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RTOG 0247: A Randomized Phase II Study of Neoadjuvant Capecitabine and Irinotecan or Capecitabine and Oxaliplatin with Concurrent Radiation Therapy for Patients with Locally Advanced Rectal Cancer

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Abstract

Purpose—To evaluate rate of pathologic complete response (pCR) and toxicity of two neoadjuvant chemoradiation (chemoRT) regimens for T3/T4 rectal cancer in a randomized phase II study.

Methods and Materials—Patients with T3 or T4 rectal cancer < 12 cm from the anal verge were randomized to preoperative RT (50.4 Gy in 1.8 Gy fractions) with (1) concurrent capecitabine (1200 mg/m²/d M-F) and irinotecan (50 mg/m² weekly × 4 doses) (arm 1), or (2) concurrent capecitabine (1650 mg/m²/d M-F) and oxaliplatin (50 mg/m² weekly × 5 doses) (arm 2). Surgery was performed 4–8 weeks after chemoRT, and adjuvant chemotherapy 4–6 weeks after surgery. The primary endpoint was pCR rate, requiring 48 evaluable patients per arm.

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Results—146 patients were enrolled. Protocol chemotherapy was modified due to excessive GI toxicity after treatment of 35 patients; 96 were assessed for the primary endpoint—final regimen described above. Patient characteristics were similar for both arms. Following chemoRT, tumor downstaging was 52% and 60%, and nodal downstaging (excluding N0 patients) was 46% and 40%, for arms 1 and 2, respectively. The pCR rate for arm 1 was 10% and for arm 2 was 21%. For arms 1 and 2, respectively, preop chemoRT grade 3/4 hematologic toxicity was 9% and 4%, and grade 3/4 non-hematologic toxicity was 26% and 27%.

Conclusions—Preoperative chemoRT with capecitabine plus oxaliplatin for distal rectal cancer has significant clinical activity (10/48 pCRs) and acceptable toxicity. This regimen is currently being evaluated in a phase III randomized trial (NSABP R04).

Keywords

Neoadjuvant; chemotherapy; radiation; rectal; cancer

INTRODUCTION

Adenocarcinoma of the rectum is a common disease with over 40,000 cases diagnosed each year in the U.S. (1) Despite the potentially high rate of curability with combined modality therapy, some patients experience significant treatment-associated morbidity, while other patients succumb to locoregional failure or distant metastasis. In addition to achieving cure, sphincter preservation is an important goal of therapy. Improvements in clinical outcome have been realized with wide acceptance of continuous infusion (CVI) 5FU-based neoadjuvant chemoRT and utilization of total mesorectal excision.

Results of large randomized trials comparing neoadjuvant pelvic radiation (RT) alone versus RT plus concurrent 5-FU have demonstrated improvement in locoregional disease control with the addition of concurrent chemotherapy. (2, 3) Attempts to improve upon this approach have focused primarily on testing new agents added to the backbone of 5-FU plus RT in order to enhance the rate of pathologic complete response (pCR). Drugs with high activity in the metastatic disease setting have been of particular interest to apply to rectal cancer clinical studies. However, integration of new RT techniques is also pertinent to this clinical research question.

The Radiation Oncology Group (RTOG) 0012 study was a phase II trial in which patients were randomly assigned to either hyperfractionated pelvic RT plus CVI 5-FU or standard pelvic RT plus CVI 5-FU and irinotecan. (4) This study was successful in that both arms achieved very high rates of pCR, 26% in each arm. However, both arms were also associated with high rates of acute grade 3 or greater toxicity (42% and 51%, respectively, for each arm) and therefore neither regimen was suitable for further development.

RTOG 0247 was designed to evaluate two experimental neoadjuvant chemotherapy regimens, capecitabine plus irinotecan or capecitabine plus oxaliplatin, with concurrent standard fractionated pelvic RT in a multi-center randomized phase II trial. We sought to examine the efficacy of these two neoadjuvant regimens as determined by the primary endpoint, pCR rate, and to evaluate adverse events for these regimens.

