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Neoadjuvant short-course radiotherapy followed by camrelizumab and chemotherapy for locally advanced rectal cancer: 3-year survival from a phase 2 study

Zhenyu Lin[1,2,3†], Peng Zhang[4†], Ming Cai[4], Gang Li[4], Tao Liu[1,5], Kailin Cai[4], Jing Wang[1], Junli Liu[1], Hongli Liu[1], Weikang Zhang[4], Jinbo Gao[4], Chuanqing Wu[4], Linfang Wang[4], Zheng Wang[4], Zhiguo Hou[6], Hongyi Kou[6], Kaixiong Tao[4*] and Tao Zhang[1,2,3*]

Abstract

Background Neoadjuvant short-course radiotherapy (SCRT) followed by camrelizumab and chemotherapy has shown an encouraging pathological complete response rate (48.1%, primary endpoint) in patients with locally advanced rectal cancer (LARC). Here, we present the 3-year survival outcomes.

Methods In this phase 2 trial, patients with previously untreated T3-4N0M0 or T1-4N + M0 rectal adenocarcinoma received 5 × 5 Gy SCRT over 5 days, followed by two cycles of camrelizumab (200 mg) and CAPOX regimen every 3 weeks after 1 week. Total mesorectal excision (TME) was scheduled 1 week after the completion of neoadjuvant treatment. The 3-year disease-free survival (DFS) and overall survival (OS) were evaluated in this analysis.

Results A total of 30 patients were enrolled, of whom 28 (93.3%) had microsatellite stable status (MSS) and 27 (90.0%) underwent TME. With a median follow-up of 40.8 months, the median DFS and OS were both not reached, with the 3-year DFS and OS rates of 80.2% (95% CI 58.6–91.3) and 93.3% (95% CI 75.9–98.3), respectively. Additionally, there was a trend toward improved 3-year DFS and OS in patients with pCR, postoperative pathological node-negative status (pN0), baseline negative circumferential resection margin as assessed by MRI, baseline negative extramural venous invasion and a PD-L1 combined positive score of 1 or higher, as compared with those without these characteristics.

Conclusions Our data support the potential efficacy of neoadjuvant SCRT followed by camrelizumab and CAPOX regimen in LARC, as indicated by 3-year survival outcomes, suggesting that this may be an alternative therapeutic strategy, especially with the potential to address an unmet need for MSS patients.

Trial registration www.ClinicalTrials.gov. NCT04231552.

Keywords Locally advanced rectal cancer, Neoadjuvant, Short-course radiotherapy, Camrelizumab, Survival

†Zhenyu Lin and Peng Zhang are equal contributors.

*Correspondence:
Kaixiong Tao
kaixiongtao@hust.edu.cn
Tao Zhang
taozhangxh@hust.edu.cn
Full list of author information is available at the end of the article

Background

Total neoadjuvant therapy (TNT) is an emerging standard of care for patients with locally advanced rectal cancer (LARC), especially those with low rectal disease or a higher risk for local or distant metastases [1]. In contrast to traditional treatment modalities (i.e., long-course chemoradiotherapy (LCRT) or short-course radiotherapy (SCRT) followed by total mesorectal excision (TME) and then adjuvant chemotherapy), TNT pulls adjuvant chemotherapy forward to the preoperative setting, further increasing compliance and reducing recurrence and metastasis [2–4]. However, the reduced probabilities of locoregional recurrence and distant metastasis appear insufficient to confer a substantial overall survival (OS) benefit [3–5]. This scenario underscores the need to develop novel neoadjuvant therapeutic strategies for this population.

The advent of immunotherapy has significantly improved patient outcomes and has become the mainstay of treatment for metastatic colorectal cancer with deficient mismatch repair (dMMR) status. However, its role in metastatic proficient MMR (pMMR) tumors has been modest, and the effect of introducing immunotherapy into neoadjuvant setting remains to be determined. SCRT upregulates programmed cell death-ligand 1 (PD-L1) expression and maintains it at a high level prior to surgery, which may synergize with immunotherapy at an early stage to mitigate the immunosuppressive effects and improve efficacy [6–8]. In this regard, we previously reported the primary analysis results of a phase 2 trial, in which patients with locally advanced rectal adenocarcinoma received neoadjuvant SCRT followed by camrelizumab plus CAPOX, demonstrating a pathological complete response (pCR) rate of 48.1% [9]. Additionally, a pCR rate of 46.2% was observed in pMRR patients. These results were impressive and superior to the standard neoadjuvant chemoradiotherapy.

Here, we present the secondary endpoints of this phase 2 trial, including 3-year disease-free survival (DFS) and 3-year OS.

