Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial

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Summary

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

Methods We did a multi-institutional, single-arm, open-label, non-randomised, phase 2 trial of patients with clinically staged T2N0 distal rectal cancer treated with neoadjuvant chemoradiotherapy at 26 American College of Surgeons Oncology Group institutions. Patients with clinical T2N0 rectal adenocarcinoma staged by endorectal ultrasound or endorectal coil MRI, measuring less than 4 cm in greatest diameter, involving less than 40% of the circumference of the rectum, located within 8 cm of the anal verge, and with an Eastern Cooperative Oncology Group performance status of at least 2 were included in the study. Neoadjuvant chemoradiotherapy consisted of capecitabine (original dose 825 mg/m² twice daily on days 1–14 and 22–35), oxaliplatin (50 mg/m² on weeks 1, 2, 4, and 5), and radiation (5 days a week at 1·8 Gy per day for 5 weeks to a dose of 45 Gy, followed by a boost of 9 Gy, for a total dose of 54 Gy) followed by local excision. Because of adverse events during chemoradiotherapy, the dose of capecitabine was reduced to 725 mg/m² twice-daily, 5 days per week, for 5 weeks, and the boost of radiation was reduced to 5·4 Gy, for a total dose of 50·4 Gy. The primary endpoint was 3-year disease-free survival for all eligible patients (intention-to-treat population) and for patients who completed chemotherapy and radiation, and had ypT0, ypT1, or ypT2 tumours, and negative resection margins (per-protocol group). This study is registered with ClinicalTrials.gov, number NCT00114231.

Findings Between May 25, 2006, and Oct 22, 2009, 79 eligible patients were recruited to the trial and started neoadjuvant chemoradiotherapy. Two patients had no surgery and one had a total mesorectal excision. Four additional patients completed protocol treatment, but one had a positive margin and three had ypT3 tumours. Thus, the per-protocol population consisted of 72 patients. Median follow-up was 56 months (IQR 46–63) for all patients. The estimated 3-year disease-free survival for the intention-to-treat group was 88·2% (95% CI 81·3–95·8), and for the per-protocol group was 86·9% (79·3–95·3). Of 79 eligible patients, 23 (29%) had grade 3 gastrointestinal adverse events, 12 (15%) had grade 3–4 pain, and 12 (15%) had grade 3–4 haematological adverse events during chemoradiation. Of the 77 patients who had surgery, six (8%) had grade 3 pain, three (4%) had grade 3–4 haemorrhage, and three (4%) had gastrointestinal adverse events.

Interpretation Although the observed 3-year disease free survival was not as high as anticipated, our data suggest that neoadjuvant chemoradiotherapy followed by local excision might 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.

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Introduction

Transabdominal rectal resection following the principles of total mesorectal excision has been the mainstay treatment for patients with localised rectal cancer for decades.[1] Although effective in providing local tumour control, total mesorectal excision is associated with significant morbidity and long-lasting complications. These include sexual and urinary dysfunction, significant defecatory problems, or a permanent stoma.[2–4] Consequently, many patients have a significant decrease in their quality of life after total mesorectal excision. Alternatives to total mesorectal excision that are capable of achieving the same proportion of cured patients, while preserving organ function, would substantially improve patients' quality of life.

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Research in context

Evidence before this study

We searched PubMed for English language publications between Jan 1, 1995, and July 31, 2015, using the search terms "early rectal cancer", "neoadjuvant therapy", "radiotherapy", "chemotherapy", "local excision", "transabdominal resection", "local recurrence", and "quality of life". Local excision of stage 1 rectal cancer is appealing because it could potentially cure the cancer while preserving the organ. However, local excision alone for patients with T2N0 rectal cancer is associated with higher proportions of patients having of local recurrence, and worse survival compared with patients treated with a transabdominal resection. The use of neoadjuvant chemoradiotherapy to reduce the risk of local recurrence in patients with early-stage rectal cancer treated with local excision is an extrapolation of results obtained for patients with advanced rectal cancer treated with transabdominal rectal resection. Several retrospective, single-institution case series have reported low rates of local recurrence in selected patients with T2–3N0 rectal cancer receiving neoadjuvant chemoradiotherapy before local excision. However, these studies are limited by small sample sizes, variable clinical staging criteria and imaging modalities, heterogeneous tumour characteristics, and varying chemoradiotherapy regimens. Additionally, information about functional outcomes and quality of life is insufficient.

Added value of this study

This study shows that neoadjuvant chemoradiotherapy results in a high proportion of patients achieving a tumour response, and low 3-year local recurrence rate, in a defined population of patients with early-stage distal rectal cancer. It also suggests that most patients with distal T2N0 rectal cancer treated with neoadjuvant chemoradiotherapy and local excision can preserve the rectum while achieving a survival equivalent to patients treated with transabdominal rectal resection. Finally, our study suggests that neoadjuvant chemoradiotherapy followed by local excision has minimum effect on anorectal function and quality of life.

Implications of all the available evidence

The results of this study taken together with previous evidence suggest that neoadjuvant chemoradiotherapy followed by local excision might 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.

