Neoadjuvant Chemotherapy With CAPOX Versus Chemoradiation for Locally Advanced Rectal Cancer With Uninvolved Mesorectal Fascia (CONVERT): Final Results of a Phase III Trial

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DOI https://doi.org/10.1200/JCO-25-00731

ABSTRACT

PURPOSE The neoadjuvant chemoradiotherapy (nCRT) might accentuate surgical complications and toxicity in the treatment of locally advanced rectal cancer (LARC) while neoadjuvant chemotherapy (nCT) alone shows promise as an alternative treatment. However, which patients deserve most from the nCT need further clarify. This trial aimed to assess the non-inferiority of nCT with capecitabine plus oxaliplatin (CAPOX) versus nCRT with capecitabine in LARC with uninvolved mesorectal fascia (MRF).

METHODS Patients with LARC within 12 cm from the anal verge and uninvolved MRF were randomly assigned to receive 4 cycles of CAPOX chemotherapy alone (nCT group) or CRT with concurrent Capecitabine (nCRT group). The primary end point is 3-year locoregional recurrence-free survival (LRRFS). Secondary end points, such as 3-year disease-free survival (DFS), 3-year overall survival (OS), and adverse events (AEs), were also reported.

RESULTS A total of 663 patients were enrolled and 589 patients received the allocated treatment (nCT, n = 300; nCRT, n = 289). LRRFS was analyzed with a median follow-up of 48 months. 3-year LRRFS was 97.4% (95% CI, 95.5 to 99.3) in the nCRT group and 96.3% (95% CI, 94.0 to 98.6) in the nCT group, resulting in a hazard ratio (HR) of 1.40 (95% CI, 0.53 to 3.68). The nCT and nCRT achieved similar 3-year DFS (89.2% *v* 87.9%; HR, 0.88 [95% CI, 0.54 to 1.44]) and 3-year OS (95.0% *v* 94.1%; HR, 0.86 [95% CI, 0.42 to 1.76]). The nCT group showed a lower incidence of grade 2 to 4 long-term AEs (16.0% *v* 26.3%, $P = 0.002$) and proctitis (33.6% *v* 41.7%, $P = 0.049$) compared with nCRT group.

CONCLUSIONS The non-inferiority of nCT was not confirmed with a very low incidence of local recurrence in both group. But nCT offers comparable DFS and OS while mitigating the burden of toxicity as compared to nCRT. These insights shed light on a potential paradigm shift in the treatment for LARC with uninvolved MRF.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

Accepted January 7, 2026
Published February 19, 2026

J Clin Oncol 00:1-11

View Online Article

INTRODUCTION

The therapeutic landscape for locally advanced rectal cancer (LARC) has traditionally been anchored by the administration of neoadjuvant chemoradiotherapy (nCRT), followed by total mesorectal excision (TME) and adjuvant chemotherapy.[1,2] The emergence of total neoadjuvant therapy (TNT) has garnered substantial attention.[3] Notably, the RAPIDO and PRODIGE 23 trials have illuminated the potential of TNT in improving disease-free survival (DFS) and pathologic complete responses (pCRs), particularly for patients with high-risk factors.[4,5] While radiation therapy undoubtedly plays a pivotal role in improving the therapeutic outcome for LARC,[6] clinical benefits are often accompanied

CONTEXT

Key Objective

Selected patients may achieve comparable oncologic outcomes with chemotherapy alone while avoiding radiotherapy-induced toxicity. This trial aimed to assess the noninferiority of neoadjuvant chemotherapy (nCT) with capecitabine plus oxaliplatin (CAPOX) versus neoadjuvant chemoradiotherapy (nCRT) in locally advanced rectal cancer (LARC) with uninvolved mesorectal fascia (MRF).

Knowledge Generated

nCT with CAPOX demonstrated comparable 3-year locoregional recurrence-free, disease-free, and overall survival while significantly reducing grade 2 to 4 long-term adverse events and proctitis.

Relevance *(A.H. Ko)*

As treatment paradigms for LARC continue to evolve, this trial offers further evidence that nCT alone represents a viable strategy for selected patients and can result in good long-term efficacy while avoiding radiation-associated toxicities.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

by equivalent costs. Radiation therapy may give rise to radiation-related adverse events (AEs), increase surgical complexity, and lead to the occurrence of complications.[7,8] Moreover, it can significantly affect the patient's quality of life, affecting functions such as bowel, urinary, and sexual functions.[9,10] Consequently, the indiscriminate use of radiation therapy for the LARC is increasingly under scrutiny.[11]

Neoadjuvant chemotherapy (nCT) has arisen as an alternative strategy that overcomes the limitations associated with conventional nCRT.[12-14] The FOWARC study demonstrated that nCT with the FOLFOX regimen showed no statistically significant difference in DFS and local recurrence rates compared with nCRT.[15,16] However, the FOWARC study included patients with high-risk factors (T4b-/mesorectal fascia [MRF]–involved), for whom nCT alone might struggle to control local recurrence effectively. In addition, the study design of FOWARC lacked the power to demonstrate the noninferiority or superiority of nCT. On the other hand, the PROSPECT study demonstrated the noninferiority of nCT in terms of DFS, but it only included low-risk patients (T2N+/T3N−/T3N+), which also limits the clinical applicability of this conclusion.[17]

MRF-involved LARC represents a distinct subgroup characterized by adverse tumor biology, a suboptimal treatment response, and poorer prognosis.[18,19] Consequently, we hypothesize that nCT alone may not adequately control MRF-involved LARC. By contrast, for LARC with uninvolved MRF, nCT alone may serve as a viable alternative to nCRT. To explore this hypothesis, the CONVERT study was initiated, with the aim of investigating whether nCT, specifically the capecitabine plus oxaliplatin (CAPOX) regimen, is noninferior to nCRT in LARC patients with uninvolved MRF, without increasing the risk of disease recurrence.

METHODS

Trial Design and Participants

The CONVERT trial is a phase III, open-label, multicenter, noninferiority, randomized trial, conducted at 21 hospitals across China (Figs 1 and 2). The trial (ClinicalTrials.gov identifier: NCT02288195) adhered rigorously to the guidelines set forth by the CONSORT. The trial protocol received approval from the central ethics committee of the Sun Yat-sen University Cancer Center (Guangzhou, China), along with the endorsement of local ethics committees spanning all participating hospitals. All participants provided written informed consent.

We recruited patients age 18-75 years with previously untreated, pathologically confirmed LARC that had been clinically staged as cT2N+ or cT3-4aNany disease, whereas those with a primary tumor staged as cT4b, or located adjacent to the MRF, or experiencing symptomatic bowel obstruction were deemed ineligible. All eligible patients were required to have an Eastern Cooperative Oncology Group performance status of ≤1 and adequate hematologic, liver, and renal function. Tumor location was stipulated to have a distal edge situated between 5 and 12 cm from the anal verge, taking into consideration the limited data available on the effectiveness of nCT in cases of low rectal cancer. Commencing in April 2019, the study protocol was amended to include patients with tumors located within 5 cm from the anal verge, following the findings from the FOWARC study, which indicated that tumor location did not influence the response to chemotherapy.[16] Other exclusion criteria included previous pelvic radiation or chemotherapy or other invasive malignancy within 5 years or symptomatic bowel obstruction.

