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ORGAN PRESERVATION FOR CLINICAL T2N0 DISTAL RECTAL CANCER USING NEOADJUVANT CHEMORADIOTHERAPY AND LOCAL EXCISION: RESULTS OF A MULTICENTER PHASE 2 STUDY

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Disclosures

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Summary

Background—Local excision is an organ-preserving treatment alternative for patients with stage I rectal cancer. However, local excision alone is associated with a high risk of local recurrence and inferior survival compared to transabdominal rectal resection. Here we investigate the oncologic and functional outcomes of neoadjuvant chemoradiotherapy and local excision for T2N0 rectal cancer.

Methods—This was a prospective, multi-institutional, single arm phase 2 trial for patients with clinically-staged T2N0 distal rectal cancer, treated with neoadjuvant chemoradiotherapy consisting of capecitabine (original dose 825mg/m^2, twice daily, on days 1-14 and 22-35) , oxaliplatin (50mg/m^2 weeks 1, 2, 4, 5), and radiation (5 days/week at 1.8 Gy/day for 5 weeks to a dose of 45 Gy, then a boost, for a total dose of 54 Gy) followed by local excision. Due to adverse events during chemoradiotherapy, the dose of capecitabine was reduced to 725 mg /m^2, twice daily, 5 days/week, for 5 weeks, and the total dose of radiation to 50.4 Gy. Patients were followed at scheduled intervals and evaluated for recurrence and survival. Anorectal function (ARF) and quality of life (QOL) were assessed at baseline and one year after surgery, using validated instruments. The primary endpoint was 3-year disease-free survival for all eligible patients and for patients who completed chemotherapy and radiation, and had ypT0, ypT1, or ypT2 tumors, and negative resection margins. This trial is registered with ClinicalTrials.gov, number NCT00114231.

Findings—Seventy-nine eligible patients were accrued to the trial, and started nCRT. Three patients did not complete nCRT or LE per-protocol. Four additional patients completed protocol treatment, but one had a positive margin and three had ypT3 tumours. Median follow-up was 56 months. Of the 79 patients, five (6%) developed distant recurrence, and three (4%) recurred locally. All but two underwent salvage surgery. Three-year disease-free survival and overall survival for the entire group were 88% (0.88 (95% CI: 0.81, 0.96) and 95% (95% CI: 0.90, 1.00), respectively. Overall 14 (29%) of 79 patients had grade 3-4 gastrointestinal adverse events, 12 (16%) of 79 patients had grade 3-4 pain as an adverse event, 12 (16%) of 79 patients had grade 3-4 hematological adverse events, and 9 (11%) of 79 patients had grade 3 dermatologic adverse events during chemoradiation. Six (8%) of the 77 patients who had surgery had grade 3 pain, 3(4%) of 77 patients had grade 3-4 hemorrhage, 3 (4%) of 77 patients had gastrointestinal adverse events, 2 (3%) of 77 patients had infectious/febrile neutropenia, 2 (3%) of 77 patients had hematological adverse events, and one (1%) had neurological adverse events. The rectum was preserved in 72 of the 79 (91%) patients. ARF and QOL were unchanged one year after surgery compared to baseline.

Interpretation—Most patients with T2N0 rectal cancer treated with nCRT and LE achieved organ preservation without deterioration of their quality of life. The estimated 3-year DFS rate was within the defined margin of efficacy. Our data suggest that nCRT followed by LE may be

considered as an organ-preserving alternative in carefully selected patients with clinically-staged T2N0 tumours who refuse, or are not candidates for, transabdominal resection.

INTRODUCTION

Transabdominal rectal resection following the principles of total mesorectal excision (TME) has been the mainstay treatment for patients with localized rectal cancer for decades.[1] While effective in providing local tumour control, TME is associated with significant morbidity and long-lasting consequences. These include sexual and urinary dysfunction, significant defecatory problems, or a permanent stoma.[2-4] Consequently, many patients experience a significant decline in quality of life QOL after TME. Alternatives to TME that are capable of achieving the same cure rate, while preserving function, would improve patients' QOL significantly.

The need for TME in patients with tumours localized to the bowel wall, which have not spread to the mesorectal lymph nodes, has long been questioned.[5] Local excision (LE) has been proposed as an alternative for these patients. However, LE in early-stage cancer is associated with higher local recurrence (LR) rates than TME.[6-8] Furthermore, while patients who develop LR after LE can theoretically undergo salvage TME, many have incomplete resections, with recurrence extending beyond the tissues removed by standard TME.[9-11] Survival after LE is therefore inferior compared to TME, particularly in patients with T2N0 tumours.[12-14]

A number of studies have proven that radiotherapy (RT) or chemoradiotherapy (CRT) before TME is associated with a lower rate of LR, compared to either TME alone, or TME followed by CRT. Based on these studies, neoadjuvant CRT (nCRT) followed by TME has become the standard treatment for patients with locally advanced rectal cancer (LARC).[15, 16] The benefits of nCRT in LARC patients treated with TME have hastened interest in use of nCRT before LE for early-stage rectal cancer. Several retrospective case series, and a single-institution prospective study, have suggested that nCRT before LE may result in local tumour control comparable to that of TME for tumours of similar stage.[17-20] However, these studies are limited by small size, variable clinical staging criteria, heterogeneous tumour characteristics, and varying nCRT regimens. Prospective data from larger multi-center trials are needed.

The American College of Surgeons Oncology Group (ACOSOG) designed a prospective multi-institutional, phase 2 trial to investigate the feasibility of using nCRT before LE to achieve organ preservation in patients with endorectal ultrasound (ERUS)- or endorectal coil magnetic resonance imaging (EC-MRI)-staged T2N0 rectal cancer located within 8 cm of the anal verge. Select secondary endpoints of this trial have already been reported.[21] Given more mature follow-up on all patients enrolled, we now report the primary endpoints of tumour recurrence and survival at 3 years, and anorectal function and QOL at 1 year.

METHODS

Study Design and Participants

The study design has been reported previously.[21] This was a phase 2, single arm, non-randomized, open-label trial conducted at American College Of Surgeons Oncology Group Institutions. Patients with clinical T2N0 rectal adenocarcinoma staged by ERUS or EC-MRI, measuring < 4 cm in greatest diameter, involving < 40% of the circumference of the rectum, and located within 8 cm of the anal verge, were included. All patients underwent complete colonoscopy, rigid proctoscopy, digital rectal exam (DRE), abdominal and pelvic CT, and chest x-ray or chest CT. All had Eastern Cooperative Oncology Group Performance Score (ECOG PS) of ≤ 2. Patients with tumours fixed to adjacent structures on DRE were ineligible. The protocol schema is shown in Figure 1. The study was approved by the Institutional Review Boards at all participating institutions. Data was submitted to the ACOSOG statistical center.