METHODS AND MATERIALS

Patient Characteristics

All patients gave written informed consent in accordance with each center's institutional review board guidelines. Eligible patients were at least 18 years of age; had Zubrod

performance of 0 to 2; adequate hematologic, renal, cardiac, and hepatic function; potentially resectable adenocarcinoma of the rectum originating at or below 12 cm from the anal verge without evidence of distant metastases; and clinical stage T3, based on endorectal ultrasound, or clinical stage T4, based on endorectal ultrasound or physical exam.

Exclusion criteria included pregnancy or lactation, distant metastasis, synchronous colon carcinomas, anal canal extension, prior chemotherapy or radiation for malignancies, serious uncontrolled concurrent medical or neurologic conditions, clinically significant cardiac disease, major surgery within 4 weeks of study entry, upper gastrointestinal disease that may interfere with drug absorption, or uncontrolled coagulopathy.

Pre-randomization evaluations included a medical history and physical examination, blood counts, serum chemistry and liver function panel, pregnancy testing, chest radiography, CT scan of abdomen and pelvis, and lower endoscopic examination.

Treatment

Planned treatment consisted of 1:1 randomization to one of two arms in which preoperative pelvic RT was administered with (1) concurrent capecitabine (1200 mg/m²/d orally Monday-Friday during RT) and irinotecan (50 mg/m² IV weekly × 4 doses) (arm 1), or (2) concurrent capecitabine (1650 mg/m²/d orally Monday-Friday during RT) and oxaliplatin (50 mg/m² IV weekly × 5 doses) (arm 2), see Figure 1. These chemotherapy doses represent a modification of the initial study design which demonstrated excessive toxicity in the initial 35 patients treated. Pelvic RT was delivered according to the conformational standards established by RTOG and consisted of 1.8 Gy/fraction, 5 fractions/week, with 45 Gy in 25 fractions plus a boost dose of 5.4 Gy in 3 fractions for a total dose of 50.4 Gy over 5 ½ weeks. Either two-dimensional or three-dimensional delivery was allowed. Surgery was planned for all patients at 4–8 weeks following completion of RT. For both arms, postoperative chemotherapy (FOLFOX) was administered 4–6 weeks after surgery as follows: oxaliplatin 85 mg/ m² IV over 2 hours (day 1, every 14 days); leucovorin 400 mg/ m² IV over 2 hours (day 1, every 14 days); 5-FU bolus 400 mg/ m² IV push (day 1, every 14 days); 5-FU infusion 2400 mg/ m² IV continuous infusion over 46 hours (beginning day 1, every 14 days).

Follow-up Evaluations

Patients were evaluated weekly during concurrent chemoRT, prior to surgery, and before each cycle of postoperative chemotherapy. Patients were then followed every 3 months for the first 2 years after completion of therapy; every six months for the next 3 years, and annually thereafter. Follow-up imaging studies were performed at the discretion of the treating physician.

Statistical Considerations

The primary endpoint of this study was pathologic complete response following neoadjuvant combined-modality in clinically staged T3 or T4 rectal cancer, for each of the two experimental regimens investigated. An experimental arm that results in a pCR rate of at least 25% would merit further study. Forty-eight analyzable patients were required per arm for 90% power to reject the null hypothesis that the true pCR rate of a regimen is ≤ 10% with a type I error level of 5%. Adjusting the sample size by 10% to guard against ineligibility, 53 patients per arm were targeted, for a total of 106 patients.

pCR was defined as no evidence of residual cancer histologically; disease progression or death before surgery was considered less than pCR (even without surgical specimen). All cases were reviewed by the study's surgical oncology co-chair for determination of pCR.

The following analysis rules were applied to each treatment arm, based on the Fleming method. (5) There was one planned interim look at the pCR data after the first 24 patients were entered. If at that time, only 1 patient had experienced a pCR, it would be concluded that the null hypothesis would not be rejected and the arm would be dropped from further randomization. Alternately, if there were ≥ 7 pCRs among the first 24 patients, the null hypothesis would be rejected and the treatment arm results reported. Otherwise, accrual would continue to the full sample size. At the final analysis, to preserve the overall 0.05 type I error, the null hypothesis would be rejected if there were at least 9 pCRs achieved for a given arm. Exact 95% confidence intervals were calculated for the pCR rate on each arm. (6)

An important secondary endpoint included the incidence of preoperative, postoperative, and overall treatment-related hematologic and non-hematologic grade 3–4 adverse events (AEs) with each of the two regimens. All AEs were scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Each arm was monitored for excessive toxicity using the method of Fleming. (5) The frequency of grade 3 or 4 non-hematologic toxicities (excluding nausea/vomiting controllable with antiemetics, alopecia) was considered acceptable if it was $\leq 10\%$ and modifications were considered if its frequency was $> 30\%$. If there were ≥ 5 patients with grade 3 or 4 toxicities among the first 15 patients in a treatment arm, or if there were ≥ 7 such cases among the first 30 patients entered, the treatment plan would have been modified for the remaining patients to be entered.