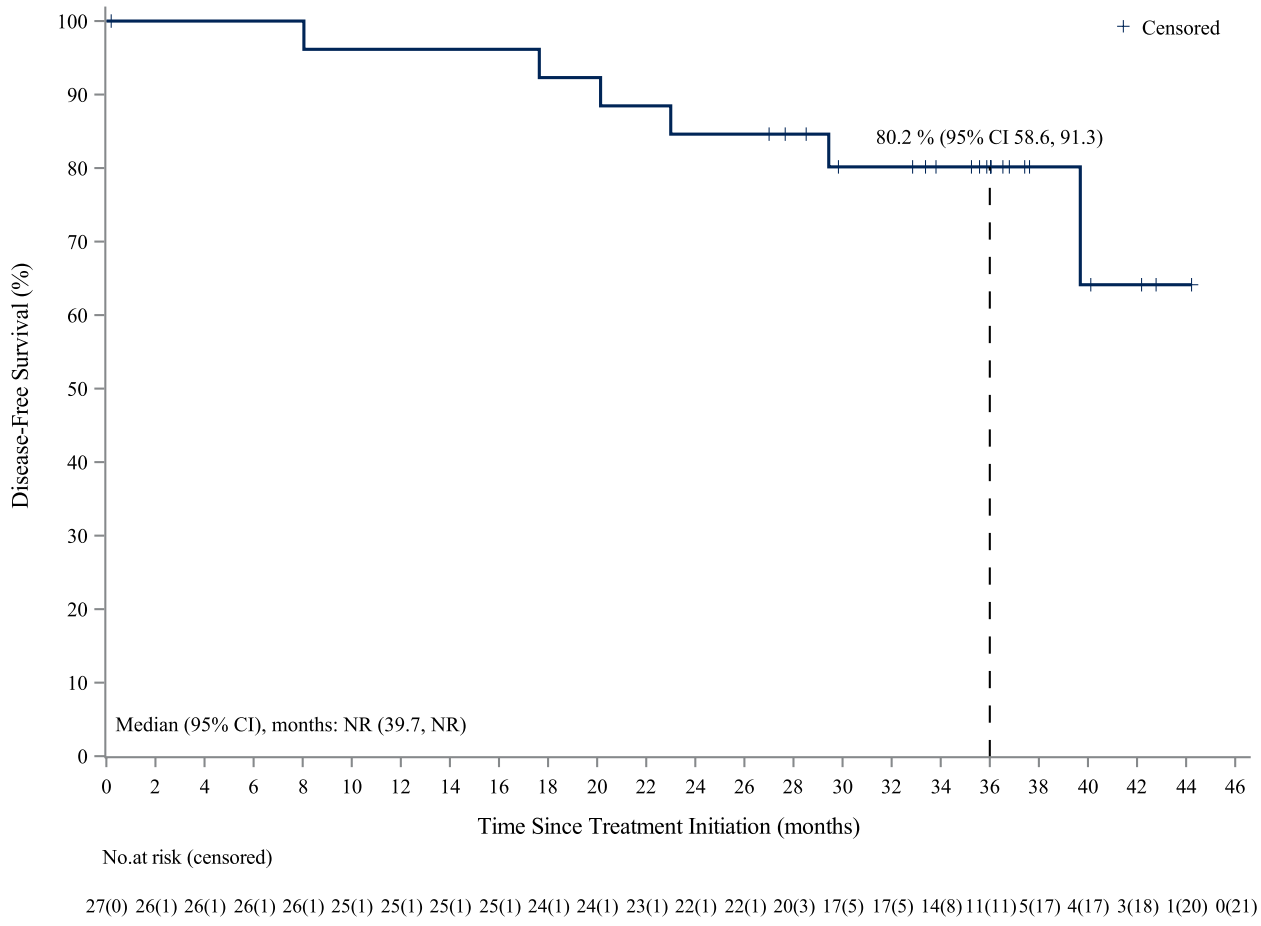

Fig. 1 Kaplan–Meier curves for 3-year disease-free survival. CI, confidence interval; NR, not reached

Methods

Study design and participants

This non-randomized, single-center, single-arm phase 2 trial (NCT04231552) was done at our center. This trial was done in accordance with the Declaration of Helsinki and Good Clinical Practices and the study protocol was approved by the Ethics Committee of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology. Written informed consent was obtained from all enrolled patients.