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

Several studies[15,16] have shown that radiotherapy or chemoradiotherapy before total mesorectal excision is associated with a lower proportion of patients having local recurrence than either total mesorectal excision alone or total mesorectal excision followed by chemoradiotherapy. On the basis of these studies, neoadjuvant chemoradiotherapy followed by total mesorectal excision has become the standard treatment for patients with locally advanced rectal cancer.[15,16] The benefits of neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer undergoing total mesorectal excision have hastened interest in the use of neoadjuvant chemoradiotherapy before local excision for early-stage rectal cancer. Several retrospective case series,[17–19] and a single-institution prospective study,[20] have suggested that neoadjuvant chemoradiotherapy before local excision might result in local tumour control similar to that of total mesorectal excision for tumours of similar stages. However, these studies are limited by small sample size, variable clinical staging criteria, heterogeneous tumour characteristics, and varying neoadjuvant chemoradiotherapy regimens. Prospective data from large multicentre 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 neoadjuvant chemoradiotherapy before local excision to achieve organ preservation in patients with endorectal ultrasound-staged or endorectal coil magnetic resonance imaging (EC-MRI)-staged T2N0 rectal cancer located within 8 cm of the anal verge. Some secondary endpoints of this trial have already been reported.[21] Because of the longer follow-up to investigate the primary endpoints of all patients enrolled, we now report the primary endpoints of tumour recurrence and survival at 3 years, and anorectal function and quality of life at 1 year.

Methods

Study design and participants

The study design has been reported previously.[21] ACOSOG Z6041 was a phase 2, single-group, non-randomised, open-label trial done at 26 ACOSOG institutions. Patients with clinical T2N0 rectal adenocarcinoma staged by endorectal ultrasound or EC-MRI, measuring smaller than 4 cm in greatest diameter, involving less than 40% of the circumference of the rectum, and located within 8 cm of the anal verge,

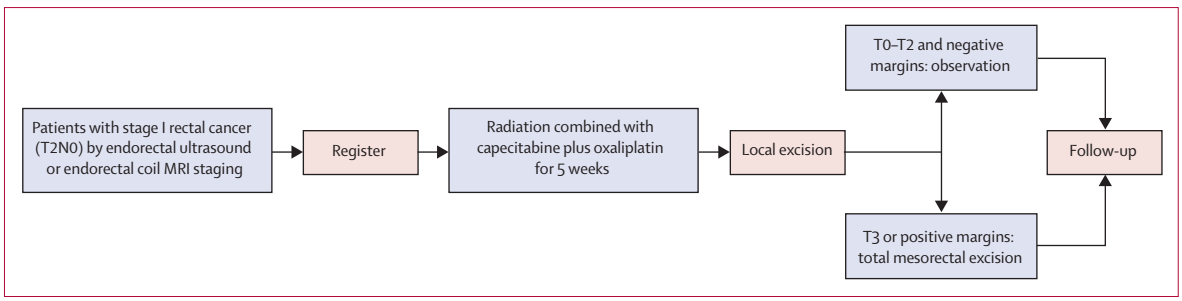

Figure 1: **ACOSOG Z6041 trial protocol overview**

and an Eastern Cooperative Oncology Group performance status of 2 or lower were included in the study. Patients meeting the study's eligibility criteria were recruited at the participating institution, and each patient (or patient representative) provided written informed consent. All patients underwent complete colonoscopy, rigid proctoscopy, digital rectal exam, abdominal and pelvic CT, and chest radiography or chest CT. Patients with tumours judged to be fixed to adjacent structures upon having a digital rectal examination were ineligible. The study was approved by the institutional review boards at all participating institutions.

Procedures

Figure 1 shows a schematic of the trial protocol. External beam radiotherapy 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. The original dose of radiotherapy was 1·8 Gy per day, 5 days a week for 5 weeks to a dose of 45 Gy to planning target volume 1, then a boost of 9 Gy to planning target volume 2 (defined as the gross tumour volume plus 2 cm) for a total dose of 54 Gy. This was accompanied by capecitabine (825 mg/m², twice daily, on days 1–14 and 22–35) and oxaliplatin (50 mg/m² on weeks 1, 2, 4, and 5). The original dose of neoadjuvant chemoradiotherapy was found to have unfavourable toxic effects, which led to a revised dose regimen after 53 patients had been recruited and the protocol was amended accordingly. The radiotherapy was reduced to a total of 50·4 Gy by reducing the 9 Gy boost to 5·4 Gy, and capecitabine was reduced to 725 mg/m², twice daily, 5 days a week for 5 weeks. The dose of oxaliplatin was not changed.

Surgery was done 4–8 weeks after completion of neoadjuvant chemoradiotherapy. Local excision was done using conventional transanal excision or transanal endoscopic microsurgery. Full-thickness excision of the tumour with a 1 cm surrounding margin of normal rectal wall was needed. All participating surgeons were required to have done at least three local excisions with negative margins, and completed a skills verification programme.

Staging of surgical specimens was done according to American Joint Committee on Cancer criteria. Specimens without evidence of dysplastic epithelium or invasive cancer were classified as having pathological complete response. Specimens with dysplastic epithelium at the original tumour site, but without evidence of invasion, were staged as ypTis (carcinoma in situ), rather than pathological complete response.

Patients received an initial postoperative exam 1 month after surgery. digital rectal exam, proctoscopy, and endorectal ultrasound were given every 4 months for 3 years, and every 6 months for the next 2 years.