If both regimens had acceptable pCR rates, then pCR rates and AEs would be compared to choose a treatment regimen to pursue for further investigation. With 48 patients in each arm, there would be a greater than 90% probability of correctly selecting the better treatment when there is an absolute difference of 15% in pCR rates between the experimental treatment arms.

RESULTS

One hundred forty-six patients from 59 institutions were entered on the study from March 2004 to February 2007. In January of 2005, both arms were temporarily closed due to excessive GI adverse events (AE) associated with neoadjuvant therapy. Seven out of 18 patients developed grade 3/4 diarrhea in arm 1. In arm 2, 5/17 patients developed grade 3 diarrhea and 1 patient died following hospitalization for diarrhea. The protocol was amended to decrease the duration of neoadjuvant capecitabine in both arms from 7 days to 5 days per week, and oxaliplatin in arm 2 was decreased from 60 to 50 mg/m². The study reopened in April 2005 with a new targeted sample size of 141 patients including the 35 patients previously enrolled. The 35 patients accrued prior to the amendment were not included in the primary endpoint analysis. The data and analysis reported below pertains to the 111 patients enrolled following this amendment. Five patients were retrospectively declared ineligible and 2 patients received no protocol therapy, leaving 104 analyzable patients. Patient disposition is presented in Figure 2. The distribution of pretreatment patient characteristics in the two arms is shown in Table 1. There were no statistically significant differences between the two arms besides Zubrod performance status. More patients on arm 2 had a Zubrod status = 1 than on arm 1 (31% vs. 13%, $p = 0.034$).

Response Rates

Five patients on arm 1 and 1 on arm 2 did not undergo planned protocol surgery due to disease progression, toxicity, or patient/physician choice; the overall rate of resection for the study was 94%. The interim stopping rules for evaluation of pCR were not crossed. Of the first 48 evaluable patients, the pCR rate was 5/48 (10.4%; 95% C.I.=[3.5%, 22.7%]) in arm 1 and 10/48 (20.8%; 95% C.I.=[10.5%, 35.0%]) in arm 2 (Table 2). Since there were only 5

pCRs on arm 1, there is not enough evidence to reject the null hypothesis of 10% pCR rate. Since there are 10 pCRs on the arm 2, the null hypothesis of 10% pCR rate is rejected in favor of the alternative hypothesis of 25%. For all evaluable patients for pCR, the pCR rate was 6/51 (11.8%; 95% C.I.=[4.4%, 23.9%]) in arm 1 and 12/52 (23.1%; 95% C.I.=[12.5%, 36.8%]) in arm 2. Tumor downstaging was observed in 25/48 (52%) patients in arm 1 and in 29/48 (60%) patients in arm 2. Lymph node downstaging (excluding N0 preoperatively staged patients) was observed in 12/26 (46%) patients in arm 1 and 10/25 (40%) patients in arm 2.

High rates of sphincter preservation were observed in both arms as demonstrated by requirement for abdominoperineal resections (APR). Only 26% (n=25/98) of patients required APR—12 patients from arm 1 and 13 patients from arm 2. .

