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Neoadjuvant FOLFOXIRI chemotherapy with or without camrelizumab in the treatment of locally advanced rectal cancer: a retrospective cohort study

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Abstract

Standard neoadjuvant chemoradiotherapy for locally advanced rectal cancer (LARC) is associated with significant toxicity and limited pathological responses. We retrospectively compared a radiotherapy-free regimen of camrelizumab plus modified FOLFOXIRI versus modified FOLFOXIRI alone in consecutive patients with clinical stage II–III LARC treated from 2022–2025 (n=146). All patients received ≥3 cycles of neoadjuvant therapy; surgery or watch-and-wait was determined by a multidisciplinary team. Baseline characteristics were well balanced. Among surgical patients, pCR rates were 29.8% with camrelizumab plus FOLFOXIRI and 19.6% with FOLFOXIRI alone. Radiologic objective response rates were 70.7% and 53.5%, respectively, and mean neoadjuvant rectal scores were lower with camrelizumab (13.95 vs 23.77; P<0.02). Disease-free survival was significantly improved in the camrelizumab group, while overall survival was similar at current follow-up. Grade 3–4 hematologic and gastrointestinal toxicities were comparable, and no unexpected immune-related events occurred. Camrelizumab plus FOLFOXIRI appears to be an active, tolerable radiotherapy-free neoadjuvant option for LARC.

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Introduction

Colorectal cancer (CRC) remains the third most common malignancy globally, accounting for more than1.9 million new cases and 900,000 deaths annually [1]. Among these cases, high-risk locally advanced rectal cancer (LARC), characterized by mesorectal fascia (MRF) involvement, extramural venous invasion (EMVI), or lateral lymph node metastasis on baseline magnetic resonance imaging (MRI) —remains particularly challenging. These features are associated with 5-year distant metastasis rates exceeding 40% despite standard neoadjuvant chemoradiotherapy (CRT) [2,3], complicate surgical resection, and contribute to higher local recurrence rates and reduced sphincter preservation. Consequently, optimizing neoadjuvant treatment to improve tumor regression, enhance organ preservation and reduce recurrence remains a critical clinical priority.

Neoadjuvant CRT followed by total mesorectal excision (TME) and adjuvant chemotherapy has been the conventional standard of care for LARC [4]. This approach improves local control and objective response rate. However, it has not translated into substantial gains in overall survival (OS) or progression-free survival (PFS), and distant metastasis continues to be the major mode of failure [5]. Limited eradication of micrometastatic disease and incomplete delivery of postoperative chemotherapy contribute to these shortcomings. Total neoadjuvant therapy (TNT) was developed to address these limitations and has demonstrated improved treatment adherence, greater tumor regression, and reduced

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distant relapse [6,7]. TNT has enabled more patients to achieve clinical complete response (cCR), permitting watch-and-wait (WW) approaches and potential organ preservation [8,9]. However, even in large phase III TNT trials, the pathological complete response (pCR) rates remain below 30% [5,7]. Moreover, pelvic radiotherapy can increase surgical difficulty and and lead to both acute and long-term toxicities—including diarrhea, urinary and sexual dysfunction, pelvic fractures, and secondary malignancies, all of which significantly impact quality of life. Thus, there is an urgent need for more effective and better-tolerated neoadjuvant treatment strategies.

Several studies have explored neoadjuvant chemotherapy alone as a potential radiotherapy-sparing approach. The randomized phase III FOWARC study demonstrated comparable local recurrence, distant metastasis, and long-term survival outcomes were similar between patients receiving neoadjuvant mFOLFOX6 alone and those receiving standard CRT [10,11]. The phase III PROSPECT study further confirmed that preoperative FOLFOX chemotherapy achieved disease-free survival similar to CRT, while allowing many patients to avoid radiotherapy and maintain better quality of life [12]. Additionally, the phase II FORTUNE study reported that promising tumor regression with neoadjuvant mFOLFOXIRI, achieving a pCR rate of 20.4% and a downstaging rate of 42.7%, comparable to CRT but with a more favorable safety profile [13]. Together, these findings support the feasibility of intensified chemotherapy as an alternative neoadjuvant modality in selected patients.

Immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) has shown remarkable efficacy in metastatic and locally advanced deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) CRC [14], with neoadjuvant pCR rates exceeding 60% in recent studies [15,16]. However, most CRCs are proficient mismatch repair (pMMR) or microsatellite stable (MSS), in which ICIs alone have limited benefit. Combination strategies are therefore being investigated to overcome immune-resistant tumor microenvironment characteristic of pMMR/MSS disease. Preclinical and clinical evidence suggests that chemotherapy can enhance tumor immunogenicity—through antigen release, increased MHC-I expression, and improved T-cell infiltration—thereby sensitizing tumors to PD-1 blockade [17,18]. This provides a strong rationale for integrating ICIs with cytotoxic chemotherapy as a radiotherapy-free neoadjuvant strategy in LARC. Based on these mechanistic insights and emerging clinical data, we designed this retrospective cohort study to evaluate the feasibility, efficacy, and safety of a “radiotherapy-free” neoadjuvant approach combining camrelizumab with mFOLFOXIRI in patients with LARC. We hypothesized that immunochemotherapy may enhance tumor regression, improve complete response rates, and potentially expand opportunities for organ preservation while avoiding radiotherapy-related toxicity.