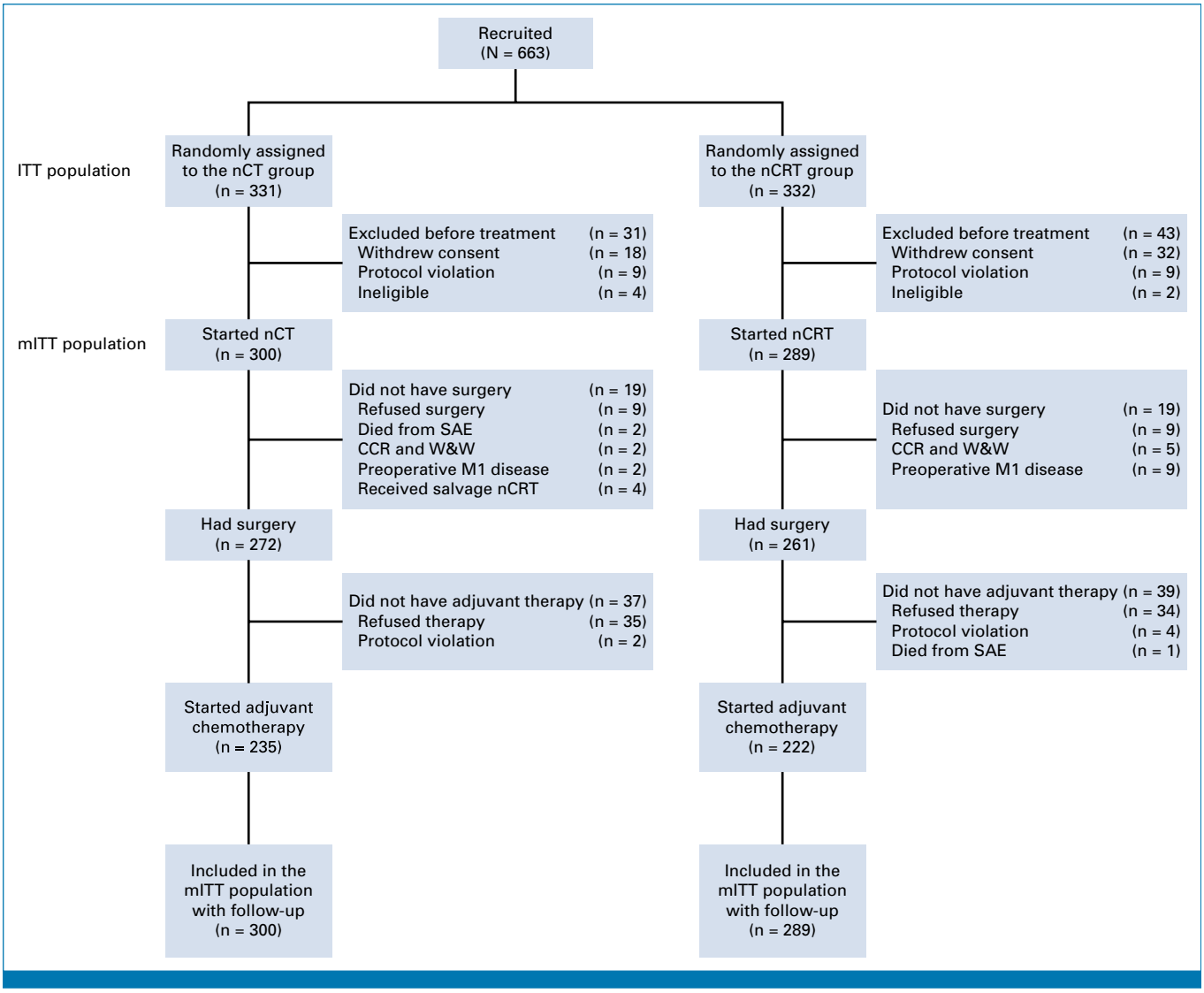

FIG 1. CONSORT diagram and trial profile. The ITT population comprised all patients who were randomly assigned to treatment. The mITT population comprised all patients who were randomly assigned to treatment and received at least one dose of study treatment. cCR, clinical complete response; ITT, intention-to-treat; mITT, modified intention-to-treat; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; SAE, serious adverse event; W&W, watch and wait.

Random Assignment and Masking

Contrast-enhanced computed tomography (CT) scans of the chest and abdomen, as well as pelvic magnetic resonance imaging (MRI), were conducted at baseline to rule out metastases. Pelvic MRI was mandatory for all patients, unless contraindicated, in which case pelvic CT scans and endoscopic ultrasound (EUS) were used for evaluation. Clinical T stage was determined using both MRI and EUS in accordance with the American Joint Committee on Cancer 7th edition,[20] with any disparities resolved through consultation with surgeons and radiologists. A stratified randomized block design was used to allocate patients (1:1) to either the nCT group or the nCRT group. The random assignment process was centralized, and patients were assigned through a phone call or an internet interface hosted by the Fudan University Shanghai Cancer Center (Shanghai, China). Stratification factors for this allocation included tumor location and clinical nodal staging. Neither investigators nor participants were blinded to the treatment allocations.

Procedures

Patients in the nCT group received four cycles of CAPOX regimen (oxaliplatin, 130 mg/m^2 intravenous drip once on day 1 plus capecitabine, 1,000 mg/m^2 twice daily for 14 days, once every 3 weeks), followed by restaging with pelvic MRI and EUS 1 week after chemotherapy. Patients without disease progression were scheduled for surgery with TME 2-4 weeks after chemotherapy, whereas those with evidence of local disease progression in the nCT group underwent

