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Phase II Trial of Low Dose Whole Pelvic Radiotherapy with Concurrent Neoadjuvant FOLFOX for Patients with Newly Diagnosed T3N0M0, T2N1M0, or T3N1M0 Rectal Adenocarcinoma

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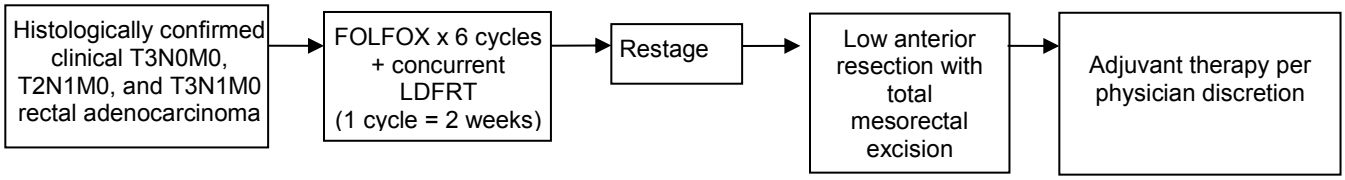
SCHEMA

T3N0M0, T2N1M0, or T3N1M0 Rectal Adenocarcinoma



FOLFOX: 5-fluorouracil (5-FU), leucovorin, and oxaliplatin

Oxaliplatin: 85 mg/m^2 intravenously (IV) over 2 hours
Leucovorin: 200 mg/m^2 IV bolus over 2 hours
5-FU: 400 mg/m^2 IV bolus over 5–15 minutes, then 2,400 mg/m^2 continuous IV infusion over 46-48 hours

Low dose fractionated radiation therapy (LDFRT)

Intensity-modulated, bone marrow sparing, whole pelvic radiation therapy
40 cGy fractions twice per day delivered at least 4–6 hours apart on the first 2 days of each chemotherapy cycle for a total of 6 cycles

	Day 1	Day 2
Oxaliplatin	↓	
Leucovorin	↓	
5-FU	↓	↓
LDFRT	↓↓ (each fraction separated by a minimum of 4 hours)	↓↓(each fraction separated by a minimum of 4 hours))

Primary Objective: To determine whether the addition of concurrent LDFRT to neoadjuvant full dose FOLFOX results in a pCR response rate of at least 35%.

Secondary Objective: To assure that neoadjuvant concurrent LDFRT-FOLFOX maintains a high rate of pelvic R0 resection compared to standard preoperative chemoradiation and total mesorectal excision surgery.

Accrual Goal: 30 patients.

1.0 BACKGROUND

1.1 Potential Role for Decreased-Intensity Neoadjuvant Therapy for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision (TME).

It is estimated that about 40,000 new cases of rectal cancer are diagnosed in the U.S. annually, and these are expected to result in approximately 22,000 deaths[1]. Treatment for locally advanced (T3/T4/N+) rectal cancers has evolved over the course of several decades. Before 1990, surgery alone without total mesorectal excision (TME) was the accepted standard of care for stage II and III rectal cancers. However, this approach was found to be suboptimal because of high local recurrence rates of greater than 50%. In an attempt to decrease local recurrences, which commonly cause significant morbidity, investigators conducted trials asking whether adjuvant 5-FU-based chemotherapy and radiation therapy provided any benefit. The Gastrointestinal Tumor Study Group 9173 (GITSG 9173) and North Central Cancer Treatment Group (NCCTG) trials in particular showed a significant decrease in local recurrence following adjuvant chemoradiation compared with observation[2,3]. These data led to a 1990 consensus statement being issued by the National Cancer Institute (NCI) recommending that surgery followed by adjuvant chemotherapy and radiation therapy (RT) should become the new standard of care[4].

Several randomized trials also evaluated the role of neoadjuvant RT for locally advanced rectal cancer. At least in theory, neoadjuvant therapies have several advantages over postoperative therapies including better tumor oxygenation and smaller radiation treatment ports. The Swedish and Dutch Rectal Cancer trials both randomized patients to short-course neoadjuvant RT (25 Gy in 5 fractions) without concurrent chemotherapy[5,6]. Notably, patients in the Swedish trial did not undergo TME while those in the Dutch trial did receive TME. These trials collectively demonstrated a local control benefit for both neoadjuvant short-course radiotherapy and TME.

Although both neoadjuvant and postoperative treatment strategies were shown to provide a local control, the current standard of care for stage II and III rectal cancers is neoadjuvant chemoradiation, based on data published from the German Rectal Study Group. Sauer et al. compared neoadjuvant with postoperative chemoradiation (50.4 Gy plus continuous infusion 5-FU) in 823 patients with resectable rectal cancer[7]. Neoadjuvant therapy had several benefits over postoperative chemoradiation including a lower 5-year local recurrence rate (6% and 13%, respectively; $P = 0.006$), less acute and late toxicity, and a higher percentage of sphincter-preserving surgeries in patients who were initially scheduled for an abdominoperineal resection (APR). No differences were found in the frequency of distant metastases or in overall survival. An 8% pathologic complete response rate (pCR) was observed in the neoadjuvant arm. The NSABP R-03 trial also prospectively compared preoperative to postoperative chemoradiation in a randomized fashion[8]. Although it closed early because of poor accrual, this trial confirmed a benefit in favor of neoadjuvant therapy. After a median follow up of 8.4 years, the neoadjuvant arm had improved 5-year disease-free survival without a significant difference in overall survival. The pCR rate in the neoadjuvant arm

was 15%. Thus, preoperative pelvic chemoradiation followed by TME-based resection is now the standard of care for locally advanced rectal cancer. Based on data extrapolated from colon cancer, these patients are also routinely recommended to receive adjuvant 5-FU-based chemotherapy.

This proposed study does not seek to introduce novel treatment agents. Instead, it aims to make modifications in standard-of-care trimodality therapy intended to maintain excellent long-term outcomes while potentially decreasing significant treatment-related toxicity. The rationale for this concept stems from a confluence of factors related to contemporary management of locally advanced rectal cancer.

1.1.1 Neoadjuvant RT with standard pelvic RT doses may result in overtreatment of some patients.

Although neoadjuvant chemoradiation reduces toxicity compared to adjuvant chemoradiation, the potential remains for a minority of patients to demonstrate significant acute and/or late adverse effects. This has resulted in debate regarding whether all locally advanced rectal cancer patients should receive the same intensive neoadjuvant treatment regimen.[9] Some centers have suggested eliminating RT in patients with more favorable disease who are at a lower risk of local recurrence, especially in the era of TME.[10-12] Because of the lack of data supporting a chemotherapy-only approach, neoadjuvant chemoradiation remains the standard of care for all locally advanced rectal cancer patients.

1.1.2 Standard pelvic RT doses are associated with both short and long-term morbidity.

Standard neoadjuvant chemoradiation can result in considerable acute toxicity, which is seen in up to 50% of patients.[13] Treatment time is also substantial in that it requires 28 daily radiation treatments over 5.5 weeks as well as additional visits to receive either oral or intravenous 5-FU. Most importantly, the late effects of pelvic radiation can be significant, including fibrosis and autonomic nerve injury and may be accompanied by increased fecal incontinence, urgency/frequency, and higher rates of bladder and sexual dysfunction when compared to patients that do not receive pelvic radiation.[7,14,15] In addition, because the pelvis is an active site of hematopoiesis, patients who undergo pelvic radiation may have diminished ability to withstand subsequent myelosuppressive therapy, a consideration that is more relevant in an era in which a greater number of chemotherapeutic options are available for metastatic disease. Pelvic fracture after modest trauma such as an uncomplicated fall also occurs more commonly in patients after pelvic irradiation with standard RT dosing.[16]

1.1.3 Neoadjuvant radiation delays initiation of full dose systemic therapy.

Current rectal cancer treatment paradigms do not deliver full dose systemic chemotherapy such as FOLFOX until 14-18 weeks from initiation of neoadjuvant chemoradiotherapy and this delay is potentially disadvantageous because it allows a window for metastatic dissemination of disease. The standard treatment timeline is as follows: 5.5 weeks of neoadjuvant chemoradiation; 4-6 weeks recovery; surgical resection; 4-6 weeks postoperative recovery; and then initiation of adjuvant therapy. As

a result, no full dose chemotherapy is delivered to treat potential micrometastases until more than 3 months after treatment onset. The delay in full-dose systemic therapy may open a window of opportunity for growth of small-volume disease outside the pelvis. Our hypothesis is that delivering full dose chemotherapy such as FOLFOX earlier in the treatment course may decrease the likelihood of disease dissemination outside of the pelvis.