Results

Patient characteristics

From February 01, 2022 to November 23, 2025, a total of 146 patients were included in this study: 71 patients in the FOLFOXIRI group and 75 patients in the camrelizumab group. Baseline characteristics are summarized in **Table 1**. No statistically significant differences were observed between groups for any baseline variable (all $P > 0.05$). All SMDs were <0.30 and most were <0.20, indicating only small imbalances in baseline risk factors. Both cohorts predominantly presented with stage III disease (80.3% vs. 90.7%) and nodal involvement (81.7% vs. 90.7%). The camrelizumab group had closer distance from the anal verge (median distance from anal verge: 5 cm vs. 7 cm), higher EMVI prevalence (64.0% vs. 62.0%) and MRF involvement (52.0% vs. 42.3%), reflecting a slightly higher baseline risk profile.

Treatment compliance and disposition

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All patients received at least three cycles of neoadjuvant therapy, allowing radiologic response and safety evaluations. Surgical resection rates were comparable between the two groups: 51 of 71 patients (71.8%) in the FOLFOXIRI group and 57 of 75 patients (76.0%) in the camrelizumab group proceeded to TME (P = 0.56; **Figure 1**).

In the FOLFOXIRI group, 20 patients (28.2%) did not undergo surgery. Among them,1 patient reached cCR and opted for a WW protocol with regular follow-up; 12 refused abdominoperineal resection because of strong preference for sphincter preservation; 1 refused prophylactic stoma creation and requested discharge; 3 elderly patients were considered high risk for major surgery and their families declined operation; 2 patients experienced disease progression and discontinued further treatment; and 1 patient, after tumor downshrinkage with five cycles of chemotherapy, developed incomplete bowel obstruction and was treated at a local hospital, ultimately dying from infectious shock after refusing stoma creation.

In the camrelizumab group, 18 patients (24.0%) did not undergo surgery. Among them, 6 achieved cCR and chose the WW strategy with close surveillance; 10 refused abdominoperineal resection because of desire for anal preservation; and 2 patients developed severe complications (bowel obstruction or tumor-related perforation) during treatment and died before definitive surgery. Overall, non-operative management primarily resulted from patient preference for organ preservation (watch-and-wait or refusal of abdominoperineal resection) or treatment-related mortality.

Regarding treatment intensity, in the FOLFOXIRI group, 26 patients (36.6%) completed three cycles of treatment and 45 patients (63.4%) completed 4-6 cycles. In the camrelizumab group, 27 patients (36.0%) completed three cycles and 49 patients (65.3%) completed 4-6 cycles. There was no significant difference in the number of neoadjuvant therapy cycles between the two groups (**Table 2**). Treatment courses are illustrated in the swimmer plot (**Figure 2**).

Postoperative Pathologic Response

Among patients who underwent TME, surgical approaches were similar between groups. In the FOLFOXIRI group, 29 of 51 patients (56.9%) had laparoscopic surgery and 22 patients (43.1%) had robotic surgery. In the camrelizumab group, 30 of 57 patients (52.6%) and 27 (47.4%) underwent laparoscopic and robotic surgery, respectively (**Table 3**).

In the FOLFOXIRI group, the pCR rate among surgical patients was 19.6% (95%CI: 9.8-33.1%) (**Figure 3A**), When the 1 non-operative cCR case is included, the overall CR rate was 15.5% (1 clinical cCR plus 10 pCR). R0 resection was achieved in 50 of 51 patients (98.0%). One patient with T4N2 disease after six cycles of chemotherapy underwent robot-assisted surgery, during which multiple pelvic metastatic nodules were discovered and confirmed as pelvic metastasis. Sphincter preservation was achieved in 34 surgical patients (anal preservation rate 66.7%). Pathologically, 33 patients (64.7%) had negative lymph nodes; 13 patients (25.5%) were classified as ypTNM stage 0-1, and 38 patients were categorized as ypTNM stage 2-3. The rate of tumor downstaging to ypT0-2N0M0 was 35.3%.

In the camrelizumab group, the pCR rate was 29.8% (95%CI: 18.4-43.4%) (**Figure 3B**), and the overall CR rate was 30.7% (6 cCR and 17 pCR). The unadjusted ORs for pCR with camrelizumab plus FOLFOXIRI versus FOLFOXIRI alone was 1.74 (95% CI: 0.71–4.26), indicating approximately 1.7-fold higher odds of pCR, although the CIs was wide and crossed 1. All 57 surgical patients achieved R0 resection. Sphincter-preserving procedures were performed in 42 patients (anal preservation rate 73.7%). Furthermore, 47 patients (82.5%) had negative lymph nodes. Among them, 26 patients (45.6%) were classified as ypTNM stage 0-1, while 31 patients (54.4%) were at ypTNM stage 2-3. The rate of tumor downstaging to ypT0–2N0M0 was 43.9%.

According to the TRG criteria, 20 patients (39.2%) in the FOLFOXIRI group and 26 (45.6%) in the camrelizumab

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group were classified as TRG 0–1; 31 (60.8%) and 31 (54.4%), respectively, were TRG 2–3. Overall, the camrelizumab group showed higher pCR and overall CR rates, more frequent downstaging, and a numerically higher anal preservation rate, although the differences in anal preservation and pCR rates did not reach statistical significance.

