original reports

Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR)

Jing Jin, MD[1,2]; Yuan Tang, MD[1]; Chen Hu, PhD[3]; Li-Ming Jiang, MD[4]; Jun Jiang, MD[4]; Ning Li, MD[1]; Wen-Yang Liu, MD[1]; Si-Lin Chen, MD[1]; Shuai Li, MD[5]; Ning-Ning Lu, MD[1]; Yong Cai, MD[5]; Yong-Heng Li, MD[5]; Yuan Zhu, MD[6]; Guang-Hui Cheng, MD[7]; Hong-Yan Zhang, MD[8]; Xin Wang, MD[9]; Su-Yu Zhu, MD[10]; Jun Wang, MD[11]; Gao-Feng Li, MD[12]; Jia-Lin Yang, MD[13]; Kuan Zhang, MD[14]; Yihebali Chi, MD[15]; Lin Yang, MD[15]; Hai-Tao Zhou, MD[16]; Ai-Ping Zhou, MD[15]; Shuang-Mei Zou, MD[17]; Hui Fang, MD[1]; Shu-Lian Wang, MD[1]; Hai-Zeng Zhang, MD[16]; Xi-Shan Wang, MD[16]; Li-Chun Wei, MD[18]; Wen-Ling Wang, MD[19]; Shi-Xin Liu, MD[20]; Yuan-Hong Gao MD[21]; and Ye-Xiong Li, MD[1]

abstract

PURPOSE To ascertain if preoperative short-term radiotherapy followed by chemotherapy is not inferior to a standard schedule of long-term chemoradiotherapy in patients with locally advanced rectal cancer.

MATERIALS AND METHODS Patients with distal or middle-third, clinical primary tumor stage 3-4 and/or regional lymph node–positive rectal cancer were randomly assigned (1:1) to short-term radiotherapy (25 Gy in five fractions over 1 week) followed by four cycles of chemotherapy (total neoadjuvant therapy [TNT]) or chemoradiotherapy (50 Gy in 25 fractions over 5 weeks, concurrently with capecitabine [chemoradiotherapy; CRT]). Total mesorectal excision was undertaken 6-8 weeks after preoperative treatment, with two additional cycles of CAPOX (intravenous oxaliplatin [130 mg/m^2, once a day] on day 1 and capecitabine [1,000 mg/m^2, twice a day] from days 1 to 14) in the TNT group and six cycles of CAPOX in the CRT group. The primary end point was 3-year disease-free survival (DFS).

RESULTS Between August 2015 and August 2018, a total of 599 patients were randomly assigned to receive TNT (n = 302) or CRT (n = 297). At a median follow-up of 35.0 months, 3-year DFS was 64.5% and 62.3% in TNT and CRT groups, respectively (hazard ratio, 0.883; one-sided 95% CI, not applicable to 1.11; $P < .001$ for noninferiority). There was no significant difference in metastasis-free survival or locoregional recurrence, but the TNT group had better 3-year overall survival than the CRT group (86.5% *v* 75.1%; $P = .033$). Treatment effects on DFS and overall survival were similar regardless of prognostic factors. The prevalence of acute grade III-V toxicities during preoperative treatment was 26.5% in the TNT group versus 12.6% in the CRT group ($P < .001$).

CONCLUSION Short-term radiotherapy with preoperative chemotherapy followed by surgery was efficacious with acceptable toxicity and could be used as an alternative to CRT for locally advanced rectal cancer.

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INTRODUCTION

Long-course concurrent chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is a first-line treatment for locally advanced rectal cancer (LARC).[1-3] Subsequential postoperative chemotherapy is controversial if significant improvement in overall survival (OS) is not achieved, probably because of its poor tolerance and compliance.[4-6] Usually, only approximately 50% of patients finish adjuvant chemotherapy after CRT and surgery.[4-6] Additionally, short-course radiotherapy (5 Gy in five fractions) followed by surgery is another treatment option for resectable rectal cancer.[7,8] Two randomized controlled trials (RCTs) showed comparable outcomes between preoperative short-course radiotherapy and long-course CRT in terms of OS, disease-free survival (DFS), local control, and late toxicity.[9,10] Those results motivated investigators to transfer postoperative chemotherapy to preoperative radiotherapy to improve the compliance and completion rate of chemotherapy, enhance the treatment intensity, and provide potential survival benefit in LARC.[11-13]

Phase II studies have shown a higher pathological complete response (pCR) rate after addition of preoperative chemotherapy to CRT.[12,13] Recently, a phase III trial (PRODIGE 23) demonstrated that neoadjuvant chemotherapy before CRT improved DFS significantly and showed better tolerance and compliance compared with adjuvant chemotherapy.[14] An early Polish II RCT demonstrated that short-course radiotherapy followed by chemotherapy and surgery for LARC resulted in

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The optimal neoadjuvant treatment strategy for locally advanced rectal cancer is still being explored and refined. One option includes a total neoadjuvant therapy (TNT) strategy comprising hypofractionated radiation (5 Gy × 5) followed by chemotherapy. The STELLAR trial evaluated whether this TNT approach is noninferior to standard chemoradiotherapy (CRT) in this patient population.

Knowledge Generated

This study demonstrates noninferiority for the primary end point, 3-year disease-free survival, in patients receiving TNT versus standard CRT (64.5% *v* 62.3%, respectively; $P < .001$ for noninferiority). Although the compliance rate was high, TNT was associated with an approximately twofold rate of grade 3-plus toxicity compared with CRT (26.5% *v* 12.6%; $P < .001$).

Relevance

This finding provides additional evidence supporting the clinical practice of hypofractionated radiotherapy followed by neoadjuvant chemotherapy for locally advanced rectal cancer.

improved OS and lower acute toxicity, compared with long-course CRT.[15] Moreover, another recent RCT (RAPIDO) showed that short-course radiotherapy and neoadjuvant chemotherapy and surgery improved distant metastasis (DM)–free survival (MFS) significantly, but not OS or locoregional control.[16]

Given the potential advantage in the treatment strategy of total neoadjuvant therapy (TNT) and limited clinical prospective data in 2015,[12,15] we believed that short-term radiotherapy could improve the treatment efficiency and save medical resources, and neoadjuvant chemotherapy had the advantage of high completion. Hence, we designed a multicenter RCT to compare short-term radiotherapy plus neoadjuvant chemotherapy with CRT followed by surgery and adjuvant chemotherapy in LARC. We hypothesized that short-course radiotherapy followed by neoadjuvant chemotherapy may not be inferior to standard CRT in LARC, even if the patients would undergo slightly more but still acceptable toxicities. We reported the 3-year results of survivals, compliance, and toxicities.

