.2.1 Sample Size Derivation

The primary objective of this study is to determine if IMRT, given with concurrent chemotherapy (capecitabine and oxaliplatin), reduces the rate of ≥ grade 2 treatment-related gastrointestinal adverse events (per CTCAE v. 3.0) occurring preoperatively, compared to the rate with conventional radiation. The rate of these adverse events from the conventional radiation/capecitabine/oxaliplatin arm of RTOG 0247 was 40%. Using a chi-squared test, a

sample size of 71 patients will ensure at least 80% probability of detecting a minimum reduction of 12% in the adverse events described above at a significance level of 0.10 (1-sided). Adjusting this figure by 5% to allow for patients determined to be ineligible or who do not start protocol treatment, **a total sample size of 75 patients will be required** for this study.

13.2.2 Patient Accrual

It is projected that there will be a period of approximately 6 months with very slow accrual at the beginning of this study to allow for both institutional IRB approval and IMRT approval by the RTOG QA Center. Following this initial period, it is projected that the study will accrue 4 patients/month (based on the most recent RTOG rectal study, RTOG 0247) and that accrual will be completed in approximately 18 months. If the average monthly accrual is less than 2 cases per month 12 months after it is opened, the study will be re-evaluated with respect to feasibility.

13.3 Suspension of Accrual Due to Excessive Rate of Adverse Events or Abdominoperineal Resections

13.3.1 Unacceptable Rate of Adverse Events

The rate of unacceptable adverse events related to protocol treatment (grade 3 and 4 non-hematologic adverse events, excluding nausea/vomiting controllable with antiemetics, and alopecia) will be evaluated at two time points during accrual: after 24 and 48 patients have been entered and are evaluable and again on all evaluable patients after the study has finished accrual. The study chairs have determined that a rate of 40% or greater will be considered unacceptable. According to Fleming's method[15] with a maximum overall significance level of 0.05 if there are:

11 or more unacceptable adverse events out of the first 24 evaluable patients, or
16 or more unacceptable adverse events out of the first 48 evaluable patients,

the study will have exceeded the limit for unacceptable adverse events. The final analysis will use a rejection rule of 22 or more unacceptable adverse events out of 71 evaluable patients. If the number of unacceptable adverse events crosses a boundary, as described in the rules above, then the conclusion will be that the unacceptable adverse event rate is greater than 40%. If this occurs, the study chairs, the RTOG Gastrointestinal Cancer Committee chair, and the statistician will review the adverse event data and make appropriate recommendations about the study to the RTOG Executive Committee. These stopping rules provide 90% power for concluding that the unacceptable adverse event rate is equal to or exceeds 40% when in fact that is the true rate.

13.3.2 Fatal Treatment Morbidity

If a fatal adverse event occurs (1) within 30 days of protocol treatment completion, regardless of relationship to protocol treatment, or (2) at any time and is related to protocol treatment, the event will be reported to the study chairs and the RTOG Gastrointestinal Cancer Committee chair for review. At this time it will be determined if accrual to the trial must be suspended pending this review for patient safety. The data manager will, after requesting additional supporting documentation if necessary, have all documents scanned and transmitted electronically to the study chairs and the head of the RTOG Data Safety Monitoring Board (DSMB) for their review. This will take place within 2 weeks of each reported adverse event if at all possible.

13.3.3 Unacceptable Rate of Abdominoperineal Resections(APRs)

The rate of unacceptable APRs will be evaluated at two time points during accrual: after 24 and 48 patients have been entered and are evaluable and again on all evaluable patients after the study has finished accrual. The study chairs have determined that an APR rate of 50% or greater will be considered unacceptable. According to Fleming's method[15] with a maximum overall significance level of 0.05 if there are:

14 or more unacceptable adverse events out of the first 24 evaluable patients, or
21 or more unacceptable adverse events out of the first 48 evaluable patients,

the study will have exceeded the limit for APRs. The final analysis will use a rejection rule of 29 or more unacceptable adverse events out of 71 evaluable patients. If the number of

unacceptable APRs crosses a boundary, as described in the rules above, then the conclusion will be that the APR rate is greater than 50%. If this occurs, the study chairs, the RTOG Gastrointestinal Cancer Committee chair, and the statistician will review the APR data and make appropriate recommendations about the study to the RTOG Executive Committee. These stopping rules provide 95% power for concluding that the unacceptable adverse event rate is equal to or exceeds 50% when in fact that is the true rate.