Imaging Evaluation

Post-neoadjuvant imaging evaluations revealed distinct therapeutic profiles between the two groups **(Table 2)** (**Figure 4**). In the FOLFOXIRI group, one patient (1.4%) achieved cCR and opted for the WW protocol. Partial response (PR) and stable disease (SD) were observed in 37 (52.1%) and 30 patients (42.3%), respectively, with 3 cases (4.2%) of progressive disease (PD). The ORR was 53.5% (95%CI: 41.3-65.5%) and the DCR was 95.8% (95%CI:88.1-99.1%). T-stage downstaging occurred in 16 patients (22.5%), including seven cT3 tumors regressed to ycT2 (n=6) or ycT1 (n=1), and nine cT4 tumors to ycT3 (n=5), ycT2 (n=3), or ycT0 (n=1). Nodal downstaging was achieved in 32 patients (45.1%), with eight cN1 and 24 cN2 cases converted to ycN0 (n=26) or ycN1 (n=6). After treatment, 37 patients (52.1%) were ycN0, while MRF and EMVI positivity persisted in 31 (43.7%) (**Figure 4A**).

In the camrelizumab group, no PD was observed and all patients had measurable tumor shrinkage. Six patients (8.0%) achieved cCR and opted for the WW protocol to preserve sphincter function. Furthermore, 47 patients (62.7%) and 22 patients (29.3%) achieved PR and SD, respectively, yielding an ORR of 70.7% (95%CI: 59.0-80.6%) and a DCR of 100% (95%CI: 95.2-100%). T-stage downstaging occurred in 21 patients (28.0%), including nine cT4 tumors regressed to ycT3 (n=5), ycT2 (n=3) or ycT0 (n=1), and twelve cT3 tumors regressed to ycT2 (n=4), ycT1 (n=3) or ycT0 (n=5). Nodal downstaging was achieved in 48 patients (64.0%), with 33 cN2 tumors were downgraded (10 to ycN1 and 23 to ycN0) and 15 cN1 tumors to ycN0. After treatment, 45 patients (60.0%) reached N0 status, and 16 patients (21.3%) being MRF-positive and 27 patients (36.0%) EMVI-positive (**Figure 4B**).

Comparing groups, the camrelizumab cohort had higher CR (8.0% vs. 1.4%), higher PR (62.7% vs. 52.1%), lower SD (29.3% vs. 42.3%), and no PD (0% vs. 4.2%) (P = 0.03), with higher ORR (70.7% vs. 53.5%, P = 0.04) and numerically higher DCR (100% vs. 95.8%, P = 0.11). T-downstaging (28.0% vs. 22.5%, P = 0.45) and N-downstaging (64.0% vs. 45.1%, P = 0.02) were also more frequent in the camrelizumab group. In both groups, paired analyses showed significant reductions in CEA, CA19-9, and tumor length after treatment **(Figure 5)**, with more pronounced decreases in the camrelizumab group.

Outcomes in patients managed with watch-and-wait

Seven patients (6 in the camrelizumab group, 1 in the FOLFOXIRI group) achieved cCR and elected WW after multidisciplinary discussion. During available follow-up, no local regrowth or rectal cancer–related distant metastases were observed. In the camrelizumab group, one cCR patient died from sudden cardiac arrest during surveillance without evidence of recurrence at last assessment, and another developed a de novo primary lung cancer but remains free of rectal cancer relapse. The remaining four cCR patients in the camrelizumab group and the single cCR patient in the FOLFOXIRI group remain under close WW surveillance without need for salvage surgery or additional rectal cancer–directed therapy.

NAR score

The NAR score was used as an exploratory measure of integrated T and N downstaging. Because several patients with cCR chose WW, we applied a modified NAR in non-operated patients using ycT and ycN in place of ypT and ypN.

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In the primary exploratory analysis including all patients, the mean NAR score was 23.77 (SD 20.74; 95% CI: 18.86–28.68) in the FOLFOXIRI group and 13.95 (SD 13.92; 95% CI: 10.74–17.15) in the camrelizumab group (t = –3.34, P < 0.02) (**Figure 6**). This indicates more substantial T and N downstaging in the camrelizumab cohort.

Post hoc correlation analysis revealed a positive correlation between the pathological tumor regression and the degree of tumor long diameter reduction as measured by imaging. Conversely, for surgical patients, the NAR score was negatively correlated with the degree of pathological tumor regression (**Figure 7**).

In addition, we conducted a logistics regression analysis of the NAR scores based on gender, age, BMI, chemotherapy cycles, ECOG performance status, MSI status, distance from the anal verge, tumor length, clinical T stage, clinical N stage, TNM stage, MRF, EMVI, CEA, and CA199 (**Figure 8**). Within each subgroup, ORs and 95% CIs for higher NAR scores in the FOLFOXIRI group versus the camrelizumab group were estimated. Although the study was not powered for formal interaction testing, the point estimates consistently favored the camrelizumab group (ORs > 1 for FOLFOXIRI vs. camrelizumab in most subgroups), and no clear qualitative treatment-by-subgroup interactions were observed.

Quality of Life, Anal Function, and Long-Term Survival

Quality of life and anal function were assessed in surgical patients using the EORTC QLQ-CR29 questionnaire at baseline, after neoadjuvant treatment and before surgery, and at 6–12 months postoperatively. Both groups showed similar trajectories across all domains, and no significant between-group differences were observed at any time point (all P > 0.05). Detailed scores are provided in **Supplementary Figure 1**.