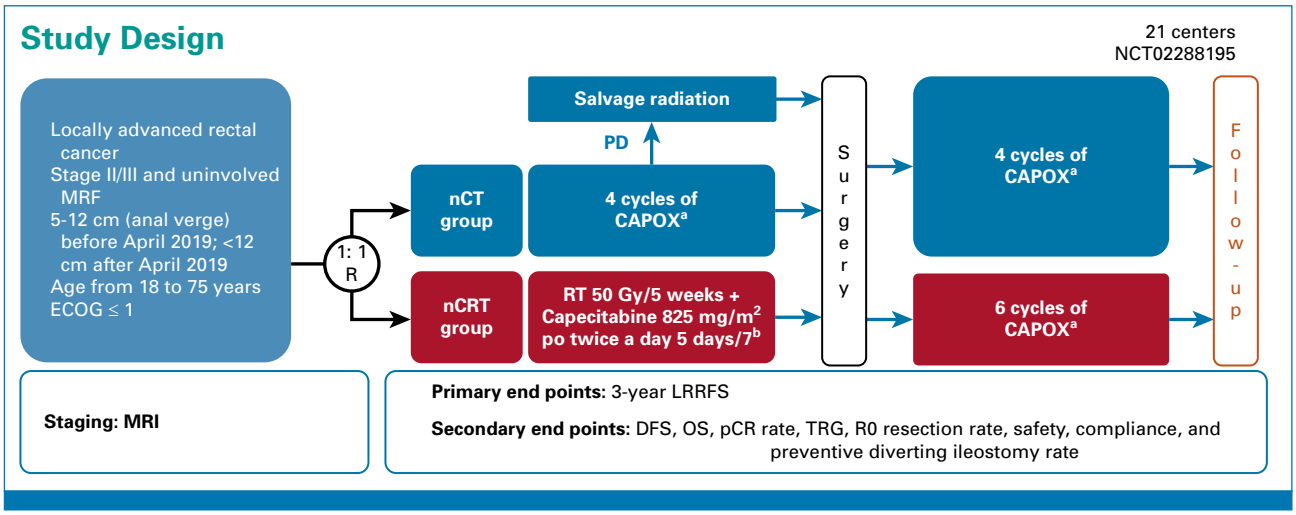

FIG 2. Study design. [a]Oxaliplatin 130 mg/m^2 intravenous drip once on day 1, repeated every 21 days. Capecitabine 1000 mg/m^2 orally twice daily on days 1-14, repeated every 21 days. [b]Capecitabine 825 mg/m^2 twice daily administered orally and concurrently with radiation therapy for 5 days per week. The total dosage of RT was 50 Gy in 25 fractions to the GTV and 45 Gy in 25 fractions to the CTV delivered by IMRT. CTV, clinical target volume; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; LRRFS, locoregional recurrence-free survival; MRF, mesorectal fascia; MRI, magnetic resonance imaging; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; OS, overall survival; pCR, pathologic complete response; PD, progressive disease; RT, radiotherapy; TRG, tumor regression grade.

chemoradiation as in the nCRT group before surgery. Postoperative CRT was recommended for patients with microscopic or macroscopic disease in the surgical margin. Postoperative adjuvant chemotherapy with four cycles of the CAPOX regimen was recommended.

Patients assigned to the nCRT group received 825 mg/m^2 of oral capecitabine twice daily with concurrent radiation therapy 5 days/week for 5 weeks. The total radiotherapy dosage was 50 Gy in 25 fractions to the gross tumor volume and 45 Gy in 25 fractions to the clinical target volume delivered by intensity-modulated radiation. The restaging with pelvic MRI and EUS was performed 5 weeks after CRT, and the surgery with TME was performed 6-10 weeks after chemoradiotherapy. Postoperative adjuvant chemotherapy with six cycles of the CAPOX regimen was recommended.

End Points

The primary objective was to assess whether the nCT with CAPOX would be noninferior to nCRT with capecitabine in LARC with uninvolved MRF. The primary end point is 3-year locoregional recurrence-free survival (LRRFS), which was defined as time interval between the date of random assignment and any local or regional progression/relapse.

Secondary end points such as pCR rate, tumor regression grade, pelvic R0 resection rate, postoperative morbidity and rate of receiving preoperative or postoperative chemoradiation have been reported in the initial result,[21] whereas secondary end points, such as 3-year DFS, 3-year overall survival (OS), and AEs are reported here. DFS is defined as the time interval between the date of random assignment and the date of the locoregional recurrence or metastasis, or death from any cause, whichever occurred first. OS is defined as the time interval between the date of random assignment and the date of death. AEs were categorized into short-term AEs, long-term AEs, and surgery-related AEs, the latter of which have been presented in the initial result. Short-term AEs were defined as those occurring during the period of neoadjuvant and adjuvant therapy and were attributed to chemotherapy or radiotherapy. Long-term AEs were defined as those persisting 1 year after the start of the trial. The severity of AE and the laboratory findings were graded by the investigators according to Common Terminology Criteria for Adverse Events, version 4.

Statistical Analysis

The use of a noninferiority margin of 1.6 for the hazard ratio (HR) and a type I error of 5% ensured an 80% power to show noninferiority between the nCT and nCRT groups. Based on previous studies,[6,22] assuming a 3-year LRRFS of 93% for the nCRT group and allowing approximately 5% of patients to be excluded from the per-protocol population, an enrollment of 650 patients was planned.

As a noninferiority study, the analysis of the primary end point is based on modified intention-to-treat (mITT) populations that received at least one dose of assigned neoadjuvant therapy. When comparing the two groups, categorical variables are compared using the χ^2 or Fisher's exact test, and continuous variables are compared using the *t*-test. Kaplan-Meier and log-rank methods are used for

survival analysis, and the Cox proportional hazards model is used for prognosis analysis. A two-sided P value of <.05 is considered to indicate statistical significance. All statistical analyses were performed using the SPSS software (version 24.0; SPSS, Chicago, IL). A detailed description of the statistical analysis plan is provided in the Data Supplement (online only).

RESULTS

From June 1, 2014, to October 1, 2020, 663 patients at 21 centers were recruited and randomly assigned to the nCT (n = 331) or nCRT (n = 332) group. Seventy-four patients did not receive any protocol treatment after random assignment (31 in the nCT group and 43 in the nCRT group). The remaining patients in the nCT (n = 300) and nCRT (n = 289) groups were included in the mITT population. Their baseline characteristics were well-balanced (Table 1, all P > .05). The median follow-up for end points was 48 months.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Modified Intention-to-Treat Population

Characteristic	Treatment Group	
	nCT (n = 300)	nCRT (n = 289)
Age, years, median (range)	60 (31-75)	60 (28-75)
Sex, No. (%)		
Male	188 (62.7)	177 (61.2)
Female	112 (37.3)	112 (38.8)
Clinical T category, No. (%)		
cT2	16 (5.3)	11 (3.8)
cT3	201 (67.0)	202 (69.9)
cT4a	83 (27.7)	76 (26.3)
Clinical N category, No. (%)		
cN0	92 (30.7)	77 (26.7)
cN1	147 (49.0)	133 (46.0)
cN2	61 (20.3)	79 (27.3)
Distance from the anal verge, No. (%)		
>10 cm	10 (3.3)	8 (2.8)
5-10 cm	166 (55.3)	163 (56.4)
≤5 cm	124 (41.3)	118 (40.8)
EMVI, No. (%)		
Positive	52 (17.3)	63 (21.8)
Negative	248 (82.7)	226 (78.2)
LLN, No. (%)		
Positive	27 (9.0)	36 (12.5)
Negative	273 (91.0)	253 (87.5)
BMI, No. (%)		
<24	230 (76.7)	218 (75.4)
≥24	70 (23.3)	71 (24.7)

Abbreviations: EMVI, extended maximum vertical lymphatic infiltration; LLN, lateral lymph node; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy.