MATERIALS AND METHODS

Eligibility Criteria

Patients age 18-70 years with Eastern Cooperative Oncology Group score 0-1, clinical primary tumor (cT) stage 3-4 and/or regional lymph node (N)–positivity without distant metastases, and rectal adenocarcinoma with tumor location in the distal or middle third of the rectum were randomly enrolled. Inclusion criteria were no previous anticancer treatments, white blood cell count $\geq 3.5 \times 10^9$/L, hemoglobin ≥ 100 g/L, platelet count $\geq 100 \times 10^9$/L, and creatinine $\leq 1.0\times$ the upper limit of normal. Patients with recurrent disease, a medical contraindication to the planned treatment or magnetic resonance imaging (MRI), or a second primary malignancy were excluded. Patients underwent MRI to determine the involvement of the mesorectal fascia (MRF) as the tumor distance of the MRF < 1 mm regardless of a primary tumor, metastatic lymph nodes, or MRI-extramural vascular invasion (EMVI). MRI-EMVI was defined as an intermediate signal intensity apparent within vessels, obvious irregular vessel contours, or nodular expansion of the vessel by a tumor.

Random Assignment and Stratification

STELLAR is a multicenter, open-label, randomized phase III study. STELLAR was designed by the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) in Beijing, China. Patients were enrolled from 16 hospitals in 11 provinces of China. All patients provided written informed consent. The protocol was approved by the local ethics committee and registered at ClinicalTrials.gov (identifier: NCT02533271). Random assignment was carried out by a computer-generated allocation with stratification by location, clinical stage, and MRF. We used a telephone call to an independent central trial office for assurance of blindness of random assignment. Treatment allocation was not be masked.

Patients were assigned to short-term radiotherapy followed by chemotherapy (TNT group) or long-term concurrent chemoradiotherapy (CRT group). The protocol design, random assignment, MRI, study quality of assurance and control (NCC2015XC-06), and treatment planning of radiotherapy were reviewed by the local ethics committee. All patients underwent pretreatment and post-treatment MRI assessment centrally and independently by three radiologists.

Work-Up

Pelvic MRI was required to identify T/N stage, status of MRF, and EMVI score appropriately. In addition, digital rectal examination, colonoscopy with biopsy, endorectal ultrasound (optional), chest computed tomography (CT),

liver MRI/CT, and biochemical examination with serum carcinoembryonic antigen were performed. The distance from the lower pole of the tumor to the anal verge was measured during colonoscopy. According to the results of colonoscopy, we defined the rectum segment 0-5 cm from anal edge as the distal rectum and 5.1-10 cm as the middle third of rectum. The serum/plasma at different stages of treatment and fresh tumor tissue before treatment were collected in each patient.

Treatment Procedure

The TNT group had short-term radiotherapy (5 Gy × 5) followed by four cycles of CAPOX (oxaliplatin 130 mg/m^2, once a day, on day 1 and capecitabine 1,000 mg/m^2, twice a day, from day 1 to day 14) at 7-14 days after completion of radiotherapy. The CRT group had 50 Gy in 25 fractions over 5 weeks, concurrently with capecitabine (825 mg/m^2, twice a day). Postoperative chemotherapy comprised two cycles of CAPOX in the TNT group or six cycles of CAPOX in the CRT group.

Patients received intensity-modulated radiation therapy (IMRT). The clinical target volume (CTV) included the primary tumor, regional lymph nodes, and pelvic regions at risk according to consensus reached by the Radiation Therapy Oncology Group and Roels.[17,18] The mesorectum, presacral space, internal iliac nodes, obturator nodes, and ischiorectal fossa were covered within the CTV, and if rectal tumor was staged T4b, external lilac nodes should be included. The superior border was defined as the sacral promontory. The inferior border was 2-3 cm distal to the lower pole of the tumor. Expansion of the CTV to the planning target volume was 0.5-1.0 cm, and 95% of the planning target volume was given the prescribed dose of 50 Gy. The quality assurance and control of radiotherapy were performed in all participating centers. The target delineation and radiotherapy plan of first five patients were sent to the quality control center office for verification, and thereafter, they were checked at each center.

Patients were re-evaluated with digital rectal examination, MRI of the pelvis, colonoscopy, endorectal ultrasound (optional), chest CT, and liver MRI/CT 5-6 weeks after preoperative therapy. The TME procedure was recommended in both groups 6-8 weeks after preoperative treatment. The protocol also allowed for a watch-and-wait strategy if patients achieved a clinical complete response (cCR), requested organ preservation, or refused radical surgery (nonoperative management). The cCR was defined according to the criteria set by Maas et al in 2011.[19]

Pathology

Pathology staging was provided by examination of the surgical specimen. The mesorectal surface (circumferential resection margin) was stained with India ink to make an assessment. The maximum distance of tumor invasion outside the muscularis propria was recorded, as well as the closest point of approach to the inked circumferential margin. Circumferential resection margin involvement was defined as tumor invasion $\leq$ 1 mm from the mesorectal surgical margin, and R1 resection as tumor in the surgical margin. The tumor was sampled to determine histology type, grade, direct tumor spread, perineural invasion, tumor deposits, and vascular invasion. Tumor regression grade was reported according to the classification system devised by Dworak et al.[20] A pCR was defined as the absence of tumor cells at the primary site and regional lymph nodes.

Follow-Up

Follow-up investigations were scheduled every 3 months during the first 2 years, then every 6 months for next 3 years, and annually thereafter. Evaluation comprised physical examination, blood tests, serum carcinoembryonic antigen level, and CT of the chest, abdomen, and pelvis. Acute adverse events were codified using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.[21] For those in which a watch-and-wait strategy was used, an intensive follow-up protocol was recommended.

End Points and Statistical Analyses

The primary end point was DFS, which was defined as the time from the date of random assignment to the first occurrence of locoregional failure, DM, second primary tumor, or death from any cause. The primary hypothesis was that DFS in the TNT group would not be inferior to that in the CRT group. After preoperative radiotherapy and surgery, the DFS rate fluctuates from 50% to 65%.[22-25] Assuming a 3-year DFS rate in the CRT group of 65%, we considered the 3-year DFS rate in the TNT group to be $\geq$ 54% (eg, a margin of 11% or equivalent, hazard ratio [HR] $<$ 1.43). Guarding against a 5% ineligibility rate or dropout rate, the accrual target was 600 patients, with the final analysis to occur after $\geq$ 194 DFS events to provide $\geq$ 80% power at a one-sided type 1 error of 0.05. The choices of type 1 error and power were made to provide an appropriate compromise between feasibility, timeliness, and statistical rigor of evidence generation.