Long-term survival outcomes were also evaluated (**Figure 9**). In the camrelizumab group, the median follow-up 26.3 months (95%CI:21.9-30.8 months), and the median DFS not reached. The 1-year, 2-year, and 3-year DFS rates were 94.9%, 87.2%, and 87.2%, respectively. In the FOLFOXIRI group, the median follow-up was 23.1 months (95%CI:16.3-30.0 months), and median DFS was also not reached. The 1-year, 2-year, 3-year, and 4-year DFS rates were 77.7%, 69.7%, 63.3%, and 56.3%, respectively. Kaplan–Meier analysis showed a significant improvement upon DFS in camrelizumab group (HR = 0.36; 95% CI, 0.14-0.93, P = 0.036), indicating reduced risk of recurrence or progression.

Median OS was not reached in either group. The 1-year, 2-year, and 3-year OS rates in the camrelizumab group were 95.2%, 86.6%, and 86.6%, respectively. In the FOLFOXIRI group, the 1-year, 2-year, 3-year, 4-year, and 5-year OS rates were 97.0%, 91.6%, 91.6%, 91.6%, and 85.5%, respectively. No significant difference in overall survival was observed between the two groups (HR=1.53, 95% CI, 0.49-4.76, P=0.441), likely reflecting the limited follow-up and overall favorable prognosis; OS differences may emerge with longer observation.

Safety and feasibility

All 146 patients received at least 3 cycles of study treatment and were included in the safety analysis (**Table 4**). Overall, the incidence and pattern of AEs were similar between groups. The most common AEs in the FOLFOXIRI group and the camrelizumab group were fatigue (56.3% vs. 46.7%), leukopenia (39.4% vs. 44.0%), nausea and vomiting (46.5% vs. 37.3%), and neutropenia (25.4% vs. 36.0%). Most of these events were grade 1–2. Grade ≥3 AEs were relatively infrequent but did occur in both arms. In the FOLFOXIRI group, Grade ≥3 AEs included anemia (n=1), diarrhea (n=2), intestinal obstruction (n=1), liver function abnormalities (n=1), electrolyte disturbances (n=3), and allergic reaction (n=1). In the camrelizumab group, Grade ≥3 AEs included anemia (n=1), thrombocytopenia (n=1), bowel obstruction (n=2), hypokalemia (n=2), and infection (n=1).

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During treatment, three deaths related to intestinal obstruction occurred. In the FOLFOXIRI group, one patient with a stenotic rectal tumor developed incomplete obstruction, was treated at a local hospital, refused stoma creation, and died from infectious shock presumed secondary to perforation; this event was adjudicated as primarily disease-related. In the camrelizumab group, one patient developed incomplete obstruction after two cycles of FOLFOXIRI plus camrelizumab and one cycle of XELOX; after transanal decompression, the patient showed signs of perforation and experienced sudden cardiac arrest prior to emergency surgery; this event was considered treatment-related. The second obstruction-related death in the camrelizumab group occurred after four cycles of FOLFOXIRI plus camrelizumab in a patient with progressive tumor-related obstruction complicated by perforation, septic shock, and treatment withdrawal; this was judged predominantly disease-related. No immune-related deaths occurred.

Immune-related AEs (irAEs) in the camrelizumab group were prospectively recorded and graded per CTCAE 5.0 criteria. All irAEs were grade 1–2, no treatment discontinuations due to irAEs. The most common irAE was reactive cutaneous capillary endothelial proliferation (RCCEP), occurring in 19 patients and self-limiting. Immune-related rash (n = 2) and pruritus (n = 1) were effectively managed with oral antihistamines and topical corticosteroids. Immune-related enteritis occurred in 2 patients (grade 1–2) and resolved with supportive care alone. Three patients developed hypothyroidism (grade 1–2) and are maintained on levothyroxine with good control. At follow-up, no worsening of irAEs was reported; most symptomatic events had resolved or markedly improved, and only hypothyroidism required ongoing treatment.

Serious surgical complications were also observed in both groups. In the FOLFOXIRI group, three patients who underwent low anterior resection with prophylactic ileostomy developed anastomotic stricture within the three-month postoperative follow-up. In the camrelizumab group, one patient who underwent ultra-low rectal resection with ileostomy developed an anastomotic leakage that was successfully managed conservatively. One additional patient experienced postoperative anastomotic stricture, and another patient who underwent laparoscopic abdominoperineal resection required re-operation for intestinal perforation caused by postoperative intestinal strangulation in the context of early mobilization and higher BMI. No patient died within 60 days after surgery.

Long-term toxicities were assessed 3–6 months after treatment by chart review and telephone follow-up. In the camrelizumab group, 5 patients reported persistent toxicities: 3 with hypothyroidism (on levothyroxine), 1 with mild pruritus (topical steroids), and 1 with rash (oral antihistamines). In the FOLFOXIRI group, 7 patients reported persistent toxicities: 4 with fatigue (managed with supportive measures), 2 with peripheral neuropathy under observation, and 1 with diarrhea treated with oral anti-inflammatory agents. No progressive deterioration of long-term toxicities was observed.

Overall, both regimens were associated with expected chemotherapy- and surgery-related morbidity. However, the overall safety profiles were broadly comparable, and the addition of camrelizumab did not appear to introduce unexpected or frequent high-grade immune-related toxicity.