	Original dose group (n=53)	Revised dose group (n=26)	Overall (n=79)
Age (years)	62 (30–80)	63 (45–83)	62 (30–83)
Sex			
Male	33 (62%)	20 (77%)	53 (67%)
Female	20 (38%)	6 (23%)	26 (33%)
Ethnic origin			
White	47 (89%)	25 (96%)	72 (91%)
African American	2 (4%)	0	2 (3%)
Native Hawaiian or Pacific Islander	1 (2%)	0	1 (1%)
Asian	1 (2%)	1 (4%)	2 (3%)
American Indian or Alaska native	1 (2%)	0	1 (1%)
Unknown	1 (2%)	0	1 (1%)
ECOG/Zubrod performance status			
0	47 (89%)	20 (77%)	67 (85%)
1	5 (9%)	5 (19%)	10 (13%)
2	1 (2%)	0	1 (1%)
Missing	0	1 (4%)	1 (1%)
Tumour size (cm)	2·8 (0·8)	2·9 (0·7)	2·8 (0·8)
Tumour location			
Anterior	11 (21%)	4 (15%)	15 (19%)
Posterior	29 (55%)	10 (38%)	39 (49%)
Left lateral	10 (19%)	7 (27%)	17 (22%)
Right lateral	3 (6%)	4 (15%)	7 (9%)
Missing	0	1 (4%)	1 (1%)
Distance from distal anal verge (cm)	4·88 (1·91)	5·30 (2·05)	5·02 (1·95)

Data are median (range), n (%), or mean (SD). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

Colonoscopy was needed at 3 years. Other tests for local recurrence or distant metastasis were done if indicated.

Outcomes

The primary endpoint was 3-year disease-free survival. Evidence of local recurrence, distant metastasis, or death from any cause within 3 years counted as events in the time-to-event Kaplan-Meier analysis[22] of disease-free survival.

Secondary endpoints were the proportion of patients having negative resection margins after local recurrence, the proportion of patients with a pathological complete response, the procedure-specific morbidity and mortality after neoadjuvant chemoradiotherapy and local excision, the effect of neoadjuvant chemoradiotherapy followed by local excision on anorectal function and quality of life, and overall survival.

We assessed anorectal function and quality of life at the time of enrolment and 12 months after surgery using the Fecal Incontinence Severity Index (FISI)[23] and the Functional Assessment of Cancer Therapy-Colorectal (FACT-C)[24] 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 consists of five subscales: four measuring concerns related to general health-related quality of life (physical wellbeing, social or family wellbeing, emotional wellbeing, and functional wellbeing) and one subscale measuring concerns related specifically to colorectal cancer (the Colorectal Cancer Subscale). The FACT-C total score is the sum of all five subscales. A higher score represents improved quality of life and overall function.

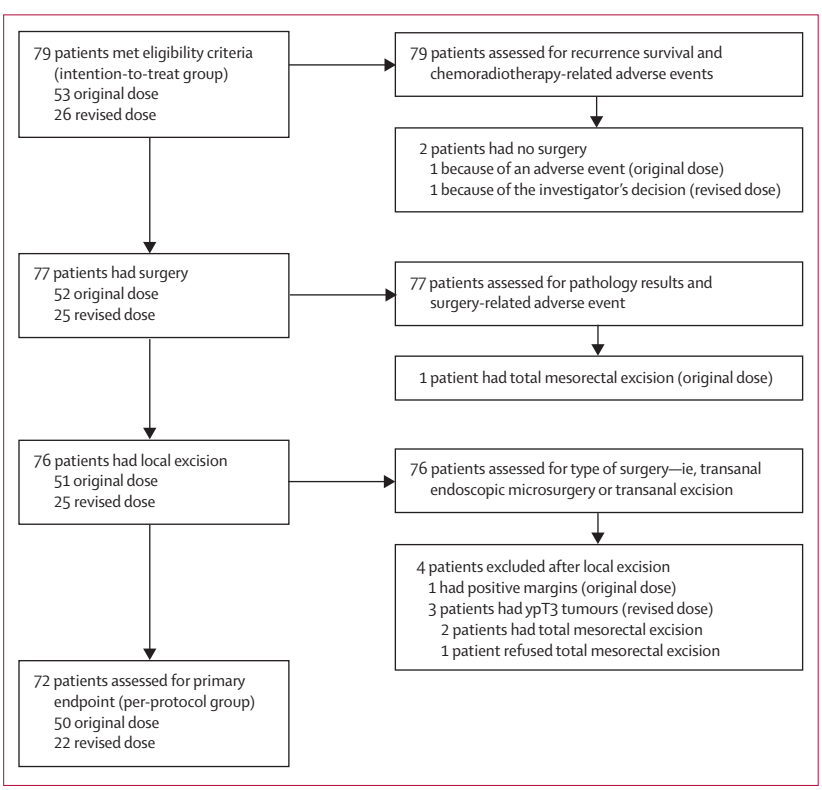

Figure 2: **Trial profile**
OD=original dose group. RD=revised dose group.