1.1.4 Advancements in systemic therapy and surgical techniques have substantially improved outcomes over the last decade.

Local control is critically important because of the high morbidity associated with pelvic recurrence. Traditional surgery, now outmoded, involved blunt digital dissection of the mesorectum and often resulted in tearing the mesorectal fascia and/or incomplete resection of the nodal basin around the rectum with a positive radial margin. In this setting, postoperative chemoradiation reduced local recurrence by sterilizing tumor deposits left in the pelvis from inadequate surgery. The introduction and acceptance of TME and subsequent standardization of sharp dissection of the lymph node–bearing tissue resulted in low positive radial margin rates, which translated into fewer local recurrences. This has spurred a debate about whether RT remains necessary in the patient who has undergone an appropriate and successful TME. This question was addressed in the TME trial set up by the Dutch Colorectal Cancer Group that randomized between standardized and quality-controlled TME surgery alone and TME surgery preceded by short-term preoperative RT.[17] This study helped clarify the contribution of neoadjuvant radiation to rectal cancer therapy and underscored the importance of proper surgical technique. First, the authors demonstrated that neoadjuvant radiation does not influence long-term survival. Second, they confirmed that neoadjuvant radiation improves local control even after TME is performed. Third, the rate of local recurrence for patients treated without RT was substantially lower than the 25% local recurrence noted in the historical rectal cancer trials. The Dutch study thus demonstrated that superior surgical technique is able to dramatically reduce local recurrence.

In addition to surgical advances, significant advances have been made in systemic chemotherapy for patients with colorectal cancer.[18-20] Response rates for patients with primary and metastatic colorectal cancer treated with modern chemotherapy regimens such as 5-FU, leucovorin, oxaliplatin (FOLFOX) have routinely exceeded 50% and are frequently as high as 60%-70%.[19,20] In the context of improved surgical technique, improved chemotherapy, and better radiologic staging, many have questioned whether rectal cancer treatment can be streamlined and/or simplified.

1.1.5 Neoadjuvant FOLFOX chemotherapy without radiation therapy as a potentially new option for locally advanced rectal cancer.

This current protocol builds on work conducted by investigators at the Memorial Sloan-Kettering Cancer Center. In a single-institution trial (MSKCC07-021) that started in March 2007, 32 rectal cancer patients were treated with neoadjuvant FOLFOX chemotherapy instead of standard whole pelvic chemoradiation over 5.5 weeks. Patients also received bevacizumab for the first 4 cycles of therapy. Two patients did

not complete neoadjuvant FOLFOX secondary to cardiac complications likely attributable to bevacizumab. Of the 30 who did complete neoadjuvant treatment, all had R0 resections including TME. Eight of those 30 had pathologic complete responses (pCR) (27%). One patient died postoperatively, and 3 patients experienced a recurrence. All 3 recurrent patients had distant metastasis to the lung. With a mean follow–up of 27 months no study participant had a pelvic recurrence, which is notable since none received pelvic RT. These results were so striking that they have led to an ongoing National Cancer Institute-sponsored phase II/III clinical trial (NCT01515787) evaluating the use of neoadjuvant chemotherapy alone in locally advanced rectal cancer patients who are planned to undergo a low anterior resection with total mesorectal excision. The phase II component of the trial aims to assure that neoadjuvant FOLFOX maintains a high rate of pelvic R0 resection compared to standard pelvic chemoradiation and is also non-inferior with respect to time to local recurrence. The phase III component of the trial aims to compare the pCR rate between neoadjuvant FOLFOX and standard pelvic chemoradiation. Lastly, this trial also will evaluate treatment-related toxicity from each of the respective treatment arms.

1.2 Rationale for using whole pelvic low dose fractionated radiation therapy (LDFRT) for locally advanced rectal cancer patients.

Gastrointestinal carcinomas are known to be radiosensitive, which has resulted in extensive use of RT for rectal cancer. As previously discussed, while standard whole pelvic RT is highly effective in decreasing the probability of pelvic recurrence for rectal cancer patients a significant drawback of using standard RT doses includes potentially serious RT-related morbidity. The likelihood of serious acute and late RT-related morbidity is well known to correlate with the total RT dose prescribed as well as the dose delivered per fraction. Because locally advanced rectal cancer patients may harbor occult metastatic disease outside of the pelvis neoadjuvant full dose chemotherapy (i.e. FOLFOX) should be combined with concurrent standard pelvic RT prior to reap the benefits of optimal systemic and locoregional treatment. However, this is not done in practice because the cumulative toxicity would be unacceptably high. Thus, an optimal combination of chemotherapy and pelvic RT is needed to address both potentially distant occult metastatic disease and gross pelvic disease, respectively.

Traditional thoughts in radiation biology of tumors suggested that doses of at least 120 cGy were required to overcome the initial shoulder of the cell survival curve. In practice, the standard dose per fraction is considered to be 150-220 cGy per fraction although the vast majority of patients are treated with either 180 cGy or 200 cGy fractions. Laboratory and clinical data suggest that a new paradigm using LDFRT as a chemopotentiator may allow full-dose drug therapy with improved efficacy without adding to the toxicity of the systemic treatment.[21-26] This chemopotentiating effect is possible through a phenomenon known as hyper-radiation sensitivity (HRS) by which there is more effective tumor cell killing than would be predicted when using doses per fraction below 100 cGy. This is followed by a change in slope of the survival response with increasing doses per fraction, indicating increased radioresistance (IRR) (Figure 1). This phenomenon was first described by Joiner and colleagues in the Gray Laboratory in 1986 and has since been well described by a number of laboratories.[27] It also has

been documented in the clinical setting; in a study by Harney et al. patients with paired cutaneous metastases from sarcoma and melanoma had longer time to tumor regrowth after LDFRT than with conventional radiation.[26] *In vitro* studies have established a link between (HRS/IRR) and evasion of the early G2/M cell cycle checkpoint.[21,28,29] Exaggerated HRS/IRR responses were found for enriched populations of G2-phase cells in one study, indicating that the mechanism likely involved events in the G2-phase of the cell cycle. Two G2 checkpoints have been described, and the more recently discovered "early" checkpoint is rapidly activated after radiation exposure. It is believed to prevent cell cycle progression through G2 of cells with unrepaired radiation-induced DNA damage. The signaling cascade regulating the early G2/M checkpoint is initiated through ataxia telangiectasia mutated (ATM) activity. Joiner and colleagues have shown that inhibition of ChK1 and Chk2, two proteins integral to the G2/M transition, can influence the cell-cycle response to low-dose radiation.[28] It is believed that failure of the cell to repair DNA damage in G2-phase cells leads to increased apoptosis. Nonetheless, inhibition of ChK1 and ChK2 also lead to IRR at radiation doses > 0.2 Gy. This is consistent with reports indicating that low dose radiation can stimulate repair of DNA damage. Interestingly, low dose radiation can also stimulate antioxidant capacity, apoptosis, and induction of immune responses, which collectively may provide effective local tumor control.[30] In addition, hypoxia and nitric oxide levels can also affect cells sensitivity to radiation. Reduction of nitric oxide level enhances the radiosensitivity of hypoxic non-small cell lung cancer. Therefore, the identification of cellular pathways that are responsive to low-dose radiation and their contribution to chemopotentiation is highly significant because this will provide a better measurement of the therapeutic response and contribute to the rational design of mechanism-based clinical trials.