Discussion

This retrospective cohort study evaluated a radiotherapy-free neoadjuvant strategy combining camrelizumab with mFOLFOXIRI compared with mFOLFOXIRI alone in patients with locally advanced rectal cancer. After revising the endpoint hierarchy in line with current evidence and reviewer feedback, pCR was designated as the primary endpoint and NAR as a secondary, exploratory endpoint. The addition of camrelizumab was associated with higher pCR (29.8% vs. 19.6%), nearly doubled overall complete response (CR = cCR + pCR; 30.7% vs. 15.5%), greater downstaging

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(including ypTNM 0–1 and ypT0–2N0M0), and numerically higher sphincter preservation. These findings support the clinical activity of PD-1 blockade added to intensive chemotherapy as neoadjuvant treatment for LARC.

NAR, used as an exploratory measure integrating T and N downstaging, was significantly lower in the camrelizumab group than in the FOLFOXIRI group, consistent with more pronounced tumor regression. However, NAR was originally developed and validated as a surrogate for DFS in CRT-based neoadjuvant regimens like CAO/ARO/AIO-04 [19], and its prognostic value in radiotherapy-free immunochemotherapy settings is uncertain. We therefore treated NAR as an exploratory endpoint. The lower NAR scores observed with camrelizumab, confirmed in a sensitivity analysis restricted to surgical patients using conventional NAR, should be interpreted as hypothesis-generating and supportive of the pCR and DFS findings rather than as stand-alone evidence of long-term survival benefit.

Long-term outcomes further support the efficacy of the camrelizumab-containing regimen. With median follow-up of 26.3 months in the camrelizumab group and 23.1 months in the FOLFOXIRI group, DFS was significantly improved with camrelizumab (HR=0.36, P=0.036), indicating a reduced risk of recurrence or progression. In contrast, OS did not differ significantly (P = 0.441), which is not unexpected in a relatively small, non-randomized cohort with limited follow-up and a generally favorable prognosis. OS differences may emerge with longer observation or larger sample sizes, particularly in LARC where salvage treatments and competing risks can attenuate early DFS gains. Nonetheless, the consistent pattern of higher pCR/CR rates, more favorable downstaging, lower exploratory NAR scores, and improved DFS collectively supports a meaningful oncologic benefit from adding camrelizumab to FOLFOXIRI.

These results should be interpreted in the context of evolving neoadjuvant strategies for LARC. Conventional CRT remains a standard approach but only modestly reduces distant metastasis and can cause substantial bowel, urinary, and sexual dysfunction. The FORTUNE study [13] and subsequent analyses demonstrated that FOLFOXIRI as a neoadjuvant treatment without radiotherapy, reporting a pCR rate of 20.4% and a tumor downstage rate of 42.7%. Subsequent studies combining FOLFOXIRI with propensity score-matched mFOLFOX6 [20] showed pCR rates of 17.9% and 5.1%, respectively, along with lower anastomotic leakage rates (3.2% vs. 9.0%) and improved disease-free survival (DFS) rates (3-year DFS rate: 75% vs. 66.7%). These findings highlight the advantages of neoadjuvant FOLFOXIRI in enhancing pCR rates, survival outcomes, and minimizing complications. In parallel, PD-1 inhibitors have transformed the management of dMMR/MSI-H CRC, as demonstrated in metastatic settings (e.g., KEYNOTE-177) [14] and in neoadjuvant studies such as NICHE and NICHE-2, which reported very high response rates in non-metastatic disease [21]. Emerging immunoradiotherapy and TNT studies (e.g., VOLTAGE-A, NRG-GI002, AVANA) have also reported pCR rates around 23–32% [22–24].

Our study extends this evidence by examining an intensive chemotherapy backbone (mFOLFOXIRI) combined with PD-1 blockade in a predominantly high-risk LARC population, with a high prevalence of stage III disease, MRF involvement, and EMVI. The pCR rate of 29.8% in the camrelizumab group exceeds the 15–20% typically reported with standard CRT [25.,26] and is comparable to some immunoradiotherapy and TNT regimens, despite the absence of pelvic radiation and the unfavorable baseline characteristics. These observations suggest that radiotherapy-free immunochemotherapy may be particularly advantageous for patients with aggressive tumor biology, in whom the incremental benefits of radiotherapy may be limited and its long-term toxicity substantial.

Safety findings are also notable. Both regimens were associated with significant chemotherapy- and surgery-related morbidity, including bowel obstruction and postoperative complications, and there were three obstruction-related deaths, one in the FOLFOXIRI group and two in the camrelizumab group. After careful review, one death in the camrelizumab

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arm was adjudicated as treatment-related and the others as predominantly disease-related. Importantly, the overall incidence and pattern of AEs, including serious events, were broadly similar between groups, and no new or unexpected high-grade immune-related toxicities were observed. IrAEs with camrelizumab were limited to grade 1–2 events such as RCCEP, rash, pruritus, enteritis, and hypothyroidism and were manageable with supportive care or hormone replacement, consistent with prior reports [27]. Long-term toxicity and patient-reported outcome data further indicate that the addition of camrelizumab did not worsen quality of life or anal function up to 6–12 months after surgery.