Statistical analysis

We calculated the estimated sample size using the per-protocol patient population based on the study by Steele and collegues[25] reporting an estimated 4-year disease-free probability of 80% and a 3-year disease-free rate of about 83% in patients with T2 rectal cancer treated with local excision followed by chemoradiotherapy. We estimated that a probability of at most 80% would be deemed unacceptably low, while a probability of at least 91% would be very promising from the clinical point of view. Assuming a significance level of 0·1, 70 assessable patients were needed to distinguish a null 3-year disease-free survival event rate of 80% from an alternative rate of 91% with 90% power. We estimated that up to 5% of patients would not tolerate neoadjuvant chemo-radiotherapy, up to 10% would exhibit pathological ypT3 tumours or positive resection margins, and up to 15% would not be assessable for the primary endpoint; therefore, we targeted a total accrual of 83 patients to ensure at least 70 assessable patients for per-protocol analyses. In addition to computation of 3-year disease-free survival, the survival profile of enrolled patients was summarised graphically over 5 years of follow-up using the Kaplan-Meier estimator. We analysed differences between grouped survival profiles using the log-rank test.[22] We used the Wilcoxon rank-sum test[26] and Fisher's exact test[27] to compare continuous and categorical variables between dose groups. All reported p values were based on two-sided tests; CIs assumed a significance of 0·05. We compared anorectal function and QoL at baseline, and 12 months after surgery using the Wilcoxon signed rank test.

We assessed 3-year disease-free survival in all protocol eligible patients (intention-to-treat population) and all patients that had neoadjuvant chemotherapy and local excision, and had ypT0, ypT1, or ypT2 tumours with negative margins (per-protocol population). We did post-hoc analyses comparing survival and safety outcomes in the original and revised dosage groups. All the analyses were done with SAS (version 9.2). Data was submitted to the ACOSOG statistical centre for statistical analysis.

This study 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. All authors participated in the data interpretation. The corresponding author had access to the analysed data, not the raw data, but had final responsibility for the decision to submit the manuscript.

Results

Between May 25, 2006, and Oct 22, 2009, 79 eligible patients were recruited to the trial and began neoadjuvant chemoradiotherapy. Baseline characteristics are shown in table 1. Patient disposition and analysis groups are shown in the trial profile (figure 2). Two patients did not have surgery. The pathological 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%) had ypT1 tumours, 24 (31%) had ypT2 tumours, three (4%) had ypT3 tumours, and one (1%) had a ypTx tumour. Because of toxic effects, one patient was unable to complete the full course of chemoradiotherapy. For this reason, the patient's treating surgeon did not believe that local excision would succeed, and opted for total mesorectal excision. Final pathological evaluation showed a T2N0 tumour.

The estimated 3-year disease-free survival for the intention-to-treat group was 88·2% (95% CI 81·3–95·8), and for the per-protocol group was 86·9% (79·3–95·3; figure 3). 3-year overall survival in the intention-to-treat group was 94·8% (89·9–100·0) and for the per-protocol group was 95·7% (91·1–100·0; figure 4). Five of the recurrences developed in patients receiving the original dose and three in patients receiving the revised dose. We also assessed 3-year disease-free survival and overall survival by original dose versus revised dose groups for the intention-to-treat group (appendix). Survival was higher for patients treated in the original group compared with the revised group, but the differences were not significant. We identified no differences in 3-year disease-free survival or overall survival between patients treated with transanal microscopic endosurgery and transanal excision (appendix).

Of 76 patients who had neoadjuvant chemotherapy and local excision, 29 (38%) had transanal endoscopic microsurgery and 47 (62%) had transanal excision. One patient had positive resection margins and underwent abdominoperineal resection, as specified 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 abdominoperineal resection within 6 weeks of local excision (figure 2). Neither abdominoperineal resection specimen indicated cancer; both patients were alive and without evidence of disease at 40 months and 47 months from local excision. The third patient refused abdominoperineal resection and developed pelvic recurrence. The remaining 72 patients underwent neoadjuvant chemoradiotherapy and local excision and had ypT0–2 and negative resection margins, comprising the per-protocol group.

The proportions of all patients having adverse events during neoadjuvant chemoradiotherapy and stratified by dose groups are presented in table 2 and 3. Surgery-related adverse effects are presented in table 4.

All patients have been followed-up for a median 56 months (IQR 46–63) after surgery, with no treatment-related deaths. Five patients died from non-cancer-related causes 8–38 months after surgery. At the end of follow-up, eight (10%) of 79 patients had developed recurrence: five (6%) of 79 had distant metastases and three (4%) of 79 had local recurrence as initial sites of failure. None of the patients had both distant metastases and local recurrence. The eight patients with recurrent tumours received salvage treatment and their tumour and survival status are reported at the end of follow-up (table 5). Two patients with local recurrence underwent salvage abdominoperineal resection, with negative margins. One patient whose abdominoperineal resection specimen showed tumour limited to the muscularis propria developed further pelvic recurrence and died of

