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ORIGINAL ARTICLE – COLORECTAL CANCER

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

Julio Garcia-Aguilar, MD, PhD[1], Qian Shi, PhD[2], Charles R. Thomas Jr. , MD[3], Emily Chan, MD, PhD[4], Peter Cataldo, MD[5], Jorge Marcet, MD[6], David Medich, MD[7], Alessio Pigazzi, MD[1], Samuel Oommen, MD[8], and Mitchell C. Posner, MD[9]

[1]Department of Surgery, City of Hope, Duarte; [2]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester; [3]Knight Cancer Institute, Oregon Health and Science University, Portland; [4]Vanderbilt University Medical Center, Nashville; [5]Department of Surgery, University of Vermont, Burlington; [6]Tampa General Hospital, Tampa; [7]Allegheny Cancer Center, Pittsburgh; [8]John Muir Hospital, Concord; [9]University of Chicago Medical Center, Chicago

ABSTRACT

Purpose. We designed American College of Surgeons Oncology Group (ACOSOG) Z6041, a prospective, multicenter, 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 perioperative complications (PCs).

Methods. Clinically staged T2N0 rectal cancer patients were treated with capecitabine and oxaliplatin during radiation followed by LE. Because of toxicity, capecitabine and radiation doses 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 years; 83% Eastern Cooperative Oncology Group performance score 0; 92% white; mean tumor size 2.9 cm; and average distance from anal verge 5.1 cm. Five patients were considered ineligible. Therapy was completed per protocol in 79 patients, but two patients did not undergo LE. Among 77 eligible patients who underwent LE, 34 patients achieved a pathologic complete response (44%) and 49 (64%) tumors were downstaged (ypT0–1), but 4 patients (5%) had ypT3 tumors. Five LE specimens contained lymph nodes; one T3 tumor had a positive node. All but one patient had negative margins. Thirty-three (39%) of 84 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 pathologic complete response 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.

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 experience high cure rates, with 5-year survival reported between 87 and 90% and recurrence rates lower than 7%.[1–4] However, TME is associated with 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 it 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, although 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

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J. Garcia-Aguilar, MD, PhD
e-mail: jgarciaaguilar@coh.org

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treated with TME have increased interest in investigating whether CRT could also reduce recurrence after LE in patients with early rectal cancer.[10–13] Several retrospective case series and a small prospective study suggest that CRT before 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 multicenter trials are needed.

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

METHODS

Study Design and Patients

The study was a single-arm, multicenter phase II trial (Fig. 1a). A central institutional review board and the institutional review board at each participating institution approved the study. All patients provided written informed consent before entering the trial. Before enrollment, patients underwent a complete colonoscopy, rigid proctoscopy, either an endorectal ultrasound (ERUS) or endorectal coil MRI, abdominal and pelvic computed tomography (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 Cooperative Oncology Group performance status of ≤ 2 and invasive rectal