Locoregional Recurrence-Free Survival

In the mITT population, local or regional progression/relapse was observed in 17 patients (10 in the nCT group and seven in the nCRT group) within the 3-year follow-up period. The anatomic sites of local recurrence included the presacral area (n = 2 in the nCT group and n = 3 in the nCRT group), mesorectal space (n = 2 in the nCT group and n = 2 in the nCRT group), anastomotic site (n = 2 in the nCT group and n = 1 in the nCRT group), lateral area (n = 3 in the nCT group), and anterior area (n = 1 in the nCT group and n = 1 in the nCRT group). The noninferiority of nCT was not confirmed with a HR of 1.40 (95% CI, 0.53 to 3.68). The 3-year LRRFS was 97.4% (95% CI, 95.5 to 99.3) in the nCRT group and 96.3% (95% CI, 94.0 to 98.6) in the nCT group (Fig 3A). None of the subgroups showed significant interaction effects at a two-sided significance level of 0.05 (Fig 3B and Appendix Table A1, online only). In the nCT group, univariate and multivariate analysis revealed no factors associated with worse LRRFS (Appendix Table A2). It is noteworthy that patients with tumors <5 cm from the anal verge exhibited high HR for LRRFS in the nCT group although these findings did not achieve statistical significance (HR, 3.60, P = .063). It is worth noting that two patients in the nCT group and five patients in the nCRT group were assessed to have complete clinical response (cCR) after treatment and underwent a watch-and-wait approach. All seven of these patients remained tumor-free during the 3-year postoperative follow-up period.

DFS and OS

Locoregional recurrence or metastasis or death occurred in 30 patients in the nCT group and 33 patients in the nCRT group within the 3-year follow-up period. The 3-year DFS rate was 89.2% (95% CI, 85.6 to 92.9) in the nCT group and 87.9% (95% CI, 84.1 to 91.8) in the nCRT group, with a HR of 0.88 (95% CI, 0.54 to 1.44; Fig 3C). Overall, 30 patients (14 in the nCT group and 16 in the nCRT group) died within the 3-year follow-up period. The 3-year OS was 95.0% (95% CI, 92.4 to 97.5) in the nCT group and 94.1% (95% CI, 91.3 to 96.9) in the nCRT group, with a HR of 0.86 (95% CI, 0.42 to 1.76; Fig 3D). None of the subgroups showed significant interaction effects at a two-sided significance level of 0.05 (Appendix Figs A1 and A2).

Short-Term AEs

During the neoadjuvant and adjuvant treatment periods, there was no statistically significant difference in the incidence of any-grade AEs between the nCT and nCRT groups (78.0% v 73.3%, P = .189), nor in the incidence of grade 3 to 4 AEs (15.3% v 13.1%, P = .449; Table 2). The incidence of neutropenia was lower in the nCT group compared with the nCRT group (39.3% v 48.1%, P = .032), whereas the incidence of thrombocytopenia was higher in the nCT group (28.7% v 20.1%, P = .015). All other AEs occurred without statistically significant differences between the nCT and nCRT groups.

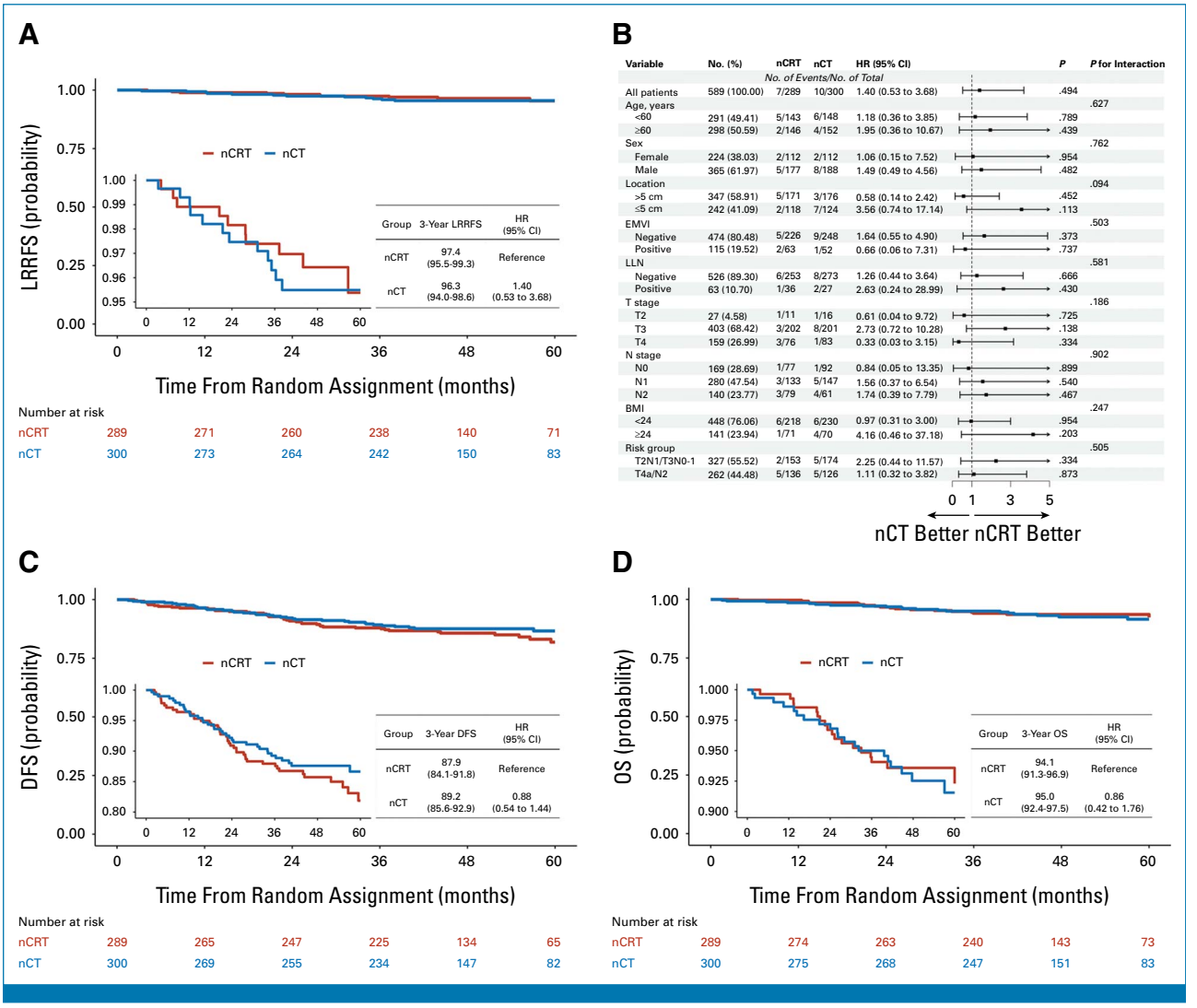

FIG 3. The Kaplan-Meier curves for (A) LRRFS, (C) DFS, and (D) OS. (B) The LRRFS for patient subgroups. DFS, disease-free survival; EMVI, extended maximum vertical lymphatic infiltration; HR, hazard ratio; LLN, lateral lymph node; LRRFS, locoregional recurrence-free survival; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; OS, overall survival.

Long-Term AEs

There was no statistically significant difference in the incidence of any-grade long-term AEs between the nCT and nCRT groups (40.7% *v* 48.1%, *P* = .070; Table 2). However, the incidence of grade 2 to 4 AEs was significantly lower in the nCT group compared with the nCRT group (16.0% *v* 26.3%, *P* = .002). Patients who underwent radiotherapy had a significantly higher probability of developing proctitis than those who did not receive radiotherapy (33.6% *v* 41.7%, *P* = .049). One year after radiotherapy, 12.5% of patients still suffered from radiation dermatitis. All other AEs occurred without statistically significant differences between the nCT and nCRT groups.