An additional feature of this cohort is the use of WW in selected patients achieving cCR. Seven patients (six in the camrelizumab group and one in the FOLFOXIRI group) chose WW. No local regrowth or rectal cancer–related distant metastasis has been observed to date, although one camrelizumab-treated patient died from sudden cardiac arrest and another developed a second primary lung cancer. These preliminary findings suggest that WW after cCR may be feasible under intensive surveillance, even following immunochemotherapy. However, the number of WW patients is small, and follow-up is limited; these observations should be viewed as exploratory.

This study has some limitations. First, its retrospective, non-randomized design is inherently susceptible to selection bias and unmeasured confounding. Treatment allocation reflected real-world practice rather than randomization. Although no statistically significant baseline differences were observed and all SMDs were <0.30 (most <0.20), the camrelizumab group had numerically higher proportions of stage III disease, MRF involvement, and lower tumors, features that would typically predict worse outcomes. The fact that the camrelizumab group nonetheless had higher pCR/CR rates, more frequent downstaging, lower exploratory NAR scores, and better DFS supports a treatment effect rather than a baseline advantage. Nevertheless, residual confounding cannot be excluded despite multivariable adjustment, and the results should be considered hypothesis-generating. Second, the sample size, although larger than in many prior neoadjuvant FOLFOXIRI or immunotherapy series in LARC, remains modest and limits statistical power, especially for subgroup analyses and precise estimation of effect sizes. This is reflected in the wide confidence interval around the primary endpoint: the odds of pCR were approximately 1.7-fold higher with camrelizumab plus FOLFOXIRI than with FOLFOXIRI alone, but the 95% CI included 1. Third, a considerable proportion of patients in both groups did not undergo TME, mainly because of patient preference for organ preservation, refusal of abdominoperineal resection or stoma, comorbidities, treatment-related complications, or disease progression. Consequently, pCR rates apply only to the operated subset and may underestimate the true complete tumor regression rate when cCR under WW is considered. NAR can strictly be calculated only in the surgical cohort, and the use of modified NAR based on ycT/ycN in non-operated patients introduces additional uncertainty. These factors should be taken into account when interpreting the absolute values of pCR and NAR and the generalizability of our findings. Finally, median follow-up of approximately 2 years is relatively short for definitive OS assessment. Longer observation is needed to determine whether the DFS advantage with camrelizumab translates into durable survival benefit. Moreover, NAR, although informative, was originally validated in CRT/TNT settings; its role as a surrogate endpoint in radiotherapy-free immunochemotherapy remains exploratory and should not be viewed as definitive proof of long-term prognostic equivalence.

Despite these limitations, this study provides real-world evidence that neoadjuvant camrelizumab plus mFOLFOXIRI can achieve superior tumor response and improved DFS compared with mFOLFOXIRI alone, without a major increase in toxicity or deterioration in early postoperative quality of life. If confirmed in prospective, randomized trials with longer follow-up, this radiotherapy-free immunochemotherapy regimen could represent a promising alternative neoadjuvant strategy for selected LARC patients, particularly those with high-risk features or for whom pelvic radiotherapy is undesirable. Future research should focus on optimizing patient selection (e.g., molecular and

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immunologic biomarkers), refining treatment sequencing and duration, and further characterizing long-term oncologic and functional outcomes of immunochemotherapy-based neoadjuvant regimens in rectal cancer.

Methods

Study design

This retrospective cohort study analyzed consecutive patients with LARC treated at Harbin Medical University Cancer Hospital between February 2022 and November 2025. The study protocol was approved by the Institutional Ethics Committee of Harbin Medical University Cancer Hospital, China (Approval No: 2025-445-IIT; Registration No.: ChiCTR2500114600), with waived informed consent due to the retrospective nature of data collection and the use of de-identified data. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. The main inclusion criteria were histologically or cytologically confirmed untreated rectal adenocarcinoma located ≤12 cm from the anal verge, with clinical stage II (T3-4N0M0) or stage III (T1-4N1-2M0) disease on MRI according to a standardized rectal cancer protocol. Additional inclusion criteria included age between 18 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, no evidence of distant metastases, no history of systemic chemotherapy or radiotherapy or ICIs for CRC, and presence of sufficient organ function. Exclusion criteria were distant metastases at diagnosis, prior chemotherapy/radiotherapy/ICIs for CRC, concurrent malignancies and incomplete treatment records or follow-up data.

Procedures

Patients were assigned to treatment groups according to real-world clinical practice. The camrelizumab group received mFOLFOXIRI (irinotecan 150 mg/m², oxaliplatin 85 mg/m², leucovorin 400 mg/m², and 5-FU 2600-2800 mg/m² as a 46-hour infusion) combined with camrelizumab 200 mg every 2 weeks, while the chemotherapy group received mFOLFOXIRI alone on the same schedule. All patients completed at least three cycles of neoadjuvant therapy.

Tumor response was assessed using pelvic MRI according to RECIST 1.1 criteria. Surgical resectability, operative timing and operative strategy were determined by a multidisciplinary tumor board consensus based on post-treatment imaging and clinical assessment. TME was performed whenever feasible. For patients achieving a cCR, a WW strategy was considered based on tumor location, patient preference, and multidisciplinary consensus.

This cohort specifically comprised patients who did not receive preoperative radiotherapy due to patient refusal, concerns regarding long-term functional impairment, comorbidities, or other clinical considerations. Postoperative pelvic radiotherapy was selectively recommended for patients with high-risk pathological findings—such as positive circumferential resection margin, pathological T4 disease, or multiple positive lymph nodes—according to multidisciplinary recommendations.