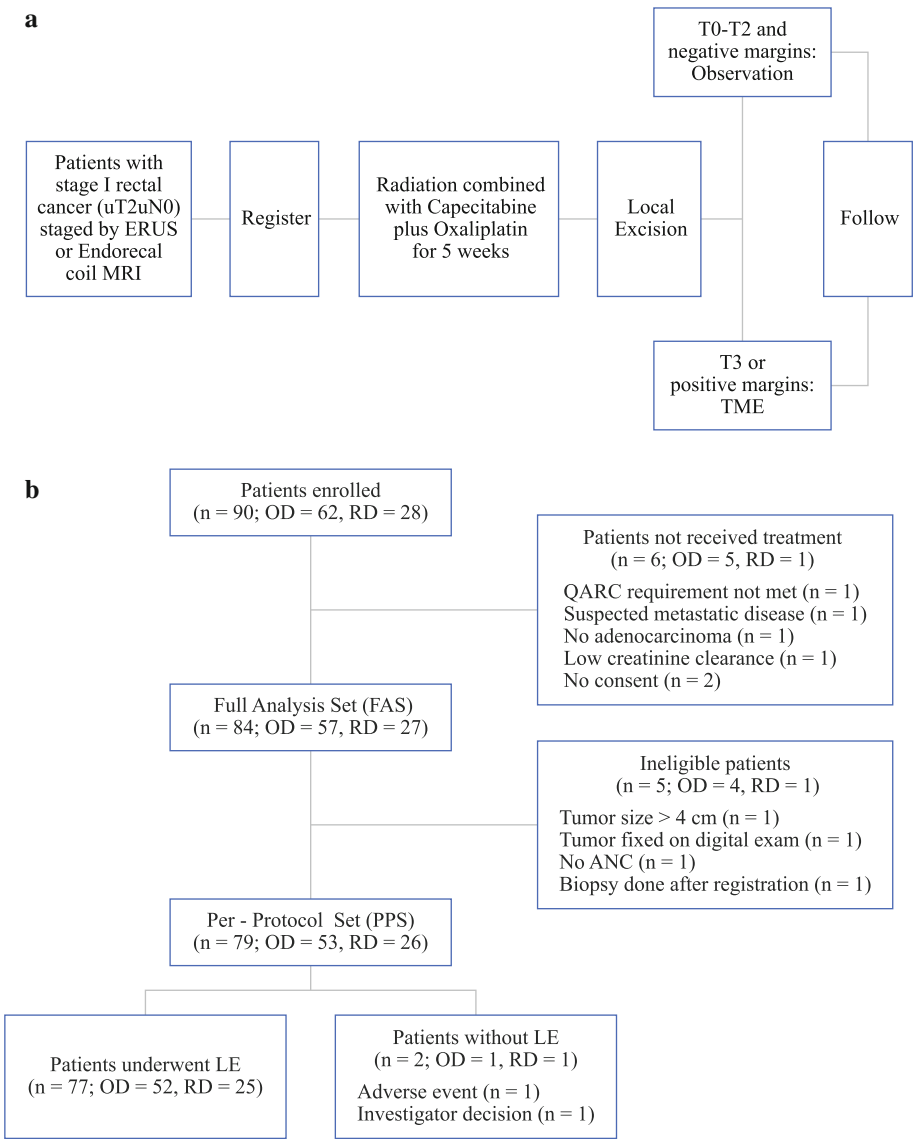

FIG. 1 **a** ACOSOG Z6041 trial protocol schema. **b** Patient disposition. *QARC* Quality Assurance Review Center, *OD* original dose group, *RD* revised dose group, *ANC* absolute neutrophil count

adenocarcinoma with the distal margin located within 8 cm 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 ≤4 cm and ≤40% of the rectum circumference, determined by ERUS or endorectal coil MRI. Patients with tumors fixed to adjacent structures, as established by digital rectal examination, were ineligible.

Neoadjuvant CRT

ICRU-50 prescription methods and nomenclature were used. External beam radiotherapy (EBRT) with megavoltage linear accelerators (≥6 MV) was delivered to a 3–4-field pelvis arrangement after CT-based simulation and computer-assisted treatment planning. Intensity-modulated radiotherapy was allowed after a protocol modification, primarily to increase accrual. Patients were treated 5 days/week at 1.8 Gy/day for 5 weeks to a dose of 45 Gy to planning target volume (PTV) 1, followed by a boost to PTV2 (defined as gross tumor volume plus 2 cm) for a total dose of 54 Gy. After an unfavorable toxicity profile, total EBRT dose was reduced from 54 to 50.4 Gy. 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 perianal skin when feasible. Posterior borders of the lateral fields were at least 1.5 cm posterior to the sacral hollow and coccyx. The anterior border included the internal iliac nodal drainage. After 45 Gy, fields were reduced to include a 2-cm margin around the tumor volume.

Patients received capecitabine (825 mg/m^2 days 1–14 and 22–35) and oxaliplatin (50 mg/m^2 weeks 1, 2, 4, and 5) during radiation. As a result of higher-than-expected toxicity, capecitabine dosage was reduced to 725 mg/m^2 twice a day, 5 days a week, for 5 weeks. Oxaliplatin dose was not 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). LE was performed by conventional transanal excision or transanal endoscopic microsurgery. Full-thickness excision of the tumor area with a 1-cm surrounding margin of normal rectal wall was required. All surgeons were required to have performed at least three transanal rectal tumor excisions with negative margins and completed a surgeon skill 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 examination.