13.4 Analysis Plan

13.4.1 Interim Reports

Interim reports will be prepared every 6 months until the primary endpoint has been accepted for presentation or publication. In general, these reports include:

- the patient accrual rate with projected completion date,
- institutional accrual,
- exclusion rates and reasons,
- pretreatment characteristics,
- compliance rates of treatment delivery with respect to the protocol prescription, and
- the frequency and severity of adverse events.

13.4.2 CDUS Reports

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.3 Data Safety Monitoring Board (DSMB) Review

To monitor the safety of this study, the RTOG DSMB will officially review this study twice per year in conjunction with the RTOG semi-annual meeting and on an “as needed” basis in between meetings.

13.4.4 Analysis for Reporting the Initial Treatment Results

The analysis for reporting the initial primary endpoint results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. Only patients that meet the eligibility requirements of this protocol and start protocol treatment will be included. The usual components of this analysis are:

- tabulation of all cases entered and any patients excluded from the analysis with reasons for exclusion,
- patient accrual rate,
- institutional accrual,
- distribution of important prognostic baseline and other pretreatment variables,
- frequency and severity of adverse events,
- compliance rates of treatment delivery with respect to the protocol prescription, and
- observed results with respect to the endpoints described in Section 13.1.

Patterns of failure will be reported at least 2 years after the last patient has been entered. Time to local, regional, and distant failure and time to progression will be estimated using the cumulative incidence method.[16] Overall survival rates will be estimated using the Kaplan-Meier method.[17]

13.5 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered differences in prognosis by race, ethnicity and gender. If the distributions allow, an exploratory statistical analysis will be performed to examine the possible differences between the genders and among the race and ethnicity categories.

Projected Distribution of Gender and Minorities

Ethnic Category	Gender		
	Females	Males	Total

Ethnic Category	Gender		
	Females	**Males**	**Total**
Hispanic or Latino	3	4	7
Not Hispanic or Latino	25	43	68
Ethnic Category: Total of all subjects	28	47	**75**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	2	3	5
Native Hawaiian or other Pacific Islander	0	1	1
White	25	42	67
Racial Category: Total of all subjects	28	47	**75**

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APPENDIX I

Informed Consent Template for Cancer Treatment Trials
(English Language)

RTOG 0822

A PHASE II EVALUATION OF PREOPERATIVE CHEMORADIOTHERAPY UTILIZING INTENSITY MODULATED RADIATION THERAPY (IMRT) IN COMBINATION WITH CAPECITABINE AND OXALIPLATIN FOR PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have rectal cancer.

As treatment for your rectal cancer, you will require radiation therapy and chemotherapy given at the same time. Both radiation therapy and chemotherapy can cause side effects. When given at the same time, they have a greater risk of causing side effects. Prior studies have established that the most common side effects are gastrointestinal side effects (such as diarrhea), which at times can be severe enough to require unplanned treatment breaks or chemotherapy dose reductions (either of which can compromise the effectiveness of the cancer treatment) or in rare cases require discontinuation of therapy. Modern radiation therapy delivery techniques have the potential to reduce the risk of gastrointestinal side effects when compared with standard radiation delivery techniques.

Why is this study being done?

It is possible to reduce the amount of radiation delivered to the normal tissues that surround your cancer by using an advanced radiation therapy delivery technique called intensity-modulated radiation therapy (IMRT – see description below). The purpose of this study is to determine whether reducing the amount of radiation, given along with chemotherapy, to these normal tissues will reduce the side effects associated with standard radiation and chemotherapy treatment for rectal cancer.