Procedures

External beam RT with megavoltage linear accelerators (≥ 6 MV) was delivered to a 3-4 field pelvis arrangement, following CT-based simulation and computer-assisted treatment planning. Intensity-modulated RT (IMRT) was allowed (IMRT guidelines available at:http://www.acosog.org). The original dose (OD) of RT consisted of 1.8 Gy/day 5 days/week for 5 weeks to a dose of 45 Gy to PTV1, then a boost to PTV2 (defined as GTV plus 2cm) for a total dose of 54 Gy. This was accompanied by capecitabine (825mg/m^2, twice daily, on days 1-14 and 22-35) and oxaliplatin (50mg/m^2 weeks 1, 2, 4, 5). The OD of nCRT was found to have unfavorable toxicities; this led to a revised dose (RD) regimen after 53 patients had been accrued. The RT was reduced to a total of 50.4 Gy, and capecitabine was reduced to 725 mg /m^2, twice daily, 5 days/week, for 5 weeks. The dose of oxaliplatin was not changed. Surgery was performed 4-8 weeks after completion of nCRT. LE was done using conventional transanal excision (TAE) or transanal endoscopic microsurgery (TEM). Full-thickness excision of the tumour with a 1 cm surrounding margin of normal rectal wall was required. All participating surgeons had performed at least 3 LEs with negative margins, and completed a skills verification program.

Staging of surgical specimens was performed according to AJCC criteria. Specimens without evidence of dysplastic epithelium or invasive cancer were classified as having pathologic complete response (pCR). Specimens with dysplastic epithelium at the original tumour site, but without evidence of invasion, were staged as ypTis (carcinoma *in situ*), rather than pCR.

Patients received an initial post-operative exam 1 month after surgery. DRE, proctoscopy and ERUS were given every 4 months for 3 years, and every 6 months for the next 2 years. Colonoscopy was required at 3 years. Other tests for LR or distant metastasis (DM) were performed if indicated.

Outcomes

The primary endpoint was 3-year disease-free survival (DFS). Evidence of LR, DM, or death from any cause within 3 years counted as events in the time-to-event Kaplan-Meier analysis[22] of DFS. All protocol-eligible patients were considered on an intent-to-treat analysis. Per-protocol analyses were also performed, for which patients were considered evaluable if they underwent nCRT and LE and had ypT0, ypT1, or ypT2 tumours with negative margins.

Secondary endpoints were the proportion of patients having negative resection margins after LR, the proportion of patients with a pCR, the procedure-specific morbidity and mortality following nCRT and LE, and the impact of nCRT followed by LE on anorectal function and QOL.

Anorectal function and QOL were evaluated at the time of enrollment and 12 months after surgery using the Fecal Incontinence Severity Index (FISI)[25] and the Functional Assessment of Cancer Therapy-Colorectal (FACT-C)[26] questionnaires. The FISI addresses varying frequencies of leakage of gas, mucus, liquid or solid stool, with higher scores indicative of worse anorectal function. The FACT-C questionnaire comprises 5 subscales: 4 measuring concerns related to general health -related –QOL, Physical Well-Being (PWB), Social/ Family Well Being (SFWB), Emotional Well-Being (EWB), Functional Well-Being (FWB); and 1 subscale measuring concerns related specifically to colorectal cancer - the Colorectal Cancer Subscale (CCS). The FACT-C total score is the sum of all 5 subscales. A higher score represents better QOL and overall function.

Statistical analysis

The sample size was calculated using the per-protocol patient set. A 3-year DFS probability of < 0.80 was considered unacceptably low, while a probability of > 0.91 was considered clinically promising. Assuming a significance level of 0.1, 70 evaluable patients were needed to distinguish a null 3-year DFS event rate of 0.80 from an alternative rate of 0.91 with 90% power. We estimated that up to 5% of patients would not tolerate nCRT, up to 10% would exhibit pathological ypT3 tumours or positive resection margins, and up to 15% would not be evaluable for the primary endpoint; therefore, we targeted a total accrual of 83 patients, to ensure at least 70 evaluable patients for per-protocol analyses. In addition to computation of 3-year DFS, the survival profile of enrolled patients was summarized graphically over 5 years of follow-up using the Kaplan-Meier estimator. Differences between grouped survival profiles were assessed with the Log-rank test[22]. The Wilcoxon rank-sum test[23] and Fisher's exact test[24] were used to compare continuous and categorical variables between dose groups. All reported P-values were based on two-sided tests; confidence intervals assumed a significance of 0.05. Anorectal function and QOL at baseline, and 12 months following surgery, were compared using the Wilcoxon Signed Rank test.

The trial is registered with ClinicalTrials.gov, number NCT00114231.

Role of the Funding Source

The ACOSOG participated in the study design, data collection, data storage, and data analysis, but had no role in writing the report. Only LAR, QS and XWC had access to the raw data. The corresponding author had access to the analyzed data, not the raw data, but had final responsibility for the decision to submit the manuscript.

RESULTS

Seventy-nine eligible patients were accrued to the trial from May 25th 2006 to October 22nd 2009, and began nCRT. They represent the intention-to-treat group (Table 1). Patient disposition and analysis groups are presented in Figure 2. Two patients did not have surgery. The pathologic results for all 77 patients undergoing surgery have been previously published.[21] Of these 77 patients, 38 (49%) had ypT0 or ypTis tumours; 11 (14%) ypT1 tumours; 24 (31%) ypT2 tumours; 3 (4%) ypT3 tumours; 1 (1%) ypTx tumour. The proportions of all patients experiencing AEs during nCRT and stratified by dose groups are presented in Table 2. Surgery-related toxicities are presented in Table 3.

In total, 76 patients had nCRT and LE, either TEM (29 patients or 38%) or TAE (47 patients or 62%). One patient had positive resection margins and underwent APR, as required per protocol, with no residual tumour identified in the surgical specimen. The patient died 10 months later from surgery-related complications. Three additional patients had ypT3 tumours, and two of these underwent APR within six weeks of LE. Neither APR specimen revealed cancer; both patients were alive and without evidence of disease at 40 and 47 months from LE, respectively. The third patient refused APR and developed pelvic recurrence. The remaining 72 patients underwent nCRT and LE and had ypT0-2 and negative resection margins, comprising the per-protocol group.

