Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy for initially unresectable locally advanced colon cancer: short-term outcomes of an open-label, single-centre, randomised, controlled, phase 3 trial

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Summary

Background Neoadjuvant chemotherapy (NACT) is commonly used to downstage the tumor in locally advanced colon cancer (LACC) and improve the R0 resection rate. Neoadjuvant chemoradiotherapy (NACRT) is the standard treatment for locally advanced rectal and esophageal cancers, but its benefits in LACC remain poorly understood. This study aimed to compare the effects and safety of NACRT and NACT on R0 resection and survival rates in initially unresectable LACC.

Methods This was an open-label, single-center, randomized, controlled trial conducted between May 11, 2019 and May 30, 2022. Forty-five patients with initially unresectable LACC were randomly allocated to the NACT (control, n = 20) or NACRT (research, n = 25) group. The NACT group received XELOX (oxaliplatin 100–130 mg/m^2, qd, d1, every 3 weeks; and capecitabine 1000 mg/m^2, bid, d1-d14, every 3 weeks) for 4 cycles. The NACRT group, in addition to chemotherapy, received daily irradiation (GTV 45–50 Gy/25 F; CTV 42.5–45 Gy/25 F). Surgery was scheduled 6–12 weeks after neoadjuvant treatment and adjuvant chemotherapy was administered if the patient developed resectable LACC. The primary endpoint was the 5-year overall survival (OS) rate. The secondary outcomes included the 3-year progression-free survival (PFS) and R0 resection rates. This study was registered with ClinicalTrials.gov (NCT03970694).

Findings In short-term outcome analysis, NACRT significantly improved the R0 resection rate (80% for NACRT vs. 20% for NACT, P < 0.001). The NACRT and NACT groups had a 3-year OS of 87.6% and 75% (P = 0.037) and a 3-year PFS of 76% and 45% (P = 0.049), respectively. The 5-year OS was not reached. In the NACRT group, no local or regional recurrence was observed in patients who underwent surgery during the follow-up period, compared to two patients in the NACT group. Both NACT and NACRT were well tolerated, with no significant differences in severe adverse events. The most commonly observed grade 3–4 AE was myelosuppression (39% for NACRT and 47% for NACT, P = 0.609). No grade 5 AEs were observed between the two groups.

Interpretation Adding radiation to NACT increased the R0 resection rate, prolonged the PFS, and potentially improved OS in selected patients with initially unresectable LACC. The trial findings indicate that this approach is safe, feasible, and may confer a survival benefit.

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Keywords: Locally advanced colon cancer; Neoadjuvant chemoradiotherapy; Neoadjuvant chemotherapy; R0 resection

Research in context

Evidence before this study

We searched PubMed and Web of Science for the keywords ["locally advanced colon cancer (LACC)", "Neoadjuvant chemotherapy (NACT)", "Neoadjuvant chemoradiotherapy (NACRT)"] up to December 31, 2023, with no language restrictions. We identified several prospective randomized controlled trials on NACT for patients with LACC, as well as retrospective studies on NACRT for the same patient population. However, we found no evidence of phase III randomized controlled trials regarding the efficacy of NACRT in LACC.

Added value of this study

To our best knowledge, this study is the first randomized clinical trial to compare NACRT with NACT to manage LACC. We have demonstrated that NACRT, compared to NACT alone, might provide greater benefits to patients with initially unresectable LACC. Given the current lack of results from other phase III clinical trials in this field, the findings of our head-to-head study would provide higher-level evidence for future clinical practice.

Implications of all the available evidence

Our results supported the further evaluation of radiation in combination with NACT in treating initially unresectable LACC. NACRT may be a valuable treatment option for this patient population. Future prospective multicenter studies with larger cohorts, ideally randomized controlled trials, are needed to validate our findings.

Introduction

Treatment of localized colon cancer typically involves complete mesocolic excision to ensure radicality. However, since 10–26% of colon cancers are at a locally advanced stage,[1,2] extensive surgical resection leads to lower rates of adjacent organ preservation and increased positive surgical margins, postsurgical complications, and risk of local recurrence.[3–5]

The degree of resection radicality significantly affects the long-term survival and local control (LC) in patients with locally advanced colon cancer (LACC).[6,7] The incomplete resection with microscopic positive margins is a significant predictor of poor survival.[8] Moreover, about 5% of colon cancers are initially inoperable due to extensive tumor infiltration, organ adherence, or lymph node metastasis.[4] Therefore, converting unresectable LACC to a treatable status through neoadjuvant treatment is essential for these patients. Limited trials have demonstrated that neoadjuvant chemotherapy (NACT) helps manage resectable LACC, downstaging the tumors and improving their regression rates with acceptable toxicity compared to postoperative therapy.[9–12] However, few trials have investigated therapies that can convert unresectable LACC into a treatable disease.