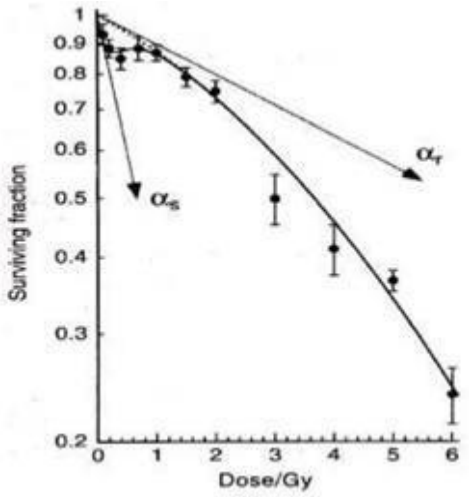


Figure 1. Induced Repair Model of Cell Survival. *Shown are the parameters of the "induced repair" (IR) model of cell survival, which provides a statistically better fit in the low dose region than the linear quadratic model in cell lines exhibiting hyperradiosensitivity (HRS). The presence of HRS is supported by αs/αr ≠ 1 and dc ≠ 0 Gy. For the Joiner data in Figure 1, αs/αr = 13.6 and dc = 0.21Gy. The best-fit parameters of the "induced-repair" or the linear-quadratic (LQ) model were obtained using JPM® SAS software (Cary, NC), also used to analyze our data. This data is unpublished.*

1.2.1 Preclinical HRS data for colorectal cancer cells.

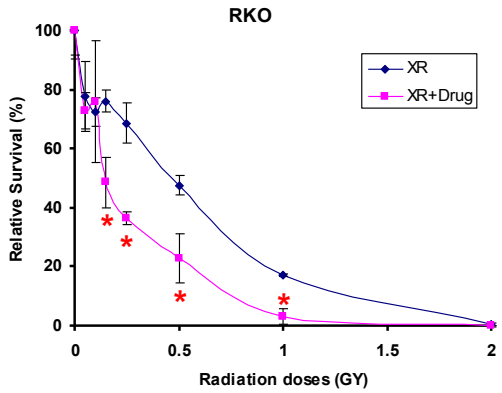
Preclinical data demonstrates increased radiation sensitivity in a variety of tumor cell lines including colorectal cells.[31-35] Investigators at the University of Kentucky have demonstrated that LDFRT can increase radiosensitivity in colorectal cells irrespective of

p53 status.[34] Colony-forming assays were performed in HCT-116 (wild-type p53) and HT-29 (mutant p53) colorectal cell lines after exposure to LDFRT 50-60 cGy, paclitaxel 1-10 nanomolar (nM), or LDFRT and paclitaxel. LDFRT and paclitaxel given concurrently showed enhanced radiosensitization among the HCT-116 cells (surviving fraction (SF)(2)=0.138; D(0)=103 cGy) although not in HT-29 cells (SF(2)=0.608; D(0)=306 cGy). However, both HCT-116 and HT-29 cells had increased radiosensitivity when 50 or 100 cGy fractions were given to a total of 200 cGy after pretreatment with paclitaxel.

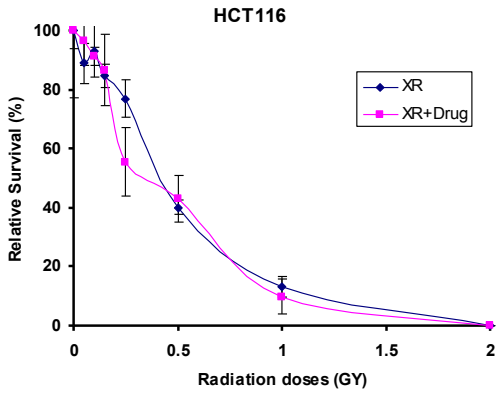
Unpublished preclinical data from the University of Maryland Medical Center also support that a HRS phenomenon occurs in colorectal cells in response to LDFRT. Colorectal carcinoma RKO and HCT-116 cells were plated at 200 cells per well in p6 well plates in triplicate. Plating efficiency were 53 and 43 % respectively. The cells were irradiated twice daily 4.5 hours apart for 2 days. The dose per fraction ranged from 0.05 Gy up to 2 Gy, as shown in Figure 2. On the first day of radiation the cells were exposed to 5-FU 1.15 millimolar (mM), oxaliplatin 0.18 mM and leucovorin 2mM. On day two of irradiation the cells were exposed to 5-FU 1.15 mM. The chemotherapy doses were adjusted to produce 50% survival in a cell based assay. Cells were allowed to grow for 7-10 days following initial treatment after which the colonies (≥ 50 cells) were fixed, stained and counted. Relative survival is expressed as a percentage of surviving colonies in reference to the mean plating efficiency of three sham-irradiated control plates. Chemotherapy enhancement ratio (ER) by radiation was calculated using the following formula based on surviving fraction (SF): mDCF ER = $SF_{mDCF\ alone}$/ $SF_{mDCF\ +\ radiation}$. Ratio above 1 indicate enhancement. There was clear chemopotentiation from LDFRT in the RKO cell line. The HCT-116 cell line showed potentiation at 0.25 Gy.

Figure 2. A-B) Clonogenic survival assays performed on RKO and HCT-116 colorectal cancer cell lines. Relative survival is expressed as a percentage of untreated cells. C-D) Chemotherapy enhancement ratio (ER) by radiation was calculated using the following formula based on surviving fraction (SF): mDCF ER = $SF_{mDCF\ alone}$/ $SF_{mDCF\ +\ radiation}$

A.



B.



C.

Dose Gy	FOLFOX ER
0	1
0.05	1.06
0.1	0.95
0.15	1.57
0.25	1.88
0.5	2.09
1	5.6
2	0

D.

Dose Gy	FOLFOX ER
0	1
0.05	0.92
0.1	1.02
0.15	0.97
0.25	1.38
0.5	0.93
1	1.32
2	0

Fig. 2

1.2.2 Clinical experience with LDFRT.

Based on promising preclinical data, clinical studies have been performed in a variety of cancer types with LDFRT in addition to standard chemotherapy. Investigators at the University of Kentucky published their experience using carboplatin and paclitaxel with 4 fractions of 80 cGy each in locally advanced head and neck cancer patients.[25] They observed toxicities similar to those expected from chemotherapy alone and concluded that the addition of LDFRT was “extremely well tolerated.” Moreover, they reported excellent response rates. Regine et al. conducted a phase I trial of low-dose abdominal RT (60 vs. 70 cGy fractions, total 8 fractions) and gemcitabine 1,250 mg/m^2 among patients with unresectable pancreatic/small bowel carcinomas.[36] The authors concluded that abdominal LDFRT using 60-cGy fractions was well tolerated when given concurrently with full-dose gemcitabine. A multi-institutional phase II trial using this regimen suggested improved efficacy of the combined regimen in improving overall survival. Sixty-one percent of enrolled patients experienced at least stable disease, and median survival in this poor prognosis population was 13 months. More important, no additional toxicity was observed with the low-dose radiation other than that expected from the high dose of gemcitabine. More recently, Wrenn et al. published results of a phase I study of low-dose whole-abdominal RT and full-dose cisplatin in optimally debulked stage III/IV endometrial cancer patients.[37] Because treatment was well

tolerated, the authors concluded that further investigation was warranted to determine treatment efficacy.

1.2.3 Experience with using bone marrow–sparing intensity-modulated radiation therapy (IMRT).
In addition to our experience using LDFRT, we have also successfully used IMRT to spare bone marrow based on the phase II study reported by Rochet and coworkers.[38] By utilizing this approach, we have been able to safely deliver significantly higher doses of whole-abdominal RT similar to that proposed in this protocol; patients treated in this fashion have not required treatment breaks because of hematologic toxicity. Moreover, a bone marrow–sparing approach is prudent given our strategy of using concurrent FOLFOX, which causes more hematologic toxicity than 5-FU alone.

1.3 Proposed study overview.
The current standard of care for treatment of locally advanced rectal cancer consists of neoadjuvant whole pelvic RT with radiosensitizing single-agent 5-FU followed by surgery and adjuvant full dose chemotherapy (typically FOLFOX). For all clinical T3, T4, and/or lymph node positive rectal cancer patients the standard neoadjuvant radiation dose per fraction is 180 cGy delivered on consecutive weekdays over 5.5 weeks for a total of 5040 cGy. A potentially paradigm-changing approach is currently being investigated in a phase II/III trial in which neoadjuvant RT is omitting in favor of using full dose FOLFOX chemotherapy based on provocative data published from Memorial Sloan Kettering Cancer Center. We hypothesize that whole pelvic LDFRT using 40 cGy fractions for a total of 960 cGy can be safely added concurrently to neoadjuvant full dose FOLFOX as an alternative to standard neoadjuvant 5-FU chemoradiation. We further hypothesize that using LDFRT as a chemopotentiatior will significantly increase the pCR rate as reported by the Memorial Sloan Kettering pilot study of 27%. Lastly, due to the significantly lower radiation dose per fraction and lower total radiation dose we expect that this novel strategy will not cause higher rates of severe toxicity compared to neoadjuvant FOLFOX alone.