Definition of IMRT: Several normal tissues in your pelvis (including the small and large bowel, bladder, femoral heads and others) lie near the rectal tumor and regional lymph nodes. Standard radiation techniques deliver radiation to the tumor target (rectal tumor and nearby lymph nodes at high risk for spread), but in doing so also deliver some radiation dose to the nearby normal tissues that we otherwise do not need to radiate. The higher the radiation dose to these normal tissues, the greater the risk of developing side effects. IMRT is a more sophisticated radiation planning and delivery technique that can lower the amount of radiation

dose that the normal tissues receive while maintaining effective treatment to the tumor target. IMRT accomplishes this through the use of multiple computer-controlled radiation beams that are optimized through computer planning to minimize the radiation dose to normal tissues without compromising treatment to the tumor target.

How many people will take part in the study?

About 75 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A history and physical examination
- A colonoscopy (examination of your rectum and colon with a lighted flexible camera) and a biopsy (a piece of your tumor is taken for examination under the microscope) – these tests help to establish your cancer's location in the rectum and rule out other cancers in the rectum or colon
- One of the following scans of the abdomen and pelvis to assess the size and extent of the rectal tumor and assess the potential spread of the rectal tumor to nearby lymph nodes or other organs such as the liver:
  - Computed tomography (CT) scan: An imaging study that uses x-rays to look at one part of your body
  - Magnetic resonance imaging (MRI) scan: An imaging study that uses a strong magnetic field to look at one part of your body
  - The combination of a positron emission tomography (PET) scan plus a CT scan of your entire body (whole body PET-CT): A computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker in your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body.
- CT scan or x-ray of the chest to assess whether the tumor may have spread to the lungs or other areas in the chest (not needed if you have a whole body PET-CT)
- Transrectal ultrasound (a probe placed in the rectum to help image the tumor) may be needed. Your study doctor can tell you whether or not you will need this performed.
- Blood tests
- For women able to have children, a pregnancy test (blood test)
- If your doctors are concerned that you are at significant risk of complete obstruction of your rectum by the tumor, a diverting colostomy (re-routing your bowel to a bag outside your body to prevent obstruction) may be performed. You can discuss this with your study doctor.

During the study …
If the exams, tests, and procedures show that you can be in the study, and you chose to take part, you will need the following tests and procedures. They are part of regular cancer care.

During the first 6 weeks of your treatment while you are receiving chemotherapy and radiation at the same time:

- Weekly history and physical examination
- Weekly blood tests

After you have completed chemotherapy and radiation but before you have surgery to remove your tumor:

- A history and physical examination
- A PET-CT scan (optional – your doctor will let you know if this is recommended)
- CT or MRI scan of the abdomen and pelvis (not needed if you have a PET-CT scan)
- A CT scan or x-ray of the chest (not needed if you have a PET-CT scan)
- Blood tests

During the chemotherapy that is given after you have surgery:

- A history and physical examination before each cycle of chemotherapy (every 14 days)
- Blood tests before each cycle of chemotherapy (every 14 days)

When you are finished taking the study treatment….
You will be seen in follow-up every 3 months for the first 2 years following treatment completion, every 6 months for the next 3 years, and then annually. During these visits you will need the following exams, tests, and procedures:

- A history and physical examination
- Blood to assess your bone marrow, kidney and liver function as well as your tumor marker (CEA)
- A CT or MRI scan of the abdomen and pelvis – if needed (your study doctor will let you know if this is required)
- A PET-CT scan (optional – your doctor will let you know if this is recommended)
- A colonoscopy (at your 12 month follow-up visit only – if negative, then every 2 years thereafter)

You will receive the following treatments…

CHEMOTHERAPY PLUS RADIATION THERAPY

- Radiation: You will receive radiation treatments once per day, 5 days per week, for a total of 28 treatments as an outpatient. This will take approximately 5 ½ weeks.

- Chemotherapy: You will receive two drugs.
  - (1) You will receive capecitabine in pill form as an outpatient during the time you are receiving radiation. The first dose will be given to you the evening before your first radiation treatment. You will then receive it twice daily through Thursday, with a final weekly dose on Friday morning.

