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A Phase II Trial of Neoadjuvant Chemoradiation and Local Excision for T2N0 Rectal Cancer: Preliminary Results of the ACOSOG Z6041 Trial

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Abstract

Purpose—We designed ACOSOG Z6041, a prospective, multi-center, single-arm, Phase II trial to assess the efficacy and safety of neoadjuvant chemoradiation (CRT) and local excision (LE) for T2N0 rectal cancer. Here, we report tumor response, CRT-related toxicity and peri-operative complications (PCs).

Methods—Clinically-staged T2N0 rectal cancer patients were treated with capecitabine and oxaliplatin during radiation followed by LE. Due to toxicity, capecitabine and radiation dosage were reduced. LE was performed 6 weeks after CRT. Patients were evaluated for clinical and pathologic response. CRT-related complications and PCs were recorded.

Results—Ninety patients were accrued; 6 received non-protocol treatment. The remaining 84 were: 65% male; median age, 63; 83% ECOG PS=0; 92% white; mean tumor size, 2.9cm; average distance from anal verge, 5.1cm. Chemotherapy and radiation were completed per protocol in 81% and 88% of patients, respectively. Five patients were considered ineligible. Among 77 eligible patients who underwent LE, 34 patients achieved a pCR (44%) and 49 (64%) tumors were down-staged (ypT0-1), but 4 patients (5%) had ypT3 tumors. Five LE specimens contained lymph nodes;

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one T3 tumor had a positive node. All but one patient had negative margins. Thirty-three of 84 (39%) patients developed CRT-related Grade ≥3 complications. Rectal pain was the most common PC.

Conclusions—CRT before LE for T2N0 tumors results in a high pCR rate and negative resection margins. However, complications during CRT and after LE are high. The true efficacy of this approach will ultimately be assessed by the long-term oncologic outcomes.

Introduction

The mainstay of treatment for rectal cancer is total mesorectal excision (TME). For most rectal cancers TME is compatible with sphincter preservation, but for distal tumors TME results in a permanent colostomy. Most patients with early rectal cancer who undergo TME benefit from high cure rates, with 5-year survival reported between 87–90% [1] and recurrence rates lower than 7%. [2–4] However, TME is associated with significant mortality (1–6%) and morbidity. [5–8] Local excision (LE) is an alternative to TME for early stage rectal cancer because it is associated with lower morbidity and mortality, and alleviates the need for a colostomy or the distressing sequelae of a low colorectal anastomosis. However, LE alone often results in high local recurrence rates that albeit occasionally salvageable by TME, could ultimately reduce long-term survival. [9] Consequently, LE as a curative surgical approach for early rectal cancer has yet to gain widespread acceptance.

The oncologic benefits of neoadjuvant chemoradiation (CRT) in patients with locally advanced rectal cancer treated with TME [10–13] have hastened interest in investigating whether CRT could also reduce recurrence after LE in patients with early rectal cancer. Several retrospective case series and a small prospective study suggest that CRT prior to LE reduces recurrence to a level comparable with TME. [14–21] However, these studies are collectively limited by their small size, variable clinical staging criteria and imaging modalities, heterogeneous tumor populations, and use of varying CRT regimens. Thus, prospective data from larger multi-center trials is needed.

To address this the American College of Surgeons Oncology Group (ACOSOG) designed a prospective Phase II trial using neoadjuvant CRT followed by LE in patients with ultrasound or MRI-staged T2N0 rectal cancer (Z6041 trial). We report tumor response, CRT-related toxicity and complications following surgery.

Methods

Study design and patients

The study was a single-arm, multi-center Phase II trial (Figure 1a). A central Institutional Review Board (IRB) and the IRB at each participating institution approved the study. All patients provided written informed consent before entering the trial. Prior to enrollment patients underwent a complete colonoscopy, rigid proctoscopy, either an endorectal ultrasound (ERUS) or endorectal coil MRI, abdominal and pelvic CT, and chest x-ray or chest CT. Central review of all staging ERUS or endorectal coil MRI images was performed for quality assurance.