Patients have been followed for a median 56 months (IQR 46-63 months) after surgery, with no treatment-related deaths. Five died from non-cancer-related causes 8-38 months after surgery. At the end of the follow-up period, eight of 79 patients (10%) have developed recurrence: five of 79 (6%) with DM and three of 79 (4%) with LR as initial sites of failure. None have developed both DM and LR. Characteristics of the eight patients with recurrent tumour, salvage treatment received, and tumour and survival status at the end of follow-up are presented in Table 4. Two patients with LR underwent salvage APR, with negative margins. One patient whose APR specimen showed tumour limited to the muscularis propria developed further pelvic recurrence, and died of disease 48 months after LE. The second patient had carcinoma *in situ* in the APR specimen, and remains alive and free of disease 48 months after LE. One patient with a ypT3 tumour in the surgical specimen refused TME and developed LR.

The estimated 3-year DFS for the intent-to-treat group was 0.88 (95% CI: 0.81, 0.96), and for the per-protocol group 0.87 (95% CI: 0.79, 0.95) (Figure 3). Three-year OS for the intent-to-treat group was 0.96 (95% CI: 0.90, 1.00), and for the per-protocol group 0.96 (95% CI: 0.91, 1.00) (Figure 4). Five of the recurrences developed in patients receiving the OD, three in patients receiving the RD. The 3-year DFS and OS by OD versus RD groups for the intent-to-treat group are presented in Supplemental Figure 1. We found no

differences in 3-year DFS or overall survival between patients treated with TEM and TAE (Supplemental Figure 2).

At the end of follow-up, 72 (91%) of 79 patients receiving nCRT and LE had rectal preservation. All 72 patients completed the baseline FISI and FACT-C questionnaires, but only 62 (86%) completed them one year after surgery. We found no significant deterioration in the overall FISI scores or any of the subscales one year after surgery, compared to baseline (Table 5). We found no difference in the overall FACT-C scores between baseline and one-year evaluations (Table 5). However, patients experienced deterioration in the physical well-being subscale, and an improvement in the emotional well-being subscales (Table 5).

DISCUSSION

The results of this multi-institutional prospective trial indicate that the vast majority of patients with clinically staged T2N0 rectal cancer treated with nCRT and LE preserved the rectum. The LR rate for all patients was 4%, and the estimated 3-year DFS for the intention-to-treat group and for the per-protocol groups were within the margin of efficacy defined in the study design. However, the lower limit of the 95% confidence interval of 3-years DFS for the per-protocol group, the one used for the sample size calculation, reached the threshold for considering it unacceptably low. Thus, while the results are encouraging, the study did not achieve its goal using the strictly pre-set statistical parameters. The results of this trial also demonstrated that nCRT and LE do not cause significant alterations in anorectal function and overall QOL measured one year after surgery, compared to baseline. Furthermore, half of the clinically staged T2N0 patients treated with nCRT and LE had pCR, and only one in 76 had a positive resection margin.

The changes in nCRT introduced in response to the unexpectedly high toxicity observed with the original nCRT regimen resulted in a reduction in the pCR and 3-year DFS rates. The results of recent phase 3 trials indicate that adding oxaliplatin to a fluoropyrimidine as a radiosensitizer in patients with rectal cancer increases toxicity without enhancing tumour response, compared to fluoropyrimidine alone.[27-29] Based on this information, discontinuing oxaliplatin altogether may have been more effective in preventing toxicity, without affecting tumour response, than reducing the dose of capecitabine and radiation.

A transabdominal rectal resection is the recommended treatment for patients with T2N0 rectal cancer, and TME is the gold standard against which other surgical procedures should be compared.[1] The 3-year DFS and OS in this trial are within the range of the rates reported for Stage I tumours treated with either laparoscopic or open TME in the recently published COLOR II trial.[30] However, the COLOR II trial did not stratify the results of patients with Stage I disease by T categories. Retrospective case series and a cohort study from the National Cancer Database have reported 5-year LR rates ranging from 6% to 15% for T2N0 rectal cancers treated with transabdominal resection alone,[12, 13, 31] higher than the 4% LR rate in this study. Recent population-based analysis from the NCDB and the Surveillance, Epidemiology and End Results (SEER) database have reported 5-year OS rates close to 76% for patients with T2N0 rectal cancer treated with transabdominal resection alone, lower than

the estimated 5-year overall survival observed in this trial. However, comparisons between this trial and prospective studies or retrospective series of patients treated with transabdominal rectal resection are limited by patient selection bias. Patients in the Z6041 trial had tumours located within 8 cm of the anal verge, while patients in the TME series had tumours located anywhere in the rectum. As cancers located in the lower third of the rectum pose a higher risk of LR than cancers in the mid and upper rectum, a higher risk of recurrence should be expected in the Z6041 trial. On the other hand, the Z6041 trial was limited to tumours smaller than 4 cm in diameter, a selection criterion not applied in the transabdominal rectal resection series. In addition, results for the Z6041 trial are reported by clinical stage, whereas results in the transabdominal resection series were reported by pathological stage. Both ERUS and EC-MRI are known to overstage or understage some tumours.[32, 33] It is likely that some of the ypT0, ypTis or ypT1 tumours in this trial may have been initially overstaged as T2 by ERUS. Conversely, the ypT3 tumours in this trial may represent either tumour progression during nCRT, or understaging by ERUS. Finally, LR tends to occur later in patients treated with nCRT and surgery, compared to those treated with surgery alone.[15] In our series all patients received neoadjuvant radiation, compared to 59% in the COLOR II trial. Therefore, more patients in the Z6041 trial are likely to develop tumour relapse on longer follow-up.

Proving equivalence in oncologic efficacy between nCRT plus LE and TME for treatment of early rectal cancer would require a well-designed prospective, randomized trial. Given the relatively good prognosis of stage I rectal cancer, the required sample size will be large. In addition, patients' acceptance of randomization between LE and TME is questionable. Therefore, completion of such a study would be challenging. Lezoche, et al. reported the results of a prospective single-institution trial comparing nCRT and LE and transrectal partial mesorectal excision to nCRT and laparoscopic TME in patients with ultrasound-staged T2N0M0 rectal cancers, smaller than 3 cm in diameter, located within 6 cm of the anal verge, with well or moderately differentiated histology.[19] After five years of follow-up, 8% of patients in the LE group and 6% in the TME group have developed LR, rates not very different than in this trial. Although underpowered to prove equivalence between nCRT plus LE and nCRT plus TME in uT2uN0 rectal cancer, Lezoche's study also suggests that nCRT plus LE may be an alternative to TME for patients with distal rectal cancer seeking organ-preserving treatment to avoid a permanent colostomy.