The optimal treatment modality for LACC remains unclear owing to the lack of high-level clinical evidence. Neoadjuvant chemoradiotherapy (NACRT) is the standard treatment for locally advanced rectal and esophageal cancers, given its ability to improve resection radicality, survival outcomes, and quality of life.[13–18] However, the benefits of NACRT in LACC remain poorly understood, with only a few small-sample retrospective studies reporting its outcomes.[19–21] We have previously presented several reports of over 100 patients with initially unresectable LACC receiving NACRT and subsequent surgical resection based on real-world clinical practice, with promising survival benefits.[22–24] The encouraging results indicate that radiotherapy may be more beneficial than previously appreciated for the treatment of colon cancer. Nonetheless, no study has directly compared NACRT with NACT for LACC. Our randomized trial aims to investigate whether adding radiation to NACT can provide more surgical opportunities for patients with unresectable LACC, thereby improving their survival rates.

Methods

Study design and participants

This was an open-label, single-center, randomized, controlled phase 3 trial conducted in China. All patients provided written informed consent before enrollment. The trial was registered at ClinicalTrials.gov, number NCT03970694. The research protocol (Supplement 1) was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (IRB: B2018-144-01) and adhered to the Declaration of Helsinki and Guidelines for Good Clinical Practice, and the local laws and regulations of China.[25] The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit platform (www.researchdata.org.cn).

Participants

Eligible participants were aged 18–75 years with newly diagnosed LACC, where the distance from the lower

edge of the tumor to the anal edge was ≥15 cm (from the sigmoid colon to the ileocecal region). All patients attended multidisciplinary team conferences for discussions. Preoperative staging required fulfilling at least one of the following criteria: surgical exploration confirming unachievable R0 resection; tumor invasion of adjacent organs/adhesion to structures (T4b stage), unachievable R0 resection based on imaging; severe pericolonic lymph node involvement adjacent to large abdominal vessels based on imaging, leading to difficult lymphadenectomy and increasing the risk of intraoperative vascular rupture and massive hemorrhage; multidisciplinary team evaluation determining the need for extensive multi-visceral resection, expected to result in severe structural damage and loss of organ function, significantly impacting the postoperative quality of life. Other eligibility criteria included no obvious signs of intestinal obstruction or relieved obstruction after proximal enterostomy and the absence of distant metastasis based on preoperative CT/MRI/PET-CT. The detailed inclusion and exclusion criteria are outlined in the research protocol (Supplement 1). All these assessments were conducted before randomization.

Sample size calculation

Sample size calculation was based on the initial study design assumptions: a two sided alpha level of 0.05 with an 80% power, improvement of 5-year OS from 45% in the control group to 65% in the research group, 4-year enrollment period. The study and control groups were expected to enrolled at least 74 and 75 patients, respectively. Accounting for a 20% dropout rate, the final sample size was 186, with 93 patients in each group.

Random assignment and masking

The research group and control group were randomized in a 1:1 ratio. The study population was randomized by the Central Office of the Clinical Trials Center of Sun Yat-sen University Cancer Center. The random assignment was not masked, and the patients, providers, and data managers were aware of the treatment allocation.

Procedures

Patients were randomly allocated to the NACRT (research group) or the NACT group (control group). The NACT group received XELOX for 4 cycles, while the NACRT group received additional radiotherapy to the primary tumor. The XELOX regimen consisted of oxaliplatin 130 mg/m^2, qd, d1, every 3 weeks and capecitabine 1000 mg/m^2, bid, d1-d14, every 3 weeks. For concurrent chemotherapy during radiotherapy, the mXELOX regimen with oxaliplatin (100 mg/m^2) was administered. In the NACRT group, all patients underwent 3 mm slice thickness contrast-enhanced CT simulation scanning with site-specific immobilization. The Gross Tumor Volume (GTV) included primary tumor lesions, surrounding tissues and organs infiltrated by the tumor, and positive lymph nodes indicated by MRI or CT imaging. The Clinical Target Volume (CTV), in addition to the GTV, includes sections of the colon at both ends of the primary tumor and the corresponding lymphatic drainage region. Additionally, for patients with T4b sigmoid colon cancer that invades the bladder, the CTV included presacral, internal iliac, and external iliac lymphatic drainage region. The prescribed radiation doses were: GTV 45–50 Gy/25 F, 1.8–2.0 Gy/F; CTV 42.5–45 Gy/25 F, 1.7–1.8 Gy/F. Volumetric intensity-modulated arc therapy was used for treatment planning, and cone-beam CT was mandatory for image-guided radiation therapy once a week. After neoadjuvant treatment, the clinical response was evaluated using colonoscopy, CT, and MRI five weeks after radiotherapy or two weeks after the fourth cycle of chemotherapy. If the tumor had converted to a resectable status, surgery was performed 6–12 weeks after the end of neoadjuvant treatment, following the complete mesocolic excision (CME) principles. Adjuvant chemotherapy with XELOX was routinely administered after the CME. Delayed resection was performed in cases with concern for tumor stability or when imaging reassessed that achieving R0 resection was still unachievable after neoadjuvant treatment. In these cases, up to four additional cycles of chemotherapy were administered. Second-line chemotherapy was initiated if tumor progression occurred.