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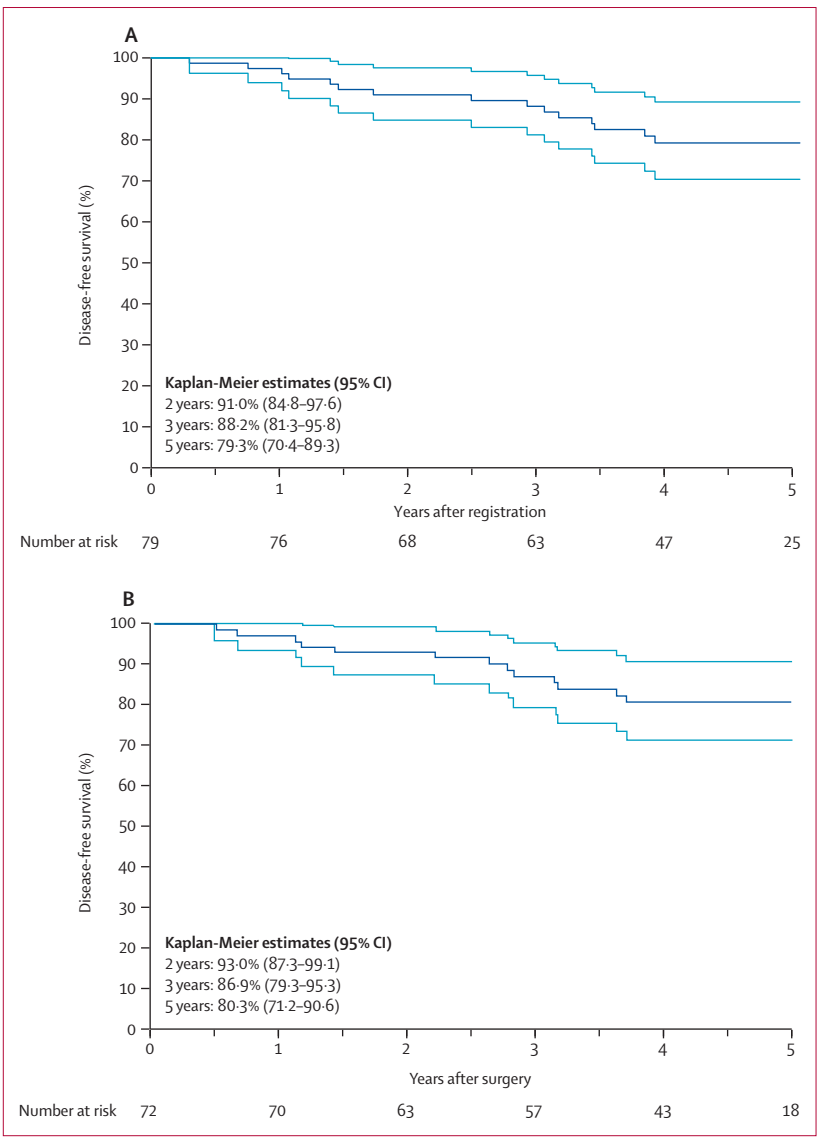

Figure 3: **Kaplan-Meier estimates of disease-free survival for the intention-to-treat group (A) and the per-protocol group (B)**
Light blue lines represent 95% CI.

disease 48 months after local excision. The second patient had carcinoma in situ in the abdominoperineal resection specimen, and remains alive and free of disease 48 months after local excision. One patient with a ypT3 tumour in the surgical specimen refused total mesorectal excision and developed local recurrence.

At the end of follow-up, 72 (91%) of 79 patients receiving neoadjuvant chemoradiotherapy had rectal preservation. 71 patients in the per-protocol group completed the baseline FISI and FACT-C questionnaires, but only 62 (87%) completed them 1 year after surgery. We identified no substantial deterioration in the overall FISI scores or any of the subscales 1 year after surgery, compared with baseline (table 6). We identified no difference in the overall FACT-C scores between baseline and 1-year assessments (table 6). However, we noted deterioration in the physical wellbeing subscale and an improvement in the emotional wellbeing subscales (table 6).