The justification for CRT and LE as an alternative to TME in patients with early-stage rectal cancer is the possibility of achieving equivalent oncologic results while preserving QOL. The baseline FISI total score in our patients was equivalent to those reported in patients with low rectal cancer enrolled in a prospective trial comparing functional outcomes after TME and different types of colorectal anastomosis. However, while in this study the FISI score remained essentially unaltered one year after CRT and LE, patients treated with TME had a significant deterioration in the FISI score at that time point, independent of the type of anastomosis.[34] In this study the FACT-C overall score and the CCS subscale remained unchanged one year after surgery, compared to baseline. These findings are consistent with the recently published results of the NSABP R04[35] trial that also reported no significant differences in the FACT-C scores (baseline vs. 1 year after surgery) in rectal cancer patients treated with nCRT and TME. The study has several important limitations. This is a single

arm phase II trial, and the possibility of selecting fitter patients for nCRT and LE cannot be excluded. The sample size is relatively small. The follow-up is still short and, while most recurrences tend to arise in the first three years after treatment, nCRT delays the appearance of LR and it is possible that more patients may develop recurrence in the future. Finally, not all patients completed the 1-year FISI and FACT-C questionnaires, either because they passed away, developed recurrence, or simply did not return them. Therefore, our study may underestimate the real impact of nCRT and LE on ARF and QOL.

In conclusion, this study shows that nearly half of patients with clinically-staged T2N0 distal rectal cancer can achieve a pCR in response to nCRT. Rates of recurrence and survival are similar to patients with stage I tumours treated with TME. The majority of patients treated with nCRT and LE preserve the rectum with minimal deterioration in ARF and QOL up to one year after LE. While follow-up is still short, this study suggests that nCRT followed by LE may be an alternative to transabdominal rectal resection for carefully selected patients with T2N0 distal rectal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg. 1982; 69(10):613–6. [PubMed: 6751457]
2. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Annals of surgery. 2010; 251(5):807–18. [PubMed: 20395841]
3. Lange MM, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. Nature reviews Urology. 2011; 8(1):51–7. [PubMed: 21135876]
4. Floodeen H, Lindgren R, Hallbook O, Matthiessen P. Evaluation of Long-term Anorectal Function After Low Anterior Resection: A 5-Year Follow-up of a Randomized Multicenter Trial. Diseases of the colon and rectum. 2014; 57(10):1162–8. [PubMed: 25203371]
5. BC M. Factors influencing the prognosis of early cancer of the rectum. Proc R Soc Med. 1966; 59(7):607–8. [PubMed: 5939502]
6. Garcia-Aguilar J, Mellgren A, Sirivongs P, Buie D, Madoff RD, Rothenberger DA. Local excision of rectal cancer without adjuvant therapy: a word of caution. Annals of surgery. 2000; 231(3):345–51. [PubMed: 10714627]
7. Paty PB, Nash GM, Baron P, et al. Long-term results of local excision for rectal cancer. Annals of surgery. 2002; 236(4):522–29. discussion 9-30. [PubMed: 12368681]
8. Madbouly KMRF, Erkek BA, Senagore AJ, Baeslach CM, Khandwala F, Fazio VW, Lavery IC. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? Diseases of the colon and rectum. 2005; 48(4):719–21.

9. Weiser MRLR, Wong WD, Shia J, Guillem JG, Temple LK, Minsky BD, Cohen AM, Paty PB. Surgical salvage of recurrent rectal cancer after transanal excision. Diseases of the colon and rectum. 2005; 48(6):1169–75. [PubMed: 15793645]
10. Stipa F, Giaccaglia V, Burza A. Management and outcome of local recurrence following transanal endoscopic microsurgery for rectal cancer. Diseases of the colon and rectum. 2012; 55(3):262–9. [PubMed: 22469792]
11. Friel CM, Cromwell JW, Marra C, Madoff RD, Rothenberger DA, Garcia-Aguilar J. Salvage radical surgery after failed local excision for early rectal cancer. Diseases of the colon and rectum. 2002; 45(7):875–9. [PubMed: 12130873]
12. Mellgren A, Sirivongs P, Rothenberger DA, Madoff RD, Garcia-Aguilar J. Is local excision adequate therapy for early rectal cancer? Diseases of the colon and rectum. 2000; 43(8):1064–71. discussion 71-4. [PubMed: 10950004]
13. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Annals of surgery. 2007; 245(5):726–33. [PubMed: 17457165]
14. Stitzenberg KB, Sanoff HK, Penn DC, Meyers MO, Tepper JE. Practice patterns and long-term survival for early-stage rectal cancer. J Clin Oncol. 2013; 31(34):4276–82. [PubMed: 24166526]
15. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. The lancet oncology. 2011; 12(6):575–82. [PubMed: 21596621]
16. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012; 30(16):1926–33. [PubMed: 22529255]
17. Borschitz T, Wachtlin D, Mohler M, Schmidberger H, Junginger T. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol. 2008; 15(3):712–20. [PubMed: 18163173]
18. Nair RM, Siegel EM, Chen DT, et al. Long-term results of transanal excision after neoadjuvant chemoradiation for T2 and T3 adenocarcinomas of the rectum. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2008; 12(10):1797–805. discussion 805-6. [PubMed: 18709419]
19. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg. 2012; 99(9):1211–8. [PubMed: 22864880]
20. Kim CJ, Yeatman TJ, Coppola D, et al. Local excision of T2 and T3 rectal cancers after downstaging chemoradiation. Annals of surgery. 2001; 234(3):352–8. discussion 8-9. [PubMed: 11524588]
21. Garcia-Aguilar J, Shi Q, Thomas CR Jr. et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol. 2012; 19(2):384–91. [PubMed: 21755378]
22. Fleming, TRHD. Counting Processes and Survival Analysis. John Wiley & Sons; 1991.
23. Mann HBW, Donald R. On a Test of Whether one of Two Random Variables is Stochastically Larger than the Other. Annals of Mathematical Statistics. 1947; 18((1)):50–60.
24. Fisher RA. On the interpretation of $\chi 2$ from contingency tables, and the calculation of P. Journal of the Royal Statistical Society. 1922; 85(1):87–94.
25. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Diseases of the colon and rectum. 1999; 42(12):1525–32. [PubMed: 10613469]
26. Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. Qual Life Res. 1999; 8(3):181–95. [PubMed: 10472150]
27. Aschele CCL, Lonardi S, et al. Primary tumour response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01

randomized phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29(20):2773–80. [PubMed: 21606427]