Study termination

Patient enrollment was terminated prematurely in July 2021 due to significant differences in the conversion and R0 resection rates between the two groups. Short-term analysis yielded a 99% power calculation based on the R0 resection rate. In addition, the enrolled patients were not selected based on mismatch repair (MMR) status. The early termination was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center (B2018-144-07). The study protocol will be improved and refined in future clinical trials that are newly launched.

Outcomes

The primary outcome of this trial was the 5-year OS rate. Secondary outcomes included the 3-year progression-free survival (PFS) and R0 resection rates. Owing to the early termination of the study, the R0 resection rate was the primary concern for short-term outcome analysis. OS was defined as the interval between the time of randomization and death from any cause. PFS was measured from randomization to progressive disease (PD; according to RECIST version 1.1) that precluded surgery, local or distant recurrence, or death from any cause. The R0 resection rate was defined as the percentage of patients whose post-operative pathology indicated the absence of tumor cells within 1 mm of any resection margin as observed under a microscope. LC

was defined as the interval between the time of randomization and primary lesion progression during treatment/local recurrence after R0 resection. The complete response rate is defined as the proportion of patients who achieved either a pathological complete response or a clinical complete response. Acute adverse events (AEs) occurring during and within 30 days of radiotherapy and chemotherapy were evaluated and graded according to the Common Terminology Criteria for Adverse Events Version (CTCAE) 5.0.

Statistical analysis

The initial analysis was based on a modified intention-to-treat population (mITT), which included randomized patients who received at least two cycles of chemotherapy per randomized assignment. The per-protocol population (eligible and randomized participants who adhered to treatment assigned) and the as-treated population (eligible patients analyzed per treated received) were used as a key sensitivity analysis. AEs were summarized according to as-treated population. Categorical data were compared using the chi-squared test or Fisher's exact test, as appropriate. Survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios and 95% confidence interval were calculated using a Cox proportional hazard model. Odds ratios and 95% confidence interval were calculated using a Logistic regression model. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS (version 23.0; IBM Corp., Armonk, NY, USA) and R statistical software (version 3.6.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All investigators read, discussed, and approved the final version of this manuscript. All investigators had full access to the dataset and took responsibility for the authenticity and integrity of the dataset as well as the decision to submit for publication.

Results

Patients and tumor characteristics

From July 2019 to July 2021, 49 patients with initially unresectable LACC who met the inclusion criteria were enrolled in the trial and underwent randomization. Four patients in the NACRT group were deemed ineligible after enrollment due to consent withdrawal or protocol entry violations and did not receive the assigned intervention. Ultimately, 25 and 20 patients were included in the NACRT and NACT groups for analysis based on the mITT population. Details of patient recruitment and outcomes after initiation of protocol-directed therapy are shown in Fig. 1.

The patient and tumor characteristics are summarized in Table 1. The detailed reasons for not performing radical resection at the initial diagnosis for each