Specifically, this phase II trial intends to determine whether 6 cycles of neoadjuvant FOLFOX with concurrent LDFRT followed by comprehensive restaging and TME achieves favorable outcomes for patients with T3N0M0, T3N1M0, or T2N1M0 rectal cancer. As mentioned above, the current standard of care for all locally advanced rectal cancer patients includes radiosensitizing 5-FU and concurrent whole pelvic RT to 5040 Gy in 180 Gy once daily fractions. Per the proposed protocol, T3N0M0, T3N1M0, or T2N1M0 rectal cancer patients who are eligible to undergo a low anterior resection would receive whole pelvic RT to 960 cGy in 40 cGy fractions delivered twice daily on days 1-2 of each cycle of FOLFOX chemotherapy for a total of 6 cycles.

Eligible study subjects include adults who are candidates for curative intent sphincter-sparing surgery and who lack high-risk features, particularly tumor encroaching upon the mesorectal fascia (within 3 mm) as determined by pre-treatment endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) or distal rectal tumors (<5 cm from the anal verge).

This study has the potential to dramatically influence our approach to treating rectal cancer by improving on the single-institution experience reported by Schrag and coworkers at Memorial Sloan–Kettering. Based on the previously reported ability of LDFRT as a chemopotentiator to improve treatment outcomes with no significant increase in toxicity as seen in other disease sites, we anticipate that the addition of LDFRT to neoadjuvant chemotherapy will augment the encouraging data published from Memorial Sloan–Kettering.

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether the addition of concurrent LDFRT to neoadjuvant full dose FOLFOX results in a pCR response rate of at least 35%.

2.2 Secondary Objective

To assure that neoadjuvant concurrent LDFRT-FOLFOX maintains a high rate of pelvic R0 resection compared to standard preoperative chemoradiation and total mesorectal excision surgery.

3.0 ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 ≥ 18 years old at diagnosis.
3.1.2 ECOG Performance Status 0, 1, or 2.
3.1.3 Biopsy-proven diagnosis of rectal adenocarcinoma.
3.1.4 Clinical AJCC 7th edition stage T2N1M0, T3N0M0 or T3N1M0 based on physical examination, CT scan chest or chest x-ray AND CT abdomen or MRI abdomen AND pelvic MRI or endorectal ultrasound (ERUS).
3.1.5 Preoperative lower gastrointestinal endoscopy (proctoscopy, sigmoidoscopy, colonoscopy) confirming tumor extent as no less than 5 cm and no greater than 12 cm from the anal canal. If endoscopy is not rigid, CT or MRI can be used to indicate location from anal canal.
3.1.6 Evaluation by a surgical oncologist, radiation oncologist, and medical oncologist ≤ 28 days prior to registration.
3.1.7 Confirmation that the patient is able to undergo a low anterior, sphincter-sparing resection with total mesorectal excision ≤ 28 days prior to registration.
3.1.8 In the absence of treatment on a clinical trial, the patient would be recommended to receive neoadjuvant chemoradiation followed by curative intent surgery.
3.1.9 The following laboratory values obtained ≤ 14 days prior to registration:

- Absolute neutrophil count (ANC) ≥ 1500/mm^3.
- Platelet count ≥ 100,000/mm^3.
- Hemoglobin > 8.0 g/dL. May transfuse to meet eligibility.
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN).
- SGOT (AST) ≤ 3 x ULN.
- SGPT (ALT) ≤ 3 x ULN.

- Creatinine ≤ 1.5 x ULN.

3.1.10 Baseline CEA within 14 days of registration
3.1.11 Negative serum pregnancy test (B-HCG) within 14 days prior to registration for women of childbearing potential.
3.1.12 Did the patient provide study-specific informed consent prior to study entry?
3.1.13 Willingness to return to the enrolling medical site for all study assessments.

3.2 Exclusion Criteria
3.2.1 Clinical T4 tumor.
3.2.2 Surgeon indicates the need for an abdominal perineal resection (APR) at baseline.
3.2.3 Previous pelvic RT.
3.2.4 Autoimmune disease such as scleroderma, lupus, or inflammatory bowel disease.
3.2.5 Tumor < 3 mm from the mesorectal fascia as seen on MRI or endorectal ultrasound.
3.2.6 Tumor-induced symptomatic bowel obstruction.
3.2.7 Chemotherapy (including hormonal therapy) within the past 5 years from date of registration.
3.2.8 Other invasive malignancies within past 5 years from date of registration.
3.2.9 Pregnant or nursing women.
3.2.10 Men or women of childbearing potential who are unwilling to employ adequate contraception.
3.2.11 Other co-morbid conditions that, based on the judgment of the physicians obtaining informed consent, would make the patient inappropriate for this study.
3.2.12 Any conditions that would preclude a patient from completing all study assessments.

4.0 REGISTRATION
Patients can be registered only after all eligibility criteria are met. The date of registration/enrollment is considered to be the day the Eligibility Checklist is signed by the verifying physician. Once a patient is enrolled, a unique case number will be assigned to the patient in ONCORE.

5.0 TREATMENT PLAN
Treatment must begin within 14 days of registration.

5.1 Chemotherapy
Neoadjuvant FOLFOX (5-FU + leucovorin + oxaliplatin)
This regimen will be repeated every 2 weeks for 6 cycles; (1 cycle = 14 days).

Given first: Oxaliplatin 85 mg/m^2 IV in D5W 500 mL over 2 hours, Day 1
Given second: Leucovorin 200 mg/m^2 IV bolus in D5W 250 mL over 2 hours, Day 1
Given third: 5-FU 400 mg/m^2 IV bolus in a syringe given over 5–15 minutes, Day 1, then 2,400 mg/m^2 in 240 mL of 0.9% Sodium Chloride via continuous IV infusion over 48 hours, Days 1–2

Note: Oxaliplatin is administered first, prior to leucovorin; alternatively leucovorin may be administered (via separate infusion containers) concurrently with oxaliplatin.

5.1.1 If necessary to accommodate holidays, patient schedule or other justified circumstance approved by the PI, the schedule may be modified by ± 3 days.

5.1.2 Chemotherapy dose modification is at the discretion of the treating medical oncologist, although any patient who requires dose modification below dose level -2 will be removed from study participation. There are no restrictions on dose modifications for the sixth cycle of FOLFOX.

5.1.3 Patients who cannot tolerate 6 cycles of FOLFOX or those who require dose modification below dose level -2 or those who are found to be ineligible for the study based on central review of either the baseline or the follow up MRI or those that withdraw consent will receive preoperative combined modality chemoradiation with infusional 5-FU. There are no restrictions on dose modifications for the 6th cycle of neoadjuvant FOLFOX.

5.1.4 Patients receiving oxaliplatin on this study should be counseled to avoid cold drinks, chewing ice chips, and exposure to cold water or air because the sensory neurotoxicity often seen with oxaliplatin appears to be exacerbated by exposure to cold. The period of time during which the patient appears to be at risk for these cold-induced sensory neuropathies is not well documented. Patients should exercise caution regarding cold exposure during the treatment period. Peripheral sensory neuropathies can occur at any time after receiving oxaliplatin therapy.

5.1.5 Concurrent medications are at the discretion of the treating physician.
Current Greenebaum Comprehensive Cancer Center recommended:
Ondansetron 16 mg PO daily, if patient unable to take orally give 8 mg IV.
Dexamethasone 12 mg PO daily, if; unable to take orally give IV.

5.1.6 Adjuvant chemotherapy is at the discretion of the treating physician and is not considered part of protocol therapy.

5.2 Radiation therapy

5.2.1 Simulation: Will be performed prior to initiation of therapy with patients in the supine position and arms above the head. One Vac-Lock bag will be used for positioning and immobilization placed at the level of the pelvis. No oral or IV contrast is required. CT simulation from the cranial extent of L1 to the level of the lesser trochanter will be performed to ensure adequate coverage and dosimetric parameters.

5.2.2 Volumes: The gross tumor volume (GTV) should be contoured using all available imaging as well as information from physical examination and proctoscopy.

The clinical target volume (CTV) should include the GTV as well as elective lymph node regions (internal iliac, mesorectal, presacral). Since patients with low lying rectal tumors and T4 rectal tumors will not be included in this study, the external iliac and inguinal lymph nodes should not be included as they are not felt to be at a significant clinical risk of subclinical involvement. A planning target volume (PTV) should be created using a 0.5 cm uniform expansion from the CTV to account for daily set up variability provided daily kilovoltage (kV) imaging is used for image guidance. If daily kV imaging is not available, then larger PTV margins should be used based on the discretion of the treating physician. Normal structures to be contoured include small bowel (up to 1 cm superior to PTV), bladder, femoral heads, and pelvic bones (including the sacrum, ilium, ischium, and pubic bones as a surrogate for bone marrow).