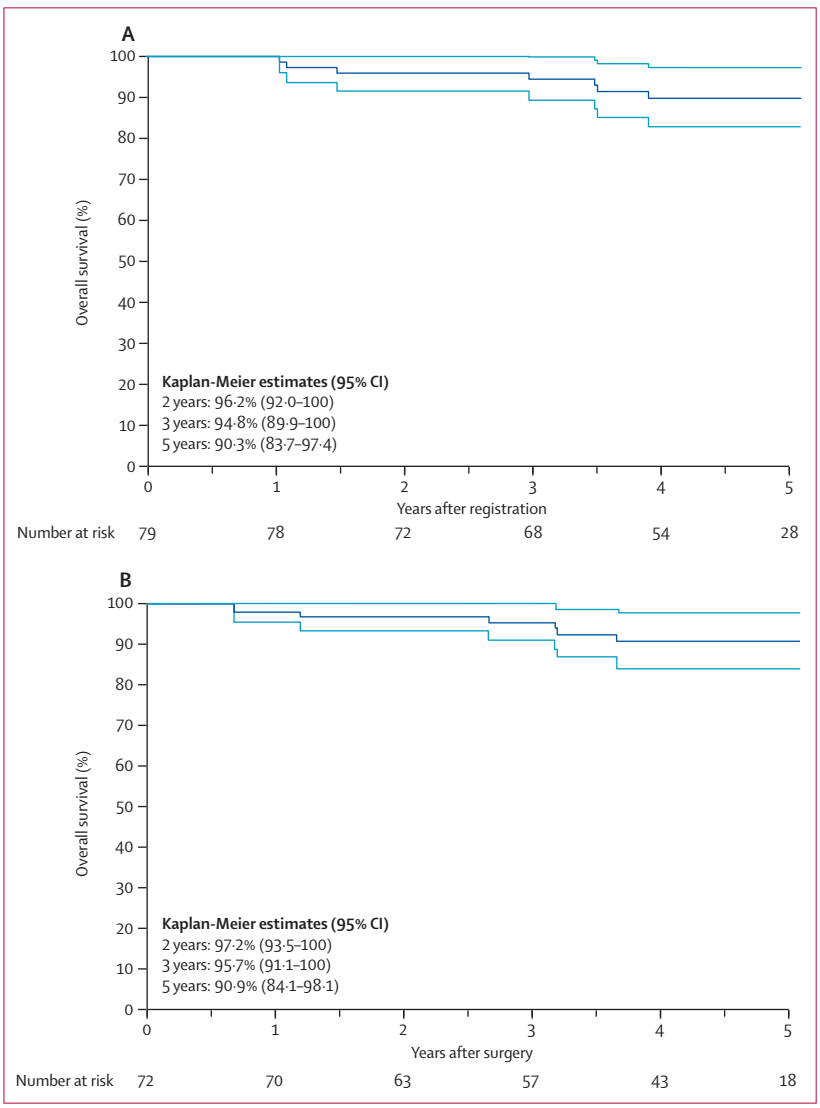

Figure 4: **Kaplan-Meier estimates of overall survival for the intention-to-treat group (A) and the per-protocol group (B)**
Light blue lines represent 95% CI.

Discussion

The results of this multi-institutional trial suggest that we were able to preserve the rectum of most patients with clinically staged T2N0 rectal cancer treated with neoadjuvant chemoradiotherapy and local excision. The local recurrence rate for all patients was 4% at the end of follow-up, and the estimated 3-year disease-free survival for the intention-to-treat and per-protocol groups were within the margin of efficacy defined in the study protocol, although lower than initially anticipated. However, the lower limit of the 95% CI of 3-years disease-free survival for the per-protocol group used for the sample size calculation reached the threshold for deeming it unacceptably low. Therefore, although the results are encouraging, the study did not achieve its goal with the strictly preset statistical variables. The results of this trial also showed that neoadjuvant chemoradiotherapy and local excision do not cause substantial changes in anorectal function and overall quality of life measured 1 year after surgery, compared with baseline. Furthermore, nearly half of the patients with clinically staged T2N0 treated with neoadjuvant chemoradiotherapy and local excision had pathological complete response, and only one in 76 had a positive resection margin.

The changes in neoadjuvant chemoradiotherapy introduced in response to the unexpectedly high toxic effects noted with the original neoadjuvant chemo-radiotherapy regimen resulted in a reduction in the proportion of patients achieving a pathological complete response and in 3-year disease-free survival. The results of phase 3 trials[28–30] show that adding oxaliplatin to a fluoropyrimidine as a radiosensitiser in patients with rectal cancer increases toxic effects without enhancing tumour response, compared with fluoropyrimidine alone. On the basis of this information, discontinuing oxaliplatin altogether might have been more effective in preventing toxic effects, 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 total mesorectal excision is the gold standard against which other surgical procedures should be compared.[1] The 3-year disease-free survival and overall survival in this trial are within the range of the rates reported for stage I tumours treated with either laparoscopic or open total mesorectal excision in the COLOR II trial.[31] However, the COLOR II trial did not stratify the results of patients with stage I disease by T staging categories. Retrospective case series[12] and a cohort study[13] from the National Cancer Database have reported 5-year local recurrence rates ranging from 6% to 15% for T2N0 rectal cancers treated with transabdominal resection alone,[12,13] higher than the

	Original dose group (n=53)			Revised dose group (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
Haematological	1 (2%)	4 (8%)	1 (2%)	11 (42%)	6 (23%)	1 (4%)	12 (15%)	10 (13%)	2 (3%)
Infectious or 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 or 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%)
Haemorrhage	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 or 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 2: **Adverse events during neoadjuvant chemoradiotherapy**