The detailed eligibility criteria of this trial have been previously described [9]. In brief, eligible patients were aged 18 to 75 years with previously untreated T3–4 N0M0 or T1–4 N+ M0 rectal adenocarcinoma, who had an inferior margin of 10 cm or less from the anal verge, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients received 5× 5 Gy SCRT over 5 days. After 1 week, camrelizumab (200 mg, intravenously, on day 1) and CAPOX (oxaliplatin: 130 mg/m^2, intravenously, on day 1, and capecitabine: 1000 mg/m^2, oral twice daily, on days 1–14) were administered every 3 weeks for two cycles, and TME was planned 1 week after the completion of neoadjuvant treatment. Adjuvant chemotherapy regimens were administered at the discretion of the investigator 3 to 4 weeks after surgery.

Outcomes and assessments

The primary endpoint was pCR rate in patients who received at least one dose of camrelizumab and underwent surgery, as previously published [9]. Secondary endpoints included 3-year DFS and 3-year OS. DFS was defined as the time from surgery to disease recurrence or death from any cause. OS was defined as the time from treatment initiation to death from any cause. The other secondary endpoints, including R0 resection rate, complication rate and safety, have been reported elsewhere [9].

All resection specimens were processed and examined according to the standardized protocol [10]. Tumor regression grade was categorized with Ryan's criteria [11]. Adverse events (AEs) were assessed and graded as

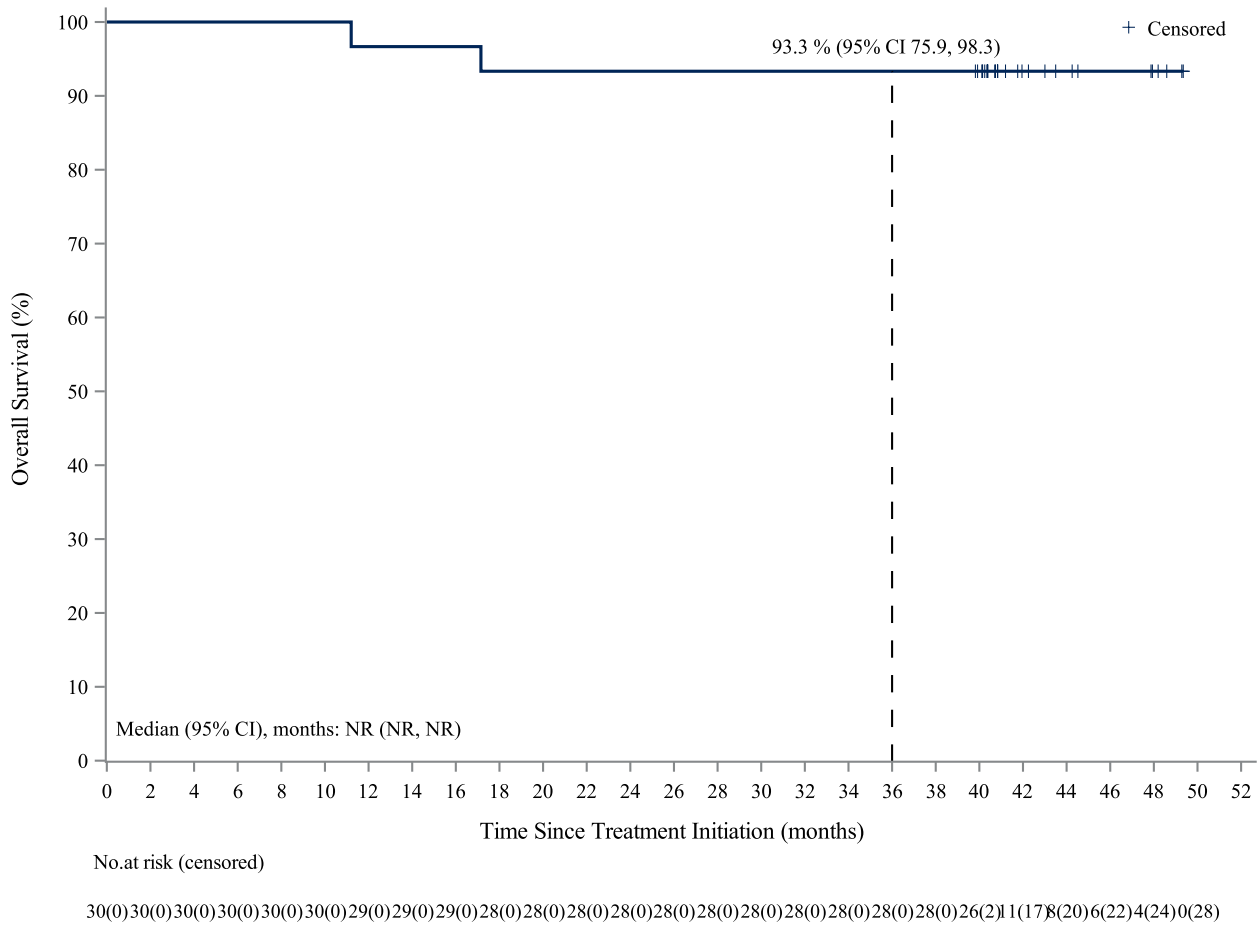

Fig. 2 Kaplan–Meier curves for 3-year overall survival. CI, confidence interval; NR, not reached

per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Postoperative follow-up was performed every 3 months for the first 3 years, every 6 months for the third to fifth years, and every year thereafter.