5.2.3 Technique: To limit dose to bone marrow, LDFRT will be delivered using intensity modulated radiation therapy (IMRT). IMRT may be delivered using either static beams or volumetric-modulated arc therapy (VMAT). Since the total prescribed radiation dose used in this study is well below the established tolerance levels of all normal tissues that will be contoured, no specific normal dose constraints should be used. However, a priority should be made to limit the volume of the pelvic bones (as a surrogate for bone marrow) receiving the prescription dose.

5.2.4 Dose: 40 cGy fractions will be administered twice daily on Days 1 and 2 of each cycle of FOLFOX with each radiation fraction being delivered a minimum of 4 hours apart. This will be repeated every 2 weeks for a total dose of 960 cGy.

5.2.5 Treatment Planning Objectives:
100% of the PTV should be covered by at least 95% of the prescription dose. 100% of the CTV should be covered by at least 95% of the prescription dose. No greater than 110% of the prescription dose should be delivered to no greater than 0.03 cc of the PTV.

6.0 RESTAGING

Restaging will take place 4 weeks (±1 week) after completion of 6 cycles of FOLFOX and LDFRT. The patient will see the physician and have labs and imaging completed per Appendix I scheduling. Repeat imaging should include the same modality used at baseline. For example, if a baseline MRI was performed, a post-LDFRT-FOLFOX MRI should be repeated. If a baseline endorectal ultrasound (ERUS) was performed, a post-LDFRT-FOLFOX ERUS and CT scan should be repeated.

The decision to proceed to TME directly, or alternatively receive standard chemoradiation off protocol followed by TME, will be based on radiological and clinical tumor response.

Patients will proceed directly to TME unless any of the following occurs, at which time they will be discontinued from treatment on this study and be recommended to pursue appropriate treatment off-study.

- If there is any evidence of progressive disease (PD) by either imaging or clinical assessment.
- If a patient with radiologically measurable disease has an overall radiologic tumor response status of stable disease (SD).
- If a patient with disease that is not radiologically measurable has a clinical tumor response of 20% or less as determined by endoscopy.

6.1 Radiological tumor evaluation

Assessment will be according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.[39]

6.1.1 Timing of restaging evaluation: Patients should undergo re-evaluation 4 weeks (± 1 week) after the completion of 6 cycles of FOLFOX and LDFRT.

6.1.2 Definitions of measurable and non-measurable disease

6.1.2.1 Measurable disease (standard definition per RECIST):

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as at least 2.0 cm with chest x-ray, or as at least 1 cm with CT scan, CT component of a PET/CT or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is at least 1 cm in diameter as assessed using calipers or imaging.
- A malignant lymph node (LN) is considered measurable if its short axis is at least 1 cm when assessed by CT scan or pelvic MRI

6.1.2.2 Non-measurable disease (standard definition per RECIST):

- All other lesions or sites of disease are considered non-measurable disease, including pathological nodes (those with a short axis at least 1 cm to less than 1.5 cm. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) or considered non-measurable as well.

6.1.3 Guidelines for evaluation of measurable disease

6.1.3.1 Measurement methods

- All measurements should be recorded in metric notation (i.e. decimal fractions of centimeters) using a ruler or calipers.
- The same technique and method of assessment must be used at baseline and during follow-up.

6.1.3.2 Acceptable modalities for measurable disease

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- For this study, when an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: The CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Evaluation of disease by MRI is preferred. However, for patients who are not able to undergo an MRI or for clinicians who prefer it, an ERUS is acceptable. If ERUS is performed as an alternative to MRI at baseline, then an ERUS must also be performed at the time of restaging.
- In cases where ERUS is the modality selected to evaluate the primary rectal tumor, an accompanying CT for complete pelvic disease staging will also be interpreted by the on-site radiologist.
- A standard CT of the abdomen and pelvis or chest, abdomen and pelvis with oral and intravenous contrast is required. In the event that radiologic studies yield inconsistent interpretation of T stage or N stage the modality that assigns the highest T stage or the highest N stage should be used for purposes of protocol eligibility.

6.1.4 Measurement of effect – imaging response to neoadjuvant LDFRT-FOLFOX

"Adapted RECIST" as defined in this protocol consists of the following:

6.1.4.1 Target Lesions & Target Lymph Nodes

- The Rectal Primary tumor is the primary target lesion. In addition, associated pelvic lymph nodes should be recorded and measured at baseline.

- The primary rectal lesion is measured and followed as a bi-dimensional product to avoid measurements that include the GI tract lumen whether collapsed or filled with air, feces or contrast material that does not represent tumor tissue. The Bi-Dimensional Product (BDP) is the product of the longest diameter for the rectal primary tumor and the thickest wall. The BDP will be used as reference to further characterize

any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Bi-Dimensional Product (PBDP): The product of the longest diameter of the rectal primary tumor multiplied by the thickest wall will be calculated and reported as the post-bi-dimensional product (PBDP). If the radiologist is able to provide an actual measure for the target even if it is below 0.5 cm. If the target is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the rectal primary has likely disappeared, the measurement should be recorded as 0 cm.

- Given increased error in measuring smaller structures, and given differing qualities of MRI and their resolution, diminutive nodes are those measuring 0-0.4 cm. These will not be considered evaluable for change. Evaluable nodes are those 0.5 cm or greater in the mesorectal and superior hemorrhoidal location.

- To be labeled as a target lymph node: up to 4 nodes in the mesorectal, superior hemorrhoidal and internal iliac regions may be considered “target” lymph nodes if they measure 0.5 cm or greater in short axis.

- To categorize the primary tumor as consistent with clinical stage N2 disease, ≥4 lymph nodes must measure >1 cm in short axis.

6.1.4.2 Imaging Response Criteria

6.1.4.2.1 All target lesions and target lymph nodes followed by imaging and physical examination must be measured on reevaluation at evaluation times specified in Section 6.1. Specifically, a change in objective status to either a PR or CR cannot be made without re-measuring target lesions and target lymph nodes.

6.1.4.2.2 For purpose of restaging, a target lymph node must measure 0.5 cm or more in short axis.

- Target lymph nodes, which at baseline measure between 0.5 and 1 cm short axis inclusive, must increase 0.3 cm in size to be considered PD. Nodes between 1.1 and 2 cm short axis inclusive must increase in size 0.4 cm to be considered PD. Nodes 0.2 cm and greater in short axis must increase in size by 25%, (e.g., 0.2 cm to 2.5 cm, or 2.5 cm to 3.1 cm) to be considered PD.

- An internal target iliac lymph node (“obturator,” etc.), must be

1 cm in short axis diameter to be considered evaluable and will follow same rules as above for absolute increase in size.

- Complete LN response requires radiological disappearance of initially abnormal lymph nodes or maintenance of 1.9 cm or less size of LN from this baseline "normal" definition.

6.1.4.2.3 Evaluation of the Rectal Primary and Target Lymph Nodes.

1. Complete Response (CR)	All of the following must be true: a. Disappearance of the rectal primary. b. Each target lymph node must have decreased short axis to <0.5 cm. c. No new sites of disease.
2. Partial Response (PR):	At least a 20% decrease in PBDP (bi-dimensional product of primary rectal lesion) taking as reference the BDP. No new sites of disease. And no PD of any target lymph nodes.
3. Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
4. Progression (PD)	At least one of the following must be true: At least one new malignant lesion, which also includes any LN that was normal at baseline (< 0.5 cm short axis) and increased to ≥ 0.5 cm short axis during follow-up. At least a 20% increase in PBDP (bi-dimensional product of rectal primary lesion).

6.1.4.3 Overall radiologic tumor response status after neoadjuvant LDFRT-FOX

The radiologic response status after neoadjuvant LDFRT-FOLFOX is determined by combining the patient's status including primary rectal tumor, target lymph nodes, and new disease as defined below:

Primary Rectal Tumor & Target Lymph Nodes	New Sites of Disease	Overall Radiographic Tumor Response Status
CR	No	CR
PR	No	PR
SD	No	SD
Not all evaluated	No	Not evaluated
PD	Yes or No	PD

6.2 Clinical tumor evaluation

Baseline and re-evaluation proctoscopy should be performed by the surgeon. The surgeon should perform pre and post treatment examinations. A gastroenterologist may perform proctoscopy in lieu of the surgeon, but then must also perform the follow-up examination. Proctoscopy includes colonoscopy, flexible sigmoidoscopy as well as rigid proctoscopy.

Follow-up proctoscopy should be performed within 3-5 weeks after the completion of LDFRT-FOLFOX.