Post Hoc Exploratory Analysis

According to the patient selection criteria of the PROSPECT study,[17] there were 327 patients that met the criteria for cT2N1/cT3N0-1 and 262 patients with high-risk factors (cT4a/cN2) in our study. In the population that met the criteria for cT2N1/cT3N0-1, there was no statistically significant difference in long-term outcomes including 3-year LRRFS (*P* = .321; Fig 4A), 3-year DFS (*P* = .490; Fig 4C), and 3-year OS (*P* = .631; Fig 4E). In the population with high-risk factors (cT4a or cN2), there was no statistically significant difference in long-term outcomes including 3-year LRRFS (*P* = .872; Fig 4B), 3-year DFS (*P* = .907; Fig 4D), and 3-year OS (*P* = .986; Fig 4F). The treatment effect is consistent between cT2N1/cT3N0-1 and cT4a/cN2 subgroups (*P* for interaction = .505; Fig 3B).

DISCUSSION

The final results of the CONVERT trial show that nCT offers comparable LRRFS, DFS, and OS while mitigating the burden of long-term toxicity as compared with nCRT. However, the upper limit of the confidence intervals of the HRs for LRRFS

TABLE 2. The Short-Term AEs and Long-Term AEs in the Modified Intention-to-Treat Population

AE	nCRT (n = 289), No./n (%)	nCT (n = 300), No./n (%)	*P*
Short-term AEs			
Any grade	212/289 (73.3)	234/300 (78.0)	.189
Grade ≥2	106/289 (36.7)	123/300 (41.0)	.282
Grade ≥3	38/289 (13.1)	46/300 (15.3)	.449
Grade = 4	8/289 (2.8)	8/300 (2.7)	.940
Leukopenia/neutropenia	139/289 (48.1)	118/300 (39.3)	.032
Anemia	62/289 (21.5)	65/300 (21.7)	.950
Thrombocytopenia	58/289 (20.1)	86/300 (28.7)	.015
Nausea	74/289 (25.6)	96/300 (32.0)	.087
Vomiting	50/289 (17.3)	58/300 (19.3)	.524
Neurologic	71/289 (24.6)	96/300 (32.0)	.045
Long-term AEs			
Any grade	139/289 (48.1)	122/300 (40.7)	.070
Grade ≥2	76/289 (26.3)	48/300 (16.0)	.002
Grade ≥3	13/289 (4.5)	9/300 (3.0)	.338
Grade 4	1/289 (0.3)	1/300 (0.3)	>.999
Urologic	53/289 (18.3)	52/300 (17.3)	.750
Sexual dysfunction	16/177 (9.0)	16/188 (8.51)	.914
Anastomotic stenosis	36/261 (13.8)	36/272 (13.2)	.866
Pain	40/289 (13.8)	39/300 (13.0)	.765
Proctitis[a]	111/266 (41.7)	94/280 (33.6)	.049
Neurologic	38/289 (13.1)	50/300 (16.7)	.272
Radiodermatitis	36/289 (12.5)	NA	<.001

Abbreviations: AEs, adverse events; APR, abdominoperineal resection; ISR, intersphincteric resection; NA, not applicable; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy.
[a]Patients who underwent ISR or APR (20 in the nCT group and 23 in the nCRT group) were excluded from the denominator for proctitis incidence.

exceeds the noninferiority margin, suggesting that the noninferiority of nCT was not confirmed.

During the design of the CONVERT study in 2014, we assumed a lower LRRFS rate because, at that time, the local recurrence rate for LARC was still close to 10%.[6,22] However, with advancements in surgical techniques and perioperative management in recent years, both groups achieved exceptionally high LRRFS rates (97.4% *v* 96.3%), making it difficult to demonstrate noninferiority. We noted that the HR for local recurrence in the PROSPECT study (HR, 1.18 [95% CI, 0.44 to 3.16]) and the FOWARC study (HR, 0.95 [95% CI, 0.43 to 2.12]) also had upper confidence intervals that were relatively high.[16,17] With such low local recurrence rates, it is evident that a larger sample size would be required to accumulate a sufficient number of local recurrence events to prove noninferiority. In addition, the PROSPECT study opted to administer additional radiotherapy to 53 patients (9.1%) with less than a 20% regression, whereas our study administered salvage radiotherapy to only four patients (1.3%) with progressive disease (PD), which might have contributed to a slight decrease in outcomes for the nCT group, thereby increasing the HR. On the other hand, the PROSPECT study chose DFS as the primary end point and successfully demonstrated the noninferiority of nCT with selective radiotherapy (HR, 0.92 [95% CI, 0.74 to 1.12]). In our study (HR, 0.88 [95% CI, 0.54 to 1.44]) and the FOWARC study (HR, 0.94 [95% CI, 0.63 to 1.41]), a lower HR for 3-year DFS was also observed, suggesting that nCT might have noninferiority in controlling DFS. It is worth noting that in our initial report, the perioperative distant metastasis rate for the nCT group was significantly lower than that for the nCRT group (0.7% *v* 3.1%; $P = .034$).

Although the CONVERT study did not demonstrate the noninferiority of nCT, there were no statistically significant differences in LRRFS, DFS, or OS between the nCT and nCRT groups. This suggests that for patients with cT2N+ and cT2-4aNx tumors with negative MRF, nCT can achieve similar long-term outcomes compared with traditional nCRT. We observed that the long-term survival data from the CONVERT study were significantly better than those from the FOWARC study but slightly worse than those from the PROSPECT study, which may be attributed to differences in patient selection among the three studies. The worse long-term outcomes in the FOWARC study could be due to the inclusion of patients with T4b- and MRF-positive tumors. Previous studies have shown that patients with MRF-involved or T4b tumors have an exceedingly high risk of recurrence.[23,24] Considering the long-term outcomes of our study in conjunction with the differences observed in the FOWARC trial, we believe that these two factors should be regarded as high-risk factors to avoid when opting for nCT. Conversely, the better long-term outcomes in the PROSPECT study may result from the exclusion of patients with poorer prognoses, such as those with cT4 tumors or cN2 tumors. In addition, up to 20% of patients had high rectal tumors located more than 10 cm from the anal verge, a group unlikely to receive neoadjuvant radiotherapy.[25,26] Our analysis of cT4a or cN2 patients revealed similar 3-year LRRFS, 3-year DFS, and 3-year OS between the nCT group and the nCRT group, indicating that nCT could be a potential option for this subset of patients. However, because of the exploratory nature of this analysis and the small sample size, further research is needed to support this conclusion.