Statistical analysis

This analysis was conducted on patients who received at least one dose of camrelizumab and underwent TME for 3-year DFS and on all enrolled patients for 3-year OS. The Kaplan–Meier method was used to estimate 3-year DFS and OS, and the corresponding 95% confidence intervals (CIs) were estimated using the Greenwood method. Subgroup analyses for 3-year DFS and OS were based on the following characteristics: pCR (no versus yes), postoperative pathological node status (positive (pN +) versus negative (pN0)), baseline PD-L1 combined positive score (CPS; <1 versus ≥ 1), baseline circumferential resection margin (CRM) as assessed by MRI (positive versus negative), and baseline extramural venous invasion (EMVI; positive versus negative). The 3-year DFS and OS and their corresponding 95% CIs for subgroups were calculated using the same method as for the overall population aforementioned. In addition, DFS and OS were compared between subgroups using the log-rank test. Given the exploratory nature, all reported *p*-values were two-sided nominal ones. Statistical analyses were performed using SAS software, version 9.4.

Results

Between November 7, 2019, and September 14, 2020, 30 patients were enrolled, of whom 27 patients received at least one dose of camrelizumab plus CAPOX and underwent TME. The baseline characteristics of these 30 patients have been previously described [9]. Twenty-six (86.7%) patients had positive lymph nodes, of which 10 (33.3%) had N2 disease. Twenty-one (70.0%) and 12 (40.0%) patients had positive CRM and EMVI, respectively. Half of the patients (50.0%) had the lower edge of the tumor less than 5 cm from the anus. Additionally, the majority of patients were microsatellite stable (MSS; 28 (93.3%)) and had a PD-L1 CPS of less than 1 (20 (66.7%)).

Of the 27 patients who underwent TME, 21 (77.8%) patients received subsequent adjuvant chemotherapy with the CAPOX regimen. The median number of adjuvant cycles was 4 (range 1–6). Of the 21 patients, 17 (81.0%) patients received at least three cycles of adjuvant chemotherapy, with six (28.6%) patients receiving six cycles. Two patients who received 6 cycles of adjuvant chemotherapy experienced dose reductions due to weight loss and hand-foot syndrome, respectively. Three patients discontinued oxaliplatin during adjuvant therapy, one each for grade 2 thrombocytopenia, grade 2 gastrointestinal reaction, and unknown cause. No grade 5 AEs or emergent toxicities were observed.

As of the data cutoff date (January 4, 2024), the median follow-up duration was 40.8 months (IQR 40.3–44.3). Of the 27 patients who underwent TME, six (22.2%) experienced disease recurrence or death. Of these, local recurrence and distant metastasis occurred in one (3.7%) and five (18.5%) patients, respectively. The median DFS was not reached (95% CI 39.7-not reached), with a 3-year DFS rate of 80.2% (95% CI 58.6–91.3; Fig. 1). Two (6.7%) of the 30 patients succumbed to mortality, with a median OS of immaturity. The estimated 3-year OS rate was 93.3% (95% CI 75.9–98.3; Fig. 2).

Subgroup analysis showed that patients with pCR (100.0% versus 63.5%), postoperative pathological node-negative status (pN0; 94.4% versus 50.0%), a PD-L1 CPS of 1 or higher (100.0% versus 74.3%), baseline negative CRM as assessed by MRI (100.0% versus 69.5%) and negative EMVI (100.0% versus 54.5%) had a trend toward improved 3-year DFS compared to those without these characteristics (Table 1 and Fig. 3). Regarding 3-year OS, similar improvement trends were observed across the vast majority of subgroups, although the difference was not statistically significant (Table 2 and Fig. 4).