6.2.1 Guidelines for evaluation of clinically evaluable disease

6.2.1.1 Definition of clinically evaluable disease

To be clinically evaluable, a tumor must be directly visualized at proctoscopy and estimated to have a clinical bidimensional product (BDP) of ≥ 1 cm.

6.2.1.2 Clinical tumor response based on proctoscopy can be classified as the following:

- Complete response (100%)
- Major response (51-100% smaller)
- Moderate response (21-50% smaller)
- Minimal response (0-20% smaller)
- Progression (tumor enlargement)
- Unable to determine

6.2.1.3 Treatment decision after re-evaluation following LDFRT-FOLFOX

- If there is evidence of progressive disease on imaging or clinical assessment, the patient should be referred for standard neoadjuvant chemoradiation off protocol followed by TME.
- If a patient with radiologically measurable disease has an overall imaging tumor response status of stable disease, the patient should be referred for standard neoadjuvant chemoradiation off protocol followed by TME.

- If a patient with disease that is not radiologically measurable has a minimal clinical tumor response, the patient should be referred for standard neoadjuvant chemoradiation off protocol followed by TME.
- Otherwise, the patient should proceed directly to TME.

7.0 SURGERY

Following restaging, patients without evidence of progressive disease, stable disease, or clinical tumor response of 20% or less will undergo a total mesorectal excision (TME) to be performed about 6-8 weeks after completion of LDFRT-FOLFOX. Total mesorectal excision is performed off study as part of standard of care.

Follow up visits will be off protocol and scheduled as per standard of care. Patients will be followed only for survival.

8.0 PATHOLOGICAL TUMOR ASSESSMENT

8.1 Definition of surgical margin status

8.1.1 Margin type

- Proximal: most cephalad portion of the specimen
- Distal: most caudad portion
- Radial: outer circumference of the specimen

8.1.2 Margin positivity

- Positive: tumor ≤ 1 mm from any edge of the primary tumor specimen
- Close: tumor >1 but ≤ 3 mm from any edge of the primary tumor specimen
- Negative: no tumor within 3 mm from any edge of the primary tumor specimen

8.2 Degree of pathologic treatment response

8.2.1 Pathological complete response (pCR)

A pCR indicates that no gross or microscopic tumor is identified anywhere within the primary tumor specimen or any lymph nodes.

8.2.2 Pathologic response other than a pCR

The definition of a non-pCR will include any surgical specimen that has any evidence of residual tumor manifest in the primary or regional lymph nodes.

For patients who do not meet criteria for a pCR, the extent of response to pre-operative therapy will be graded using the Tumor Regression Grade (TRG) schema that is included in the AJCC 7th edition. This was also used by Rodel in the pre/postoperative rectal cancer study and was subsequently adopted by the AJCC [Rodel (JCO 2005; 23:8688-8696)]. This schema evaluates the

degree to which the primary rectal tumor specimen has responded to neoadjuvant treatment.

Tumor regression grade (TRG)	Response categorization	Description
TRG 0	Complete	No viable cancer cells
TRG 1	Moderate	Single cells or small groups of cancer cells
TRG 2	Minimal	Residual cancer outgrown by fibrosis
TRG 3	Poor	Minimal or no tumor kill; extensive residual cancer

9.0 ADJUVANT THERAPY

Adjuvant therapy will be prescribed at the discretion of the treating physician(s). Although not required by this protocol, patients with close or positive margins or other features felt by the treating physician(s) to be high risk factors for locoregional recurrence are recommended to receive standard adjuvant chemoradiation.

10.0 DATA SAFETY MONITORING AND ADVERSE EVENT (AE) MONITORING AND REPORTING

10.1 Data and Safety Monitoring / Quality Assurance Committee

This study will be governed by the UMGCC Data Safety Monitoring / Quality Assurance Committee (DSMQAC). The study will be sent to the DSMQAC for a mandatory interim review after the first 6 patients have been accrued. Once the DSMQAC has reviewed and approved the initial 6 patients on the study, 24 additional patients will be enrolled. The study will be reviewed by the DSMQAC on an annual basis and a report will be uploaded in the continuing review submitted to the Institutional Review Board (IRB).

On the basis of an optimal two-stage design to test the null hypothesis that P<=0.05 (poor pCR response rate) versus the alternative that P>=0.25 (UMGCC DSMQAC committee feels that 25% response rate is a reasonable threshold) has an expected sample size of 16.76 and a probability of early termination of 0.63. If preoperative concurrent LDFRT and FOLFOX is actually not effective, there is a 0.05 probability of concluding that it is. If the treatment combination is actually effective, there is a 0.10 probability of concluding that it is not. After treating 9 patients in the first stage, the study will be terminated if 0 respond. If the trial goes on to the second stage, a total of 30 patients will be studied. If the total number responding is less than or equal to 3, the treatment combination will be rejected.

10.2 Results Reporting on ClinicalTrials.gov

At study activation, this study will be registered within the “ClincialTrials.gov” website. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary

Endpoint of this study is 24 months after the study opens to accrual, including 15 months to accrual, about 9 months for the last patient enrolled to finish protocol treatment, and about 6 months for data cleaning and analysis. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time that all registered patient have been off treatment.

10.3 Adverse Event Data

This study is GCC investigator initiated and is not sponsor supported. All adverse events will be reported via ONCORE. Serious unexpected adverse events will be reported to the UMB IRB via CICERO according to IRB guidelines.

- Monitoring and scoring of adverse events will be performed as per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- All Adverse Events will be reported in ONCORE per DSMQAC.
  \\stccl1srv7\radonc\protocal\Protocol\DSMQAC

  https://oncoreweb1.umm.edu/login/

- The UMB IRB will be notified per UMB Human Research Protections Office (HRPO) guidelines.

http://hrpo.umaryland.edu/includes/Study_Tool_Docs/Reportable-New-Information_6-28-11.pdf

Serious Adverse Events that meet the University of Maryland Baltimore Institutional Review Board (UMB IRB) **REPORTABLE NEW INFORMATION** (RNI) will reported via https://cicero.umaryland.edu/

REPORTABLE NEW INFORMATION (University of Maryland, Baltimore Revision Date: 6/28/11)

Report the information items that fall into one or more of the following categories to the IRB within 5 business days using this form:
Information that does not fall under any of the categories does not require reporting to the IRB.
1) Information that indicates a new or increased risk, or a safety issue. For example:
a) New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
b) An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk

c) Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
d) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
e) Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
f) Any changes significantly affecting the conduct of the research
2) Any harm experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.
a) A harm is "**unexpected**" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
b) A harm is "**probably related**" to the research procedures" if in the opinion of the investigator, the research procedures more likely than not caused the harm.
3) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
4) Failure to follow the protocol due to the action or inaction of the investigator or research staff.
5) Breach of confidentiality.
6) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
7) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
8) Complaint of a subject that cannot be resolved by the research team.
9) Premature suspension or termination of the research by the sponsor or the investigator.
10) Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)
11) Audit, inspection, or inquiry by a federal agency.
12) Written reports of study monitors.
13) For Veterans Administration (VA) research all local or internal unanticipated serious adverse events. (Note: VA is not a site for recruitment for this clinical trial.)

10.5 Additional Instructions or Exclusions to Adverse Event Expedited Reporting Requirements for Commercial Agents in a non-IND trial

- Treatment expected adverse events include those listed in the Informed Consent

Form (ICF) and in the package inserts for fluorouracil, leucovorin, and oxaliplatin.

- Grade 3 or 4 myelosuppression and hospitalization resulting from such do not require expedited reporting via CICERO but will be reported in ONCORE and will be submitted as part of study results.

- Other grade 1-4 events that are expected do not require expedited reporting via CICERO, even if they result in hospitalization.

- Grade 4 events that are unexpected and that are at probably related (per UMB IRB definition) to treatment must be reported via CICERO within 5 calendar days per UMB IRB guidelines.

- All new malignancies should be reported to the IRB whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e., solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and *insitu* tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following:
  (1) Leukemia secondary to oncology chemotherapy,
  (2) Myelodysplastic syndrome,
  (3) Treatment-related secondary malignancy, or
  (4) Neoplasm other, malignant (grade 3 or 4).
  Whenever possible, the IRB reports for new malignancies should include, tumor pathology, history of prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- All pregnancies and suspected pregnancies occurring in female patients or in the partner of a male patient during therapy or within 28 days after completion of treatment on GCC 1314 must be reported to the IRB. In CTCAE version 4.0, use the event term,*"pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade4)".*

- IRB reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).