- (2) You will receive oxaliplatin intravenously (through a needle in a vein) once per week as an outpatient during each of the 5 weeks of radiation treatments. The treatment will last approximately 2 hours per time.

SURGERY

After you have recovered from the chemotherapy and radiation (about 4 to 8 weeks), you will have surgery to remove your rectal tumor and the at-risk lymph nodes. Prior to the surgery, you will be put to sleep with anesthesia.

If it is found after your surgery that you may have residual cancer that was surgically left behind at the time of your resection, you will discontinue protocol therapy.

POSTOPERATIVE CHEMOTHERAPY

After you have recovered from the surgery (about 4 to 8 weeks), you will receive additional chemotherapy. You will receive three drugs for nine cycles, with each cycle being 14 days.

- (1) You will receive oxaliplatin intravenously as an outpatient once at the beginning of each cycle. It will last approximately 2 hours.
- (2) You will receive leucovorin intravenously as an outpatient once at the beginning of each cycle. It will last approximately 2 hours.
- (3) You will receive 5-fluorouracil (5-FU) intravenously as an outpatient once at the beginning of each cycle. You will receive one dose once quickly (an intravenous "push"), followed by a continuous intravenous infusion that will last approximately 46 hours. Your doctor will discuss with you whether you receive this as an inpatient or at home.

How long will I be in the study?

Treatment will last 8 to 9 months. You will receive radiation therapy and chemotherapy for 5 to 6 weeks. You will then be given time to adequately recover prior to surgery. Surgery will be performed 4 to 8 weeks after completion of radiation therapy. You will then be given time to adequately heal and recover from your surgery. Four to 8 weeks after your surgery you will receive additional chemotherapy for about 4 and a half months.

After you are finished all study treatments, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first 2 years, then every 6 months for the next 3 years, and after that once every year. We would like to keep track of your medical condition for the rest of your life. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so that he/she can evaluate any risks from the treatment. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the radiation include those that are:

Likely

- Skin irritation in the treatment area
- More frequent bowel movements
- Diarrhea
- Tiredness
- Loss of pubic hair (temporary)
- Rectal discomfort
- Sterility in pre-menopausal women. Hormones may be given orally to replace hormones normally produced by the ovaries

Less Likely

- More frequent urination
- Urinary discomfort
- Skin peeling

Rare but Serious

- Narrowing or blockage of the bowel (which may be serious enough to require surgery)
- A hole forming in the intestine (perforation) which may require surgery to repair
- Development of an abnormal path or connection between organs called a fistula (which typically requires a surgical repair)
- Permanent sterility (men)
- Sores and bleeding from the bowel (these side effects may occur late after treatment and be serious enough to require surgery)
- Hip fracture

Risks and side effects related to capecitabine include those that are:

Likely

- Diarrhea
- Nausea/vomiting
- Loss of appetite
- Fatigue
- Mouth sores

Risks and side effects related to capecitabine continued:

- Hand-foot syndrome (painful redness and swelling of the hands and/or feet)

Less Likely

- Hair loss
- Dry skin
- Changes in skin coloring
- Increased sensitivity to sunlight
- Eye watering, eye irritation
- Fever
- Taste changes
- Decrease in blood counts that may cause infection, bleeding, and bruising
- Inflammation of the colon
- Increased sweating
- Laryngitis (irritation or swelling of the voice box that may cause voice changes or temporary voice loss)
- Bone pain
- Joint stiffness
- Increased urination at night

Rare but Serious

- Coagulation disorder (problems with your body's ability to clot blood)
- Heart disease
- Bowel perforation (a hole forming in the bowel wall)Rectal and/or gastrointestinal bleeding
- Inflammation of the esophagus
- Inflammation of the lining of the stomach
- Inflammation/infection of the intestine and intestinal tissue, which can be severe enough to destroy it (necrosis)
- Blood in vomit
- Severe infection of the bloodstream
- Pneumonia
- Severe allergic reaction
- Formation of scar tissue in the liver
- Liver disease
- High level of triglycerides in the blood, which can increase your risk for heart disease
- Problems with coordination
- Brain disease
- Loss of consciousness or reduced level of consciousness
- Confusion
- Respiratory distress
- Low blood pressure
- Blood clots/inflammation of veins