All patients had an Eastern Co-operative Oncology Group Performance Score (ECOG PS) of ≤2 and invasive rectal adenocarcinoma with the distal margin located within 8cm of the anal verge, determined by rigid proctoscopy. TN stage was T2N0 in all cases, established by either ERUS or endorectal coil MRI. Greatest tumor diameter was ≤4cm and ≤40% of the rectum circumference, determined by ERUS or endorectal coil MRI. Patients with tumors fixed to adjacent structures on digital rectal examination were ineligible.

Neoadjuvant CRT

ICRU-50 prescription methods and nomenclature were used. External beam radiation therapy (EBRT) with megavoltage linear accelerators (≥6MV) was delivered to a 3–4 field pelvis arrangement following CT-based simulation and computer-assisted treatment planning. Intensity-modulated radiotherapy (IMRT) was allowed after a protocol modification, primarily to increase accrual. Patients were treated 5 days/week at 1.8Gy/day for 5 weeks to a dose of 45Gy to planning target volume (PTV) 1, followed by a boost to PTV2, (defined as gross tumor volume, GTV, plus 2cm) for a total dose of 54Gy. Following an unfavorable toxicity profile total EBRT dose was reduced from 54Gy to 50.4Gy. All fields were treated daily. The radiotherapy treatment portals of PTV1 were constructed such that the final cephalad border of the field was at least at or above S2 and no higher than mid L5. The caudad border excluded the peri-anal skin when feasible. Posterior borders of the lateral fields were at least 1.5cm posterior to the sacral hollow and coccyx. The anterior border included the internal iliac nodal drainage. After 45Gy, fields were reduced to include a 2cm margin around the GTV.

Patients received capecitabine (825mg/m^2 days 1–14 and 22–35) and oxaliplatin (50mg/m^2 weeks 1, 2, 4 and 5) during radiation. Due to higher than expected toxicity, capecitabine dose was reduced to 725mg/m^2 twice a day, 5 days/week, for 5 weeks. Oxaliplatin dose was un-modified. Modifications in total EBRT dose and capecitabine dose were introduced simultaneously.

Surgery and pathology

Surgery was performed within 4–8 weeks after completing CRT (surgeon's choice). Local excision was performed by conventional transanal excision or transanal endoscopic microsurgery. Full-thickness excision of the tumor area with a 1cm surrounding margin of normal rectal wall was required. All surgeons were required to have performed at least 3 transanal rectal tumor excisions with negative margins and completed a surgeon-skills verification program. Before starting the tumor excision, surgeons assessed clinical response to CRT. A clinical complete response (cCR) was defined as the complete disappearance of tumor on proctoscopic exam.

Tumors were staged according to AJCC criteria. [22] Patients with ypT0-T2 N0 tumors and negative margins are being followed up as described below. Patients with ypT3 tumors, positive nodes, or positive margins were treated at the discretion of the supervising physician and alternative surgical options including TME were considered.

Follow-up

Patients receive a post-surgical exam 1 month after surgery, then every 4 months for 3 years, and then every 6 months for the following 2 years. Follow-up proctoscopy and ERUS are conducted as clinically indicated or per physician's discretion. In addition, patients undergo colonoscopy 3 years after surgery. Other diagnostic tests to detect or confirm tumor recurrence or distal metastasis are performed if clinically indicated.

Study endpoints and statistical analysis

The primary endpoint is 3-year disease-free survival (DFS). To date, all patients have finished treatment, pathological data are complete and patient follow-up is continuing. Secondary endpoints include pathologic complete response (pCR) rate, accuracy of pCR prediction, negative margin rate, morbidity and mortality following CRT and LE, and assessment of quality of life.

The original accrual goal was 83 patients. Sixty-two patients were accrued onto the original dose. Following the EBRT and capecitabine dosage reductions, the protocol was amended to accrue 40 additional patients onto the revised dose group, for a total accrual goal of 102 patients. A toxicity threshold of 30% was set for the revised dose group such that if the proportion of patients with Grade ≥3 adverse events (AEs) reached 30%, accrual would be discontinued.

Analysis pertaining to the pCR rate included all eligible patients who completed CRT and LE. The pCR rates are reported as percentages with 95% confidence intervals (CIs), overall and by dose group.