- The IRB report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported to the IRB.

10.6 Assessment of Attribution

The following attribution categories are utilized when assessing whether an adverse event is related to a medical treatment or procedure:

Definite – The adverse event is clearly related to the agent(s).
Probable – The adverse event is likely related to the agent(s).
Possible – The adverse event may be related to the agent(s).
Unlikely – The adverse event is doubtfully related to the agent(s).
Unrelated – The adverse event is clearly NOT related to the agent(s).

11.0 DOSE MODIFICATION BASED ON ADVERSE EVENTS

11.1 Radiation therapy

Treatment interruptions are discouraged although may be necessary due to acute severe complications. Documentation must be made for any such complications including the reason and length of the treatment interruption.

If chemotherapy is held, then radiation therapy will be held. If radiation is held, then chemotherapy would continue per physician discretion.

Radiation therapy may be held for grade 4 cellulitis of the perineum or grade 4 neutropenia or other radiation-associated toxicity. Radiation should be restarted subsequent to recovery at the discretion of the treating radiation oncologist as per standard practice.

Table 11.1 Radiation therapy modifications based on adverse events

System/Organ/Class	Adverse Event	Dosage Change
Blood/lymphatic system disorders	Thrombocytopenia	Grade 2 – Continue at current dose Grade 3 – Hold until recovery ≤ grade 2 then resume Grade 4 – Hold until recovery ≤ grade 2 (platelets ≥ 75 x 10^9/L) then resume
	Neutropenia	Grade 3 or 4 – Hold until recovery ≤ grade 2 then resume
	Febrile Neutropenia	Grade 3 or 4 – Hold until resolution of fever and neutropenia ≤ grade 2. Hold until the ANC ≥ 1500/mm^3 and fever has resolved then resume
Gastrointestinal disorders	Diarrhea	Grade 1 or 2 – Continue at current dose Grade 3 – If grade 3 for >4 days, hold until recovery ≤ grade 2 then resume Grade 4 – Hold until recovery ≤ grade 2 then resume

11.2 Chemotherapy

The patient will discontinue FOLFOX and be referred for treatment off protocol if the patient requires dose reduction beyond level -2 during cycles 1-5 of preoperative therapy or if FOLFOX is held due to toxicity for more than 30 days from the previous cycle.

The precise dose modification schema used and the symmetry of dose modification may be left to the discretion of the treatment physician.

Table 11.2 FOLFOX dose levels

Dose level*	5-FU infusion	5-FU bolus	Oxaliplatin
0	1200 mg/m^2/day x 2 days (2400 mg/m^2 over 48 hours)	400 mg/m^2	85 mg/m^2
-1	960 mg/m^2/day x 2 days (1920 mg/m^2 over 48 hours)	320 mg/m^2	65 mg/m^2
-2	800 mg/m^2/day x 2 days (1600 mg/m^2 over 48 hours)	270 mg/m^2	50 mg/m^2
-3	680 mg/m^2/day x 2 days (1360 mg/m^2 over 48 hours)	230 mg/m^2	40 mg/m^2

***Dose level 0 refers to the starting dose**

Table 11.3 FOLFOX dose modifications based on adverse events

System/ organ/ class	Adverse event	Agent	Dosage change
Blood and lymphatic systemic disorders	Neutropenia grade ≥2 and/or Thrombocytopenia grade ≥ 2	5-FU Oxaliplatin	Hold up to 16 days until ANC ≥ 1200 K/mcL. If recovered in ≤ 16 days, then resume at next lower dose level. Hold up to 16 days until platelets ≥ 75,000 K/mcL. If recovered in ≤ 16 days, then resume at next lower dose level.
Gastrointestinal disorders	Nausea grade 2 Nausea grade 3	Oxaliplatin	Intensify antiemetic therapy and proceed with FOLFOX at current dose level. Maximal antiemetic therapy includes a 5-HT inhibitor in addition to Compazine, lorazepam, aprepitant, and dexamethasone If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen

	Nausea grade 4		and proceed with FOLFOX when resolved to < grade 2. May decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Vomiting grade 2	5-FU Oxaliplatin	If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. Decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Vomiting grade 3		Intensify antiemetic therapy and proceed with FOLFOX at current dose level. Maximal antiemetic therapy includes a 5-HT inhibitor in addition to Compazine, lorazepam, aprepitant, and dexamethasone
	Vomiting grade 4		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. May decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Diarrhea grade 2		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. Decrease oxaliplatin one dose level if not
	Diarrhea grade 3		

			responsive to maximal antiemetic support. If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX at current dose level. If not resolved to < grade 2, hold FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX when resolved to < grade 2.
	Diarrhea grade 4		
	Oral mucositis, esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 3		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX, decreasing 5FU and oxaliplatin one dose level. If not resolved to < grade 2, hold FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX decreasing 5FU one dose level when resolved to < grade 2.
	Oral mucositis, esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 4		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX, decreasing 5FU and oxaliplatin one dose level. If not resolved to < grade 2, hold FOLFOX decreasing 5FU and oxaliplatin one dose level when resolved to < grade 2. Hold FOLFOX until mucositis improves to < grade 2 then resume with one dose level reduction of 5-FU and the previous dose level of oxaliplatin
			Hold FOLFOX until mucositis improves to < grade 2 then resume with two dose levels reduction of 5-FU and the previous dose level of oxaliplatin

Pulmonary disorders	Cough, dyspnea, hypoxia, pneumonitis or pulmonary infiltrates grade 3+	5-FU Oxaliplatin	Hold oxaliplatin until interstitial lung disease is ruled out. Continue 5-FU/leucovorin. Discontinue study if interstitial lung disease is confirmed.
Thrombotic microangiopathy	Hemolytic uremic syndrome grade 3+	5-FU Oxaliplatin	Discontinue oxaliplatin. Continue 5-FU/leucovorin.
Immune system disorders	Allergic reaction grade 1 Allergic reaction grade 2 Allergic reaction grade 3 or 4	Oxaliplatin Leucovorin	Decrease infusion rate by 50% until symptoms resolve, then resume at initial planned rate. Stop FOLFOX infusion. Administer H1 and/or H2 blockers and/or steroids according to local medical site policy. Restart infusion when symptoms resolve and pretreat before all subsequent doses. Stop infusion. Discontinue FOLFOX.
Skin and subcutaneous tissue disorders	Extravasation	Oxaliplatin	Extravasation of oxaliplatin has been associated with necrosis. If extravasation is suspected, stop the FOLFOX infusion and restart at another site.
Neurological	Neurotoxicity grade 2 persisting between treatment cycles Neurotoxicity grade 3 resolving to ≤grade 2 between treatment cycles Neurotoxicity grade 3 persisting between treatment cycles Neurotoxicity grade 4	Oxaliplatin	Continue FOLFOX with previous dose level of 5-FU and one dose level reduction of oxaliplatin for all subsequent cycles. Continue FOLFOX with previous dose level of 5-FU and one dose level reduction of oxaliplatin for all subsequent cycles. Discontinue oxaliplatin. Continue 5-FU/leucovorin. Discontinue oxaliplatin. Continue 5-FU/leucovorin.
Other non-hematologic	Grade 3 or 4	5-FU Oxaliplatin Leucovorin	Hold FOLFOX until toxicity ≤grade 1 then resume with one dose level reduction of both 5-FU and oxaliplatin.

The following describe actions in the Dosage Change column:

Omit = Treatment is not given for this cycle
Hold = Treatment can be made up as part of this cycle
Discontinue = Treatment is totally stopped

12.0 PATIENT DISCONTINUATION

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be encouraged to return to the study center to undergo treatment discontinuation assessments. The primary reason for discontinuation should be documented.

Reasons for discontinuation of a patient by the investigator include, but are not limited to, the following:

- Documented disease progression or <20% clinical response to LDFRT-FOLFOX
- Symptomatic progression, characterized by increasing tenesmus or hematochezia, decreasing stool caliber, or other signs of imminent bowel obstruction.
- Patient not able or willing to complete the prescribed radiation therapy.
- Patient not able or willing to complete 6 cycles of neoadjuvant FOLFOX.
- Patient non-compliance.
- Patient withdraws consent to participate in the study.
- Persistent (≥ 3 weeks) NCI CTCAE version 4.0 grade 3-4 adverse event or any significant adverse event that compromises the patient's ability to participate in the study.
- Investigator determination that it is not in the patient's best interest to continue participation. It is the right and duty of the Investigator to interrupt the treatment of any subject whose health or well-being may be threatened by continuation in this study. Such subjects should be withdrawn from the study and referred for standard of care treatment.