The short-term efficacy and long-term outcomes were similar between the two groups, making the AEs in our trial particularly important. The nCT group received four cycles of nCT and four cycles of adjuvant chemotherapy, whereas the nCRT group received capecitabine sequential CRT followed by six cycles of adjuvant chemotherapy. The incidence of AEs during neoadjuvant and adjuvant treatment was similar between the two groups. However, in terms of long-term AEs, the nCT group showed a significant advantage, with a lower incidence of grade 2 to 4 AEs (16.0% *v* 26.3%) and proctitis (33.6% *v* 41.7%). It should be noted that the similarity between the symptoms of proctitis and the low

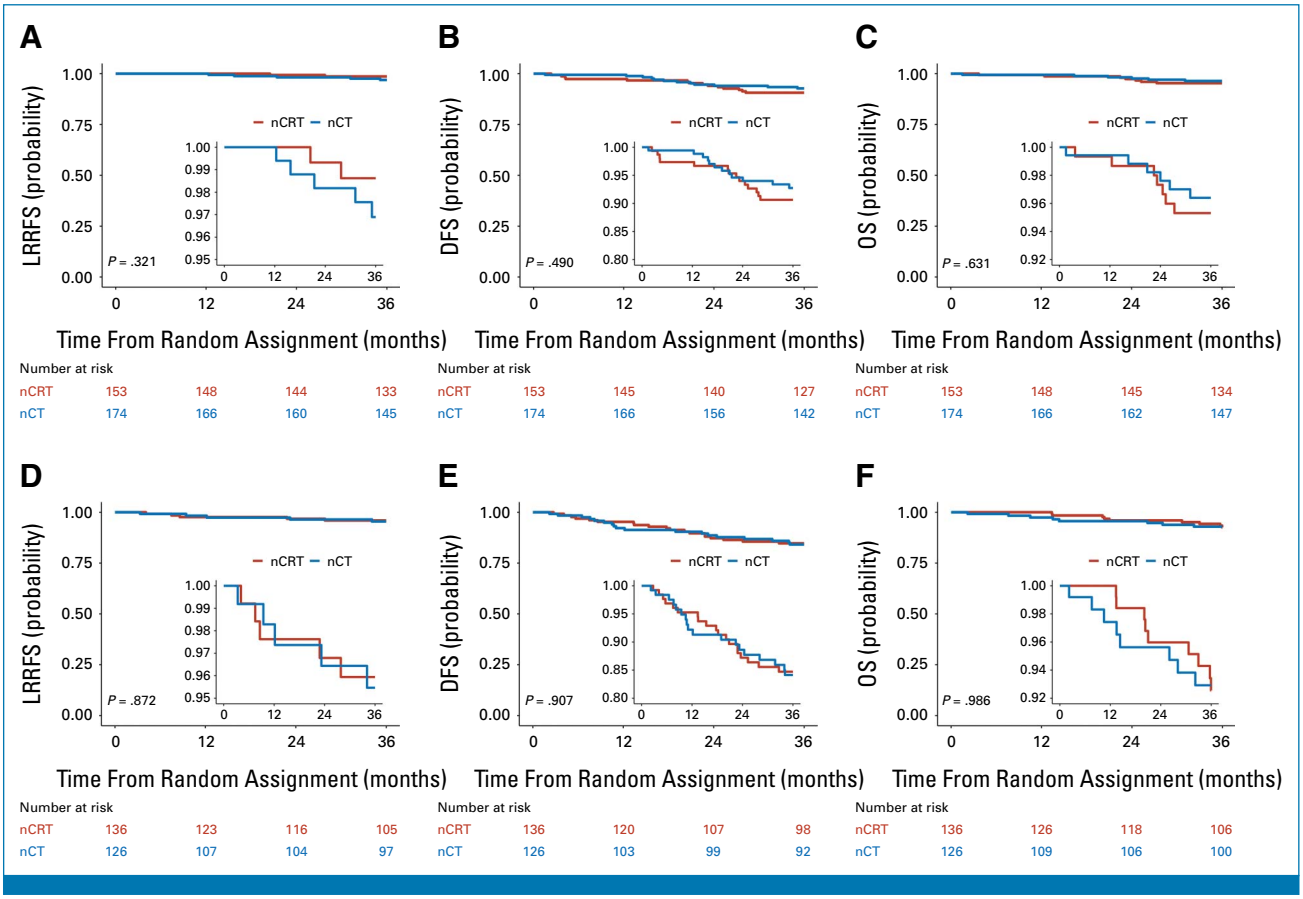

FIG 4. The Kaplan-Meier curves for (A) 3-year LRRFS, (B) 3-year DFS, and (C) 3-year OS in the population that met the criteria for cT2N1/cT3N0-1. The Kaplan-Meier curves for (D) 3-year LRRFS, (E) 3-year DFS, and (F) 3-year OS in the population with high-risk factors (cT4a or cN2). DFS, disease-free survival; LRRFS, locoregional recurrence-free survival; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; OS, overall survival.

anterior resection syndrome may result in a high proportion in the nCT group with proctitis. Meanwhile, the difference in proctitis between the two groups may be attributed to chronic radiation–induced proctitis and radiation-induced surgical difficulty, leading to poorer postoperative anal function. In addition, 12.5% of patients continued to suffer from radiation dermatitis 1 year after radiotherapy. This suggests that nCT can provide patients with a better long-term quality of life, particularly for younger patients who, with their longer life expectancy, would otherwise endure the burden of prolonged toxicities for a more extended period. Besides, for younger patients, omitting radiotherapy can markedly diminish the likelihood of pelvic second primary tumors.[27,28] In addition, while our study does not contain specific data on this matter, the omission of radiotherapy is likely to be particularly appealing to young, premenopausal women who aim to preserve their fertility or ovarian function.[29] Furthermore, we reported on postoperative complications in our initial result, with the nCT group having slightly fewer postoperative complications compared with the nCRT group, though not statistically significant (18.8% *v* 25.7%, $P = .054$). Therefore, our study demonstrates that nCT, while achieving similar short-term efficacy and long-term outcomes, has the advantage of reduced toxicity, providing favorable evidence for the substitution of nCT for nCRT in specific patient populations.

Following the commencement of our study, there has been a significant evolution in the treatment paradigm for LARC, offering more enhanceable options for the design and application of nCT regimens.[30] The FOLFOX and CAPOX regimens are the two most common chemotherapy regimens. Unlike the FOWARC and PROSPECT studies, which opted for the FOLFOX regimen, our study selected the CAPOX regimen, known for better compliance, allowing patients to take oral capecitabine at home without the need for 2-day hospital-based drug infusions. In addition, the PROSPECT study chose to administer additional radiotherapy for patients with less than a 20% regression, leading to 9.1% of patients not being able to avoid radiotherapy, significantly increasing treatment toxicity and treatment duration. By contrast, our study administered additional radiotherapy only to patients who exhibited PD after chemotherapy (1.3%), achieving similar prognosis while reducing the incidence of additional radiotherapy. Therefore, for patients who have chosen reduced-toxicity nCT and are not facing anal sphincter resection, nCT may be sufficient even if the regression is <20%. In the univariate and multivariate

analyses in the nCT group, patients with tumors <5 cm from the anal verge exhibited high HR for LRRFS although these findings did not achieve statistical significance (HR, 3.60, P = .063; HR, 3.23, P = .098). This suggests that for this subset of patients, nCT alone may be insufficient. For patients with the desire to preserve anal function, TNT offers a higher rate of cCR, which may be a better option.[31] We also note that several studies, including the MERCURY, OCUM, and QUICKSILVER trials, suggest that for some low-risk patients, direct surgery may be a better choice.[18,26,32] Thus, the risk stratification for the application of nCT should be further refined, and careful selection in conjunction with the patient's desire for anal preservation should be made.[33]