Discussion

In this study, neoadjuvant SCRT followed by immunotherapy and chemotherapy was associated with promising 3-year survival outcomes in patients with LARC. We

Table 1 Subgroup analyses of 3-year disease-free survival

Subgroups	Events/number	3-year DFS, % (95% CI)	*P*-value*
pCR			
No	6/14	63.5 (33.1, 83.0)	0.018
Yes	0/13	100.0 (100.0, 100.0)	
Postoperative pathological node status			
pN +	5/8	50.0 (15.2, 77.5)	0.003
pN0	1/19	94.4 (66.6, 99.2)	
PD-L1 CPS			
< 1	6/20	74.3 (48.7, 88.4)	0.242
≥ 1	0/6	100.0 (100.0, 100.0)	
Baseline CRM status assessed by MRI			
Positive	6/18	69.5 (41.3, 86.1)	0.036
Negative	0/9	100.0 (100.0, 100.0)	
Baseline EMVI status			
Positive	6/11	54.5 (22.9, 78.0)	0.002
Negative	0/16	100.0 (100.0, 100.0)	

* *P*-value was nominal, as determined by log-rank test. *CI*, confidence interval; *CPS*, combined positive score; *CRM*, circumferential resection margin; *DFS*, disease-free survival; *EMVI*, extramural venous invasion, *MRI*, magnetic resonance imaging; *pCR*, pathological complete response; *PD-L1*, programmed cell death-ligand 1

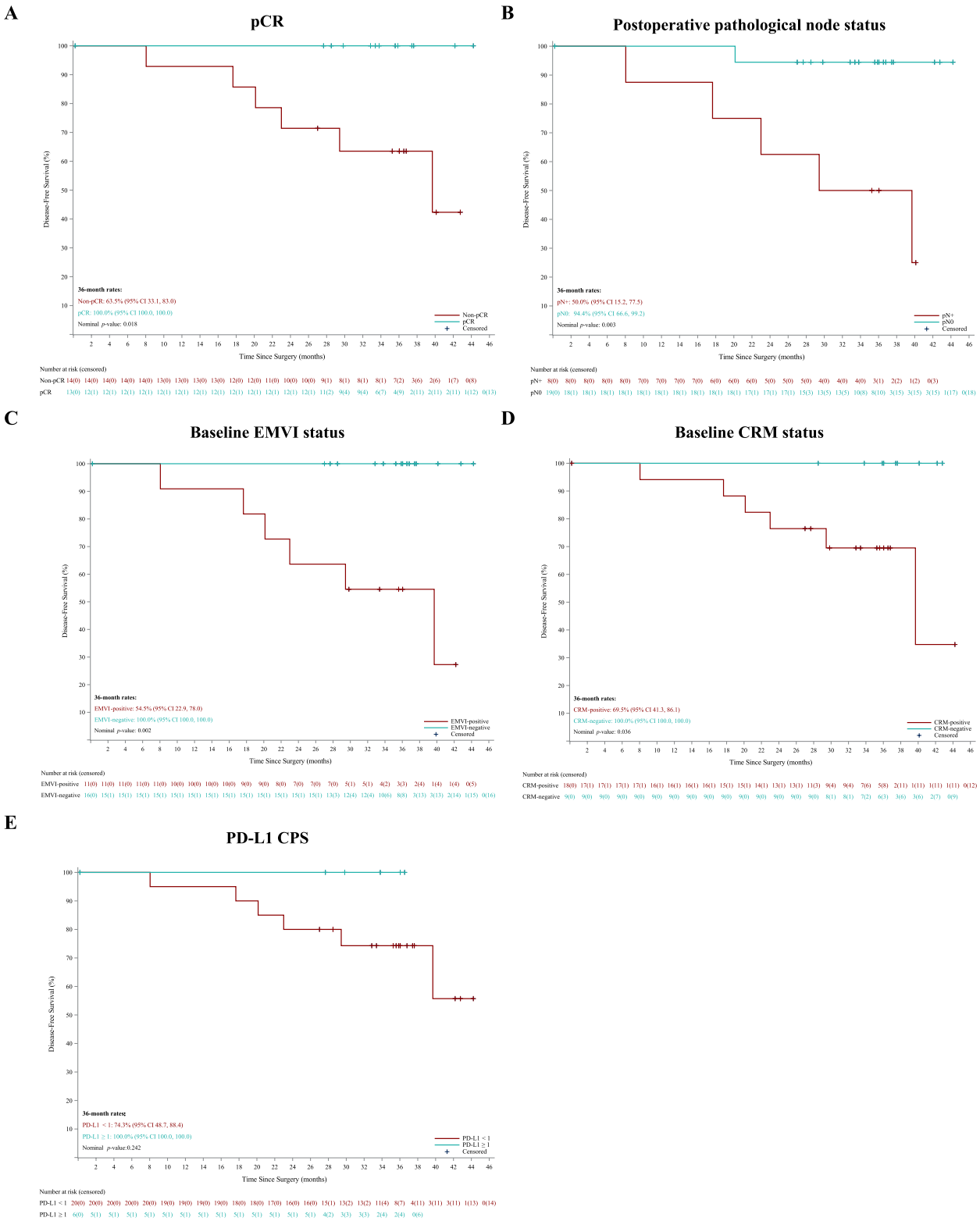

Fig. 3 Subgroup analysis of 3-year disease-free survival stratified by pCR (**A**), postoperative pathological node status (**B**), baseline EMVI status (**C**), baseline CRM status (**D**), and PD-L1 CPS (**E**). CI, confidence interval; CPS, combined positive score; CRM, circumferential resection margin; EMVI, extramural venous invasion; pCR, pathological complete response; PD-L1, programmed cell death-ligand 1