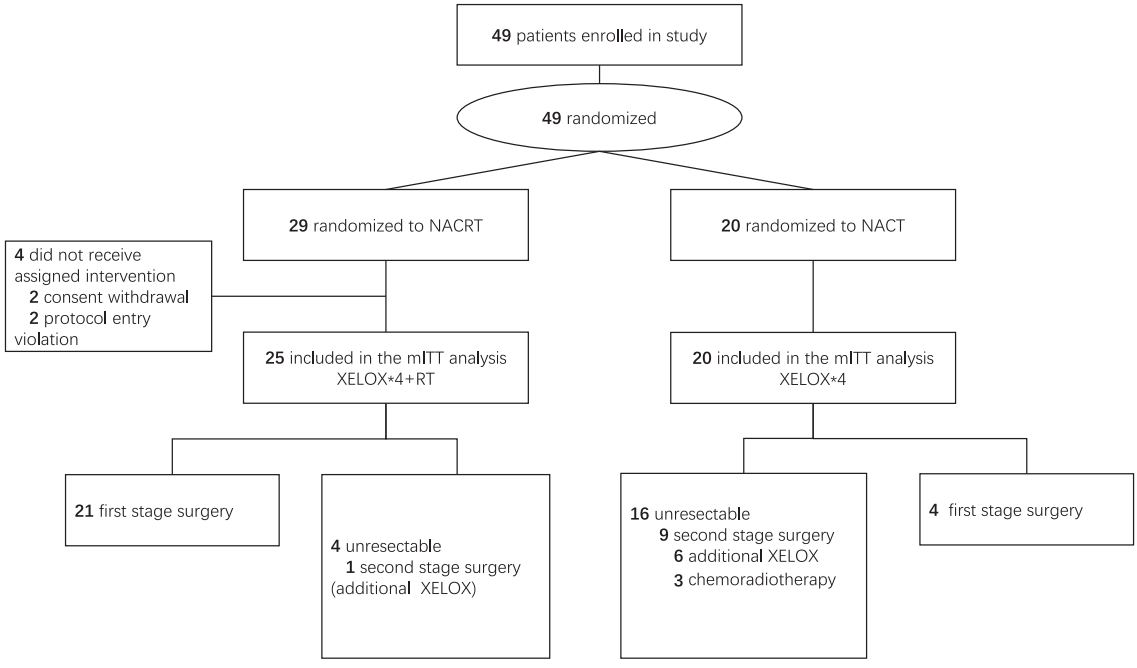

Fig. 1: CONSORT Flow chart of participants.

patient are summarized in Supplementary Table S1. Most preoperative characteristics were well-balanced between the NACRT and NACT groups. The primary tumor was in the sigmoid colon, descending colon, transverse colon, ascending colon, and the ileocecum in 23, 6, 6, 8, 7, and 1 patient, respectively. Based on pathological analysis, the tumor was an adenocarcinoma in all patients, mostly moderately differentiated. While 40 patients (89%) had clinical T4b stage disease, 43 (96%) had stage IIIc disease. The bladder and small intestine were the organs most commonly invaded by tumors. Notably, the NACT group had more patients with higher pre-treatment CEA levels, although the difference was not statistically significant.

Clinical and pathological outcomes

In the first stage of the study, all patients received four cycles of chemotherapy with or without radiotherapy. Based on the radiographic and endoscopic clinical responses, 21 patients in the NACRT group had a complete or partial response, compared to only 4 patients in the NACT group. The tumor conversion to a resectable status was significantly higher in the NACRT (n = 21, 84%) than in the NACT (n = 4, 20%) group (P < 0.001).

All patients who underwent surgery achieved R0 resection with negative margins confirmed by pathology, except for 1 patient in the NACRT group who showed tumor infiltration in the right ureter. The R0 resection rate in the first stage was significantly improved in the NACRT (20/25, 80%) than in the NACT (4/20, 20%) group (P < 0.001).

In addition, the NACRT group was also superior to NACT in terms of the downstaging rate (downstaged T: 72% vs. 10%; downstaged N: 80% vs. 20%; both P < 0.001) and organ preservation. In the NACRT group, tumors were successfully converted to a resectable status in 6/8 patients with bladder invasion, and all retained their bladders after surgery, with 4 of them undergoing partial cystectomy. In contrast, in the NACT group, only 1/6 of patients with bladder invasion underwent surgery and retained the bladder. Treatment outcomes, including surgical results and pathological findings, are detailed in Table 2.

Ten patients (9 from the NACT and 1 from the NACRT group) who did not initially achieve conversion to resectable LACC after the neoadjuvant treatment received additional downstaging treatment in the second stage and were successfully converted during the second clinical response evaluation. The NACRT patient received an additional cycle of XELOX chemotherapy, while of the NACT patients, 6 received additional cycles of XELOX chemotherapy, and 3 received additional concurrent chemoradiotherapy, as per their preference. They all underwent R0 resection after the second stage. Thus, 42 patients (25 in NACRT; 17 in NACT) were suitable for per-protocol efficacy analysis and 45 patients (28 in NACRT; 17 in NACT) were suitable for AT