13.0 PHARMACOLOGY

13.1 Oxaliplatin (Eloxatin®, OXAL)

13.1.1 Background: Oxaliplatin, a platinum derivative, is an alkylating agent. Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.

13.1.2 Formulation: Commercially available for injection as:
Solution [preservative free]: 5 mg/mL (10 mL, 20 mL, 40 mL).

13.1.3 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. Oxaliplatin solution diluted with D5W to a final concentration of 0.7 mg/mL (polyolefin container) has been

shown to retain > 90% of its original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Do not prepare using a chloride-containing solution (e.g., NaCl). Dilution with D5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light.

13.1.4 Administration: Refer to the treatment section for specific administration instructions. Administer as IV infusion over 2-6 hours. Flush infusion line with D5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

13.1.5 Pharmacokinetic information:
Distribution: Vd: 440 L.
Protein binding: > 90% primarily albumin and gamma globulin (irreversible binding to platinum).
Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivatives.
Half-life elimination: Terminal: 391 hours; Distribution: Alpha phase: 0.4 hours, Beta phase: 16.8 hours.
Excretion: Primarily urine (~ 54%); feces (~ 2%).

13.1.6 Potential Drug Interactions

13.1.6.1 Increased Effect/Toxicity: Nephrotoxic agents may increase oxaliplatin toxicity. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

13.1.6.2 Decreased Effect: Oxaliplatin may decrease plasma levels of digoxin.

13.1.7 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from established commercial supply chain or wholesaler.

13.1.8 Nursing guidelines

13.1.8.1 GI adverse events similar to cisplatin occurs with doses above 30 mg/m^2. It can be almost constant and frequently severe, but not always dose limiting. Monitor for nausea and vomiting and treat accordingly.

13.1.8.2 Dose-limiting side effects can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (>90 mg/m^2). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the health care team. Also advise patient to refrain

from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

13.1.8.3 Oxaliplatin is incompatible with NS. Flush lines with D5W prior to and following oxaliplatin infusion.

13.1.8.4 Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

13.1.8.5 Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion. If ≥ Grade 2 laryngopharyngeal dysesthesia occurs during the administration of oxaliplatin, do the following:

- Stop oxaliplatin infusion.
- Administer benzodiazepine and give patient reassurance.
- Test oxygen saturation via a pulse oximeter.
- At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.
- Rapid resolution is typical within minutes to a few hours. Can recur with retreatment.

13.1.8.6 Patients receiving oxaliplatin on this study should be counseled to avoid cold drinks, chewing ice chips, and exposure to cold water or air because the sensory neurotoxicity often seen with oxaliplatin appears to be exacerbated by exposure to cold. The period of time during which the patient is at risk for these cold-induced sensory neuropathies is not well documented. Patients should exercise caution regarding cold exposure during the treatment period.

13.2 Leucovorin

13.2.1 Background: A reduced form of folic acid, leucovorin supplies the necessary cofactor blocked by methotrexate, enters the cells via the same active transport system as methotrexate. Stabilizes the binding of 5-dUMP and thymidylate synthetase, enhancing the activity of fluorouracil.

13.2.2 Formulation: Commercially available as powder for reconstitution: 50 mg, 100 mg, 200 mg, 350 mg. Injection, solution: 10 mg/mL (50 mL).

13.2.3 Preparation, storage, and stability: Powder for injection: Store at room temperature, protect from light. Reconstitute with sterile water for injection or bacteriostatic water for injection; dilute in 100-1000 mL 0.9% NaCl or D5W. When doses > 10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol. Solutions reconstituted with bacteriostatic water for injection must be used within 7 days.

13.2.4 Nursing Guidelines

13.2.4.1 Headache may occur. Advise patient analgesics such as Tylenol

may help. Instruct patient to report any headache that is unrelieved.
13.2.4.2 Observe for sensitization reaction (rash, hives, pruritus, facial flushing and wheezing).
13.2.4.3 May potentiate the toxic effects of fluoropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal side effects (diarrhea, stomatitis). Monitor closely.
13.2.4.4 May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

13.3 Fluorouracil (Adrucil, Efudex, [5FU])

13.3.1 Background: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog). Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G1 and S phases of the cell cycle.

13.3.2 Formulation: Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

13.3.3 Preparation, storage, and stability: Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50-1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50-1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be co-administered with diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

13.3.4 Administration: Fluorouracil may be given IV push, IV infusion.

13.3.5 Pharmacokinetic information: Distribution: Vd ~ 22% of total body water; penetrates extracellular fluid, CSF and third space fluids (e.g., pleural effusions and ascitic fluid). Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active. Half-life elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.

13.3.6 Nursing Guidelines

13.3.6.1 Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.
13.3.6.2 Administer antiemetics as needed for nausea.

13.3.6.3 Diarrhea may be dose-limiting; encourage fluids and treat symptomatically.
13.3.6.4 Assess for stomatitis; oral care measures as indicated.
13.3.6.5 Monitor for neurological symptoms (headache, ataxia).
13.3.6.6 Inform patient of potential alopecia.
13.3.6.7 Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.
13.3.6.8 5-FU-induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.
13.3.6.9 Photosensitivity may occur. Instruct patients to wear sunblock when outdoors.

14.0 STATISTICS

Our hypothesis is that preoperative concurrent LDFRT and FOLFOX will result in a pCR rate of at least 35%. Thus our power analysis will rely on precision related to estimating the CR rate. Additionally, given that we will use the information from this study to design a prospective experimental study, we seek to enroll 30 patients within 24 months. As such, a sample size of 30 patients produces a two-sided 95% confidence interval with a width equal to 0.36 when the CR rate is 35%.

APPENDIX I

GCC 1314 HP-00060641 STUDY SCHEDULE (v. 13March 2017)

Procedures	**Prior to study**	**Chemo-RT Day 1 of each cycle (6 cycles total) (≤ 2 days)**	**Restaging (3-5 weeks) after completion of chemo-LDFRT**	**Surgery (6-8 weeks) after completion of chemo-LDFRT**
Informed Consent	**R**			
History and Physical exam	**C** [a]	**C**	**C**	
Performance Status	**C**	**C**	**C**	
Evaluation by Surg Onc, Med Onc, Rad Onc	**C** [a]		**C**	
Toxicity Evaluation		**C**	**C**	
Weight, BSA	**C**	**C**	**C**	
Height	**C**			
CBC with differential and platelets	**C** [b]	**C**	**C**	
CMP (Alb, TBili, Ca, Cl, CO2, Creatinine, G, TP, Na, K, BUN, AlkPhos, AST, ALT)	**C** [b]	**C**	**C**	
CEA	**C** [b]		**C**	
CT chest or chest x-ray AND CT abdomen or MRI abdomen	**C**[a]		**C**	
MRI pelvis with and without contrast or ERUS	**C** [a]		**C**	
Endoscopy (proctoscopy, sigmoidoscopy, colonoscopy)	**C**		**C**	
Serum pregnancy test B-HCG	**C** [b]			
PT/INR/PTT			**C**	
TME path evaluation				**C**

C = Conventional Care
R = Research
[a] ≤ 28 days prior to registration
[b] ≤ 14 days prior to registration

APPENDIX II

http://www.ecog.org/general/perf_stat.html

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit given to the Eastern Cooperative Oncology Group (ECOG), Robert Comis, M.D., Group Chair.

APPENDIX III

NCI CTCAE version 4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX IV

AJCC 7th Edition Rectum Cancer Staging Definitions

Source: The AJCC Cancer Staging Manual, 7th Edition (2010) published by Springer New York, Inc.

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[1]
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum[2]
T4b Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–3 regional lymph nodes
N1a Metastasis in one regional lymph node
N1b Metastasis in 2–3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in 4 or more regional lymph nodes
N2a Metastasis in 4–6 regional lymph nodes
N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b Metastases in more than one organ/site or the peritoneum

Notes:

1 Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
2 Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or

lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).
[3] Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.
[4] A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

Anatomic Stage/Prognostic Groups:

Stage	ypT	ypN	M
0	Tis	N0	M0
I	T1 T2	N0 N0	M0 M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2 T1	N1 or N1c N2a	M0 M0
IIIB	T3-T4a T2-T3 T1-T2	N1 or N1c N2a N2b	M0 M0 M0
IIIC	T4a T3-T4a T4b	N2a N2b N1-N2	M0 M0 M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

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