Table 2 Subgroup analyses of 3-year overall survival

Subgroups	Events/number	3-year OS, % (95% CI)	*P*-value*
pCR			
No	1/14	92.9 (59.1, 99.0)	0.335
Yes	0/13	100.0 (100.0, 100.0)	
Postoperative pathological node status			
pN +	1/8	87.5 (38.7, 98.1)	0.123
pN0	0/19	100.0 (100.0, 100.0)	
PD-L1 CPS			
< 1	1/20	95.0 (69.5, 99.3)	0.584
≥ 1	0/6	100.0 (100.0, 100.0)	
Baseline CRM status assessed by MRI			
Positive	2/21	90.5 (67.0, 97.5)	0.349
Negative	0/9	100.0 (100.0, 100.0)	
Baseline EMVI status			
Positive	2/12	83.3 (48.2, 95.6)	0.077
Negative	0/18	100.0 (100.0, 100.0)	

* *P*-value was nominal, as determined by log-rank test. *CI*, confidence interval; *CPS*, combined positive score; *CRM*, circumferential resection margin; *EMVI*, extramural venous invasion, *MRI*, magnetic resonance imaging; *OS*, overall survival; *pCR*, pathological complete response; *PD-L1*, programmed cell death-ligand 1

have previously reported that in this patient population, the preoperative combination of SCRT with subsequent camrelizumab and the CAPOX chemotherapy regimen resulted in an improved pCR, especially in the context of the majority of patients with pMMR/MSS status. This finding has been confirmed in the phase 3 UNION trial (NCT04928807) [9, 12]. This follow-up analysis further provides additional support for the potential benefit of this neoadjuvant combination regimen. With a median follow-up of 40.8 months, the median DFS and OS were not reached, with the 3-year DFS and OS rates of 80.2% (95% CI 58.6–91.3) and 93.3% (95% CI 75.9–98.3). Our findings appear to be numerically superior to the DFS rate of 64.5–76% and OS rate of 86.1–91% at 3 years for patients treated with standard TNT strategies [3, 4, 13, 14]. Additionally, this 3-year follow-up did not uncover any emergent or unanticipated safety signals, demonstrating the long-term safety of neoadjuvant SCRT followed by camrelizumab and CAPOX.

Recently, immunotherapy-based neoadjuvant therapy has shown efficacy in various tumors [15–17]. As for colorectal cancer, patients with dMMR/MSI-H disease are the primary beneficiaries of immunotherapy, while no breakthrough in those with pMMR/MSS disease [18]. Previous studies have shown that the combination of radiotherapy and immunotherapy produces a favorable synergistic effect [19, 20]. Therefore, an increasing number of studies (NRG-GI002, VOLTAGE-A, Averectal, et al.) have focused on LCRT or SCRT combined with PD-1/PD-L1 inhibitors in LARC patients, especially the majority with MSS LARC [21–23]. In the VOLTAGE-A trial, which evaluated LCRT followed by consolidation nivolumab, the 3-year relapse-free survival and 3-year OS rates were 79.5 and 97.4%, respectively, in MSS patients [24, 25]. In the NRG-GI002 trial, neoadjuvant FOLFOX followed by LCRT and concurrent pembrolizumab yielded a 3-year DFS rate of 64% and 3-year OS rate of 95% in LARC patients [26]. Despite the fact that direct comparisons may be challenging due to the inherent selection bias with each trial, the 3-year survival outcomes observed in our study were comparable to those of the aforementioned studies. This finding was noteworthy, given that our study included more patients with high-risk features associated with poor prognosis, including N-positive status (86.7% vs. 23–77.8% in the VOLTAGE-A and NRG-GI002 trials), positive CRM (70% vs. 8% in the VOLTAGE-A trial), and positive EMVI (40% vs. 26% in the VOLTAGE-A trial) [25–27]. These data indicated that SCRT combined with subsequent camrelizumab and chemotherapy may be a feasible neoadjuvant option for LARC patients, especially those with high-risk features.