Safety assessment involved monitoring and reporting AEs and peri-operative complications (PCs) occurring within 60 days of surgery. Adverse events were evaluated according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The ACOSOG Data Monitoring Committee reviewed AEs to evaluate ongoing safety and efficacy. Safety analysis pertaining to CRT was performed in all patients who received at least one dose of CRT. Peri-operative complications were assessed in all eligible patients who completed both CRT and LE. Adverse events related to CRT and LE are descriptive in nature. Wilcoxon Rank Sum test and Fisher's Exact test were used to compare continuous and categorical variables between dose groups. All P values were based on two-sided tests with a significance level of 0.05.

Results

Patients

Ninety patients, 62 on the original dose and 28 on the revised dose, were enrolled in the study from May 2006–October 2009 at 30 institutions. Six of the 90 patients consented but did not begin protocol treatment and were deemed un-evaluable (Figure 1b). Table 1 summarizes patient demographics, ECOG PS and pre-treatment tumor characteristics for the 84 eligible patients. All received at least one dose of CRT and were therefore included in analysis of CRT-related AEs, representing the full analysis set (FAS). Of the 84 FAS

patients, 5 were later considered ineligible (Figure 1b). The remaining 79 patients received CRT per protocol and represent the per-protocol set (PPS). Two of these patients did not have LE (Figure 1b). Analysis pertaining to tumor response (pCR) and PCs includes the 77 patients who successfully completed both CRT and LE.

Treatment

Chemotherapy and radiotherapy information for all FAS patients and by dose group is shown in Table 2. Overall 62 (72%) patients completed both chemotherapy and radiotherapy per protocol. More patients completed radiotherapy per protocol than chemotherapy. The proportion of patients who completed chemotherapy per protocol was lower for the revised dose group compared to the original dose group. The opposite was observed with radiotherapy; all patients in the revised dose group completed treatment per protocol compared to 47 patients (83%) in the original dose group. Time from beginning and end of CRT-to-surgery was not different between dosage groups. Ten patients received IMRT.

CRT-related adverse events

Overall, 33 (39%) patients, 25 (44%) in the original dose group and 8 (30%) in the revised dose group, developed Grade ≥3 AEs potentially attributable to treatment. The most common Grade ≥3 AEs by body system are presented in Table 3. There were no deaths on treatment. The toxicity threshold rate set for the revised dose group was reached when 8 of the first 27 patients accrued (30%) developed Grade ≥3 AEs possibly related to treatment and the study was closed to accrual.

Surgical and pathological data

Surgical information and pathological tumor characteristics for the 77 patients who had LE are shown in Table 4. At surgery tumors were smaller compared to baseline, and over half were considered to have a cCR to CRT. Resection margins were negative in all but one patient. Overall, 49 (64%) patients had tumors down-staged to ypT0-1, 23 (30%) were ypT2, and 4 (5%) were ypT3. Only 5 LE specimens contained lymph nodes; one patient with a T3 tumor had a positive node. This patient later underwent TME and had no tumor left in either the rectal wall or peri-rectal lymph nodes.

Thirty-four patients achieved a pCR (44%; 95% CI, 32%, 55%); 25 (48%) patients in the original dose group and 9 (36%) in the revised dose group. No pre-treatment tumor characteristic or treatment-related variable was associated with pCR. A cCR correlated with pCR in 29 out of 34 patients; sensitivity: 85%, specificity: 67% (21 of 25 patients in the original dose group; sensitivity: 84%, specificity: 67%, and 8 of 9 patients in the revised dose group; sensitivity: 89%, specificity: 69%).

Peri-operative complications

Peri-operative complication data was collected for the 77 eligible patients who underwent surgery (original dose group, n=52; revised dose group, n=25). Overall, 28 (54%) patients in the original dose group and 17 (68%) in the revised dose group developed PCs. One patient in the original dose group developed Grade 4 bleeding after LE. The most common Grade 3 complications are listed in Table 5.

Discussion

This study shows that radiotherapy concurrent with capecitabine and oxaliplatin-based chemotherapy, followed by LE for T2N0 rectal cancer results in a pCR in close to half the treated patients. In addition, nearly all eligible patients who received per-protocol CRT underwent LE with negative margins. However, despite a dosage reduction during the trial, CRT-related toxicity was high and PCs following LE were not uncommon.