Characteristic	NACRT (n = 25)	NACT (n = 20)	P value[a]
Age			
Median	53	58	0.512
Range	24–72	26–68	
Gender			
Male	18 (72%)	16 (80%)	0.729
Female	7 (28%)	4 (20%)	
KPS			
90	21 (84%)	17 (85%)	1.000
80	4 (16%)	3 (15%)	
Primary tumor location			
Sigmoid colon	15 (60%)	8 (40%)	0.235
Descending colon	4 (16%)	2 (10%)	
Transverse colon	2 (8%)	6 (30%)	
Ascending colon	3 (12%)	4 (20%)	
Ileocecus	1 (4)	0	
Primary tumor side			
Right-sided	6 (24%)	10 (50%)	0.070
Left-sided	19 (76%)	10 (50%)	
Tumor differentiation			
Well differentiated (grade 1)	1 (4%)	0	0.176
Moderately differentiated (grade 2)	20 (80%)	13 (65%)	
Poorly differentiated (grade 3)	4 (16%)	7 (35%)	
cT stage			
T3	1 (4%)	1 (5%)	1.000
T4a	2 (8%)	1 (5%)	
T4b	22 (88%)	18 (90%)	
cN stage			
N1	2 (8%)	3 (15%)	0.642
N2	23 (92%)	17 (85%)	
8th Edition of the AJCC staging			
IIIb	1 (4%)	1 (5%)	1.000
IIIc	24 (96%)	19 (95%)	
MMR status			
pMMR	21 (84%)	16 (80%)	1.000
dMMR	3 (12%)	3 (15%)	
Unknown	1 (4%)	1 (5%)	
Pre-treatment CEA			
≤5 ng/ml	14 (56%)	6 (30%)	0.081
>5 ng/ml	11 (44%)	14 (70%)	
Pre-treatment CA199			
≤35 U/ml	15 (60%)	12 (60%)	1.000
>35 U/ml	10 (40%)	8 (40%)	
Major Involved organ			
Bladder	8 (32%)	6 (30%)	0.311
Small intestine	4 (16%)	5 (25%)	
Abdominal wall	2 (8%)	5 (25%)	
Ureter	3 (12%)	3 (15%)	
Great vessel	2 (8%)	2 (10%)	
Pelvic wall	4 (16%)	0	
Uterus	2 (8%)	1 (5%)	
Ovary	2 (8%)	1 (5%)	
Liver	0	2 (10%)	
Pancreas	0	2 (10%)	

(Table 1 continues on next page)

Characteristic	NACRT (n = 25)	NACT (n = 20)	P value[a]
(Continued from previous page)			
Iliopsoas muscle	2 (8%)	0	
Prostate and seminal vesicle	0	1 (5%)	

Abbreviation: KPS, Karnofsky Performance Status; NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; MMR, mismatch repair. [a]P values were calculated with the χ^2 test (or Fisher's exact test).

Table 1: **Patient characteristics.**

efficacy analysis. In the as-treated population, the stoma rates after radical surgery were 20% in the NACRT group and 18% in the NACT group, with an average length of stay of 12 days and 11 days, respectively. No patients required reoperation or were readmitted due to postoperative complications. Second stage treatment outcomes according to the as-treated population are detailed in Supplementary Table S2.

Among the three patients in the NACRT group who did not undergo radical resection, one patient developed new liver metastasis during NACRT and another patient refused multivisceral resection (MVR), despite having the surgical opportunity for their primary tumors with potential for R0 resection. Another patient in the NACRT group and 7 patients in the NACT group who following four or more cycles of XELOX still could not undergo radical resection for their primary tumors after evaluation. They switched to second-line systemic therapy or maintenance therapy.

Characteristic	NACRT (n = 25)	NACT (n = 20)	P value[c]
First stage surgery			
Yes	21 (84%)	4 (20%)	**<0.001**
No	4 (16%)	16 (80%)	
R0 resection			
Yes	20 (80%)	4 (20%)	**<0.001**
No	5 (20%)	16 (80%)	
TRG[a]			
0–1	11 (52%)	1 (25%)	0.328
2–3	10 (48%)	3 (75%)	
pT stage[a]			
T0	3 (14%)	1 (25%)	1.000
T1	2 (10%)	0	
T2	1 (5%)	0	
T3	12 (57%)	2 (50%)	
T4	3 (14%)	1 (25%)	
pN stage[a]			
N0	15 (71%)	2 (50%)	0.382
N1	6 (29%)	2 (50%)	
Down stage T			
Yes	18 (72%)	2 (10%)	**<0.001**
No	7 (28%)	18 (90%)	
Down stage N			
Yes	20 (80%)	4 (20%)	**<0.001**
No	5 (20%)	16 (80%)	
CR			
Yes	3 (12%)	1 (5%)	0.394
No	22 (88%)	19 (95%)	
Bladder preservation[b]			
Yes	6 (75%)	1 (17%)	0.051
No	2 (25%)	5 (83%)	

Abbreviation: NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; TRG, tumor regression grade; CR, complete response. Bold values represent the P-values that are statistically significance. [a]Percent of resected patients. [b]Percent of patients with bladder involvement. [c]P values were calculated with the χ^2 test (or Fisher's exact test).