The optimal sequence (sequential or concurrent) of radiotherapy and immunotherapy as well as the best radiotherapy modality (hypofractionated or conventional) remain uncertain. Preclinical data have shown that concurrent radiotherapy and immunotherapy, rather than sequential treatment, holds greater promise for eliciting improved prognostic outcomes [7, 28]. However, this has not been demonstrated in clinical studies. The PACIFIC-2 trial reported that concurrent durvalumab and chemoradiotherapy followed by durvalumab did not improve outcomes when compared with chemoradiotherapy alone in patients with unresectable stage III non-small-cell lung cancer [29]. Additionally, the NRG-GI002 trial demonstrated no significant improvement in DFS (HR 0.95, 95% CI 0.58–1.55) with the addition of concurrent pembrolizumab to neoadjuvant FOLFOX followed by LCRT in LARC patients [26]. In contrast, sequential immunotherapy following radiotherapy has delivered remarkably encouraging outcomes, as reported by the PACIFIC trial and several single-arm studies, including ours [24, 30]. This difference in treatment sequence may be associated with the fact that radiotherapy directly impairs circulating lymphocytes along with augmenting the efficacy of immunotherapy, and this impairment may present a negative impact during concurrent treatment [28]. Additionally, the choice of radiotherapy modality is also a pivotal factor to consider when combined with immunotherapy. Preclinical evidence demonstrates that hypofractionated radiotherapy enhances antitumor immunity and reverses adaptive immune resistance compared to conventionally fractionated radiotherapy,