In recent years tumor response to CRT has emerged as an important predictor of tumor control and patient survival, [23–25] and has become an important endpoint in clinical trials of rectal cancer treated by CRT. While the pCR rate to CRT in locally advanced rectal cancer is well known, [12, 13] data on pCR rates in patients with early rectal cancer is limited. Mohiuddin, et al. was first to report a 38% pCR rate in patients with T1–T3 distal rectal cancers treated with radiation and LE. [14] Since then a number of investigators have reported pCR rates ranging from 30–73% for T2 and T3 tumors treated with CRT and LE. [15–21] However, these single institution studies are limited by their small size, varying CRT regimens, and heterogonous patient populations. Lezoche, et al. reported a 30% pCR rate in T2N0 rectal cancer patients treated with 5-fluorouracil (FU)-based CRT, and either LE or TME. [21] The higher pCR rate observed in our study could be attributable to the difference in sensitizing chemotherapy; Lezoche's patients received only 5-FU while in our trial they received capecitabine and oxaliplatin. However, it is important to note that in non-LE trials a pCR requires both the primary site and lymph nodes to be free of tumor and in our trial, lymph nodes were not examined in most cases, so this could also account for our higher pCR rate. It is noteworthy that following treatment a small number of patients (5%) had ypT3 tumors. This underscores the relatively low accuracy of ERUS and endorectal coil MRI for staging rectal cancer and suggests that some patients were under-treated while others may have been over-treated.

The CRT regimen chosen for our study was based on a regimen used by Rodel, et al. [26] Using capecitabine, oxaliplatin, and radiation before TME, they reported a Grade ≥3 AE rate of 8%. We encountered a much higher treatment-related toxicity in our patients, with 25 of the first 57 patients (44%) entered in our trial experiencing a Grade 3 or Grade 4 AE. Failure to proactively address Grade 1–2 toxicities along with discordance between physician and patient assessment of severity of treatment-related symptoms may have contributed in part to the unfavorable toxicity profile from CRT in our study. Dose reductions in capecitabine and radiation did reduce toxicity, but it still remained higher than the number reported by Rodel, et al. Potential explanations for these discrepancies include differences in criteria for dose modification, regional differences in capecitabine tolerability, and speed to recognition and interruption of dosing.

The STAR-01 [27] and ACCORD 12/0405-Prodige 2 [28] trials have assessed the effect of adding oxaliplatin to a regimen of pre-operative FU-based CRT in patients with locally advanced rectal cancer. Both studies found that patients receiving oxaliplatin reported significantly higher toxicity compared to patients who did not, with no significant difference in tumor response. [27, 28] In our study, dose reductions in capecitabine and radiation not only decreased toxicity, but also reduced the pCR rate from 48% (original dose group) to

36% (revised dose group), although this may be confounded by the smaller numbers in the revised dose group. Nonetheless, based on the results of the STAR-01 and ACCORD 12/0405-Prodige 2 trials it is possible to speculate that a reduction in oxaliplatin instead of capecitabine and radiation may have had a more beneficial effect on CRT safety without compromising pCR rate, thus contributing to a more favorable therapeutic ratio.

The presence of tumor at the resection margins after LE is not uncommon and often requires immediate TME. [29, 30] In our series only one patient had positive margins. This patient underwent abdominoperineal resection (APR) and had no residual tumor. In the CALGB 8984 trial, [31, 32] the largest prospective study on LE, patients with clinical stage I rectal cancer were registered before surgery. A second registration occurred after surgery; patients with T1 tumors were observed while patients with T2 tumors received CRT. Patients with positive margins and stage >T2 or <T1 were eliminated. Twenty out of 180 patients (11%) registered to the trial were excluded due to positive or questionable resection margins. Our data suggests that by reducing the risk of positive resection margins, neoadjuvant CRT may increase the proportion of patients with early rectal cancer who would be candidates for LE.