Tolerability and Toxicity

Adverse events in both arms were within the level that was anticipated suggesting both arms were tolerable. The percentage of patients who completed the radiation and preoperative chemotherapy per protocol or with acceptable variation was 65% on arm 1 and 73% on arm 2. Eight (16%) patients on arm 1 and 9 (18%) patients on arm 2 had RT duration > 6 weeks, and the median RT duration was 38 days on both. No deaths were observed on either arm during neoadjuvant therapy. Preoperative AEs reported as definitely, probably or possibly related to treatment are shown in Tables 3 and 4. Grade ≥ 3 AEs were reported in 27% (14 out of 52) on arm 1, and 27% (14 out of 52) on arm 2. Preoperative treatment-related grade ≥ 3 GI AEs were reported in 12% on arm 1 and 19% on arm 2. For those patients who had surgery, AEs occurring postoperatively (or on the day of surgery) and prior to chemotherapy or within 60 days of surgery (for those patients who did not receive postoperative chemotherapy) are shown in Table 5, and published online in Table 6.. Nine patients (19%) on arm 1 and 10 patients (20%) on arm 2 reported a grade ≥ 3 AE as definitely, probably or possibly related to treatment during this time period. For all patients on this trial regardless of the extent of treatment given or the timing of the AE, 37/52 (71%) on arm 1 and 36/52 (69%) on arm 2 reported a grade ≥ 3 AE definitely, probably or possibly related to treatment.

DISCUSSION

Important goals of rectal cancer therapy include improvement of survival, local control, and sphincter preservation. For the development of new neoadjuvant approaches, overall survival is indisputably the gold standard study endpoint by which efficacy is measured. However, several studies have demonstrated that pCR is predictive of other clinically relevant endpoints including sphincter preservation, relapse free survival, as well as reduction in distant metastasis. (7–11) Moreover, utilization of pCR appears to identify a favorable prognostic patient group that has an improved overall survival. Neoadjuvant rectal cancer trials have commonly adopted use of pCR as a reliable and meaningful intermediate endpoint. In the current study we found that the combination of capecitabine, oxaliplatin, and radiation results in a promising pCR rate with acceptable toxicity at recommended doses. In contrast, 5-FU, irinotecan, and radiation did not meet pre-specified benchmarks to warrant further study.

Direct comparison of pCR rates from different studies has limited value but may be useful as a rough approximation of efficacy and for hypothesis generation. In this context, a general trend towards progressive improvement in pCR can be seen in clinical trials with newer neoadjuvant regimens for rectal cancer. In two large multicenter phase 3 studies (EORTC 22921 and FFCD 9203) the rate of pCR for neoadjuvant 5-FU/leucovorin plus concurrent pelvic radiation versus radiation alone was 11–14% and 4–5%, respectively. (3, 12) Four

published studies that have examined capecitabine + pelvic RT demonstrated pCR rates in the range of 9–23% (mean= 15%).(13–16) In the ACCORD phase III study, capecitabine + RT arm yielded a pCR of 13.9%; to date, this data provides possibly the most accurate estimation of the activity of this combination. (17) We show in RTOG 0247 that the pCR rates for preoperative pelvic radiation with capecitabine plus oxaliplatin was 20.8%. This appears to be consistent with other studies that have examined similar oxaliplatin doublet regimens including the ACCORD 12 study in which the oxaliplatin arm had a pCR rate of 19.2%. (17–20) The combination of capecitabine and oxaliplatin appears to nearly double the pCR rate observed with monotherapy (5-FU) regimens such as those used in EORTC 22921 and FFCD 9203 and appears somewhat higher than the capecitabine + RT studies described above. Why however, two recently reported preoperative rectal cancer studies failed to demonstrate statistically significant improvement of pCR from the addition of oxaliplatin to fluoropyrimidines is not entirely clear. (17, 21) Plausible explanations for this observation were discussed by Tepper (22), and include dose and timing of administration, small sample size, and endpoint selection. It is also possible that, just as regional differences have been observed in the tolerability profiles of fluoropyrimidines, as suggested by Haller et al, so too may efficacy profiles of fluoropyrimidine combinations. (23) Thus, the results of the National Surgical Adjuvant Breast and Bowel Project R-04 study (a phase 3 study of RT plus capecitabine or 5FU +/- oxaliplatin) may shed a more definitive light upon this subject.