The secondary end points were OS (time from random assignment to death because of any cause), MFS (time from random assignment to first distant metastases at any time or death because of any cause), locoregional recurrence (LRR, time from random assignment to LRR at any time), and surgical complications,[26] with toxicities and completion rate related to protocol treatment. There was an interim analysis to assess toxicity and surgical complications if the first 100 patients received TME. Rates of radical resection and CR (pCR + sustained cCR) to preoperative treatment were evaluated. Postoperative complications were defined as those occurring within the first 30 days after surgery.

Survivals were summarized using the Kaplan-Meier method and analyzed using the log-rank test and Cox regression model. LRR was analyzed using competing risks methods where death without locoregional recurrence was a competing risk, summarized with cumulative incidences,

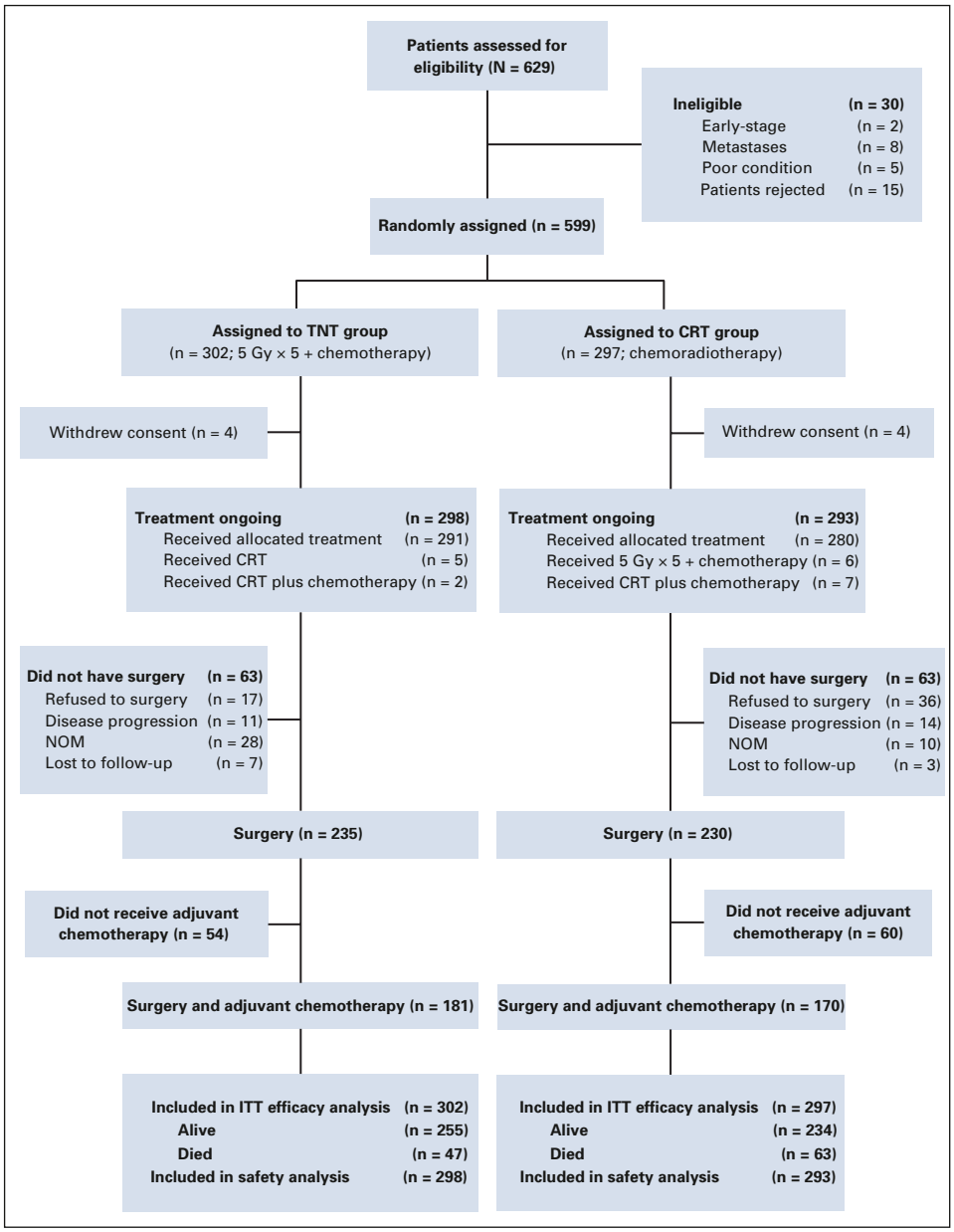

FIG 1. CONSORT diagram. TNT group: short-term radiotherapy (5 Gy × 5) followed by four cycles of CAPOX, surgery, and two cycles of CAPOX. CRT group: 50 Gy in 25 fractions over 5 weeks concurrently with capecitabine followed by surgery and six cycles of CAPOX. Disease progression included any locoregional progression, recurrence or regrowth, and/or distant metastases. CRT, chemoradiotherapy; ITT, intention-to-treat; NOM, nonoperative management; TNT, total neoadjuvant therapy.

and compared with the log-rank test.[27] Toxicities and treatment completion were summarized with the frequency and compared using chi-square or Fisher's exact tests. According to the study design, noninferiority in DFS was claimed if the upper bound of the 95% CI of HR was equal to or less than the prespecified margin (HR = 1.43). The primary end point DFS was also reported at a one-sided significance level of 0.05 using the log-rank test, along with a 95% CI of HR. All other statistical tests were carried out at a two-sided significance level of 0.05, and estimate uncertainties were based on 95% CIs. All analyses were conducted using R 4.0.1.2.10 (R Institute for Statistical Computing, Vienna, Austria).

RESULTS

Accrual and Clinical Characteristics

From August 30, 2015, to August 27, 2018, a total of 629 patients entered screening, of whom 599 were enrolled in this study (Fig 1). Of these, 302 patients were assigned to

the TNT group and 297 patients to the CRT group. After random assignment, four patients in each group withdrew consent, and a total of 591 patients received protocol treatment. Pretreatment clinical characteristics were well balanced between groups (Table 1).