28. Gerard JPAD, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28(10):1638–44. [PubMed: 20194850]
29. O'Connell MJCLBR, Petrelli NJ, Allegra CJ, Sharif S, Pitot HC, Shields AF, Landry JC, Ryan DP, Parda DS, Mohiuddin M, Arora A, Evans LS, Bahary N, Soori GS, Eakle J, Robertson JM, Moore DF Jr, Mullane MR, Marchello BT, Ward PJ, Wozniak TF, Roh MS, Yothers G, Wolmark N. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014; 32(18): 1927–34. [PubMed: 24799484]
30. Bonjer HJ1DC, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, Lacy AM, Bemelman WA, Andersson J, Angenete E, Rosenberg J, Fuerst A, Haglind E, COLOR II Study Group. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med. 2015; 372(14):1324–32. [PubMed: 25830422]
31. Rodel CLT, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial I(O-04. The lancet oncology. 2012; 13:679–87. [PubMed: 22627104]
32. Garcia-Aguilar J, Pollack J, Lee SH, et al. Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. Diseases of the colon and rectum. 2002; 45(1):10–5. [PubMed: 11786756]
33. Landmann RG, Wong WD, Hoepfl J, et al. Limitations of early rectal cancer nodal staging may explain failure after local excision. Diseases of the colon and rectum. 2007; 50(10):1520–5. [PubMed: 17674104]
34. Fazio VW, Zutshi M, Remzi FH, et al. A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. Annals of surgery. 2007; 246(3):481–8. discussion 8-90. [PubMed: 17717452]
35. Russell MM, Ganz PA, Lopa S, et al. Comparative effectiveness of sphincter-sparing surgery versus abdominoperineal resection in rectal cancer: patient-reported outcomes in National Surgical Adjuvant Breast and Bowel Project randomized trial R-04. Annals of surgery. 2015; 261(1):144–8. [PubMed: 24670844]

RESEARCH IN CONTEXT

Evidence before this study

Local excision of stage I rectal cancer is appealing because it could potentially cure the cancer while preserving the organ. However, local excision (LE) alone for T2N0 rectal cancer patients is associated with higher rates of local recurrence (LR), and inferior survival, compared to a transabdominal resection. The use of neoadjuvant chemoradiotherapy (nCRT) to reduce the risk of LR in patients with early-stage rectal cancer treated with LE is an extrapolation of results obtained for patients with advanced rectal cancer treated with transabdominal rectal resection. A number of retrospective, single-institution case series have reported low rates of LR in selected patients with T2-3N0 rectal cancer receiving nCRT before LE. However, these studies are limited by small sample sizes, variable clinical staging criteria and imaging modalities, heterogeneous tumour characteristics, and varying CRT regimens. In addition, information on functional outcomes and quality of life (QOL) is lacking.

Added value of this study

This multi-institutional prospective trial shows that nCRT results in a high rate of tumour response, and low rate of LR, in a defined population of patients with early-stage distal rectal cancer. It also indicates that most patients with distal T2N0 rectal cancer treated with nCRT and LE can preserve the rectum while achieving a survival equivalent to patients treated with transabdominal rectal resection. Finally, our study suggests that nCRT followed by LE has minimal impact on anorectal function and QOL.

Implications of all the available evidence

The results of this study suggest that nCRT followed by LE may be an alternative to transabdominal rectal resection for patients with early-stage distal rectal cancer who are unfit for major surgery, or seek preservation of the rectum.

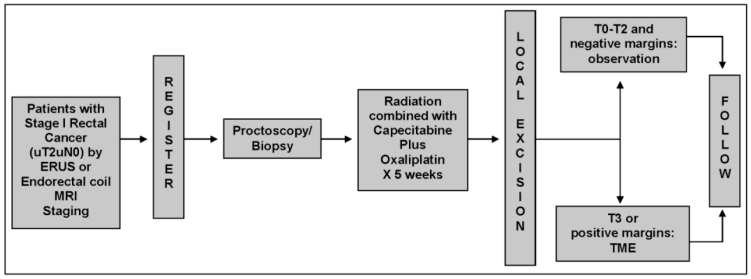

Figure 1.

ACOSOG Z6041 Trial - Protocol Schema

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

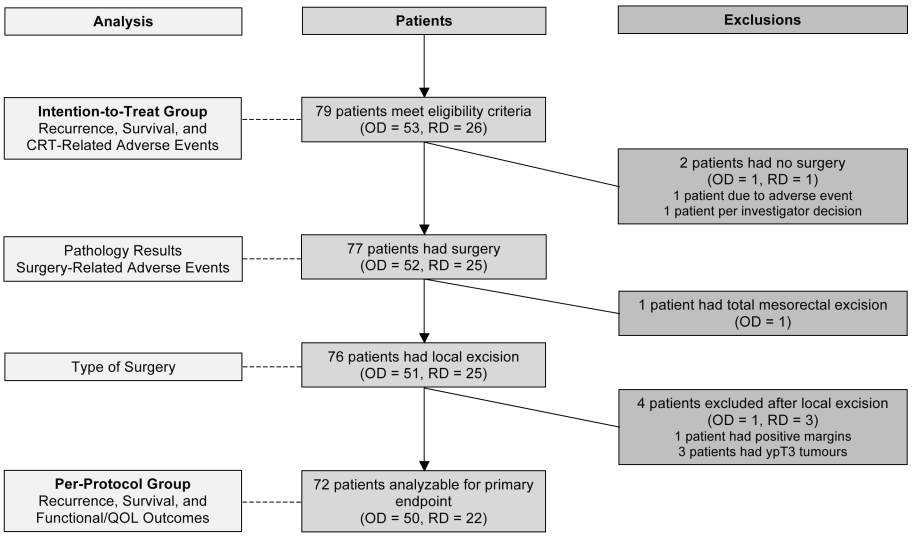

Figure 2.

