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

Jing Jin, MD1,2; Yuan Tang, MD1; Chen Hu, PhD2; Li-Ming Jiang, MD4; Jun Jiang, MD4; Ning Li, MD1; Wen-Yang Liu, MD1; Si-Lin Chen, MD1; Shuai Li, MD2; Ning-Ning Lu, MD1; Yong Cai, MD2; Yong-Heng Li, MD3; Yuan Zhu, MD4; Guang-Hui Cheng, MD7; Hong-Yan Zhang, MD8; Xin Wang, MD9; Su-Yu Zhu, MD10; Jun Wang, MD11; Gao-Feng Li, MD12; Jun Wang, MD11; Kuan Zhang, MD14; Yihebali Chi, MD15; Lin Yang, MD15; Hai-Tao Zhou, MD16; Shuang-Mei Zou, MD17; Hui Fang, MD1; Shu-Lian Wang, MD1; Hai-Zeng Zhang, MD16; Xi-Shan Wang, MD16; Li-Chun Wei, MD18; Wen-Ling Wang, MD19; Shi-Xin Liu, MD20; Yuan-Hong Gao MD21; and Ye-Xiong Li, MD1

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/m², once a day] on day 1 and capecitabine [1,000 mg/m², 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% vs 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.

J Clin Oncol 40:1681-1692. © 2022 by American Society of Clinical Oncology

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 Subsequent 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...
improved OS and lower acute toxicity, compared with long-course CRT. 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.

Given the potential advantage in the treatment strategy of total neoadjuvant therapy (TNT) and limited clinical prospective data in 2015, 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 $\geq 100 g/L$, 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 telephone call to an independent central trial of 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/m², once a day, on day 1 and capecitabine 1,000 mg/m²; 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/m², 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. 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 iliac 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 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.

**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 ≤ 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. 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. 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%.

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 ≥ 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 ≥ 194 DFS events to provide ≥ 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, 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.
and compared with the log-rank test. 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 \leq 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

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.
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). Further study will report the late adverse toxicities and quality of life.

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 preoperative therapy to surgery was 21 (range: 4-64) weeks and 14 (range: 10-57) weeks in the TNT group and CRT group, respectively. The median duration of hospital stay after surgery was 8 (range: 2-58) days in the TNT group and CRT group.

**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.
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, ypNO 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 pre-specified noninferiority (NI) margin of 1.43, so the non-inferiority 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, 70.1 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
short-course radiotherapy and neoadjuvant chemotherapy with standard CRT in patients with LARC (Table 3). In contrast to our study, the Polish II trial did not require adjuvant chemotherapy. Another RCT (PRODIGE 23) focused mainly on the comparison of preoperative chemotherapy with postoperative chemotherapy in the setting of long-course CRT. Consistent with the Polish II trial, 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, Polish II and STELLAR trials did not. The reported 3-year DM in these RCTs ranged from 20% to 30% with oxaliplatin-based chemotherapy, indicating the need for more efficacious or intensified systematic therapy. 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%), but lower than those in the Polish II trial (21%-22%). Similar to the Polish II trial, 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. 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). The Polish II trial mainly involved patients with unresectable fixed cT3 or

![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.](image-url)
T4 lesions and presented with more advanced T-stage disease than that of the other three RCTs. STELLAR and Polish II studies included only those with middle and low rectal cancer, whereas RAPIDO and PRODIGE 23 also included patients with upper rectal cancer. 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% vs 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). 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 $\geq 3$ toxicities (26.5%) than that of patients who received six cycles of CAPOX/infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in the RAPIDO trial or FOLFIRINOX (approximately 47%) in the PRODIGE 23 trial, but this proportion was similar for patients who received three cycles of neoadjuvant FOLFOX in the Polish II trial. 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, the