As the intensity of preoperative chemoRT is increased in an attempt to improve the rate of pCR, attention must also be placed upon toxicity of therapy. In the preceding RTOG study, RTOG 0012, both study arms (5-FU+ hyperfractionated RT and 5-FU+ irinotecan+ standard RT) showed high rates of pCR (26%); however, both arms were associated with high rates of acute toxicity $\geq$ grade 3, 42% and 51%, respectively. (4) In the present study, the oxaliplatin arm yielded a favorable rate of pCR but not at the expense of excess toxicity; treatment-related preoperative $\geq$ grade 3 toxicity was 27% and primarily attributable to GI toxicity. Further breakdown of toxicity shows that grade 3 hematologic toxicity was observed in 4% (2/51). These findings are very similar to other oxaliplatin preoperative chemoRT studies but clearly higher than that seen in 5-FU monotherapy studies (15% acute toxicity $\geq$ grade 3 in EORTC 22921 and FFCD 9203). (4)

Prior to the temporary closure of the study and drug dose modification, the original doses of the oxaliplatin-capecitabine arm were only moderately more intense than the final dosing—17% higher oxaliplatin dose and 28% higher capecitabine dose. At the time the study was designed selection of these original dose regimens were based upon available pilot phase I and II data. (24–32) The extent of GI toxicity seen at the higher dose levels suggests that we are very close to the acceptable limit of dose intensity of conventional chemotherapy, and that the dose-toxicity relationship for this regimen is steep. These observations also suggest that in order to gain further improvement in pCR, it will be necessary to find new ways to either decrease the toxicity of preoperative chemoRT and/or to integrate more effective new agents. An important conclusion of the study is the value of multicenter phase II data to confirm the safety experience of single/oligo-institution pilot phase I and phase II data. Pre-designated stopping rules for toxicity assessment are frequently, but not always, utilized in oncology studies that involve early development of novel agents or novel combinations of therapeutic agents. The value of preparedness for unexpected toxicity is an important take home message from this study.

Given that the primary toxicity associated with neoadjuvant chemoRT for rectal cancer is non-hematologic, it is potentially feasible to reduce the acute GI toxicity by utilizing modern conformal radiation planning and delivery techniques. RTOG 0822 will test the hypothesis that use of 3-dimensional conformal radiation and intensity modulated radiation therapy with

the capecitabine and oxaliplatin regimen (used in the present study) will reduce grade 2–5 acute GI toxicity. This study has completed accrual and is under analysis.

In summary, we show that neoadjuvant pelvic irradiation with capecitabine and oxaliplatin for clinically staged T3 and T4 rectal cancer was associated with manageable toxicity and yielded a high rate of pathologic complete response. NSABP R04 is testing whether the oxaliplatin regimen in RTOG0247 is superior to infusional 5FU/oxaliplatin, and also whether the addition of oxaliplatin improves pCR rate over fluoropyrimidines alone. While the results of RTOG 0247 are encouraging, they also highlight the need to identify more effective and less toxic regimens, through incorporation of new radiation sensitizers, novel methods of radiation delivery, and selection of patients based upon molecular classifiers.

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Figure 1.
Schema for Radiation Therapy Oncology Group 0247 phase II study.

Figure 2.
CONSORT patient flow diagram.

Table 1

Distribution of Patients

	Capecitabine/ Irinotecan/RT (n=52)		Capecitabine/ Oxaliplatin/RT (n=52)	
Age				
Median	57		56	
Min-Max	27 – 78		30 – 76	
Gender	n	%	n	%
Male	33	63	38	73
Female	19	37	14	27
Race				
American Indian/Alaska Native	0	0	1	2
Asian	2	4	0	0
Black or African American	4	8	6	12
White	46	88	45	87
Ethnicity				
Hispanic or Latino	3	6	0	0
Not Hispanic or Latino	48	92	49	94
Unknown	1	2	3	6
Zubrod Performance Status*				
0	45	87	36	69
1	7	13	16	31
Distance of Tumor from Anal Verge				
≤ 6cm	30	58	30	58
7–12 cm	22	42	22	42
T-stage (clinical)				
T3	46	88	45	87
T4	6	12	7	13
N-stage (clinical)				
N0	23	44	25	48
N1	23	44	24	46
N2	2	4	0	0
NX	4	8	3	6
AJCC Stage (6 th Edition)				
Stage IIA	20	38	21	40
Stage IIB	3	6	4	8
Stage IIIB	23	44	24	46
Stage IIIC	2	4	0	0
Unknown	4	8	3	6

* Chi square p-value = 0.034

Table 2

Pathologic Complete Response Rate First 48 Evaluable Patients on Each Arm PRIMARY ENDPOINT