Tumors were staged according to American Joint Committee on Cancer criteria.[22] Patients with ypT0–T2 N0 tumors and negative margins were followed 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 received a postsurgical examination 1 month after surgery, then every 4 months for 3 years, and then every 6 months for the next 2 years. Follow-up proctoscopy and ERUS were conducted as clinically indicated or at the physician's discretion. In addition, patients underwent colonoscopy 3 years after surgery. Other diagnostic tests to detect or confirm tumor recurrence or distal metastasis were performed if clinically indicated.

Study End Points and Statistical Analysis

The primary end point is 3-year disease-free survival. To date, all patients have finished treatment, pathologic data are complete, and patient follow-up is continuing. Secondary end points include pathologic complete response (pCR) rate, accuracy of pCR prediction, negative margin rate, morbidity and mortality after 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. After 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, overall and by dose group.

Safety assessment involved monitoring and reporting AEs and perioperative complications (PCs) occurring within 60 days of surgery. AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, 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. PCs were assessed in all eligible patients who completed both CRT and LE. AEs related to CRT and

LE are descriptive in nature. The 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 receiving the original dose and 28 receiving the revised dose, were enrolled onto the study from May 2006 to October 2009 at 30 institutions. Six of the 90 patients consented but did not begin protocol treatment and were deemed unevaluable (Fig. 1b). Table 1 summarizes patient demographics, Eastern Cooperative Oncology Group performance status, and pretreatment 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. Of these 84 patients, 5 were later considered ineligible (Fig. 1b). The remaining 79 patients received CRT per protocol and represent the per-protocol set. Two of these patients did not have LE (Fig. 1b). Analysis pertaining to tumor response (pCR) and PCs includes the 77 patients who successfully completed both CRT and LE.

TABLE 1 Baseline patient demographics and disease characteristics

Characteristic	Overall ($n = 84$)	Original dose ($n = 57$)	Revised dose ($n = 27$)
Age, years, median (range)	63 (30–83)	63 (30–80)	64 (45–83)
Sex (%)			
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, mean ± SD	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, mean ± SD	5.1 ± 2	4.9 ± 1.9	5.4 ± 2.1

ECOG PS Eastern Cooperative Oncology Group performance status

Treatment

Chemotherapy and radiotherapy information for all full analysis set patients and by dose group is shown in Table 2. Overall, 62 patients (72%) 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 intensity-modulated radiotherapy.

CRT-Related AEs

Overall, 33 patients (39%), 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 (30%) of the first 27 patients accrued developed grade ≥3 AEs possibly related to treatment, and the study was closed to accrual.

Surgical and Pathologic Data

Surgical information and pathologic 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 patients (64%) 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 perirectal lymph nodes.

Thirty-four patients experienced pCR (44%; 95% confidence interval 32–55), 25 patients (48%) in the original dose group and 9 patients (36%) in the revised dose group.

TABLE 2 Chemotherapy and radiotherapy intervention

CRT	Overall ($n = 84$)	Original dose ($n = 57$)	Revised dose ($n = 27$)
Capecitabine total dose, mg/m^2, mean ± SD	755 ± 199.6	824.9 ± 182	615.3 ± 157
No. of patients missing[a]	3	3	0
Oxaliplatin total dose, mg/m^2, mean ± SD	36.1 ± 8.8	35.9 ± 7.9	36.5 ± 10.7
No of patients missing[a]	1	1	0
Radiotherapy total dose, Gy, mean ± SD	51.8 ± 5.7	52.2 ± 6.8	51 ± 1.4
Chemotherapy completed per protocol, *n* (%)			
Yes	68 (81)	48 (84)	20 (74)
No	16 (19)	9 (16)	7 (26)
Chemotherapy delayed or modified, *n* (%)			
Yes	41 (49)	26 (46)	15 (56)
No	43 (51)	31 (54)	12 (44)
Radiotherapy completed per protocol, *n* (%)			
Yes	74 (88)	47 (83)	27 (100)
No	10 (12)	10 (18)	0 (0)
Radiotherapy interrupted, *n* (%)			
Yes	35 (42)	27 (47)	8 (30)
No	49 (58)	30 (53)	19 (70)
Days from start of CRT to surgery	88.5 ± 16	89.2 ± 13.1	87.2 ± 21.3
No. of patients missing[b]	2	1	1
Days from end of CRT to surgery	47.5 ± 14.3	47.4 ± 11.3	47.6 ± 19.6
No. of patients missing[b]	2	1	1

CRT chemoradiation therapy

[a] Patients did not receive any doses of capecitabine or oxaliplatin

[b] Patients began treatment but did not undergo surgery; therefore, days from start and end of CRT to surgery are missing

TABLE 3 Most common AEs occurring during CRT

AE	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)

CRT chemoradiation therapy

AE at least possibly attributed to CRT for CRT visits 3 to 8. No grade 5 fatal toxicity was observed

No pretreatment tumor characteristic or treatment-related variable was associated with pCR. A cCR correlated with pCR in 29 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; and sensitivity 89%, specificity 69%.