Treatment Compliance and Toxicity

All patients in the TNT group completed radiotherapy (5 Gy × 5) without dose reduction; only a few patients in the CRT group experienced dose reduction (1.4%) or interruption of radiotherapy (2.4%). In the CRT group, 4 (1.4%) and 20 (7.8%) patients decreased radiation dose and chemotherapy dose, respectively. The completion rate (reduced radiotherapy or chemotherapy doses, or delayed completion) and full-dose completion rates (completion of all radiotherapy and chemotherapy cycles) of preoperative treatment were 82.6% versus 95.2% ($P < .001$) and 74.8% versus 93.2% ($P < .001$) in the TNT and CRT groups, respectively. The prevalence of acute grade III-V toxicities during preoperative treatments was 26.5% in the TNT group versus 12.6% in the CRT group ($P < .001$). The most common grade 3-4 acute toxicity was hematologic, with 15.8% in the TNT group versus 2.0% in the CRT group ($P < .001$; Table 2). Further study will report the late adverse toxicities and quality of life.

TABLE 1. Baseline Characteristics of 599 ITT Patients

Characteristic	TNT Group	CRT Group
Total No. of patients (ITT)	302	297
Age, years		
Median (range)	55 (20-74)	56 (27-70)
Sex		
Male	218 (72.2)	208 (70.0)
Female	84 (27.8)	89 (30.0)
ECOG score		
0	259 (85.8)	254 (85.5)
1	43 (14.2)	43 (14.5)
MRI T stage		
cT2	7 (2.3)	9 (3.0)
cT3	247 (81.8)	250 (84.2)
cT3a–b	152 (50.3)	147 (49.5)
cT3c–d	95 (31.5)	103 (34.7)
cT4	48 (15.9)	38 (12.8)
cT4a	30 (9.9)	11 (3.7)
cT4b	18 (6.0)	27 (9.1)
MRI N stage		
cN0	43 (14.2)	49 (16.5)
cN1	154 (51.0)	147 (49.5)
cN2	105 (34.8)	101 (34.0)
Clinical stage		
II	43 (14.2)	49 (16.5)
III	259 (85.8)	248 (83.5)
Distance to anal verge, cm		
≤ 5	147 (48.7)	148 (49.8)
5.1-10	153 (50.1)	149 (50.2)
> 10	2 (0.7)	0 (0)
MRF involvement	170 (56.3)	167 (56.2)
EMVI	162 (53.4)	125 (42.1)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: c, clinical; CRT, chemoradiotherapy; EMVI, extramural vascular invasion; ITT, intention-to-treat; MRF, mesorectal fascia; MRI, magnetic resonance imaging; N, regional lymph node; T, primary tumor; TNT, total neoadjuvant therapy.

Of 591 patients who underwent re-evaluation with MRI, colonoscopy, and digital rectal examination after neoadjuvant therapy, 33 of 298 patients (11.1%) in the TNT group and 13 of 293 (4.4%) in the CRT group achieved cCR, regardless of watch-and-wait or surgery. Moreover, 28 patients (9.4%) in the TNT group and 10 patients (3.4%) in the CRT group achieved cCR after preoperative treatment and did not undergo further surgery. For the latter patients, two (7.1%) patients in the TNT group and one (10.0%) in the CRT group occurred regrowth. Another 53 patients (17 in the TNT group and 36 in the CRT group) who did not achieve cCR refused a surgical procedure because of personal reasons. One patient in the CRT group died of myocardial infarction a few days after CRT completion. Twenty-five patients (11 in the TNT group and 14 in the CRT group) experienced DM before planned surgery. Finally, 235 patients in the TNT group and 230 patients in the CRT group received primary tumor resection (Fig 1). The median time from the start of radiotherapy or end of neoadjuvant therapy to surgery was 21 (range: 4-64) weeks and 6 (range: 3-32) weeks in the TNT group, and 14 (range: 10-57) weeks and 9 (range: 5-36) weeks in the CRT group, respectively. The median duration of hospital stay after surgery was 8 (range: 2-58) days in the TNT group and 8 (range: 3-55) days in the CRT group. On the basis of the Dindo's classification,[26] the prevalence of grade III+ surgical complications was similar between the two groups (TNT group, 14.0% *v* CRT group, 15.7%; $P = .625$). Delayed (> 1 month) wound healing was the predominant complication without any postoperative deaths within 30 days.

Among the 465 patients who completed surgery, 54 of 235 patients (23.0%) in the TNT group and 60 of 230 patients (26.1%) in the CRT group did not undergo adjuvant chemotherapy. Of patients who received adjuvant chemotherapy (n = 351), 108 patients (60.0%) in the TNT group and 82 patients (48.3%; $P = .009$) in the CRT group completed planned cycles of adjuvant chemotherapy. The incidence of grade III-IV toxicities with adjuvant chemotherapy was 3.3% in the TNT group compared with 11.8% ($P = .003$) in the CRT group.

TABLE 2. Acute Toxicity of TNT and CRT Groups During Preoperative Treatment

Adverse Event	TNT Group	CRT Group	*P*
No. of patients (ITT)	298	293	
Hematologic			
Grade 1-2	243 (81.5)	68 (23.2)	< .001
Grade 3-4	47 (15.8)	6 (2.0)	
Leukopenia			
Grade 1-2	240 (80.5)	36 (12.2)	.01
Grade 3-4	17 (5.7)	5 (1.7)	
Thrombocytopenia			
Grade 1-2	45 (15.1)	2 (0.7)	< .001
Grade 3-4	33 (11.1)	2 (0.7)	
Neutropenia			
Grade 1-2	210 (70.5)	31 (10.6)	.573
Grade 3-4	2 (0.7)	1 (0.3)	
Anemia			
Grade 1-2	10 (3.4)	8 (2.7)	.573
Grade 3-4	2 (0.7)	1 (0.3)	
GI			
Grade 1-2	170 (57.0)	206 (70.3)	.223
Grade 3-4	31 (10.4)	22 (7.5)	
Proctitis			
Grade 1-2	87 (29.2)	205 (70.0)	.307
Grade 3-4	14 (4.7)	9 (3.1)	
Diarrhea			
Grade 1-2	38 (12.8)	27 (9.2)	.398
Grade 3-4	19 (6.4)	14 (4.8)	
Nausea			
Grade 1-2	34 (11.4)	1 (0.3)	.573
Grade 3-4	2 (0.7)	1 (0.3)	
Vomiting			
Grade 1-2	24 (8.1)	0 (0)	.160
Grade 3-4	2 (0.7)	0 (0)	
Radiation dermatitis			
Grade 1-2	86 (28.9)	96 (32.8)	.640
Grade 3-4	2 (0.7)	3 (1.0)	
Liver dysfunction			
Grade 1-2	26 (8.7)	0 (0)	.085
Grade 3-4	3 (1.0)	0 (0)	

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: CRT, chemoradiotherapy; ITT, intention-to-treat; TNT, total neoadjuvant therapy.