	Original dose group (n=53)			Revised dose group (n=26)			Overall (n=79)		
	No adverse events	1 adverse events	2 or more adverse events	No adverse events	1 adverse events	2 or more adverse events	No adverse events	1 adverse events	2 or more adverse events
Gastrointestinal	31 (58%)	12 (23%)	10 (19%)	3 (12%)	2 (8%)	21 (81%)	34 (43%)	14 (18%)	31 (39%)
Pain	42 (79%)	9 (17%)	2 (4%)	8 (31%)	6 (23%)	12 (46%)	50 (63%)	15 (19%)	14 (18%)
Dermatological	44 (83%)	8 (15%)	1 (2%)	17 (65%)	5 (19%)	4 (15%)	61 (77%)	13 (16%)	5 (6%)
Hematological	48 (91%)	4 (8%)	1 (2%)	9 (35%)	3 (12%)	14 (54%)	57 (72%)	7 (9%)	15 (19%)
Infectious or febrile neutropenia	50 (94%)	3 (6%)	0	24 (92%)	2 (8%)	0	74 (94%)	5 (6%)	0
Constitutional symptoms	45 (85%)	7 (13%)	1 (2%)	8 (31%)	9 (35%)	9 (35%)	53 (67%)	16 (20%)	10 (13%)
Metabolic or laboratory	52 (98%)	1 (2%)	0	15 (58%)	3 (12%)	8 (31%)	65 (82%)	4 (5%)	10 (13%)
Cardiovascular	51 (96%)	2 (4%)	0	20 (77%)	6 (23%)	0	71 (90%)	8 (10%)	0
Haemorrhage	52 (98%)	1 (2%)	0	21 (81%)	5 (19%)	0	73 (92%)	6 (8%)	0
Lymphatic	52 (98%)	1 (2%)	0	24 (92%)	2 (8%)	0	76 (96%)	3 (4%)	0
Neurological	49 (92%)	3 (6%)	1 (2%)	18 (69%)	2 (8%)	6 (23%)	67 (85%)	5 (6%)	7 (9%)
Coagulation	53 (100%)	0	0	24 (92%)	2 (8%)	0	77 (97%)	2 (3%)	0
Musculoskeletal	52 (98%)	1 (2%)	0	25 (96%)	1 (4%)	0	77 (97%)	2 (3%)	0
Renal or genitourinary	52 (98%)	1 (2%)	0	14 (54%)	10 (38%)	2 (8%)	66 (84%)	11 (14%)	2 (3%)
Hepatic	53 (100%)	0	0	18 (69%)	4 (15%)	4 (15%)	71 (90%)	4 (5%)	4 (5%)
Ocular or visual	53 (100%)	0	0	22 (85%)	3 (12%)	1 (4%)	75 (95%)	3 (4%)	1 (1%)
Pulmonary	51 (96%)	2 (4%)	0	25 (96%)	1 (4%)	0	76 (96%)	3 (4%)	0
Sexual or reproductive function	53 (100%)	0	0	23 (88%)	2 (8%)	1 (4%)	66 (84%)	11 (14%)	2 (3%)
Syndromes	53 (100%)	0	0	25 (96%)	1 (4%)	0	78 (99%)	1 (1%)	0
Endocrine	53 (100%)	0	0	25 (96%)	1 (4%)	0	78 (99%)	1 (1%)	0

Table 3: **Patients with adverse events during neoadjuvant chemoradiotherapy**

4% local recurrence rate in this study. Population-based analysis from the National Cancer Database and the Surveillance, Epidemiology and End Results (SEER) database have reported 5-year overall survival close to 76% for patients with T2N0 rectal cancer treated with transabdominal resection alone,[13] lower than the estimated 5-year overall survival reported 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 ACOSOG Z6041 trial had tumours located within 8 cm of the anal verge, whereas patients in the total mesorectal excision series[15,16] had tumours located anywhere in the rectum. As cancers located in the lower third of the rectum pose a higher risk of local recurrence than cancers in the mid and upper

	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
Haematological	0	1 (2%)	0	0	1 (4%)	0	0	2 (3%)	0
Haemorrhage	1 (2%)	1 (2%)	1 (2%)	4 (16%)	1 (4%)	0	5 (6%)	2 (3%)	1 (1%)
Infectious or 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: **Surgery-related adverse events for all eligible patients who underwent surgery**

	Tumour size at diagnosis (cm)	Distance from anal verge (cm)	Treatment dose	ypT tumour stage	Time to recurrence from local excision (months)	Additional treatment for recurring disease	Follow-up after local excision (months)	Survival status
Local	0·3	3·0	Original	ypT1	34	APR	42	Alive with disease
Local	3·0	5·0	Original	ypT3	6	Chemotherapy	58	Alive with disease
Local	3·4	8·0	Revised	ypT2	6	APR	48	Alive, NED
Liver	2·0	2·0	Revised	ypT1	14	Liver resection	55	Alive, NED
Lung	2·0	3·5	Original	ypT2	26	Lung resection	60	Alive, NED
Lung	2·9	6·0	Revised	ypT0	17	Lung resection	46	Alive, NED
Lung	3·0	6·0	Original	ypT0	33	Chemotherapy	55	Alive with disease
Uterus	3·0	3·0	Original	ypT0	45	Hysterectomy	63	Died from disease

APR=abdominoperineal resection. NED=no evidence of disease.

Table 5: **Characteristics of patients developing tumour recurrence by tumour recurrence location**

	Baseline (n=71)	12 months (n=62)	Mean absolute difference	p value*
FISI				
Overall	26·2 (16·7)	27·8 (17·1)	1·5 (19·4)	0·7382
Gas	7·8 (5·0)	7·9 (4·5)	−0·4 (5·4)	0·7322
Mucus	3·0 (4·1)	3·3 (4·1)	0·1 (5)	0·5831
Liquid stool	6·2 (6·9)	7·2 (6·4)	1·2 (6·9)	0·3876
Solid stool	9·5 (7·9)	9·8 (7·5)	0·6 (9·9)	0·7023
FACT-C				
Overall	112·2 (13·5)	109·3 (18·9)	−2·2 (16·5)	0·6843
Physical wellbeing	25·2 (3·8)	23·9 (4·7)	−1·2 (3·2)	0·0363
Social or family wellbeing	25·3 (3·5)	23·7 (5·2)	−1·5 (5·3)	0·0940
Emotional wellbeing	18·6 (3·9)	20·1 (3·5)	1·7 (3·7)	0·0285
Functional wellbeing	22·5 (4·7)	22·3 (5·7)	−0·1 (5·4)	0·8332
Colorectal cancer subscale	20·7 (3·1)	19·6 (3·8)	−0·8 (4·2)	0·1032

Data are mean (SD), unless otherwise indicated. *p values calculated based on results of the Wilcoxon signed-rank test.