Patient disposition and analysis

Abbreviations: OD=Original dose group; RD=Revised dose group

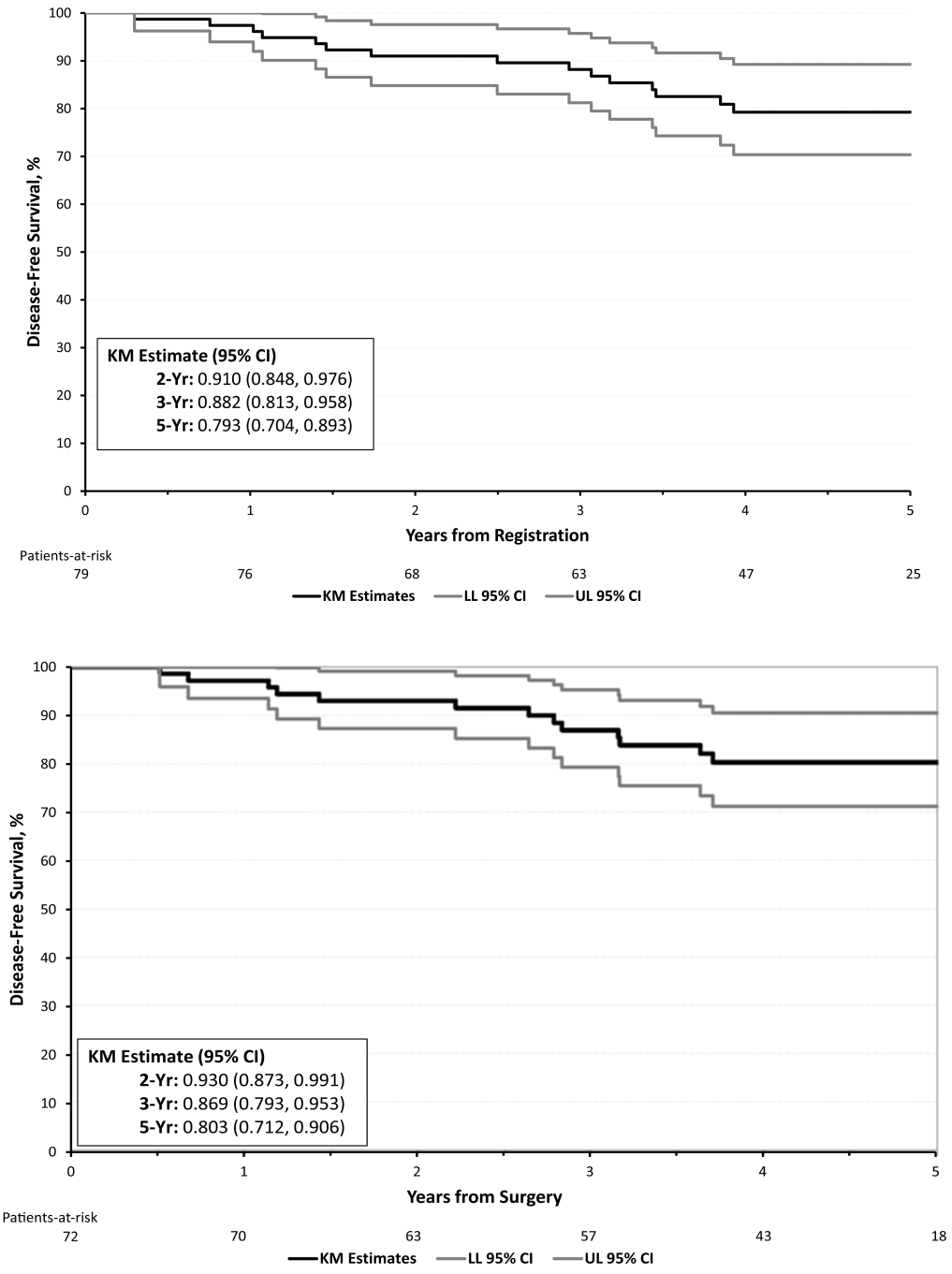

Figure 3.
Disease-free survival curves for the intention-to-treat group (A) and the per-protocol group (B)