Risks and side effects related to capecitabine continued:

- Stroke
- Radiation recall (redness, peeling, or blistering of skin in area where you received radiation)
- Fungal infection in the mouth or digestive tract
- Respiratory tract infection
- Urinary tract infection
- Bronchitis (inflammation of the air tubes leading to the lung)
- General wasting of the body caused by malnutrition
- Shortness of breath
- Nose bleed
- Contractions of the bronchi muscles
- Accumulation of fluid in the intestines, causing swelling of the body, especially of the arms and legs

Risks and side effects related to oxaliplatin include those that are:

Likely

- Fatigue
- Decreased appetite
- Nausea/vomiting
- Diarrhea
- Numbness, tingling, or change in sensations in the arms and legs

Less Likely

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Decrease in electrolyte levels that may cause muscle twitching, weakness, cramps
- Involuntary muscle contractions
- Weight loss
- Hair loss
- Injection site reaction
- Dehydration
- Taste disturbance
- Inflammation of the intestine
- Heartburn
- Inflammation of the esophagus
- Problems with coordination
- Vision abnormalities, eye infection
- Abdominal pain/cramping
- Headache
- Shortness of breath
- Vocal cord spasm
- Rash/skin peeling

Risks and side effects related to oxaliplatin continued:

- Fever
- Constipation
- Difficulty/pain with swallowing
- Mouth sores
- Cough
- Hiccups
- Insomnia
- Dizziness
- Changes in mood
- Joint pain
- Muscle pain
- Bone pain

Rare but Serious

- Allergic reaction
- Mild hearing loss
- Abnormal heart beat
- Swelling
- High blood pressure
- Blood clots, problems with clotting, hemorrhage, bleeding
- Inflammation of veins
- Hot flashes/flushes
- Bowel perforation (a hole forming in the bowel wall)
- Inflammation of the intestine and intestinal tissues that is severe enough to destroy the tissue
- Coughing of blood
- Liver disease (with a possible increased risk when combined with 5-FU)
- Scar tissue in the lung
- Inflammation of lung tissue
- Decreased electrolyte levels, which may cause kidney problems, make you disoriented

Risks and side effects related to 5-fluorouracil (5-FU) include those that are:

Likely

- Diarrhea
- Nausea/vomiting
- Loss of appetite
- Mouth sores

Risks and side effects related to 5-fluorouracil (5-FU) continued:

Less Likely

- Loss of appetite
- Skin inflammation that causes redness, swelling, blistering, oozing, and itching
- Nail changes
- Hair loss
- Taste changes
- Low blood counts
- Darkening of skin
- Hand-foot syndrome (painful redness and swelling of the hands and/or feet)
- Eye irritation, watering of the eyes, blurred vision
- Nasal discharge

Rare but Serious

- Chest pain
- Liver disease (with a possible increased risk when combined with oxaliplatin)
- Problems with coordination
- Severe, cholera-like diarrhea

Risks and side effects related to leucovorin include those that are:

Less Likely

- Hives

Rare but Serious

- Severe allergic reaction

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Pregnancy testing will be required before you can enroll. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. When receiving radiation therapy, there is a possibility that permanent sterility may result.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. While researchers hope that delivering radiation therapy with modern techniques (IMRT) will be as effective but with less side effects compared to the usual treatment for this cancer, there is no proof of this yet. We do know that the information from this study will help researchers learn more about the use of IMRT as a treatment for rectal cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?
Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?
Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Your hospital or university's institutional review board (IRB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Radiation Therapy Oncology Group

What are the costs of taking part in this study?
You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

You can say "yes" or "no" to the following study. Below, please mark your choice.

Use of Tissue for Research

[The following example of tissue consent has been taken from the NCI Cancer Diagnosis Program's model tissue consent form found at the following URL ***http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf***

Consent Form for Use of Tissue for Research

About Using Tissue for Research
You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

As a result of your participation on this study, you will also have a biopsy 4 to 8 weeks after you have completed radiation therapy. This biopsy will be done to evaluate whether the treatment is affecting your cancer.