As we discussed in our previous discussions and initial reports, our study has certain limitations. The CONVERT trial was conducted as an open-label study without blinding among investigators and participants, which inherently carries a risk of performance and assessment bias. We believe that our approach, which included standardized protocols, blinded data analysis, and patient education, effectively mitigated potential biases. Besides, 11% of patients were excluded from the mITT population, which may introduce unforeseen biases. However, the baseline characteristics were still well-balanced between the two groups. Furthermore, there remains controversy in our inclusion criteria. The question of which high-risk patients may forgo radiotherapy and which low-risk patients can proceed directly to surgery requires further investigation and discussion. Finally, it is currently believed that immunotherapy is the preferred treatment for patients with deficient mismatch repair disease, but our study did not involve the mismatch repair status. Future studies should consider incorporating microsatellite instability/mismatch repair testing as part of the study protocol to provide more comprehensive data on the molecular characteristics of tumors and their impact on treatment outcomes.

Although the noninferiority of nCT was not confirmed, the initial and final results of the CONVERT study suggest that in patients without MRF involvement, nCT could serve as a potential alternative to nCRT. These findings resonate with those of the PROSPECT and FOWARC trials, collectively providing favorable evidence for a de-escalation approach to patients with low-risk LARC. In the future, the population that stands to benefit from nCT alone requires further exploration.

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DISCLAIMER

The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

EQUAL CONTRIBUTION

W.-J.M., X.-Z.W., X.Z., Y.-M.S., C.-K.Y., and J.-Z.L. contributed equally to this work. Z.-Z.P., J.-H.Y., and P.-R.D. contributed equally as senior authors.

PRIOR PRESENTATION

Presented at the ESMO Congress 2023, Madrid, Spain, October 20-24, 2023.

SUPPORT

Supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0520301), the Sun Yat-Sen University Clinical Research 5010 Program (grant No. 2014013), the National Natural Science Foundation of China (82473395), and the China Postdoctoral Science Foundation (2024M753773).

CLINICAL TRIAL INFORMATION

NCT02288195

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-00731.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00731.

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ACKNOWLEDGMENT

We thank all patients and their families for participating in this study.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Chemotherapy With CAPOX Versus Chemoradiation for Locally Advanced Rectal Cancer With Uninvolved Mesorectal Fascia (CONVERT): Final Results of a Phase III Trial

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

Gong Chen
Speakers' Bureau: Roche, Merck Serono, Sanofi

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Univariate and Multivariate Analyses of the Effects of Prognostic Factors on Locoregional Recurrence-Free Survival in the mITT Population

	Univariate		Multivariate	
Variable	*P*	HR (95% CI)	*P*	HR (95% CI)
Group				
nCRT		Reference		Reference
nCT	.494	1.40 (0.53 to 3.68)	.430	1.48 (0.56 to 3.93)
Age, years				
<60		Reference		Reference
≥60	.215	0.53 (0.20 to 1.44)	.313	0.59 (0.21 to 1.65)
Sex				
Female		Reference		Reference
Male	.199	2.09 (0.68 to 6.40)	.110	2.56 (0.81 to 8.13)
Location				
>5 cm		Reference		Reference
≤5 cm	.283	1.68 (0.65 to 4.37)	.357	1.59 (0.59 to 4.28)
EMVI				
Negative		Reference		Reference
Positive	.896	0.92 (0.26 to 3.20)	.684	0.76 (0.21 to 2.78)
LLN				
Negative		Reference		Reference
Positive	.348	1.82 (0.52 to 6.32)	.564	1.47 (0.40 to 5.42)
T stage				
T2		Reference		Reference
T3	.133	0.31 (0.07 to 1.42)	.276	0.41 (0.08 to 2.03)
T4	.165	0.30 (0.06 to 1.64)	.361	0.44 (0.07 to 2.59)
N stage				
N0		Reference		Reference
N1	.236	2.55 (0.54 to 12.01)	.289	2.35 (0.48 to 11.40)
N2	.048	4.87 (1.01 to 23.44)	.075	4.38 (0.86 to 22.27)
BMI				
<24		Reference		Reference
≥24	.613	1.31 (0.46 to 3.71)	.976	1.02 (0.34 to 3.02)

Abbreviations: EMVI, extended maximum vertical lymphatic infiltration; HR, hazard ratio; LLN, lateral lymph node; mITT, modified intention-to-treat; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy.

TABLE A2. Univariate and Multivariate Analyses of the Effects of Prognostic Factors on Locoregional Recurrence-Free Survival in the nCT Group (n = 300)

	Univariate		Multivariate	
Variable	*P*	HR (95% CI)	*P*	HR (95% CI)
Age, years				
<60		Reference		Reference
≥60	.504	0.65 (0.18 to 2.30)	.808	0.84 (0.22 to 3.31)
Sex				
Female		Reference		Reference
Male	.265	2.41 (0.51 to 11.36)	.177	2.99 (0.61 to 14.67)
Location				
>5 cm		Reference		Reference
≤5 cm	.063	3.60 (0.93 to 13.94)	.098	3.23 (0.80 to 13.00)
EMVI				
Negative		Reference		Reference
Positive	.606	0.58 (0.07 to 4.58)	.367	0.38 (0.05 to 3.15)
LLN				
Negative		Reference		Reference
Positive	.227	2.60 (0.55 to 12.26)	.543	1.65 (0.33 to 8.36)
T stage				
T2		Reference		Reference
T3	.623	0.59 (0.07 to 4.74)	.839	0.79 (0.09 to 7.25)
T4	.239	0.19 (0.01 to 3.02)	.446	0.32 (0.02 to 5.85)
N stage				
N0		Reference		Reference
N1	.270	3.35 (0.39 to 28.66)	.330	2.96 (0.33 to 26.39)
N2	.082	7.01 (0.78 to 62.77)	.091	7.10 (0.73 to 68.75)
BMI				
<24		Reference		Reference
≥24	.226	2.18 (0.62 to 7.74)	.435	1.69 (0.45 to 6.34)

Abbreviations: EMVI, extended maximum vertical lymphatic infiltration; HR, hazard ratio; LLN, lateral lymph node; nCT, neoadjuvant chemotherapy.