Table 2: **Outcomes at the end of the first stage, according to the mITT population.**

Survival

The median follow-up time was 42.3 and 36.0 months for the NACRT and NACT groups, respectively, and no patients were lost to follow-up.

In the mITT population, the 3-year OS rates were 87.6% and 75.0%, respectively (P = 0.037; Fig. 2A), while the 3-year PFS rates were 76.0% and 45.0% in the NACRT and NACT groups, respectively (P = 0.049; Fig. 2B). In the NACRT group, no local or regional recurrence was observed in patients who underwent surgery during the follow-up period, and all post-operative failures were due to distant metastases. In contrast, two patients in the NACT group experienced local-regional recurrence after surgery. Three year-LC rates were 96.0% in the NACRT group compared to 60.0% in the NACT group, respectively (P = 0.002; Fig. 2C). The 5-year OS was not reached.

For key sensitivity analysis, consistent results were also shown in the per-protocol and as-treated population (Supplementary Table S3, Supplementary Figures S1 and S2 in Supplement 2). The NACRT group exhibits significantly higher OS, PFS and LC compared to the NACT group.

Toxicity

Both NACT and NACRT were safe and well tolerated, with no significant differences in the rates of AEs reported during and after treatment (Table 3). The most commonly observed grade 3–4 AE was myelosuppression (39% for NACRT and 47% for NACT, P = 0.609). No grade 5 AEs were observed between the two groups. No patients were deemed ineligible for surgery due to acute AEs. No severe postoperative complications, such as anastomotic leakage or intestinal obstruction, were observed after radical resection.

Discussion

This study is the first randomized clinical trial to compare NACRT with NACT to manage initially unresectable LACC. With advancements in radiotherapy,

precise irradiation of mobile primary or metastatic tumor lesions, such as those in the lungs and colon, has improved significantly, leading to better tumor control and reduced AEs.[26,27] Despite accumulating retrospective evidence suggesting that NACRT can enhance the survival of patients with colon cancer,[19–24,28] no clear clinical practice guidelines have been established. Hence, we conducted a randomized controlled trial to compare the short-term outcomes of NACRT and NACT in LACC. The initial analysis of the clinical and pathological outcomes in the first 45 patients demonstrated that NACRT is associated with a higher R0 resection rate, extended survival, and a favorable safety profile.

The ability of neoadjuvant therapy to downstage a tumor is crucial in converting unresectable LACC to a resectable disease. Some clinical trials have shown tumor downstaging in resectable LACC following NACT.[9–12] In the FOxTROT trial, NACT reduced T4 disease from 31% to 21%.[12] In the Danish trial, after NACT, 34% (24/71) of patients converted to a lower T stage, 11% progressed to a higher stage, and 66% achieved N0 status compared to the initial CT scan.[9] Overall, the results of these trials were not entirely satisfactory.

Previous studies have shown that NACRT achieved a lower T stage in 66%–82% and a lower N stage in 84%–93% of patients.[19,23,24,29] Consistent with these findings, we found that 72% and 80% of patients converted to a lower T and N stage, respectively, in the NACRT group compared to 10% and 20% patients in the NACT group after four cycles of chemotherapy. Our study also indicated a tendency towards a lower tumor regression grade with NACRT than with NACT.

The better tumor regression in this study can be attributed to the addition of local therapy, i.e., radiotherapy, which significantly improved the conversion and R0 resection rates compared to chemotherapy alone. Furthermore, NACRT may lead to higher organ preservation. Radiotherapy reduces tumor invasion, reducing the extent of radical resection required, thereby decreasing the risk of complications and the potential impact on survival, such as MVR.[5,30]

Our study revealed that the NACRT group had significantly longer PFS and OS than the NACT group, which can be primarily attributed to the higher resection rates observed in the former. Additionally, our previous studies have consistently shown that patients with better ypTMN stage have higher survival rates.[23,24] These findings confirm our hypothesis that enhancing local therapy improves pathological outcomes and positively impacts the OS.