We would like to keep some of the tissue that is left over from these biopsies to use for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://www.rtog.org/tissue%20for%20research_patient.pdf

As a result of your participation in this study, you will also have blood tests done at the following times: before you begin study treatment and during the last week of treatment. When we take the blood at these times, we would also like to take some blood to use for future research. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About
The choice to let us keep the tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and blood. Then any tissue that remains will no longer be used for research. Any remaining tissue will be returned to the institution that submitted it, and any remaining blood will be destroyed.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, your name, address, phone number, or any other information that will let the researchers know who you are will not be disclosed.

Sometimes tissue and blood are used for genetic research (about diseases that are passed on in families). Even if your tissue and blood are used for this kind of research, the results will not be put in your health records.

Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may help to develop new products in the future.

Benefits
The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks
The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue/blood may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

2. My tissue/blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to take part in more research.

Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE (3/30/10)

	Pre-Treatment			During Treatment			Follow-Up (Postoperative)			
	≤56 days prior to study entry	≤28 days prior to study entry	≤ 14 days prior to study entry	Weekly (during pre-operative chemoRT)	≤ 14 days prior to surgical resection	Prior to each cycle of post-operative FOLFOX	q3 months following post-operative FOLFOX (for yrs 1-2)	1 yr following post-operative FOLFOX; if negative q 2 yrs thereafter	q6 months following post-operative FOLFOX (for yrs 3-5)	q yr following post-operative FOLFOX (for yrs 6 and beyond)
History and physical exam	X			X	X	X	X		X	X
Medication history screen for contraindications	X									
Zubrod performance status assessment	X				X	X	X			
Diagnostic biopsy/FNA	X									
Colonoscopy	X							X		
Transrectal US (for T4, optional)	X									
Contrast-enhanced CT or MRI of the abdomen and pelvis	X				X*	(as indicated)	(as indicated)		(as indicated)	
CXR/CT chest	X				X*					
Whole-body PET-CT scan of body (optional)	X				X*					
CBC w/ diff & ANC, plt, HgB			X	X	X	X	X		X	
CMP including LFTs		X		X	X	X	X		X	
CrCl assessment		X				X				
Serum pregnancy test			X							
CEA		X			X		X		X	
Informed consent	X									
Tumor response eval					X (pathologic assessment at the time of surgery)					
Adverse event eval				X	X	X	X		X	
Tissue for banking (optional)	X				X					
Blood for banking (optional)		X		X (last week of treatment only)						

*If whole-body PET-CT done postoperatively, CT, MRI and CXR do not need to be done.

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).**
5	**Death (Karnofsky 0).**

KARNOFSKY PERFORMANCE SCALE

100	**Normal; no complaints; no evidence of disease**
90	**Able to carry on normal activity; minor signs or symptoms of disease**
80	**Normal activity with effort; some sign or symptoms of disease**
70	**Cares for self; unable to carry on normal activity or do active work**
60	**Requires occasional assistance, but is able to care for most personal needs**
50	**Requires considerable assistance and frequent medical care**
40	**Disabled; requires special care and assistance**
30	**Severely disabled; hospitalization is indicated, although death not imminent**
20	**Very sick; hospitalization necessary; active support treatment is necessary**
10	**Moribund; fatal processes progressing rapidly**
0	**Dead**

APPENDIX IV

AJCC STAGING
COLON AND RECTUM, 6TH EDITION

DEFINITION OF TNM

The same classification is used for both clinical and pathologic staging.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria*
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4 Tumor directly invades other organs or structures, and/or perforates visceral peritoneum**, ***

* Note: Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

** Note: Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.

***Note: Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
NO No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Note: A tumor nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
MO No distant metastasis
M1 Distant metastasis

APPENDIX IV (continued)