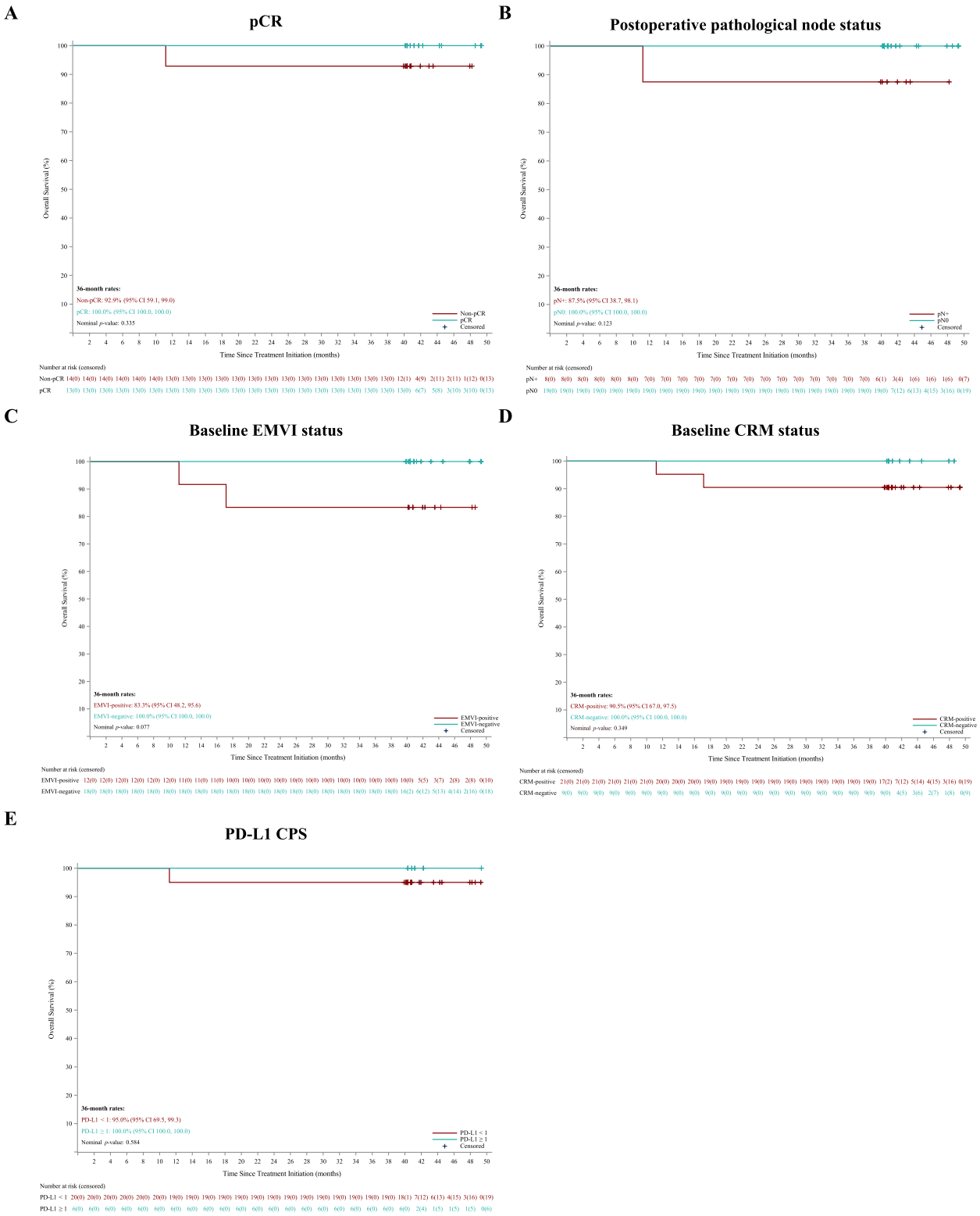

Fig. 4 Subgroup analysis of 3-year overall survival stratified by pCR (**A**), postoperative pathological node status (**B**), baseline EMVI status (**C**), baseline CRM status (**D**), and PD-L1 CPS (**E**). CI, confidence interval; CPS, combined positive score; CRM, circumferential resection margin; EMVI, extramural venous invasion; pCR, pathological complete response; PD-L1, programmed cell death-ligand 1

when combined with PD-1 blockade [31]. By implication, SCRT followed by sequential immunotherapy and chemotherapy may be a relatively more appropriate strategy, and our survival outcomes indirectly reflect its promising prospects. More clinical evidence is warrant to further identify the optimal combination of radiotherapy and immunotherapy.

A major limitation of this study is the small sample size, which may restrict the generalizability of the findings. Additionally, subgroup analyses demonstrated that pCR, postoperative pathological node status, baseline CRM, and EMVI status were associated with 3-year DFS, but these analyses were univariate. Due to the small sample size, a multivariate analysis was not feasible to further elucidate the independent predictive value of these indicators. Another is the lack of biomarker analyses beyond routine PD-L1 expression in the current report, such as tumor-infiltrating lymphocyte (TIL) immunoscore and tumor mutation burden (TMB). TIL immunoscore (e.g., based on the infiltration of CD3 + and CD8 + T cells) and high TMB (e.g., ≥ 28 mutations/Mb) have emerged as potential predictors of response to neoadjuvant immunotherapy in pMMR/MSS colorectal cancer [32]. Future studies are warranted to prioritize the integration of these biomarkers to aid in identifying patients who may benefit from neoadjuvant SCRT plus subsequent chemoimmunotherapy.

Conclusions

With over 3 years of follow-up, neoadjuvant SCRT followed by camrelizumab and CAPOX regimen was associated with promising survival outcomes in LARC patients. These suggested that this regimen may be a promising therapeutic option, especially with the potential to address an unmet need for patients with MSS tumors. Our ongoing multicenter, open-label, randomized, phase 3 UNION trial will provide more data.

Abbreviations

AEs	Adverse events
CI	Confidence interval
CPS	Combined positive score
CRM	Circumferential resection margin
DFS	Disease-free survival
dMMR	Deficient mismatch repair
ECOG PS	Eastern Cooperative Oncology Group performance status
EMVI	Extramural venous invasion
HR	Hazard ratio
IQR	Interquartile range
LARC	Locally advanced rectal cancer
LCRT	Long-course chemoradiotherapy
MSS	Microsatellite stable
OS	Overall survival
pCR	Pathological complete response
PD-L1	Programmed cell death-ligand 1
pMMR	Proficient mismatch repair
SCRT	Short-course radiotherapy
TME	Total mesorectal excision
TNT	Total neoadjuvant therapy
TIL	Tumor-infiltrating lymphocyte
TMB	Tumor mutation burden

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Authors' contributions

TZ and KT conceived and designed this study. ZL, PZ, MC, GL, TL, KC, JW, JL, HL, WZ and JG collected the data. CW, LW and ZW provided the administrative support. ZL, PZ, ZH and HK analyzed the data, and all authors participated in data interpretation. ZL and PZ drafted the manuscript and all authors reviewed. All authors read and approved the final manuscript.

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Data availability

Deidentified data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This trial was done in accordance with the Declaration of Helsinki and Good Clinical Practices and the study protocol was approved by the Ethics Committee of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology (No. S1172). All enrolled patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

ZH and HK are employees of Jiangsu Hengrui Pharmaceuticals Co., Ltd. All other authors declare that they have no competing interests.

Author details

[1]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. [2]Hubei Key Laboratory of Precision Radiation Oncology, Wuhan 430022, China. [3]Institute of Radiation Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. [4]Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. [5]Department of Digestive Surgical Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. [6]Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai 201210, China.

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