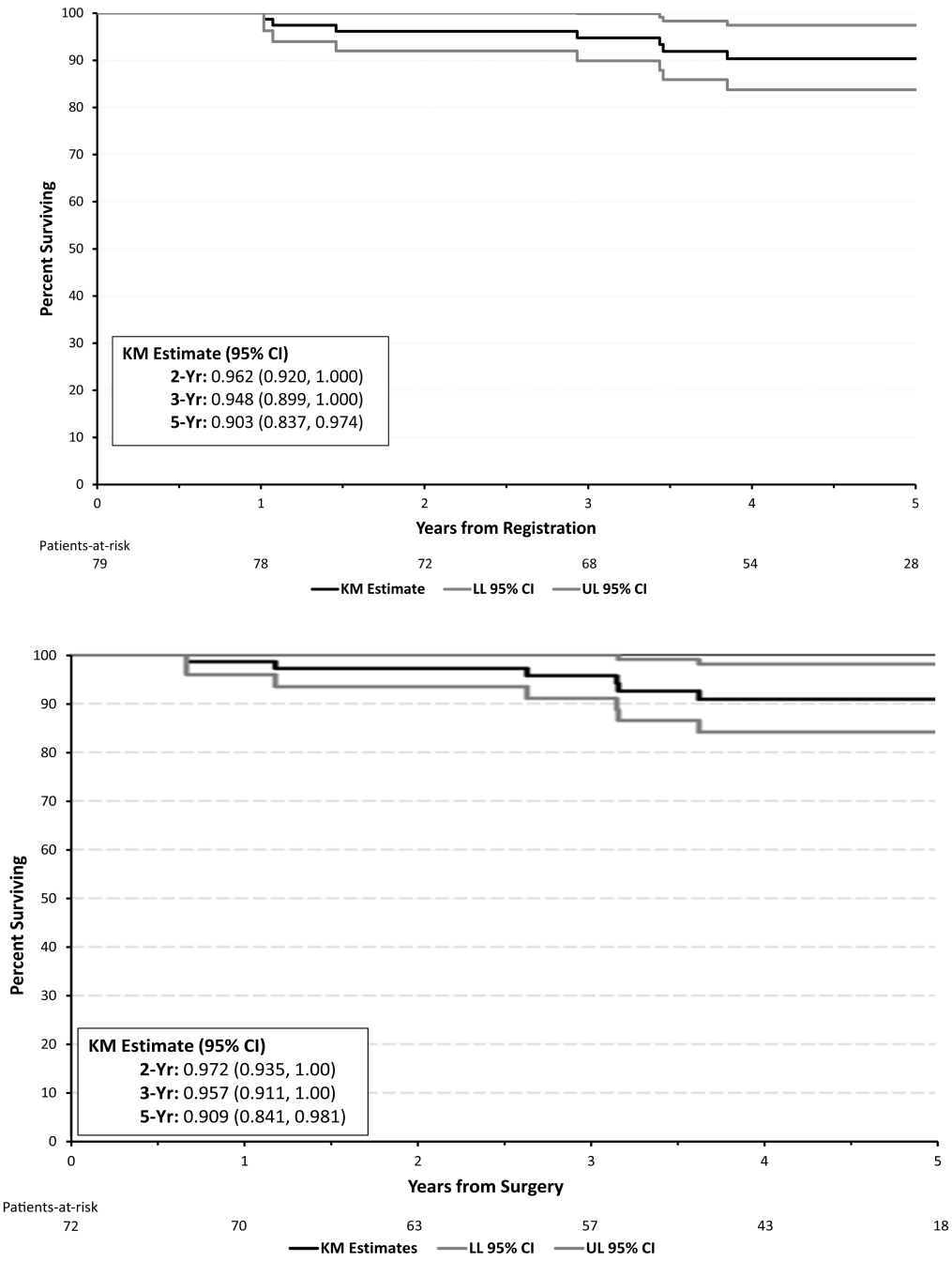

Figure 4.

Overall survival curves for the intention-to-treat group (A) and the per-protocol group (B)

Table 1

Baseline patient demographics and disease characteristics for all 79 patients accrued.

Demographic or Disease Characteristic	Original dose group (n = 53)	Revised dose group (n = 26)	Overall (n = 79)	p-value
Age, years *	62 (30-80)	63 (45-83)	62 (30-83)	0.6954[2]
Gender				
Male	33 (62%)	20 (77%)	53 (67%)	0.1926[1]
Female	20 (38%)	6 (23%)	26 (33%)	
Race				
White	47 (88.7%)	25 (96.2%)	72 (91.1%)	
African Am.	2 (3.8%)	0 (0.0%)	2 (2.5%)	
Nat. Hawaiian or Pac Isl.	1 (1.9%)	0 (0.0%)	1 (1.3%)	0.7271[1]
Asian	1 (1.9%)	1 (3.8%)	2 (2.5%)	
Am Indian or Alaska Nat.	1 (1.9%)	0 (0.0%)	1 (1.3%)	
Unknown	1 (1.9%)	0 (0.0%)	1 (1.3%)	
ECOG/Zubrod Performance Status				
0	47 (88.7%)	20 (76.9%)	67 (84.8%)	
1	5 (9.4%)	5 (19.2%)	10 (12.6%)	0.4189[1]
2	1 (1.9%)	0 (0.0%)	1 (1.3%)	
Missing	0	1 (3.9%)	1 (1.3)	
Tumor Size, cm Ψ	2.8 ± 0.8	2.9± 0.7	2.8 ± 0.8	0.7242[3]
Tumor Location				
Anterior	11 (20.8%)	4 (15.4%)	15 (19.0%)	0.2213[1]
Posterior	29 (54.7%)	10 (38.5%)	39 (49.4%)	
Left Lateral	10 (18.9%)	7 (26.9%)	17 (21.5%)	
Right Lateral	3 (5.6%)	4 (15.4%)	7 (8.8%)	
Missing	0	1 (3.8)	1 (1.3%)	
Distance from Anal Verge, (distal) cm Ψ	4.88 ± 1.91	5.30 ± 2.05	5.02 ± 1.95	0.2607[3]

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[1] Fisher's Exact Test

[2] Equal Variance T-Test

[3] Wilcoxon Rank Sum

[ψ] Mean ± SD

[*] Mean (Range)

Table 2a

Adverse events during neoadjuvant chemoradiotherapy for all 79 patients accrued.

Adverse Event Category	Original Dose (n = 53)			Revised Dose (n = 26)			Overall (n = 79)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Gastrointestinal	4 (8%)	18 (34%)	0	18 (69%)	5 (19%)	0	22 (28%)	23 (29%)	0
Pain	2 (4%)	9 (17%)	1 (2%)	16 (62%)	2 (8%)	0	18 (23%)	11 (14%)	1 (1%)
Dermatological	2 (4%)	7 (13%)	0	7 (27%)	2 (8%)	0	9 (11%)	9 (11%)	0
Hematological	1 (2%)	4 (8%)	1 (2%)	11 (42%)	6 (23%)	1 (4%)	12 (15%)	10 (13%)	(3%)
Infectious/Febrile Neutropenia	0	3 (6%)	1 (2%)	2 (8%)	0	0	2 (3%)	3 (4%)	1 (1%)
Constitutional Symptoms	5 (9%)	3 (6%)	0	17 (65%)	1 (4%)	0	22 (28%)	4 (5%)	0
Metabolic/Laboratory	1 (2%)	2 (4%)	1 (2%)	9 (35%)	2 (8%)	1 (4%)	10 (13%)	4 (5%)	2 (3%)
Cardiovascular	0	2 (4%)	1 (2%)	6 (23%)	0	0	6 (8%)	2 (3%)	1 (1%)
Hemorrhage	0	1 (2%)	1 (2%)	4 (15%)	1 (4%)	0	4 (5%)	2 (3%)	1 (1%)
Lymphatic	0	1 (2%)	0	2 (8%)	0	0	2 (3%)	1 (1%)	0
Neurological	3 (6%)	1 (2%)	0	8 (31%)	0	0	11 (14%)	1 (1%)	0
Coagulation	0	0	0	1 (4%)	1 (4%)	0	1 (1%)	1 (1%)	0
Musculoskeletal	1 (2%)	0	0	0	1 (4%)	0	1 (1%)	1 (1%)	0
Renal/Genitourinary	1 (2%)	0	0	12 (46%)	0	0	13 (16%)	0	0
Hepatic	0	0	0	8 (31%)	0	0	8 (10%)	0	0

Table 2b

Number of patients with adverse events during neoadjuvant chemoradiotherapy for all 79 patients accrued.