Acute toxicity is another important concern associated with NACRT. Studies on rectal cancer have demonstrated a favorable safety profile for doublet NACT combined with radiotherapy.[15] This study showed

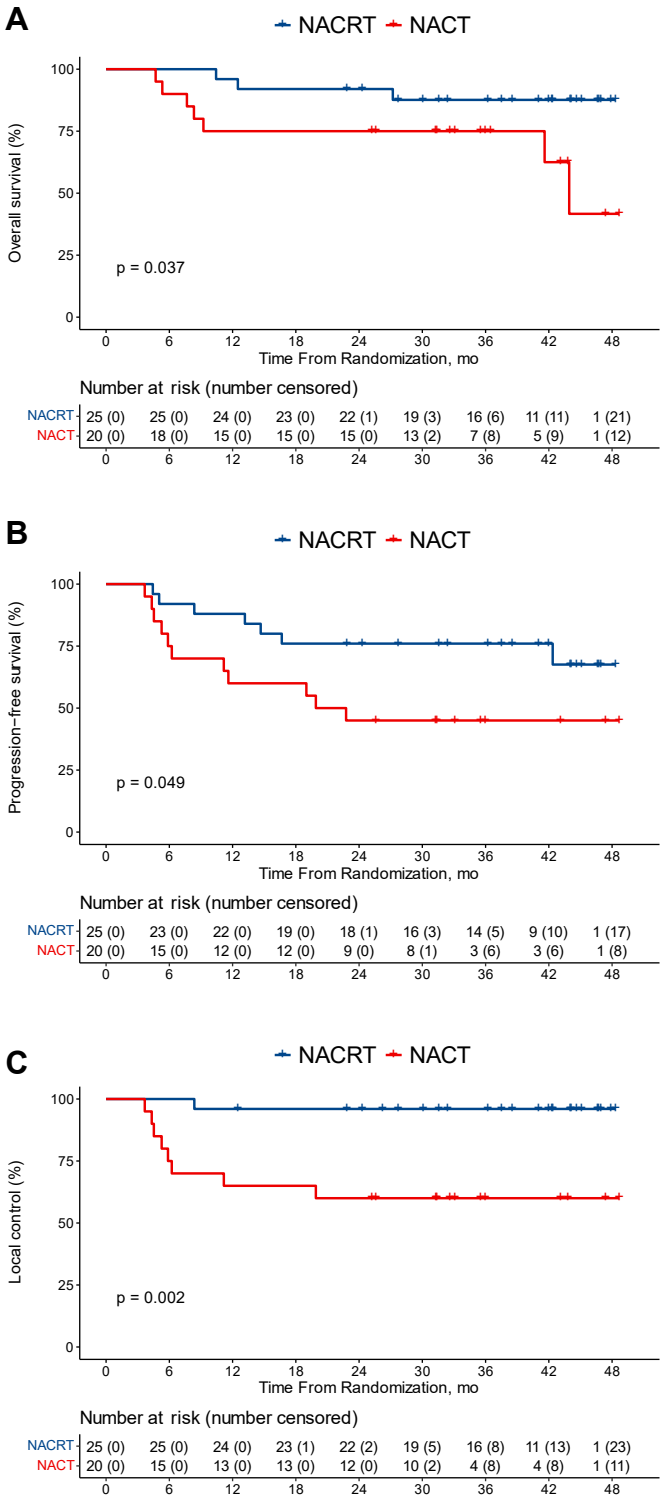

Fig. 2: Kaplan–Meier estimates of (**A**) overall survival, (**B**) progression-free survival, and (**C**) local control based on the modified intention-to-treat population*. *P-value were calculated using the log-rank test. Abbreviation: NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy.

Adverse events	NACRT (n = 28)	NACT (n = 17)	P value for events grade ≥1[a]	P value for events grade ≥3[a]
Hematological				
Any Myelosuppression				
Grade 1–2	16 (57%)	6 (35%)	0.144	0.609
Grade 3	6 (21%)	7 (41%)		
Grade 4	5 (18%)	1 (6%)		
Leukopenia				
Grade 1–2	20 (71%)	4 (24%)	0.293	0.511
Grade 3	3 (11%)	1 (6%)		
Anemia				
Grade 1–2	11 (39%)	6 (35%)	0.392	0.256
Grade 3	4 (14%)	6 (35%)		
Grade 4	3 (11%)	1 (6%)		
Thrombocytopenia				
Grade 1–2	6 (21%)	4 (24%)	0.616	0.345
Grade 3	4 (14%)	2 (12%)		
Grade 4	2 (7%)	0		
Non-Hematological				
Fatigue				
Grade 1–2	3 (11%)	1 (6%)	0.511	NA
Mucositis				
Grade 1–2	26 (93%)	13 (76%)	0.133	NA
GI toxicities				
Grade 1–2	23 (82%)	13 (76%)	0.635	0.489
Grade 3	1 (4%)	1 (6%)		
Grade 4	1 (4%)	1 (6%)		
Intestinal obstruction	2 (7%)	2 (12%)	0.489[b]	NA
Anastomotic leakage	0	0	NA	NA

Abbreviation: NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; GI, gastrointestinal; NA, not applicable. [a]P values were calculated with the χ^2 test (or Fisher's exact test). [b]P values for incidence of intestinal obstruction.