---

**FIG 3.** HRs for DFS and OS of TNT versus CRT in subgroup analysis. TNT group: short-term radiotherapy ($5 \text{ Gy} \times 5$) followed by four cycles of CAPOX, surgery, and two cycles of CAPOX. CRT group: 50 Gy in 25 fractions over 5 weeks concurrently with capcitabine 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.
### Table 3. Summary of Randomized Controlled Trials Comparing TNT and CRT Followed by Surgery in Patients With Locally Advanced Rectal Cancer

| Study          | Stage 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<sup>a</sup> | 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<sup>a</sup> | 24.7 | 11.0 |
| RAPIDO<sup>16</sup> | cT4 or N2/3 (n = 912)         | TNT: 462            | 32     | 91    | 5 Gy × 5f | — | 8 CAPOX/12 FOLFOX | 84.6 | 47.6 | 92   | —      | 23.7<sup>b</sup> | 89.1  | 20.0<sup>b</sup> | 8.3  |
|                |                                  | CRT: 450            | 30     | 92    | 50 Gy/25f | CAP | —      | 90.0 | 24.7 | 89   | 8 CAPOX/12 FOLFOX | 30.4<sup>b</sup> | 88.8  | 26.8<sup>b</sup> | 6.0  |
| Polish II<sup>15</sup> | Fixed cT3, cT4 (n = 515)   | TNT: 256            | 63     | —     | 5 Gy × 5f | — | 3 FOLFOX | 72   | 24.2 | 84   | —      | 53    | 73<sup>b</sup> | 30   | 22   |
|                |                                  | CRT: 259            | 64     | 50 Gy/25f | CAPOX | — | 64     | 23.5 | 81   | —    | —      | 52    | 65<sup>b</sup> | 27   | 21   |
| PRODIGE        | 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<sup>b</sup> | 91    | 17<sup>b</sup> | 4    |
|                |                                  | CRT: 230            | 16     | 90    | 50 Gy/25f | CAP | 98.7   | 35.6 | 95   | 12 mFOLFOX6/8 CAP | 69<sup>b</sup> | 88    | 25<sup>b</sup> | 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.

<sup>a</sup>P < .05.

<sup>b</sup>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. Third, in contrast to other RCTs, 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, we used capecitabine as concurrent chemoradiotherapy, which is not inferior to fluorouracil or oxaliplatin plus capcitabine or fluorouracil and is more convenient for patients. 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@casco.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.

**PRIOR PRESENTATION**

Presented as poster discussion at the 2021 ASCO Gastrointestinal Cancer Symposium, virtual meeting, Chicago, IL, June 4-8, 2021.

**SUPPORT**

The STELLAR trial was supported by grants from the Chinese Academy of Medical Science Innovation Fund for Medical Sciences (CIFMS, 2016-I2M-1-001); National Key Projects of Research and Development of China (2016YFC0904600); National Natural Science Foundation of China (82073352); Key Projects of Capital Health Development (2020-1-402); Collaborative Innovation Center for Cancer Medicine (CICCM, XT2015-03); Beijing Hope Run Special Fund of Cancer Foundation of China (LG2015L23) and Sanming Project of Medicine in Shenzhen (No. SZSZM201612063).

**CLINICAL TRIAL INFORMATION**

[CLINICAL TRIAL INFORMATION](https://doi.org/10.1200/JCO.21.01667)

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at DOI.
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, Yiheabali 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