Outcomes

Among the 465 patients who received surgery, 91.5% in the TNT group and 87.8% of patients in the CRT group underwent R0 resection ($P = .189$). Also, ypN0 was observed in 71.1% of cases in the TNT group versus 68.7% in the CRT group ($P = .578$); for details, see Appendix Table A1 (online only). The total rate of pCR and sustained cCR in the TNT group was 21.8%, which was significantly higher than that in the CRT group (12.3%, $P = .002$).

The median duration of follow-up was 35.0 (range, 8.3-63.9) months. In the ITT population (n = 599), locoregional recurrence (LRR), metastasis, or death as a result of any cause was observed in 202 patients (99 in the TNT group and 103 in the CRT group); for details, see Appendix Table A2 (online only). Three-year DFS was 64.5% (95% CI, 58.3 to 70.7) in the TNT group compared with 62.3% (95% CI, 56.1 to 68.5) in the CRT group. The HR for DFS between the two groups was 0.883 (one-sided 95% CI, not applicable to 1.11), with a one-sided noninferiority $P < .001$ (Fig 2A). The 95% upper bound of HR was below the prespecified noninferiority (NI) margin of 1.43, so the noninferiority hypothesis was confirmed.

One-hundred seven patients died of rectal cancer (47 in the TNT group and 60 in the CRT group); three patients in the CRT group died of a secondary malignancy. In the CRT group, three patients died of heart disease, liver metastasis, or unknown cause during the interval between radiation and surgery. In the TNT group, three patients died of liver metastasis (n = 2) or unknown cause (n = 1) during the interval between radiation and surgery. Three-year OS was 86.5% (95% CI, 82.1 to 90.8) in the TNT group compared with 75.1% (95% CI, 69.4 to 80.8) in the CRT group (HR = 0.67, 95% CI, 0.46 to 0.97; log-rank, $P = .033$; Fig 2B). There was no significant difference in MFS or LRR between the groups. Three-year MFS was 77.1% (95% CI, 71.7 to 82.6) in the TNT group and 75.3% (95% CI, 70.0 to 80.7) in the CRT group (log-rank, $P = .475$; Fig 2C). The 3-year LRR rate was 8.4% (95% CI, 4.6 to 12.2) in the TNT group and 11.0% (95% CI, 6.5 to 15.5) in the CRT group (log-rank, $P = .461$; Fig 2D). Subgroup analysis showed that the treatment effects on OS and PFS were similar regardless of clinicopathologic prognostic factors (Fig 3).

DISCUSSION

In this STELLAR study, short-course radiotherapy (5 Gy × 5) with preoperative chemotherapy before TME was not inferior to standard preoperative CRT followed by postoperative chemotherapy with regard to DFS for patients with LARC. There was no significant difference in MFS or LRR between treatment groups. Although a better 3-year OS rate was observed in the TNT group, there was no significant difference in OS upon subgroup analysis. Treatment strategy with TNT offered at least as favorable locoregional control and survival as CRT while preserving a high degree of tolerability and compliance. This finding provides additional evidence supporting the clinical practice of TNT in the modern era.

Treatment of LARC has evolved with introduction of neoadjuvant chemotherapy and radiotherapy before TME. The STELLAR study from China is the third RCT comparing