Table 3: **Treatment-related toxicities, according to the as-treated population.**

no significant increase in toxicities with the addition of radiotherapy compared to chemotherapy alone, consistent with our previous findings of <10% grade 3–4 GI toxicity. Notably, other trials, such as the FOxTROT, Danish, and Prodige 22 trials, which focused on NACT for LACC, reported a 7%–12% incidence of grade 3–4 GI toxicity.[9–11] In the NACRT group, except one patient experienced intestinal perforation and was excluded during the initial stage of neoadjuvant treatment, potentially due to rapid tumor regression after chemotherapy, no other patients were required to emergency surgery for treatment-related complications. Two patients developed intestinal obstruction during chemoradiotherapy. No severe postoperative complications were observed after the radical resection. Considering the utilization of contemporary radiotherapy techniques for target delineation and treatment delivery, we show that NACRT is safe, well-tolerated, and associated with acceptable acute toxicities in patients with LACC. Our study did not analyze and compare the late toxicities of NACRT and NACT, which needs to be further explored in future research.

Nevertheless, it is important to note that our study has some limitations and potential shortcomings. First, the selection of the study population was not based on MMR status. Since we did not incorporate these factors into our enrollment criteria during the trial design in 2019, patients with advanced disease and MSI-H/dMMR status may have lost the opportunity to benefit from immunotherapy, based on the results of Keynote 177, published in 2020.[31] Second, the intensity of the systematic therapy regimen in our study might be relatively weak. Six patients in the NACT group who received additional cycles of chemotherapy successfully converted in the second stage, indicating room for optimization. In recent years, the upfront systemic treatment for metastatic colon cancer has evolved, and triplet chemotherapy, with or without targeted therapy, has emerged as another option for locally advanced or metastatic colorectal cancer.[32–34] Third, due to the relatively small sample size, there was some imbalance in patient baselines, such as organ invasion and CEA levels. Fourth, there is some variability in the criteria for determining unresectability across different institutions, which may be influenced by factors such as imaging evaluation, treatment conditions, and clinician subjectivity. The criteria for unresectability in this study also have some limitations in generalizability. Future research should aim to establish a more comprehensive definition of unresectability criteria.

Overall, given the current lack of results from other phase III clinical trials in this field, the findings of our head-to-head study still have certain guiding implications for clinical practice. However, due to the early termination and sample size constraints, caution should be exercised when interpreting the results.

In conclusion, adding radiation to NACT increased the R0 resection rate, prolonged the PFS, and potentially improved the OS in patients with initially unresectable LACC. The initial trial results indicate that this approach is safe, feasible, and may confer a survival benefit. NACRT could be considered for further evaluation in future larger-scale clinical trials.

Contributors

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Z.-T. Zhang, Xiao, Li, Wu, and Wang contributed equally to this study. Concept and design: Gao, R. Zhang. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Z.-T. Zhang, Xiao, Li, Wu, Wang. Critical revision of the manuscript for important intellectual content: Xiao, Wang, Chang, Tian, Gao, R. Zhang, Jiang, Lin, R.-X. Zhang, Fan, Pan. Statistical analysis: Z.-T. Zhang, Xiao, Wang, Chang, Tian. Obtained funding: Wang, Chang, Gao. Administrative, technical, or material support: Chang, Tian, Jiang, Lin, R.-X. Zhang, Fan, Pan, Gao, R. Zhang. Supervision: Gao, R. Zhang. Drs Z.-T. Zhang, Xiao, Li, Wu, and Wang had directly accessed and verified the underlying data reported in the manuscript. All authors read and approved the final manuscript.

Data sharing statement

Considering patients' privacy and related regulations in China, we chose not to make the database public to everyone. However, our raw database will be deposited on the Research Data Deposit public platform (www.researchdata.org.cn). If a researcher wants to use our raw data for scientific research purposes, he or she could apply for use with our corresponding author and database administrator.

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Funding sources were not involved in the study design, data collection, analysis and interpretation, writing of the report, or decision to submit the article for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102836.

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