REFERENCES
1. Rodel C, Liersch T, Becker H, et al: Preoperative chemoradiotherapy and postoperative chemotheraphy 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. Lancet Oncol 13:679-687, 2012
2. O’Connell MJ, Colangelo LH, Beart RW, et al: Capetcitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: Surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. J Clin Oncol 32:1927-1934, 2014
3. NCCN: Clinical Practice Guidelines in Oncology. Rectal Cancer, Version 2. 2021. https://www.nccn.org/professionals/physician_gls/default.aspx#rectal
4. Glynne-Jones R, Counsell N, Quirke P, et al: Chronicle: Results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capcitabine plus oxaliplatin (XELOX) versus control. Ann Oncol 25:1356-1362, 2014
5. Breugom AJ, van Gin W, Muller EW, et al: Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo) radiotherapy and total mesorectal excision: A Dutch Colorectal Cancer Group (DCCG) randomised phase III trial. Ann Oncol 26:696-701, 2015
6. Hong YS, Kim SY, Lee JS, et al: Oxaliplatin-based adjuvant chemotherapy for rectal cancer after preoperative chemoradiotherapy (ADORE): Long-term results of a randomized controlled trial. J Clin Oncol 37:3111-3123, 2019
7. Kapitelijn E, Marinenca M, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345: 638-646, 2001
8. Pettersson D, Lorinc E, Holm T, et al: Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. Br J Surg 102: 972-978, 2015
9. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al: Spinctercetervation following preoperative radiotherapy for rectal cancer: Report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiocmetheraphy. Radiother Oncol 72:15-24, 2004
10. Ngan SY, Burmeister B, Fisher RJ, et al: Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 30:3827-3833, 2012
11. Myerson RJ, Tan B, Hunt S, et al: Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys 88:829-836, 2014
12. Garcia-Aguilar J, Chow OS, Smith DD, et al: Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. Lancet Oncol 16:957-966, 2015
13. Foka E, Aligauer M, Poliat B, et al: Randomized phase II trial of chemoradiation plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol 37:3212-3222, 2019
14. Conroy T, Bosset JF, Elteno PL, et al: Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER PRODIGE 23): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 22:702-715, 2021
15. Bujko K, Wyrwicz L, Rutkowski A, et al: Long-course oxaliplatin-based preoperative chemoradiation vs. 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: Results of a randomised phase III study. Ann Oncol 27:834-842, 2016
16. Bahadoer RR, Dijkstra EA, van Etten B, et al: Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. Lancet Oncol 22:29-42, 2021
17. Myerson RJ, Gharofalci MC, El Ni, et al: Elective clinical target volumes for conformal therapy in anorectal cancer: A radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol Biol Phys 74:824-830, 2009
18. Roels S, Dutthoy W, Haustermans K, et al: Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys 65:1129-1142, 2006
19. Maas M, Beets-Tan RG, Lamberts DM, et al: Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 29: 4633-4640, 2011
20. Dworkar O, Keilholz L, Hoffmann A: Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 12:19-23, 1997
21. Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
22. Mawdsley S, Glynne-Jones R, Counsell N, et al: Preoperative radiotherapy followed by chemotherapy before total mesorectal excision: An analysis of outcomes in a randomized trial. Int J Radiat Oncol Biol Phys 67:369-377, 2007
23. Braendengen M, Tveit KM, Benglund A, et al: Randomised phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 26:3687-3694, 2008
24. Rob MS, Colangelo LH, O’Connell MJ, et al: Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 27:5122-5130, 2009
25. Dindo D, Demartines N, Claver P: Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205-213, 2004
26. Freidlin B, Korn EL: Testing treatment effects in the presence of competing risks. Stat Med 24:1703-1712, 2005
27. Cise B, Pietrzak L, Michalski W, et al: Long-course preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: Long-term results of the randomized Polish II study. Ann Oncol 30:1298-1303, 2019.
29. Dearnaley D, Syndikus I, Mossop H, et al: Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 17:1047-1060, 2016

30. Wang SL, Fang H, Song YW, et al: Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: A randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 20:352-360, 2019

31. Wang SL, Fang F, Hu C, et al: Hypofractionated versus conventional fractionated radiotherapy after breast-conserving surgery in the modern treatment era: A multicentre randomized controlled trial from China. J Clin Oncol 38:9604-9614, 2020

32. Wang L, Lu JJ, Yin W, et al: Perspectives on patient access to radiation oncology facilities and services in mainland China. Semin Radiat Oncol 27:164-168, 2017

33. Hofheinz RD, Wenz F, Post S, et al: Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: A randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 13:579-588, 2012

34. Schmoll HJ, Stein A, Van Cutsem E, et al: Pre- and postoperative capecitabine without or with oxaliplatin in locally advanced rectal cancer: PETACC 6 trial by EORTC GITCG and ROG, AIO, AGITG, BGDO, and FFCD. J Clin Oncol 39:17-29, 2021

We are a global community of nearly 45,000 members from more than 150 countries, serving members from all subspecialties and professional roles in the pursuit of quality cancer care and progress. Membership provides the support, resources, and solutions for your professional needs:

- Stay on the cutting edge of scientific research and advances
- Streamline your pursuit of continuous learning
- Access evidence-based and data-driven quality resources
- Obtain insight into best practices for cancer care teams
- Connect and exchange views with oncology experts

To learn more about the value of membership, visit asco.org/membership. Not a member? Join today at join.asco.org.
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)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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

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

No other potential conflicts of interest were reported.
# 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)*           | 2 (0.8)*           |
| **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)*           |
| **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)*          |
| 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.

*This patient received transanal local excision.

*Two patients did not report ypN results.

*Five patients who received additional, out-of-protocol chemotherapy after CRT were excluded.
## 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)                 |
| RO 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.