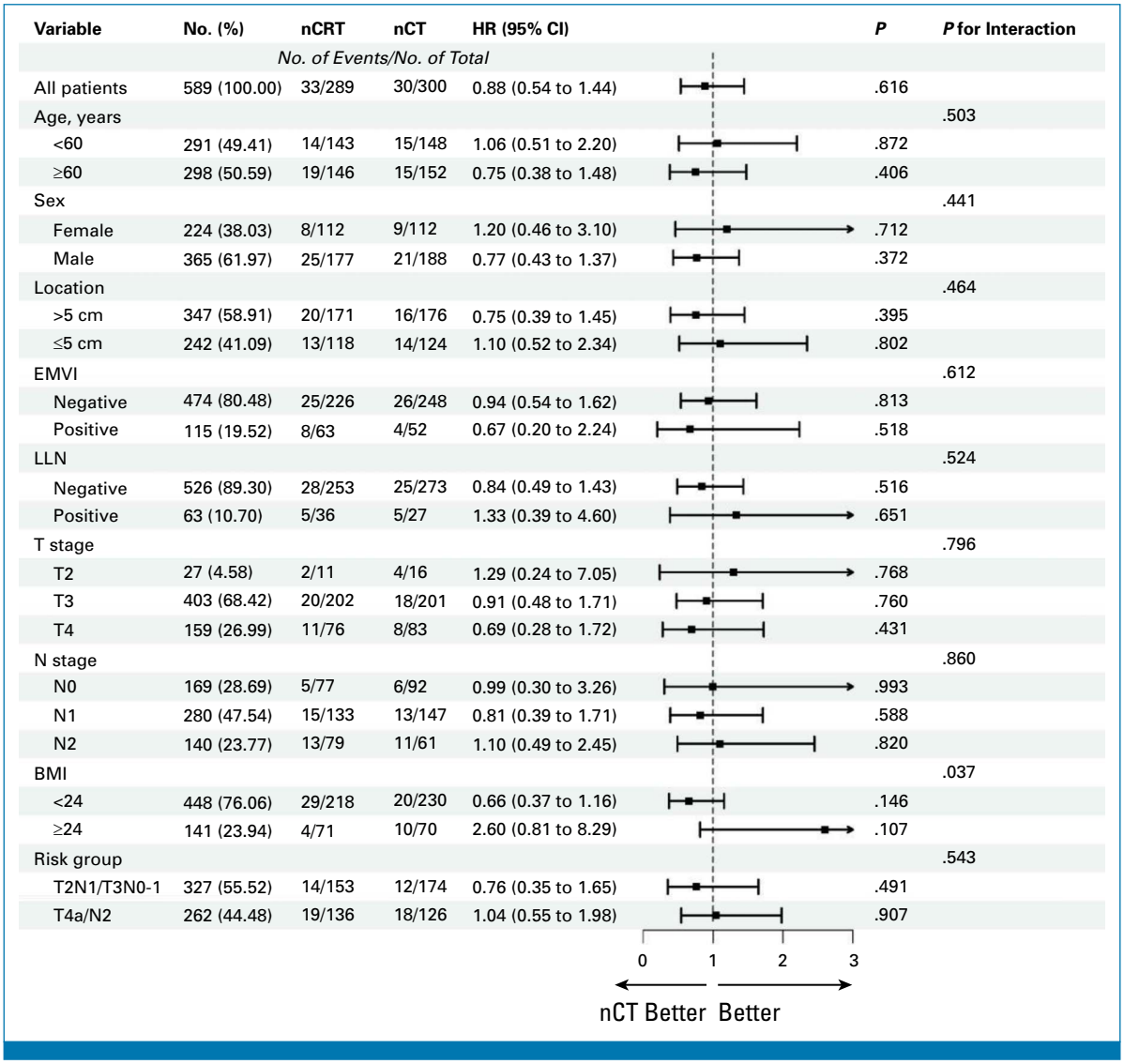

FIG A1. The DFS in patient subgroups. None of the subgroups showed significant interaction effects at a two-sided significance level of .05. DFS, disease-free survival; EMVI, extended maximum vertical lymphatic infiltration; LLN, lateral lymph node; nCT, neoadjuvant chemotherapy.

Variable	No. (%)	nCRT	nCT	HR (95% CI)	P	P for Interaction
		No. of Events/No. of Total				
All patients	589 (100.00)	16/289	14/300	0.86 (0.42 to 1.76)	.676	
Age, years						.933
<60	291 (49.41)	6/143	5/148	0.83 (0.25 to 2.70)	.751	
≥60	298 (50.59)	10/146	9/152	0.88 (0.36 to 2.16)	.779	
Sex						.756
Female	224 (38.03)	3/112	3/112	1.05 (0.21 to 5.19)	.955	
Male	365 (61.97)	13/177	11/188	0.79 (0.36 to 1.77)	.571	
Location						.662
>5 cm	347 (58.91)	8/171	6/176	0.72 (0.25 to 2.08)	.546	
≤5 cm	242 (41.09)	8/118	8/124	1.00 (0.38 to 2.67)	.997	
EMVI						.890
Negative	474 (80.48)	11/226	11/248	0.91 (0.40 to 2.10)	.830	
Positive	115 (19.52)	5/63	3/52	0.82 (0.20 to 3.43)	.787	
LLN						.152
Negative	526 (89.30)	15/253	11/273	0.69 (0.32 to 1.51)	.356	
Positive	63 (10.70)	1/36	3/27	3.93 (0.41 to 37.76)	.236	
T stage						.923
T2	27 (4.58)	2/11	2/16	0.58 (0.08 to 4.15)	.591	
T3	403 (68.42)	9/202	8/201	0.90 (0.35 to 2.34)	.831	
T4	159 (26.99)	5/76	4/83	0.78 (0.21 to 2.90)	.707	
N stage						.464
N0	169 (28.69)	1/77	3/92	2.55 (0.26 to 24.48)	.418	
N1	280 (47.54)	9/133	6/147	0.63 (0.22 to 1.76)	.373	
N2	140 (23.77)	6/79	5/61	1.10 (0.34 to 3.62)	.870	
BMI						.443
<24	448 (76.06)	15/218	12/230	0.77 (0.36 to 1.65)	.502	
≥24	141 (23.94)	1/71	2/70	2.07 (0.19 to 22.78)	.554	
Risk group						.730
T2N1/T3N0-1	327 (55.52)	7/153	6/174	0.77 (0.26 to 2.28)	.632	
T4a/N2	262 (44.48)	9/136	8/126	0.99 (0.38 to 2.57)	.986	

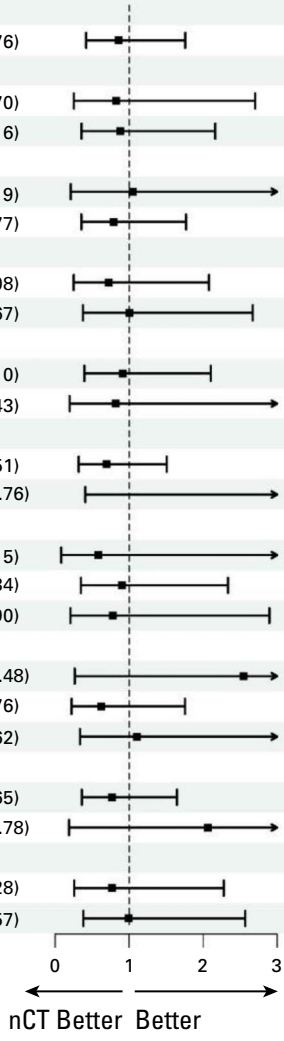

FIG A2. The OS in patient subgroups. None of the subgroups showed significant interaction effects at a two-sided significance level of .05. EMVI, extended maximum vertical lymphatic infiltration; LLN, lateral lymph node; nCT, neoadjuvant chemotherapy; OS, overall survival.