Perioperative Complications

PC data were collected for the 77 eligible patients who underwent surgery (original dose group, $n = 52$; revised dose group, $n = 25$). Overall, 28 patients (54%) in the original dose group and 17 patients (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 dose reduction during the trial, CRT-related toxicity was high, and PCs after LE were not uncommon.

In recent years, tumor response to CRT has emerged as an important predictor of tumor control and patient survival and has become an important end point in clinical trials of rectal cancer treated by CRT.[23–25] Although the pCR rate to CRT in locally advanced rectal cancer is well known, data on pCR rates in patients with early rectal cancer are 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.[12–14] Since then, several investigators have reported pCR rates ranging 30–73% for T2 and T3

TABLE 4 Pathologic 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, mean ± SD	0.9 ± 1.1	0.9 ± 1.1	0.9 ± 1
No. of patients missing	2	2	0
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[a]	1 (1)	1 (2)	0 (0)
Clinical complete response			
Yes	43 (56)	30 (58)	13 (52)
No	34 (44)	22 (42)	12 (48)

[a] Disease was not T0 because the presence of residual cancer cells was reported

TABLE 5 Most common grade 3 AEs occurring within 60 days of LE

AE	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[a]	12 (16)	7 (13)	5 (20)

[a] Number of patients who experienced any grade 3 complication

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. [21] reported a 30% pCR rate in T2N0 rectal cancer patients treated with 5-fluorouracil (5-FU)-based CRT, and either LE or TME. The higher pCR rate observed in our study could be attributable to the difference in sensitizing chemotherapy; the patients of Lezoche et al. received only 5-FU, whereas in our trial, patients 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 after 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 undertreated while others may have been overtreated.

The CRT regimen chosen for our study was based on a regimen used by Rodel et al.[26] With a regimen of 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 (44%) of the first 57 patients entered onto our trial experiencing a grade 3 or 4 AE. Failure to proactively address grades 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 quickness to recognize and interrupt dosing.

The STAR-01 and ACCORD 12/0405—Prodige 2 trials have assessed the effect of adding oxaliplatin to a regimen of preoperative 5-FU-based CRT in patients with locally advanced rectal cancer.[27,28] Both studies found that patients receiving oxaliplatin reported higher toxicity compared to patients who did not, with no marked difference in tumor response. 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, on the basis of 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 and had no residual tumor. In the CALGB 8984 trial, the largest prospective study on LE, patients with clinical stage I rectal cancer were registered before surgery.[31,32] 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 (11%) of 180 patients registered on the trial were excluded because of positive or questionable resection margins. Our data suggest 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. Perianal 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%) than in the revised dose group (4%), and it subsided in most patients within 3 months of LE, indicating that the postoperative 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 perianal area were included in the radiation field in some patients. Marks et al. [33] reported that CRT before LE does increase the rate of wound-related complications (26%) compared to LE alone (0%). However, most complications reported in their series were classified as minor (82%), and many (91%) were treated without any additional surgery or intervention. In their series, the mean dose of radiation (51.7 Gy) was similar to ours (51.8 Gy), but their patients only received sensitizing 5-FU. Taken together, these data suggest that postoperative morbidity may be a limiting factor with respect to intensity of the neoadjuvant regimen. Further, it is important to note that although CRT before LE is advantageous because it results in a low positive margin rate, it has the disadvantage of possibly causing postoperative pain.

Accurate pCR diagnosis before surgery is critical for implementation of an organ-preservation approach in selected patients with rectal cancer. Neither clinical examination 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. [37] investigated the accuracy of digital rectal examination and proctoscopy in predicting pCR after CRT in patients with locally advanced rectal cancer treated with TME. Although 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 the series of Hiotis et al. versus 44% in ours, as well as methodological differences between studies; their study was retrospective and ours was prospective.

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

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