AJCC STAGING
COLON AND RECTUM, 6TH EDITION

STAGE GROUPING

Stage		T	N	M	Dukes*	MAC*
Stage	0	Tis	N0	M0	-	-
Stage	I	T1	N0	M0	A	A
		T2	N0	M0	A	B1
Stage	IIA	T3	N0	M0	B	B2
	IIB	T4	N0	M0	B	B3
Stage	IIIA	T1-2	N1	M0	C	C1
	IIIB	T3-4	N1	M0	C	C2/C3
	IIIC	Any T	N2	M0	C	C1/C2/C3
Stage	IV	Any T	Any N	M1	-	D

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Note: The y prefix is to be used for those cancers that are classified after pretreatment, whereas the r prefix is to be used for those cancers that have recurred.

APPENDIX V

CAPECITABINE DOSING TABLE BASED UPON BODY SURFACE AREA CALCULATION

Dosing Table Based Upon Body Surface Area Calculation:
Capecitabine Starting Dose

Dose level 1650 mg/m^2/d		AM 150 mg	AM 500 mg	PM 150 mg	PM 500 mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	2000	0	2	0	2
1.25-1.36	2150	1	2	0	2
1.37-1.51	2300	1	2	1	2
1.52-1.64	2600	2	2	2	2
1.65-1.76	2800	1	3	1	2
1.77-1.91	3000	0	3	0	3
1.92-2.04	3150	1	3	0	3
2.05-2.17	3300	1	3	1	3
>2.18	3600	2	3	2	3

Capecitabine 25% Dose Reduction: Dosing Table Based Upon Body Surface Area Calculation

Dose 1237 mg/m^2/d		AM 150 mg	AM 500 mg	PM 150 mg	PM 500 mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	1500	0	2	0	1
1.25-1.36	1650	1	2	0	1
1.37-1.51	1800	1	2	1	1
1.52-1.64	1950	2	2	1	1
1.65-1.76	2150	1	2	0	2
1.77-1.91	2300	1	2	1	2
1.92-2.04	2450	2	2	1	2
2.05-2.17	2500	0	3	0	2
>2.18	2650	1	3	0	2

Capecitabine 50% Dose Reduction: Dosing Table Based Upon Body Surface Area Calculation

Dose level 825 mg/m^2/d		AM 150 mg	AM 500 mg	PM 150 mg	PM 500 mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	1000	0	1	0	1
1.25-1.36	1150	1	1	0	1
1.37-1.51	1150	1	1	0	1
1.52-1.64	1300	1	1	1	1
1.65-1.76	1450	2	1	1	1
1.77-1.91	1500	0	2	0	1
1.92-2.04	1650	1	2	0	1
2.05-2.17	1650	1	2	0	1
>2.18	1800	1	2	1	1

APPENDIX VI

PATHOLOGICAL ASSESSMENT OF A RECTAL CANCER SPECIMEN

When possible, specimens should be received fresh and opened by the pathologist. If this is not possible, then the surgeon should open the bowel in the way described below and pin it out on a cork board for fixation.

The rectum should be opened anteriorly apart from the area 2 cm above and below the tumor where the anterior part of the rectum is left intact. Below the peritoneal reflection the surgeon can usually remove between 0.5 and 1.0 cm anteriorly; thus tumors involving this area are at greater risk of circumferential resection margin (CRM) involvement. In tumors above the peritoneal reflection, involvement of the peritoneal surface can occur; it is best to avoid destroying this area and the pathologist's ability to sample it by avoiding opening the site of the tumor. If possible, a macroscopic photograph of the posterior and anterior sides of the specimen is valuable.

The opened specimen should then be pinned to a cork board and fixed for 48-72 hours. After fixation, the specimen should be removed from the board and the non-peritonealized surfaces painted with ink by the method in use locally.

The macroscopic description of the specimen is then performed. Failing to open the specimen does cause a problem with recording the tumor characteristics. However, the length, width, and area of the tumor are not prognostic, whereas CRM and peritoneal involvement are. The macroscopic description should assess the quality of the mesorectum on the specimen. There are 3 grades:

- 3/Good: Intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect is deeper than 5 mm. No coning on the specimen. Smooth CRM on slicing.