Table 6: **Baseline and 12 month FISI and FACT-C scores**

rectum, a higher risk of recurrence should be expected in the ACOSOG Z6041 trial. On the other hand, the ACOSOG Z6041 trial was limited to tumours smaller than 4 cm in diameter, a selection criterion not applied in the transabdominal rectal resection series. Additionally, results for the ACOSOG Z6041 trial are reported by clinical stage, whereas results in the transabdominal resection series were reported by pathological stage. Both endorectal ultrasound and EC-MRI are known to overstage or understage some tumours.[32,33] Some of the ypT0, ypTis, or ypT1 tumours in this trial might have therefore been initially overstaged as T2 by endorectal ultrasound. Conversely, the ypT3 tumours in this trial might represent either tumour progression during neoadjuvant chemoradiotherapy, or understaging by endorectal ultrasound. Finally, local recurrence tends to occur later in patients treated with neoadjuvant chemoradiotherapy and surgery than in those treated with surgery alone.[15] In this study, all patients received neoadjuvant radiation compared with 59% in the COLOR II trial.[31] Therefore, more patients in the ACOSOG Z6041 trial are likely to develop tumour relapse with longer follow-up.

Proving equivalence in oncological efficacy between neoadjuvant chemotherapy plus local excision and total mesorectal excision for treatment of early rectal cancer would need a well-designed, randomised trial. In view of the good prognosis of stage I rectal cancer, the sample size needed will be large. Additionally, patients' acceptance of randomisation between local excision and total mesorectal excision is questionable. Therefore, completion of such a study would be challenging. Lezoche and colleagues[20] reported the results of a prospective single-institution trial comparing neoadjuvant chemoradiotherapy and local excision and transrectal partial mesorectal excision to neoadjuvant chemoradiotherapy and laparoscopic total

mesorectal excision 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. After 5 years of follow-up, 8% of patients in the local excision group and 6% in the total mesorectal excision group had developed local recurrence, rates not very different from those in this trial. Although underpowered to prove equivalence between neoadjuvant chemoradiotherapy plus local excision and neoadjuvant chemoradiotherapy plus total mesorectal excision in uT2uN0 rectal cancer, Lezoche's study also suggests that neoadjuvant chemoradiotherapy plus local excision might be an alternative to total mesorectal excision for patients with distal rectal cancer seeking organ-preserving treatment to avoid a permanent colostomy.

The justification for chemoradiotherapy and local excision as an alternative to total mesorectal excision in patients with early-stage rectal cancer is the possibility of achieving equivalent oncological results while preserving quality of life. The baseline FISI total score in our patients was equivalent to that reported in patients with low rectal cancer enrolled in a prospective trial[34] comparing functional outcomes after total mesorectal excision and different types of colorectal anastomosis. However, although in this study the FISI score remained essentially unaltered 1 year after chemoradiotherapy and local excision, patients treated with total mesorectal excision had a substantial deterioration in the FISI score at that timepoint, independent of the type of anastomosis.[34] In this study, the Functional Assessment of Colorectal Cancer Therapy (FACT-C) overall score and the colon cancer subscale subscale remained unchanged 1 year after surgery, compared with baseline. These findings are consistent with the results of the NSABP R04 trial[35] that also reported no substantial differences in the FACT-C scores (baseline *vs* 1 year after surgery) in patients with rectal cancer treated with neoadjuvant chemo-radiotherapy and total mesorectal excision.

The study has several important limitations. It was a single-group phase 2 trial, and the possibility of selecting younger and healthier patients with fewer comorbidities for neoadjuvant chemoradiotherapy and local excision cannot be excluded. The sample size for this study is small and the length of follow-up is short. Although most recurrences tend to arise in the first 3 years after treatment, neoadjuvant chemoradiotherapy delays the appearance of local recurrence and more patients might develop recurrence in the future. Finally, not all patients completed the 1-year FISI and FACT-C questionnaires, either because they died, developed recurrence, or simply did not return them. Therefore, our study might underestimate the real effect of neoadjuvant chemoradiotherapy and local excision on anorectal function and quality of life.

Overall, this study shows that rates of recurrence and survival between patients with stage I tumours treated with chemoradiotherapy and local excision alone are similar to the results of other studies patients treated with total mesorectal excision. Most patients treated with neoadjuvant chemoradiotherapy and local excision preserve the rectum with minimum deterioration in anorectal function and quality of life up to 1 year after local excision. Although follow-up is short, this study suggests that neoadjuvant chemoradiotherapy followed by local excision might be an alternative to transabdominal rectal resection for carefully selected patients with T2N0 distal rectal cancer.

Contributors

JG-A, PAC, JEM, DSM, CSJ, SCO, BGW, AP, SMM, RKP, and RB designed the study. JG-A, LAR, OSC, QS, XWC, and PBL collected and reviewed data. LAR, QS, and XWC did the statistical analysis and prepared survival curves. JG-A and OSC wrote the manuscript and prepared the figures and tables. All authors analysed and interpreted the data and revised the report.

Declaration of interests

PAC discloses honoraria from Richard Wolf Instruments. All other authors declare no competing interests.

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