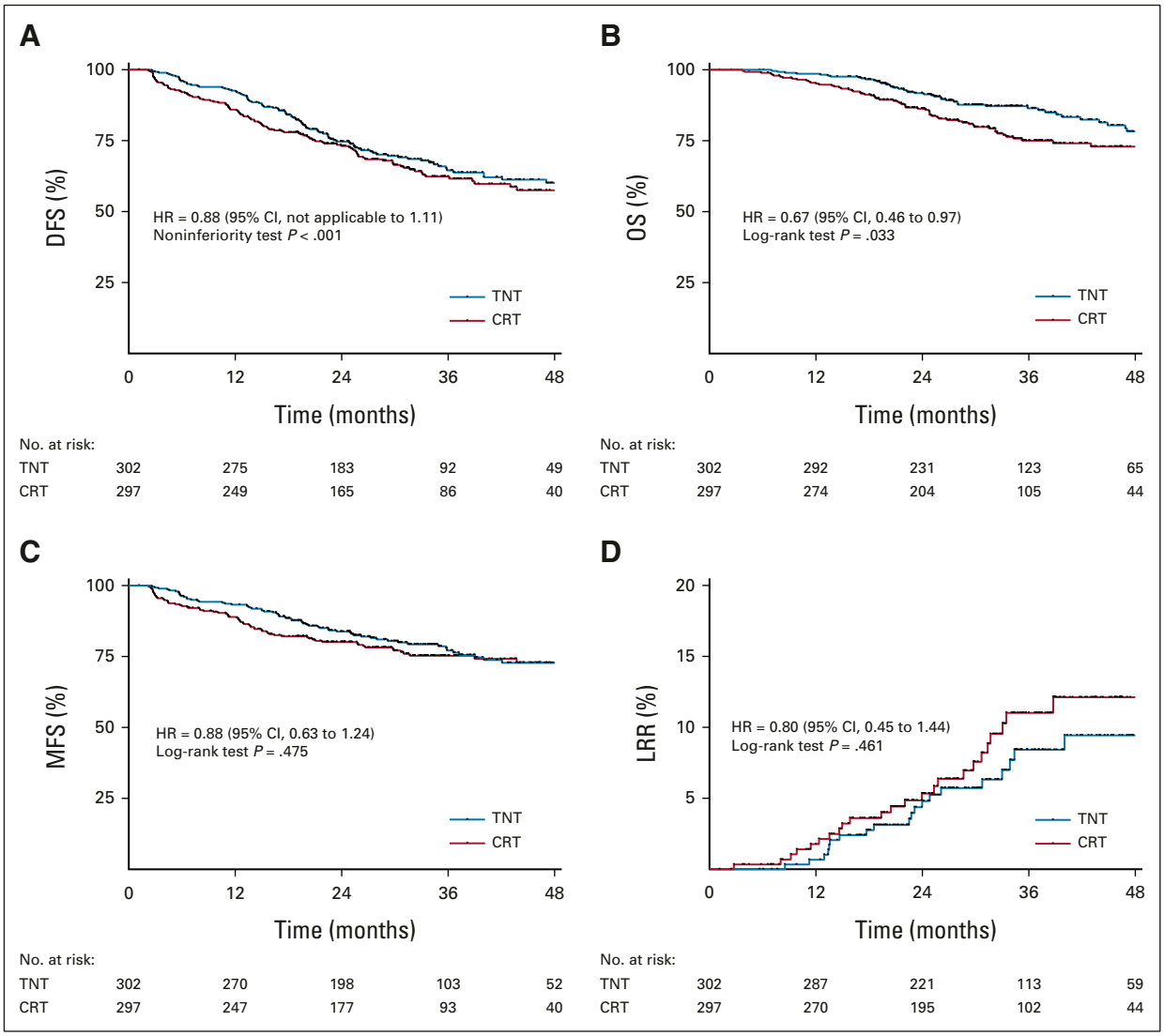

FIG 2. Kaplan-Meier curves of (A) DFS, (B) OS, (C) MFS, and (D) LRR in patients with LARC. TNT group: short-term radiotherapy (5 Gy × 5) followed by four cycles of CAPOX, surgery, and two cycles of CAPOX. CRT group: 50 Gy in 25 fractions over 5 weeks concurrently with capecitabine followed by surgery and six cycles of CAPOX. CRT, chemoradiotherapy; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; LARC, locally advanced rectal cancer; LRR, locoregional recurrence; MFS, metastasis-free survival; OS, overall survival; TNT, total neoadjuvant therapy.

short-course radiotherapy and neoadjuvant chemotherapy with standard CRT in patients with LARC (Table 3).[15,16] In contrast to our study, the Polish II trial did not require adjuvant chemotherapy.[15] Another RCT (PRODIGE 23) focused mainly on the comparison of preoperative chemotherapy with postoperative chemotherapy in the setting of long-course CRT.[14] Consistent with the Polish II trial,[15] we demonstrated that TNT and CRT resulted in similar 3-year DFS and LRR rates. Although RAPIDO and PRODIGE-23 trials reported a significant decrease in 3-year DM with TNT,[14,16] Polish II and STELLAR trials did not.[15,28] The reported 3-year DM in these RCTs ranged from 20% to 30% with oxaliplatin-based chemotherapy,[15,16] indicating the need for more efficacious or intensified systematic therapy.[14] All except one RCT presented similar LRR rates (approximately 10%) in patients with LARC; the 3-year LRR rates of 8.4% with TNT and 11.0% with CRT in the STELLAR trial were similar to those in RAPIDO and PRODIGE 23 trials (4%-8.3%),[14,16] but lower than those in the Polish II trial (21%-22%).[15] Similar to the Polish II trial,[15] we observed improved 3-year OS with TNT versus CRT, but OS benefit disappeared in the Polish II trial after a long-term follow-up at 8 years.[28] Therefore, longer follow-up at 5-10 years is needed to document the long-term effect of TNT on clinical outcomes, especially OS. The difference in LRR and survival between these RCTs may be explained by the heterogeneity of clinical features (Table 3).[14-16] The Polish II trial mainly involved patients with unresectable fixed cT3 or

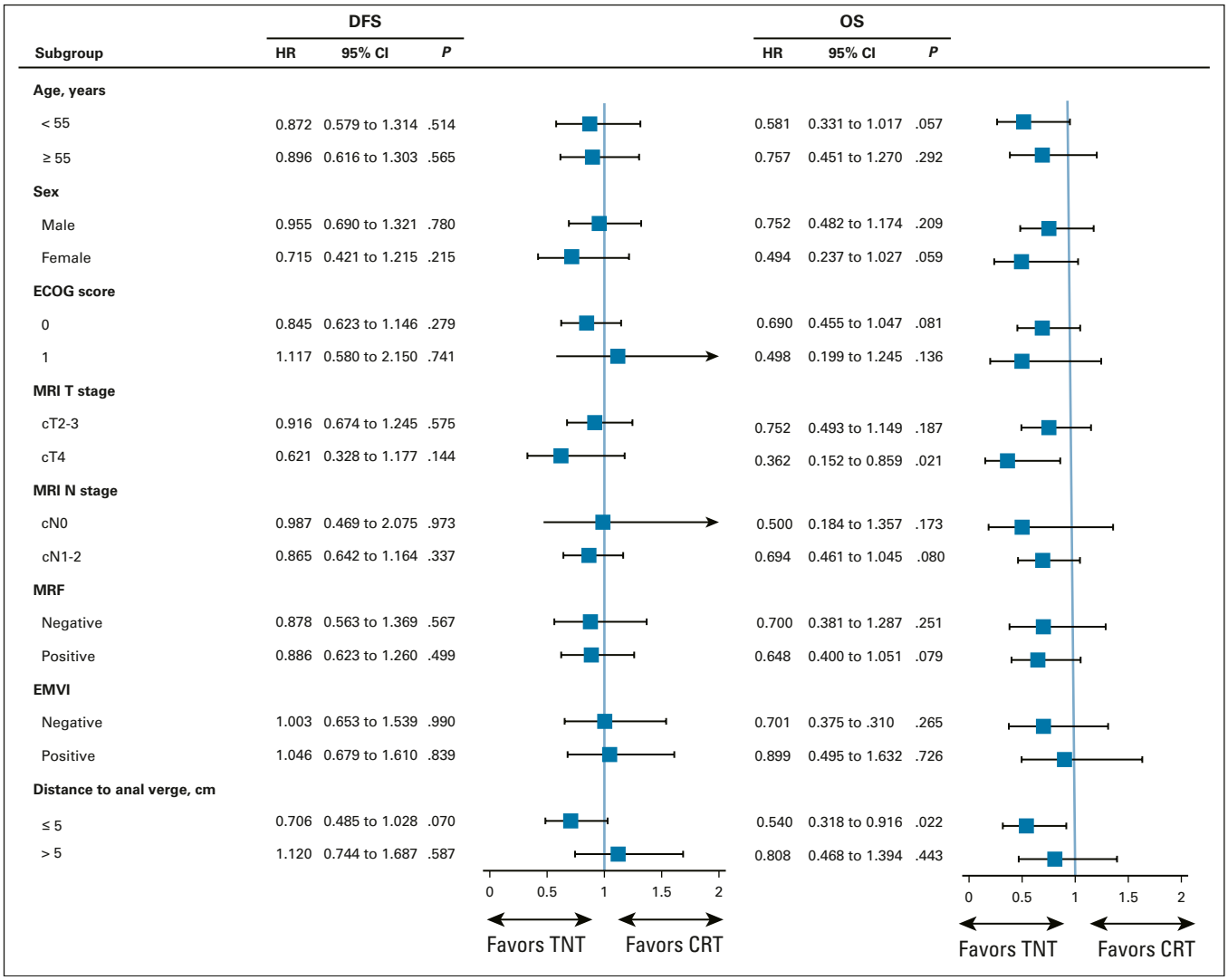

FIG 3. HRs for DFS and OS of TNT versus CRT in subgroup analysis. TNT group: short-term radiotherapy (5 Gy × 5) followed by four cycles of CAPOX, surgery, and two cycles of CAPOX. CRT group: 50 Gy in 25 fractions over 5 weeks concurrently with capecitabine followed by surgery and six cycles of CAPOX. c, clinical; CRT, chemoradiotherapy; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EMVI, extramural vascular venous invasion; HR, hazard ratio; MRF, mesorectal fascia; MRI, magnetic resonance imaging; N, regional lymph node; OS, overall survival; T, primary tumor; TNT, total neoadjuvant therapy.