- 2/Moderate: Moderate bulk to mesorectum but irregularity of the mesorectal surface. Moderate coning of the specimen towards the distal margin. At no site is the muscularis propria visible, with the exception of the area of the insertion of levator muscles. Moderate irregularity of CRM.

- 1/Poor: Little bulk to mesorectum with defects down onto muscularis propria and/or very irregular CRM.

The area of the tumor that has been left intact is now sectioned transversely as thinly as possible. If the specimen is not well fixed (i.e., 48-72 hours in formalin), then this process is more difficult.

The fixed slices are laid out under good light and photographed (if possible) and then inspected macroscopically. Measurements include: i) the maximum depth of extension of the tumor from the muscularis propria; and ii) the distance from the CRM to the tumor. If the tumor is within 1 mm on histological sections, then CRM involvement is said to have occurred. If any lymph nodes abut the CRM, then these should be taken in continuity with the CRM so that involvement by this route can be identified; similarly, if there is any evidence of isolated deposits or thickening/fibrosis in this area, the area should be sampled. Again, if tumor is less than 1 mm from the CRM, the CRM is said to be involved. Any peritumoral lymph nodes will be collected at this time. If the tumor approaches the peritoneal surface, this must also be sampled to exclude malignant cells on the surface or ulceration of the serosa by tumor. Four blocks of the primary tumor must be taken to assess the peritoneum and tumor characteristics. These may be the same blocks as those for the CRM, if there is adequate tumor represented.

After assessing the primary tumor, attention should be turned to the lymph nodes. All lymph nodes should be identified and embedded. If any lymph nodes lie against the circumferential margin, they should be taken in continuity with the margin to exclude CRM involvement. The distal margin should then be sampled and the doughnuts examined. The proximal margin does not need to be examined unless within 5 cm of the tumor. Any mucosal lesions seen should be sampled. The status of the background mucosa can be obtained from the distal margin.

Standard histological examination of the hematoxylin and eosin sections should then be performed. If tumor is within 1 mm of the CRM, then it should be deemed to be involved. This measurement should be made on the glass slide using the Vernier scale. If tumor is close to the margin but greater than 1 mm, then deeper levels should be cut to exclude involvement. If fibrosis has led to a mistaken impression of the depth of invasion from the muscularis propria, then this measurement should be corrected from the slide.

APPENDIX VII

BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:

- Ten (10) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

Serum (if requested):

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot a minimum of 0.5 ml serum (optimal 1ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected, and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at –70 to –80° Celsius.
5. Store serum at –70 to –80° Celsius until ready to ship.
6. Ship on dry ice.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma (If requested):

- ❑ Using three (3) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials "plasma".

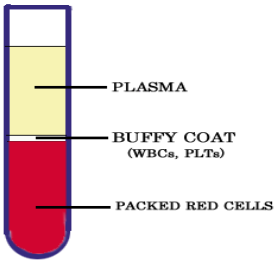
Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma (optimal 1 ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected and clearly mark specimen as "plasma".
5. Place cryovials into biohazard bag and immediately freeze at –70 to –80° Celsius.
6. Store plasma at –70 to –80° Celsius until ready to ship.
7. Ship on dry ice.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat (if requested):

For a visual explanation of Buffy coat, please refer to diagram below.



- ❑ Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) "buffy coat."

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
3. Carefully remove plasma close to the buffy coat and set plasma aside (*can be used to send plasma samples – see above instructions*).
4. Remove the buffy coat cells carefully and place into cryovials labeled "buffy coat" (*it is okay if a few packed red cells are inadvertently collected in the process*). Clearly mark the tubes with date/time of collection and timepoint collected.
5. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
6. Store buffy coat samples frozen (-70 to -80° Celsius) until ready to ship.
7. Ship on dry ice.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:

- ❑ Ship specimens overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and buffy coats together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with dry ice (4-5lbs/2-2.5kg minimum). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.*
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or contact the RTOG Biospecimen Resource by phone 415-476-7864 or Fax at 415-476-5271.