	Capecitabine/Irinotecan/RT (n=48)	Capecitabine/Oxaliplatin/RT (n=48)
Number Evaluable	48	48
Number with Pathologic Complete Response	5	10
Percentage with Pathologic Complete Response	10.4	20.8
Exact 95% Confidence Interval for Percentage with Pathologic Complete Response	(3.5, 22.7)	(10.5, 35.0)

Summary of Worst Adverse Event Definitely, Probably, or Possibly Related to Treatment Per Patient Occurring Prior to Surgery

Table 3

Adverse Event	Grade	Capecitabine/Ir inotecan/RT (n=52)	Capecitabine/O xaliplatin/RT (n=52)
Worst non-hematologic	1	15 (29%)	11 (21%)
	2	23 (44%)	27 (52%)
	3	11 (21%)	12 (23%)
	4	0 (0%)	2 (4%)
	5	0 (0%)	0 (0%)
Worst overall	1	12 (23%)	9 (17%)
	2	25 (48%)	29 (56%)
	3	14 (27%)	12 (23%)
	4	0 (0%)	2 (4%)
	5	0 (0%)	0 (0%)

Adverse events were graded with CTCAE version 3.0.

Table 4

Number of Patients with Grade 3–4 Adverse Event occurring Prior to Surgery by Category, Term, and Grade Definitely, Probably, or Possibly Related to Protocol Treatment

Category Term	Capecitabine/Irinotecan/RT (n=52) Grade				Capecitabine/Oxaliplatin/RT (n=52) Grade			
	1	2	3	4	1	2	3	4
BLOOD/BONE MARROW	13	14	5	0	18	11	2	0
Hemoglobin	18	3	0	0	13	4	1	0
Leukopenia NOS	13	11	4	0	9	3	2	0
Lymphopenia	1	0	1	0	0	2	0	0
Neutrophil count	10	4	3	0	2	3	1	0
CONSTITUTIONAL SYMPTOMS	26	7	1	0	17	12	4	0
Fatigue	20	7	1	0	17	10	4	0
DERMATOLOGY/SKIN	11	10	1	0	12	15	0	0
Dermatitis radiation NOS	4	7	1	0	5	4	0	0
GASTROINTESTINAL	17	21	6	0	18	20	9	1
Anorexia	7	2	1	0	1	7	1	0
Colitis NOS	0	0	0	0	0	1	2	0
Dehydration	0	2	1	0	0	3	4	0
Diarrhea NOS	17	14	4	0	18	14	9	0
Dry mouth	2	0	0	0	1	0	1	0
Enteritis	0	0	1	0	0	1	0	1
Nausea	14	6	0	0	16	8	1	0
Proctitis NOS	4	1	0	0	6	6	1	0
Small intestinal stricture NOS	0	0	1	0	0	0	0	0
Tooth development disorder	0	0	0	0	0	0	1	0
Vomiting NOS	2	4	0	0	4	4	1	0
INFECTION	0	1	0	0	0	1	2	0
Febrile neutropenia	0	0	0	0	0	0	1	0
Infection with Grade 3 or 4 neutrophils (ANC <1.0 × 10e9/L): Urinary tract NOS	0	0	0	0	0	1	1	0
METABOLIC/LABORATORY	14	6	3	0	12	7	4	1

Category Term	Capecitabine/Irinotecan/RT (n=52) Grade				Capecitabine/Oxaliplatin/RT (n=52) Grade			
	1	2	3	4	1	2	3	4
Aspartate aminotransferase increased	3	0	1	0	6	2	0	0
Hyperglycemia NOS	6	2	1	0	4	1	0	0
Hypoalbuminemia	5	2	0	0	2	3	2	0
Hypocalcemia	4	0	0	0	4	2	1	0
Hypokalemia	7	0	0	0	6	0	1	1
Hyponatremia	4	0	1	0	4	0	2	0
NEUROLOGY	2	3	0	0	13	5	1	0
Depression	0	1	0	0	0	0	1	0
PAIN	8	7	3	0	11	11	2	0
Abdominal pain NOS	3	5	1	0	1	4	1	0
Penile pain	0	0	0	0	0	0	1	0
Proctalgia	4	2	2	0	5	7	1	0
PULMONARY/UPPER RESPIRATORY	1	1	0	0	0	1	1	0
Hiccups	0	1	0	0	0	1	1	0

Includes adverse events where relationship to protocol treatment is missing.