Complications after LE were common in our patients. Peri-anal pain was the most common AE, experienced by 8% of patients. The source of the pain is unclear, but it was more common among patients in the original dose group (10%) compared to the revised dose group (4%), and subsided in most patients within 3 months of LE, indicating that the post-operative pain may be related to delayed healing of the LE wound in a heavily radiated tissue. The anal canal was not routinely included in the radiation field. Nonetheless, by virtue of the distal location of these tumors, the anal canal and peri-anal area were included in the radiation field in some patients. Marks, et al. reported that CRT before LE does increase the rate of wound-related complications (26%) compared to LE alone (0%). [33] However, majority of the complications reported in their series were classified as minor (82%) and a significant percentage (91%) were treated without any additional surgery or intervention. In their series, the mean dose of radiation (51.7Gy) was similar to ours (51.8Gy), but their patients only received sensitizing 5-FU. Taken together these data suggest that post-operative morbidity may be a limiting factor with respect to intensity of the neoadjuvant regimen. Further, it is important to note that while CRT before LE is advantageous as it results in a low positive margin rate, it has the disadvantage of possibly causing post-operative pain.

Accurate pCR diagnosis before surgery is critical for implementation of an organ-preservation approach in selected patients with rectal cancer. Neither clinical exam nor commonly used imaging methods have been able to diagnose pCR with a reasonable degree of accuracy in patients with locally advanced rectal cancer. [34–36] Hiotis, et al. investigated the accuracy of digital rectal exam and proctoscopy in predicting pCR after CRT in patients with locally advanced rectal cancer treated with TME. [37] While 19% of patients had a cCR, only 25% of these had a pCR. In their series, the sensitivity of cCR as a predictor of pCR was 77%, but the specificity was only 16%. In our series, cCR predicted pCR with 85% sensitivity and 67% specificity, a better predictor than previously reported. These discrepant results may be attributable to pCR rate differences; 10% in Hiotis's series versus 44% in

ours, as well as methodological differences between studies; their study was retrospective while ours was prospective.

In conclusion, our prospective multi-center trial demonstrates that CRT and LE for T2N0 rectal cancer achieves a pCR in almost half the treated patients with a negative margin rate close to 100%. However, CRT-related toxicity was high and PCs following LE were common, suggesting that while promising, this approach still requires further modification to enhance the therapeutic ratio. A successor trial is planned to decrease CRT toxicity while optimizing pCR.

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Synopsis

ACOSOG Z6041 is a prospective Phase II trial designed to assess the efficacy and safety of treating T2N0 rectal cancer patients with neoadjuvant chemoradiation and local excision. We report tumor response, chemoradiation-related toxicity and complications following surgery.