Adverse Event Category	Original Dose (n = 53)			Revised Dose (n = 26)			Overall (n = 79)		
	No AE n (%)	1 AE n (%)	2+ AEs n (%)	No AE n (%)	1 AE n (%)	2+ AEs n (%)	No AE n (%)	1 AE n (%)	2+ AEs n (%)
Gastrointestinal	31 (58.5)	12 (22.6)	10 (18.9)	3 (11.5)	2 (7.7)	21 (80.8)	34 (43.0)	14 (17.7)	31 (39.2)
Pain	42 (79.2)	9 (17.0)	2 (3.8)	8 (30.8)	6 (23.1)	12 (46.2)	50 (63.3)	15 (19.0)	14 (17.7)
Dermatological	44 (83.0)	8 (15.1)	1 (1.9)	17 (65.4)	5 (19.2)	4 (15.4)	61 (77.2)	13 (16.5)	5 (6.3)
Hematological	48 (90.6)	4 (7.5)	1 (1.9)	9 (34.6)	3 (11.5)	14 (53.9)	57 (72.1)	7 (8.9)	15 (19.0)
Infectious/Febrile Neutropenia	50 (94.3)	3 (5.7)	0	24 (92.3)	2 (7.7)	0	74 (93.7)	5 (6.3)	0
Constitutional Symptoms	45 (84.9)	7 (13.2)	1 (1.9)	8 (30.8)	9 (34.6)	9 (34.6)	53 (67.1)	16 (20.3)	10 (12.7)
Metabolic/Laboratory	52 (98.1)	1 (1.9)	0	15 (57.7)	3 (11.5)	8 (30.8)	65 (82.3)	4 (5.1)	10 (12.7)
Cardiovascular	51 (96.2)	2 (3.8)	0	20 (76.9)	6 (23.1)	0	71 (89.9)	8 (10.1)	0
Hemorrhage	52 (98.1)	1 (1.9)	0	21 (80.8)	5 (19.2)	0	73 (92.4)	6 (7.6)	0
Lymphatic	52 (98.1)	1 (1.9)	0	24 (92.3)	2 (7.7)	0	76 (96.2)	3 (3.8)	0
Neurological	49 (92.4)	3 (5.7)	1 (1.9)	18 (69.2)	2 (7.7)	6 (23.1)	67 (84.8)	5 (6.3)	7 (8.9)
Coagulation	53 (100)	0	0	24 (92.3)	2 (7.7)	0	77 (97.5)	2 (2.5)	0
Musculoskeletal	52 (98.1)	1 (1.9)	0	25 (96.2)	1 (3.8)	0	77 (97.5)	2 (2.5)	0
Renal/Genitourinary	52 (98.1)	1 (1.9)	0	14 (53.8)	10 (38.5)	2 (7.7)	66 (83.5)	11 (13.9)	2 (2.5)
Hepatic	53 (100)	0	0	18 (69.2)	4 (15.4)	4 (15.4)	71 (89.9)	4 (5.1)	4 (5.1)
Ocular/Visual	53 (100)	0	0	22 (92.3)	3 (11.5)	1 (3.8)	75 (94.9)	3 (3.8)	1 (1.3)
Pulmonary	51 (96.2)	2 (3.8)	0	25 (96.2)	1 (3.8)	0	76 (96.2)	3 (3.8)	0
Sexual /Reproductive Function	53 (100)	0	0	23 (88.5)	2 (7.7)	1 (3.8)	66 (83.5)	11 (13.9)	2 (2.5)
Syndromes	53 (100)	0	0	25 (96.2)	1 (3.8)	0	78 (98.7)	1 (1.3)	0
Endocrine	53 (100)	0	0	25 (96.2)	1 (3.8)	0	78 (98.7)	1 (1.3)	0

Table 3

Surgery-related adverse events for all eligible patients who underwent surgery (n = 77).

Adverse Event Category	Original Dose (n = 52)			Revised Dose (n = 25)			Overall (n = 77)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Hematological	0	1 (2%)	0	0	1 (4%)	0	0	2 (3%)	0
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	4	1 (4%)	0	5 (6%)	2 (3%)	1 (1%)
Infectious/Febrile Neutropenia	3 (6%)	1 (2%)	0	1 (4%)	1 (4%)	0	4 (5%)	2 (3%)	0
Pain	13 (25%)	5 (10%)	0	7 (28%)	1 (4%)	0	20 (26%)	6 (8%)	0
Gastrointestinal	8 (15%)	3 (6%)	0	11 (44%)	0	0	19 (25%)	3 (4%)	0
Neurological	0	0	0	2 (8%)	1 (4%)	0	2 (3%)	1 (1%)	0

Table 4

Characteristics of patients developing tumour recurrence

Location	Tumor Size[1]	Distance[2]	Treatment dose	ypT	Time to recurrence[3]	Additional Treatment[4]	Follow-up[5]	Survival status
Local	0.3	3.0	OD	ypT1	34	APR	42	Alive with disease
Local	3.0	5.0	OD	ypT3	6	Chemotherapy	58	Alive with disease
Local	3.4	8.0	RD	ypT2	6	APR	48	Alive, NED
Liver	2.0	2.0	RD	ypT1	14	Liver resection	55	Alive, NED
Lung	2.0	3.5	OD	ypT2	26	Lung Resection	60	Alive, NED
Lung	2.9	6.0	RD	ypT0	17	Lung resection	46	Alive, NED
Lung	3.0	6.0	OD	ypT0	33	Chemotherapy	55	Alive with disease
Uterus	3.0	3.0	OD	ypT0	45	Hysterectomy	63	Died from disease

[1]Tumour size at diagnosis measured in cm

[2]Distance from anal verge measured in cm

[3]Time to recurrence from local excision, months

[4]Treatment for recurring disease

[5]Length of follow-up after local excision, months

Table 5

Baseline and 12 month FISI and FACT-C scores.

	Baseline [ψ] (n = 72)	12 Months [ψ] (n = 66)	Mean Absolute Difference (SD)	p-value
FISI				
Overall	26.2 (16.7)	27.8 (17.1)	1.5 (19.4)	0.7382[1]
Gas	7.8 (5.0)	7.9 (4.5)	−0.4 (5.4)	0.7322[1]
Mucus	3.0 (4.1)	3.3 (4.1)	0.1 (5)	0.5831[1]
Liquid Stool	6.2 (6.9)	7.2 (6.4)	1.2 (6.9)	0.3876[1]
Solid Stool	9.5 (7.9)	9.8 (7.5)	0.6 (9.9)	0.7023[1]
FACT-C				
Overall	112.2 (13.5)	109.3 (18.9)	−2.17 (16.5)	0.6843[1]
Physical WB	25.17 (3.8)	23.85 (4.7)	−1.15 (3.2)	0.0363[1]
Social/Family WB	25.26 (3.5)	23.74 (5.2)	−1.5 (5.3)	0.0940[1]
Emotional WB	18.62 (3.9)	20.09 (3.5)	1.7 (3.7)	0.0285[1]
Functional WB	22.5 (4.7)	22.26 (5.7)	−0.1 (5.4)	0.8332[1]
Colorectal Cancer Subscale	20.66 (3.1)	19.63 (3.8)	−0.75 (4.2)	0.1032[1]

[1] Wilcoxon Signed Rank Test

[ψ] Mean (SD)