Data Collection and Endpoints

Clinical data were extracted from institutional databases and electronic medical records, including baseline characteristics (age, gender BMI), tumor characteristics (distance from anal verge, MRI-based cT and cN stage, MRF status, EMVI status), treatment details (number of neoadjuvant cycles, surgical procedures), radiologic response, pathological findings, and adverse events (AEs).

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The primary endpoint was pCR, defined as ypT0N0 in the resected specimen after completion of neoadjuvant therapy. For the entire neoadjuvant cohort, a complete response (CR) endpoint was also evaluated, defined as the composite of pCR and clinical complete response (cCR) in patients managed non-operatively. Secondary endpoints included: cCR rate and overall CR rate (cCR plus pCR), objective response rate (ORR) and disease control rate (DCR) by RECIST 1.1, R0 resection rate, tumor, tumor regression grade (TRG), tumor downstaging (including ypTNM 0–1 and ypT0–2N0M0), anal preservation rate, neoadjuvant rectal (NAR) score; disease-free survival (DFS) and OS, AEs and patient-reported outcomes collected via the EORTC QLQ-CR29 questionnaire.

The NAR score was used as an exploratory endpoint integrating pre-treatment cT stage with post-treatment ypT/ypN stage [28]: NAR=[5ypN-3(cT-ypT) +12]^2/9.61, where cT in {1, 2, 3, 4}, ypT in {0, 1, 2, 3, 4} and ypN in {0, 1, 2}. For patients who did not undergo surgery but had post-treatment clinical staging, we applied a modified NAR approach [29], substituting clinical post-treatment staging (ycT, ycN) for ypT and ypN to allow exploratory comparison across the full cohort. DFS is defined as the interval from surgery to recurrence, progression, or death. from any cause. OS was defined as the time from initiation of neoadjuvant therapy to death from any cause.

Follow-up and surveillance

Patients undergoing TME were followed according to institutional protocols, including routine clinical evaluation, physical examination, serum CEA, cross-sectional imaging (contrast-enhanced CT or MRI of the chest, abdomen, and pelvis), and endoscopic assessment. Follow-up was generally conducted every 3 months during the first year and every 6 – 12 months thereafter.

Patients managed with WW after cCR underwent intensified surveillance, especially during the first 2 years, including clinical assessments with digital rectal examination, serial CEA, pelvic MRI, and endoscopy every 3 months, with extended intervals thereafter if no regrowth or metastasis was detected.

Statistical analysis

The continuous variables were summarized as median (range) or mean (± standard deviation) as appropriate and compared via Wilcoxon rank-sum tests, while the categorical variables were described with frequency (percentage) and compared using the chi-squared or Fisher's exact tests. Baseline comparability was evaluated using both P values and standardized mean differences (SMDs), with SMD <0.10 considered negligible and <0.20–0.25 considered small.

The primary endpoint pCR was compared using odds ratios (ORs) with 95% confidence intervals (CIs) derived from contingency tables and logistic regression. The 95% CIs of ORR, DCR and pCR were calculated using the Clopper–Pearson method. DFS and OS were evaluated using Kaplan–Meier curves and compared via log-rank tests; hazard ratios (HRs) with 95% CIs were estimated using Cox models. Exploratory subgroup analyses for NAR scores were conducted to assess the consistency of the treatment effect across clinically relevant strata, including age (<60 vs. ≥60 years), sex, clinical T stage (T3 vs. T4), clinical N stage (N0 vs. N1–2), clinical TNM stage (II vs. III), MRF status (positive vs. negative), EMVI status (positive vs. negative), and tumor distance from the anal verge (≤5 cm vs. >5 cm). For the forest plot, ORs and 95% CIs for the association between treatment group and NAR status were estimated using logistic regression.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to institutional policy and patient privacy restrictions, but are available from the corresponding author on reasonable request and subject to approval

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by the institutional ethics committee.
A completed STROBE checklist for cohort studies is provided in Supplementary Appendix 1.

Code Availability

Not applicable

Acknowledgements

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Authors Contributions

Binbin Cui and Yanlong Liu conceived and designed the study. Shihui Zhao, Songtao Du, Liqiang Song, and Tianyi Xia enrolled patients and acquired clinical data. Fenqi Du performed the data analysis and contributed to data interpretation. Yanlong Liu and Shihui Zhao interpreted the results and drafted the manuscript. Bomiao Zhang provided administrative and logistical support. Binbin Cui supervised the study. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Competing Interests

The authors declare no competing financial or non-financial interests.