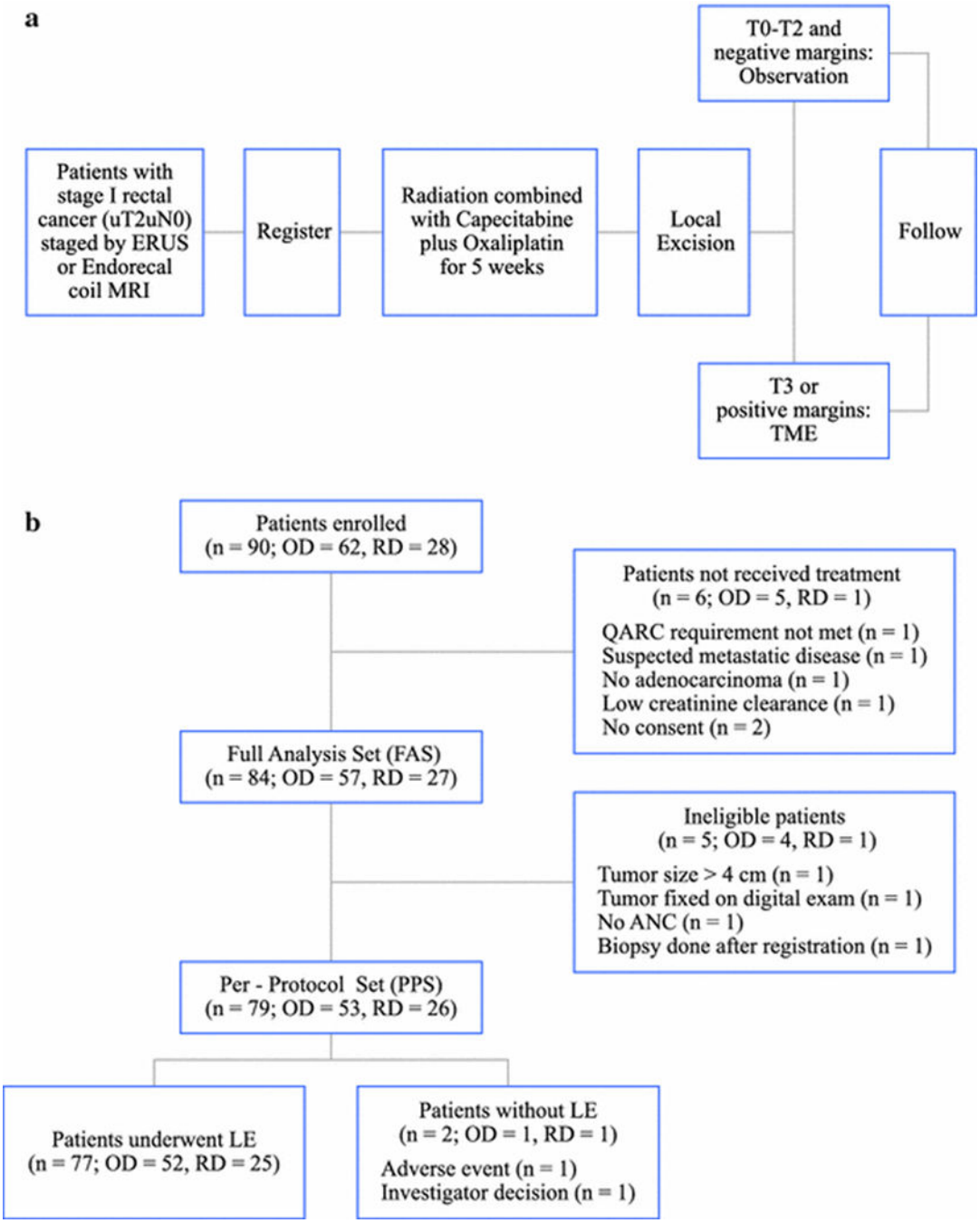

Figure 1.

a: ACOSOG Z6041 Trial - Protocol schema.

Abbreviations: ERUS: Endorectal ultrasound; TME: Total mesorectal excision

b: Patient disposition.

Abbreviations: LE - Local excision; QARC - Quality Assurance Review Center; OD - Original dose group; RD - Revised dose group; ANC - Absolute neutrophil count.

Table 1

Baseline patient demographics and disease characteristics

Demographic or Disease Characteristic	Overall n = 84	Original dose n = 57	Revised dose n = 27
Age, years *	63 (30–83)	63 (30–80)	64 (45–83)
Gender			
Male	55 (65%)	35 (61%)	20 (74%)
Female	29 (35%)	22 (39%)	7 (26%)
Race			
White	77 (92%)	51 (90%)	26 (96%)
Black	2 (2%)	2 (4%)	0 (0%)
Native Hawaiian/Pacific Islander	1 (1%)	1 (2%)	0 (0%)
Asian	2 (2%)	1 (2%)	1 (4%)
American Indian	1 (1%)	1 (2%)	0 (0%)
Unknown	1 (1%)	1 (2%)	0 (0%)
ECOG PS			
0	70 (83%)	49 (86%)	21 (78%)
1	13 (16%)	7 (12%)	6 (22%)
2	1 (1%)	1 (2%)	0 (0%)
Tumor Size, cm Ψ	2.9 ± 0.8	2.8 ± 0.8	2.9 ± 0.7
Tumor Location			
Anterior	16 (19%)	11 (19%)	5 (19%)
Posterior	43 (51%)	32 (56%)	11 (41%)
Left Lateral	18 (21%)	11 (19%)	7 (26%)
Right Lateral	7 (8%)	3 (5%)	4 (15%)
Distance from Anal Verge, (distal) cm Ψ	5.1 ± 2	4.9 ± 1.9	5.4 ± 2.1

* Median (Range);

Ψ Mean ± standard deviation. Abbreviations: ECOG PS - Eastern Co-operative Oncology Group Performance Status.