T4 lesions and presented with more advanced T-stage disease than that of the other three RCTs.[15] STELLAR and Polish II studies included only those with middle and low rectal cancer,[14] whereas RAPIDO and PRODIGE 23 also included patients with upper rectal cancer.[14,16]

We demonstrated that patients receiving short-course radiotherapy followed by four cycles of CAPOX were well-tolerated, with a compliance rate of 82.6%, but had a higher prevalence of grade ≥ 3 toxicity (26.5% *v* 12.6%) than those receiving CRT. Similarly, other RCTs demonstrated favorable compliance (approximately 85%), but higher severe toxicities with neoadjuvant chemotherapy and radiotherapy than that observed for CRT alone (Table 3).[14-16] The toxicity profile between RCTs varied depending on the heterogeneity of chemotherapy cycles and regimens in the neoadjuvant setting. Patients who received four cycles of neoadjuvant CAPOX chemotherapy in this study had a lower proportion of grade ≥ 3 toxicities (26.5%) than that of patients who received six cycles of CAPOX/infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in the RAPIDO trial[16] or FOLFIRINOX (approximately 47%) in the PRODIGE 23 trial,[14] but this proportion was similar for patients who received three cycles of neoadjuvant FOLFOX in the Polish II trial.[15] Emerging results from RCTs suggested that neoadjuvant chemotherapy with short-course radiotherapy or long-course CRT was at least or more efficacious and safe as adjuvant chemotherapy.

Our study had three main strengths. First, we used high-resolution MRI strictly as a standard assessment tool for staging to accurately define the extent of locoregional involvement. Second, consistent with other studies,[29-31] the

TABLE 3. Summary of Randomized Controlled Trials Comparing TNT and CRT Followed by Surgery in Patients With Locally Advanced Rectal Cancer

			Stage		TNT					Surgery	Postoperative	3-Year	3-Year	3-Year	3-Year
Study	Eligibility (total number)	Treatment Schedules	cT4, %	N+, %	RT	CRT	Regimen	Completion, %	≥ 3 Toxicity, %	% of ITT	Chemotherapy	DFS, %	OS, %	DM, %	LRR, %
STELLAR	cT3-4 or N+ (n = 599)	TNT: 298	15.9	84.8	5 Gy × 5f	—	4 CAPOX	82.6	26.5	77.8	2 CAPOX	64.5	86.5[a]	22.8	8.4
		CRT: 293	12.8	83.5	50 Gy/25f	CAP	—	95.2	12.6	77.4	6 CAPOX	62.3	75.1[a]	24.7	11.0
RAPIDO[16]	cT4 or N2/+	TNT: 462	32	91	5 Gy × 5f	—	8 CAPOX/12 FOLFOX	84.6	47.6	92	—	23.7[b]	89.1	20.0[a]	8.3
	EMVI/MRF+ (n = 912)	CRT: 450	30	92	50 Gy/25f	CAP	—	90.0	24.7	89	8 CAPOX/12 FOLFOX	30.4[b]	88.8	26.8[a]	6.0
Polish II[15]	Fixed cT3, cT4 (n = 515)	TNT: 256	63	–	5 Gy × 5f	—	3 FOLFOX	72	24.2	84	—	53	73[a]	30	22
		CRT: 259	64		50 Gy/25f	CAPOX	—	64	23.5	81	—	52	65[a]	27	21
PRODIGE 23[14]	cT3-4 or N+ (n = 461)	TNT: 231	18	90	50 Gy/25f	CAP	6 FOLFIRINOX	89.6	46.9	92	6 mFOLFOX6/4 CAP	76[a]	91	17[a]	4
		CRT: 230	16	90	50 Gy/25f	CAP	—	98.7	35.6	95	12 mFOLFOX6/8 CAP	69[a]	88	25[a]	6

Abbreviations: c, clinical; CAP, capecitabine; CAPOX, capecitabine, oxaliplatin; CRT, chemoradiotherapy; DFS, disease-free survival; DM, distant metastasis; EMVI, extramural vascular invasion; FOLFIRINOX, oxaliplatin, irinotecan, leucovorin, fluorouracil; FOLOX, fluorouracil, oxaliplatin; ITT, intention-to-treat; LRR, locoregional recurrence; mFOLFOX6, modified FOLFOX6, oxaliplatin, leucovorin, fluorouracil or capecitabine; MRF, mesorectal fascia; N, regional lymph node; OS, overall survival; RT, radiotherapy; T, primary tumor; TNT, total neoadjuvant therapy.

[a]$P < .05$.

[b]Three-year disease-related treatment failure.

goal of hypofractionated radiotherapy for rectal cancer is to shorten the overall treatment time without compromising outcomes, which permits improved treatment efficiency.[32] Third, in contrast to other RCTs,[14-16] all patients in the STELLAR study received IMRT. The favorable locoregional control indicates the feasibility of routine use of IMRT for rectal cancer. Consistent with two recent RCTs,[14,16] we used capecitabine as concurrent chemoradiotherapy, which is not inferior to fluorouracil or oxaliplatin plus capecitabine or fluorouracil and is more convenient for patients.[33,34] The limitation of this study was that because of the limited follow-up, the benefit of long-term OS with TNT needs further follow-up. Furthermore, while we deliberately chose the NI margin to balance the feasibility and statistical rigor, in retrospect, a narrower NI margin, a larger sample size, or a longer follow-up may be considered had TNT were not this efficacious.

In conclusion, despite the higher acute toxicity, sequential neoadjuvant short-course radiotherapy and chemotherapy could be used as an alternative to CRT and adjuvant chemotherapy for patients with middle and low LARC.