Adverse events were graded with CTCAE version 3.0.

Summary of Worst Adverse Event Definitely, Probably, or Possibly Related to Treatment per Patient occurring Post Surgery and Prior to Chemotherapy or within 60 days of Surgery for Patients who did not have Post-operative Chemotherapy

Table 5

Adverse Event	Grade	Capecitabine/Ir inotecan/RT (n=47)	Capecitabine/O xaliplatin/RT (n=51)
Worst non-hematologic	1	6 (13%)	9 (18%)
	2	14 (30%)	12 (24%)
	3	8 (17%)	8 (16%)
	4	1 (2%)	1 (2%)
	5	0 (0%)	0 (0%)
Worst overall	1	4 (9%)	9 (18%)
	2	16 (34%)	14 (27%)
	3	8 (17%)	9 (18%)
	4	1 (2%)	1 (2%)
	5	0 (0%)	0 (0%)

Adverse events were graded with CTCAE version 3.0

Number of Patients with Grade 3–4 Adverse Event occurring Post Surgery and Prior to Chemotherapy or within 60 days of Surgery for Patients who did not have Post-operative Chemotherapy by Category, Term, and Grade Definitely, Probably, or Possibly Related to Protocol Treatment

Table 6

Category Term	Capecitabine/Irinotecan/RT (n=47) Grade				Capecitabine/Oxaliplatin/RT (n=51) Grade			
	1	2	3	4	1	2	3	4
BLOOD/BONE MARROW	9	8	1	0	8	9	3	0
Hemoglobin	9	7	0	0	8	8	2	0
Lymphopenia	1	0	1	0	0	0	1	0
CARDIAC ARRHYTHMIA	0	0	1	0	0	1	0	0
Atrial fibrillation	0	0	1	0	0	0	0	0
CONSTITUTIONAL SYMPTOMS	8	6	0	0	5	5	2	0
Fatigue	6	3	0	0	5	3	1	0
Weight decreased	2	3	0	0	3	2	1	0
GASTROINTESTINAL	8	7	4	0	5	4	5	0
Dehydration	1	0	1	0	0	2	1	0
Ileus paralytic	0	0	1	0	0	0	1	0
Leak (including anastomotic), GI: Small bowel	0	0	0	0	0	0	1	0
Nausea	2	2	1	0	0	1	0	0
Rectal fistula	0	0	1	0	0	0	0	0
Small intestinal stricture NOS	0	0	1	0	0	0	3	0
INFECTION	0	4	2	0	0	1	3	1
Ano-rectal infection NOS	0	2	1	0	0	0	0	1
Infection with Grade 3 or 4 neutrophils (ANC <1.0 × 10e9/L): Wound	0	0	0	0	0	0	1	0
Infection with normal ANC or Grade 1 or 2 neutrophils: Pelvis NOS	0	0	0	0	0	0	1	0
Infection with unknown ANC: Rectum	0	0	1	0	0	0	0	0
Peritoneal infection	0	0	0	0	0	0	1	0
METABOLIC/LABORATORY	3	1	3	0	8	3	3	0
Aspartate aminotransferase increased	1	0	1	0	2	0	0	0
Blood creatinine increased	0	0	1	0	1	0	2	0
Hypoalbuminemia	1	0	1	0	2	1	1	0

Category Term	Capecitabine/Irinotecan/RT (n=47) Grade				Capecitabine/Oxaliplatin/RT (n=51) Grade			
	1	2	3	4	1	2	3	4
Hyponatremia	2	0	1	0	4	0	0	0
Hypophosphatemia	0	0	1	0	0	0	1	0
NEUROLOGY	1	3	0	0	2	1	2	0
Depression	0	3	0	0	0	0	1	0
Peripheral motor neuropathy	0	0	0	0	1	0	1	0
PULMONARY/UPPER RESPIRATORY	1	0	0	1	1	0	1	0
Dyspnea	1	0	0	1	1	0	1	0
RENAL/GENITOURINARY	0	2	0	0	0	4	1	0
Renal failure NOS	0	0	0	0	0	0	1	0
Ureteric obstruction	0	0	0	0	0	0	1	0
VASCULAR	0	0	0	1	0	0	1	0
Thrombosis	0	0	0	1	0	0	1	0

Adverse events were graded with CTCAE version 3.0.