Table 2

Chemotherapy and radiotherapy intervention

CRT	Overall n = 84	Original dose n = 57	Revised dose n = 27
Capecitabine total dose (mg/m^2) patients missing *	755 ± 199.63	824.9 ± 1823	615.3 ± 1570
Oxaliplatin total dose (mg/m^2) patients missing *	36.1 ± 8.81	35.9 ± 7.91	36.5 ± 10.70
Radiotherapy total dose (Gy)	51.8 ± 5.7	52.2 ± 6.8	51 ± 1.4
Chemotherapy completed per protocol			
Yes	68 (81%)	48 (84%)	20 (74%)
No	16 (19%)	9 (16%)	7 (26%)
Chemotherapy delayed or modified			
Yes	41 (49%)	26 (46%)	15 (56%)
No	43 (51%)	31 (54%)	12 (44%)
Radiotherapy completed per protocol			
Yes	74 (88%)	47 (83%)	27 (100%)
No	10 (12%)	10 (18%)	0 (0%)
Radiotherapy interrupted			
Yes	35 (42%)	27 (47%)	8 (30%)
No	49 (58%)	30 (53%)	19 (70%)
Days from start of CRT to surgery patients missing **	88.5 ± 162	89.2 ±13.11	87.2 ± 21.31
Days from end of CRT to surgery patients missing **	47.5 ± 14.32	47.4 ± 11.31	47.6 ± 19.61

Mean ± standard deviation is shown.

* Patients did not receive any doses of Capecitabine or Oxaliplatin.

** Patients started treatment but did not undergo surgery, therefore the days from the start and end of CRT-to-surgery are missing. Abbreviations: CRT - Chemoradiation therapy.

Table 3

Most common adverse events occurring during CRT[ψ]

Adverse Event	Overall n = 84		Original dose n = 57		Revised dose n = 27	
	Grade 3+	Grade 4+	Grade 3+	Grade 4+	Grade 3+	Grade 4+
Gastrointestinal	19 (23%)	1 (1%)	16 (28%)	1 (2%)	3 (11%)	0 (0%)
Dermatologic	8 (10%)	0 (0%)	6 (11%)	0 (0%)	2 (7%)	0 (0%)
Hematologic	9 (11%)	1 (1%)	4 (7%)	1 (2%)	5 (19%)	0 (0%)
Pain	6 (7%)	1 (1%)	4 (7%)	1 (2%)	2 (7%)	0 (0%)
Metabolic	5 (6%)	2 (2%)	3 (5%)	1 (2%)	2 (7%)	1 (4%)

[ψ]Adverse event at least possibly attributed to CRT for CRT visits 3 to 8. Note: No Grade 5 fatal toxicity was observed. Abbreviations: CRT - Chemoradiation therapy.

Table 4

Pathological tumor characteristics

Pathology	Overall n = 77	Original dose n= 52	Revised dose n = 25
Resected tumor margins free of tumor			
Yes	76 (99%)	52 (100%)	24 (96%)
No	1 (1%)	0 (0%)	1 (4%)
Pathologic tumor size, cm * patients missing	0.9 ± 1.12	0.9 ± 1.12	0.9 ± 10
Tumor T stage			
T0	34 (44%)	25 (48%)	9 (36%)
Tis	5 (7%)	3 (6%)	2 (8%)
T1	10 (13%)	7 (13%)	3 (12%)
T2	23 (30%)	14 (27%)	9 (36%)
T3	4 (5%)	2 (4%)	2 (8%)
Tx Ψ	1 (1%)	1 (2%)	0 (0%)
Clinical Complete Response			
Yes	43 (56%)	30 (58%)	13 (52%)
No	34 (44%)	22 (42%)	12 (48%)

* Mean ± standard deviation is shown.

Ψ This patient was not a T0 because the presence of residual cancer cells was reported.

Table 5

Most common Grade 3 adverse events occurring within 60 days of LE

Adverse Event	Overall n = 77	Original dose n= 52	Revised dose n = 25
Rectal Pain	6 (8%)	5 (10%)	1 (4%)
Hemorrhage	2 (3%)	1 (2%)	1 (4%)
Infection	2 (3%)	1 (2%)	1 (4%)
Urinary Retention	2 (3%)	1 (2%)	1 (4%)
Anal Incontinence	1 (1%)	1 (2%)	0 (0%)
Overall [ψ]	12 (16%)	7 (13%)	5 (20%)

[ψ] Number of patients who experienced any Grade 3 complication. Abbreviations: LE - Local excision.