AFFILIATIONS

[1]State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China
[2]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, CAMS and PUMC, Shenzhen, China
[3]Division of Biostatistics and Bioinformatics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD
[4]State Key Laboratory of Molecular Oncology and Department of Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, CAMS and PUMC, Beijing, China
[5]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiation Oncology, Peking University Cancer Hospital and Institute, Beijing, China
[6]Department of Radiation Oncology, The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, China
[7]Department of Radiation Oncology, China-Japan Union Hospital, Jilin University, Changchun, China
[8]Department of Radiation Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Anhui, China
[9]Department of Radiation Oncology, West China Hospital, Sichuan University, Chengdu, China
[10]Department of Radiation Oncology, Hunan Cancer Hospital and Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, China
[11]Department of Radiation Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China
[12]Department of Radiation Oncology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, CAMS, Beijing, China
[13]Department of Radiation Oncology, Sichuan Provincial Cancer Hospital, Chengdu, China
[14]Department of Radiation Oncology, Qinghai Red Cross Hospital, Qinghai, China
[15]State Key Laboratory of Molecular Oncology and Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, CAMS and PUMC, Beijing, China
[16]State Key Laboratory of Molecular Oncology and Department of Colorectal Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, CAMS and PUMC, Beijing, China
[17]State Key Laboratory of Molecular Oncology and Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, CAMS and PUMC, Beijing, China
[18]Department of Radiation Oncology, Xijing Hospital, Air Force Medical University, Xi'an, China
[19]Department of Oncology, Affiliated Hospital of Guizhou Medical University, Guiyang, China
[20]Department of Radiation Oncology, Jilin Provincial Cancer Hospital, Changchun, China
[21]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

CORRESPONDING AUTHOR

Jing Jin, MD, State Key Laboratory of Molecular Oncology and Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing 100021, PR China; e-mail: jinjing@csco.org.cn.

EQUAL CONTRIBUTION

J. Jin and Y.T. contributed equally as first authors. J. Jin, Y.-X.L., Y.-H.G., S.-X.L., W.-L.W., L.-C.W., H.-Z.Z., and X.-S.W. contributed equally as corresponding authors.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Jing Jin, Ye-Xiong Li
Financial support: Jing Jin, Ye-Xiong Li
Administrative support: Jing Jin, Hai-Zeng Zhang, Xi-Shan Wang, Li-Chun Wei, Wen-Ling Wang, Shi-Xin Liu, Yuan-Hong Gao, Ye-Xiong Li
Provision of study materials or patients: Yuan Tang, Ning Li, Wen-Yang Liu, Ning-Ning Lu, Yong Cai, Yong-Heng Li, Yuan Zhu, Guang-Hui Cheng, Hong-Yan Zhang, Xin Wang, Su-Yu Zhu, Jun Wang, Gao-Feng Li, Jia-Lin Yang, Kuan Zhang, Yihebali Chi, Lin Yang, Hai-Tao Zhou, Ai-Ping Zhou, Hui Fang, Shu-Lian Wang, Hai-Zeng Zhang, Xi-Shan Wang, Li-Chun Wei, Wen-Ling Wang, Shi-Xin Liu, Yuan-Hong Gao
Collection and assembly of data: Jing Jin, Yuan Tang, Si-Lin Chen, Shuai Li, Ye-Xiong Li
Data analysis and interpretation: Jing Jin, Yuan Tang, Chen Hu, Si-Lin Chen, Shuai Li, Ye-Xiong Li
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR)

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Chen Hu
Consulting or Advisory Role: Merck Sharp & Dohme, D1 Medical Technology

Ai-Ping Zhou
Consulting or Advisory Role: Pfizer, Novartis

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APPENDIX

TABLE A1. Surgical and Pathologic Characteristics of 465 Patients Who Underwent Surgery

Characteristic	TNT Group, No. (%)	CRT Group, No. (%)
Total No. of patients who underwent surgery	235	230
Type of surgery		
Abdominoperineal resection	106 (45.1)	95 (41.3)
Anterior resection	111 (47.2)	121 (52.6)
Hartmann procedure	13 (5.5)	8 (3.5)
Others	5 (2.1)	6 (2.6)
Completeness of tumor resection		
R0	215 (91.5)	202 (87.8)
R1	20 (8.5)	28 (12.2)
Pathologic T category		
ypT0	40 (17.2)	32 (13.9)
ypT1	9 (3.8)	10 (4.3)
ypT2	73 (31.1)	64 (27.8)
ypT3	106 (45.1)	113 (49.1)
ypT4	7 (3.0)	10 (4.3)
Missing	0 (0)	1 (0.4)
Pathologic N category		
ypN0	167 (71.1)	158 (68.7)
ypN1	55 (23.4)	54 (23.5)
ypN2	12 (5.1)	16 (7.1)
Missing	1 (0.4)[a]	2 (0.8) [b]
Pathologic stage		
0	39 (16.6)	27 (11.8)
I	69 (29.4)	64 (27.8)
II	61 (26.0)	67 (29.1)
IIIA	12 (5.1)	15 (6.5)
IIIB	52 (22.1)	47 (20.4)
IIIC	2 (0.9)	8 (3.5)
Missing	0 (0)	2 (0.8)[b]
Time interval to surgery, weeks, median (range)		
From start of radiotherapy to surgery	21 (4-64)	14 (10-57)
From end of radiotherapy to surgery	20 (3-63)	9 (5-36)[c]
From end of neoadjuvant therapy to surgery	6 (3-32)	9 (5-36)

Abbreviations: CRT, chemoradiotherapy; N, regional lymph node; T, primary tumor; TNT, total neoadjuvant therapy; yp, pathologic.
[a]This patient received transanal local excision.
[b]Two patients did not report ypN results.
[c]Five patients who received additional, out-of-protocol chemotherapy after CRT were excluded.

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TABLE A2. Recurrences and DM of 599 ITT patients

Recurrence and Distant Metastasis	TNT Group, No./Total No. (%)	CRT Group, No./Total No. (%)
Total No. of patients (ITT)	302	297
Deaths	47/302 (15.6)	63/297 (21.2)
DM	65/302 (21.5)	67/297 (22.6)
LRR in entire cohort	20/302 (6.6)	23/297 (7.7)
LRR only	13/302 (4.3)	15/297 (5.0)
LRR with DM	7/302 (2.3)	8/297 (2.7)
LRR in special situation		
Unresected persistent primary tumors	4/28 (14.3)	5/50 (10.0)
R1 resections	6/20 (30.0)	4/28 (14.3)
R0 resections and CRM (–)	8/215 (3.7)	13/202 (6.4)
cCR	2/28 (7.1)	1/10 (10.0)

NOTE. No patients received R2 resection.

Abbreviations: cCR, clinical complete response; CRM, circumferential resection margin; CRT, chemoradiotherapy; DM, distant metastasis; ITT, intention-to-treat; LRR, locoregional recurrence; TNT, total neoadjuvant therapy.