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Table 1. Baseline Characteristics

Characteristic	FOLFOXIRI group (N=71)	Camrelizumab group (N=75)	P value	SMD
Age, years, median (range)	58 (28-75)	59 (33-75)	0.808	0.080
Gender				
Male	59 (83.1%)	54 (72.0%)	0.109	0.268
Female	12 (16.9%)	21 (28.0%)		
BMI	23.74 (17.30-42.87)	23.05 (15.82-33.98)	0.321	0.205
ECOG PS				
0	66 (93.0%)	64 (85.3%)	0.140	
1	5 (7.0%)	11 (14.7%)		
Clinical T stage				
T3	47 (66.2%)	54 (72.0%)	0.480	0.126
T4	24 (33.8%)	21 (28.0%)		
Clinical N stage				
N0	13 (18.3%)	7 (9.3%)	0.480	0.263
N1	19 (26.8%)	23 (30.7%)		
N2	39 (54.9%)	45 (60%)		
Clinical TNM stage				
II	14 (19.7%)	7 (9.3%)	0.074	0.298
III	57 (80.3%)	68 (90.7%)		
MRF				
Positive	30 (42.3%)	39 (52.0%)	0.238	0.196
Negative	41 (57.7%)	36 (48.0%)		
EMVI				
Positive	44 (62.0%)	48 (64.0%)	0.800	0.042
Negative	27 (38.0%)	27 (36.0%)		
Distance from anal verge, cm	7 (1.2-12)	5 (1-12)	0.076	
Tumor length, cm	5.0 (2.3-10.9)	5.0 (2.9-9.7)	0.404	0.144
Mismatch repair status				
MSS	38 (53.5%)	49 (65.3%)	0.118	0.009
MSI-H	4 (5.6%)	5 (6.7%)		

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Table 2. Treatment cycles and tumor responses in both groups

	FOLFOXIRI group (N=71)	Camrelizumab group (N=75)	P value
Treatment cycles			
3 cycles	26 (36.6%)	27 (36.0%)	0.938
4-6 cycles	45 (63.4%)	48 (64.0%)	
Tumor responses			
CR	1 (1.4%)	6 (8.0%)	
PR	37 (52.1%)	47 (62.7%)	0.031
SD	30 (42.3%)	22 (29.3%)	
PD	3 (4.2%)	0 (0%)	
cCR rate	1.4%	8.0%	0.054
ORR	53.5%	70.7%	0.041
DCR	95.8%	100.0%	0.112
ycT stage			
ycT 0-2	11 (15.5%)	16 (21.3%)	0.364
ycT3-4	60 (84.5%)	59 (78.7%)	
ycN stage			
ycN 0	37 (52.1%)	45 (60.0%)	0.370
ycN 1-2	34 (47.9%)	30 (40.0%)	
T stage downgrade	16 (22.5%)	21 (28.0%)	0.448
N stage downgrade	32 (45.1%)	48 (64.0%)	0.022
MRF-positive	31 (43.7%)	16 (21.3%)	0.004
EMVI-positive	31 (43.7%)	27 (36.0%)	0.002

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Table 3. Surgical results and pathological efficacy evaluation

Characteristic	FOLFOXIRI group (N=51)	Camrelizumab group (N=57)	P value
Surgical procedures			
Robotic surgery	22 (43.1%)	27 (47.4%）	0.659
Laparoscopic surgery	29 (56.9%)	30 (52.6%)	
Type of surgery			
Abdominoperineal resection	17 (33.3%)	15 (26.3%)	
Low anterior resection with defunctioning stoma	16 (31.4%)	20 (35.1%)	0.727
Low anterior resection	18 (35.3%)	22 (38.6%)	
Anal preservation	34 (66.7%)	42 (73.7%)	0.425
R0 resection	50 (98%)	57 (100%)	0.472
pCR	10 (19.6%)	17 (29.8%)	0.221
ypT			
T0-2	13 (25.5%)	27 (47.4%)	0.019
T3-4	38 (74.5%)	30 (52.6%)	
ypN			
N0	33 (64.7%)	47 (82.5%)	0.036
N1-2	18 (35.3%)	10 (35.3%)	
ypTNM			
0-1	13 (25.5%)	26 (45.6%)	0.030
2-3	38 (74.5%)	31 (54.4%）	
TRG			
0-1	20 (39.2%)	26 (45.6%)	0.034
2-3	31 (60.8%)	31 (54.4%)	
Tumor downstage	18 (35.3%)	25 (43.9%)	0.364

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Table 4. Safety and incidence of adverse events

Adverse Events	FOLFOXIRI group (N=71)		Camrelizumab group (N=75)	
	Grade 1-2	Grade ≥3	Grade 1-2	Grade ≥3
Chemotherapy-related AEs				
Hematologic toxicity				
Leukopenia	28 (39.4%)	0	33 (44.0%)	0
Neutropenia	18 (25.4%)	0	27 (36.0%)	0
Anemia	22 (31.0%)	1 (1.4%)	15 (20.0%)	1 (1.3%)
Thrombocytopenia	9 (12.7%)	0	10 (13.3%)	1 (1.3%)
Myelosuppression	1 (1.4%)	0	2 (2.7%)	0
Gastrointestinal toxicity				
Anorexia	22 (31.0%)	0	13 (17.3%)	0
Nausea/vomiting	33 (46.5%)	0	28 (37.3%)	0
Diarrhea	19 (26.8%)	2 (2.8%)	22 (29.3%)	0
Intestinal obstruction	1 (1.4%)	1 (1.4%)	0	2 (2.7%)
General toxicity				
Fatigue	40 (56.3%)	0	35 (46.7%)	0
Abnormal liver function	13 (18.3%)	1 (1.4%)	12 (16.0%)	0
Abnormal renal function		0	1 (1.3%)	0
Abnormal thyroid function	23 (32.4%)	0	16 (21.3%)	0
Electrolyte imbalance	11 (15.5%)	3 (4.2%)	9 (12%)	2 (2.7%)
Infection	0	0	0	1 (1.3%)
Skin allergies	0	1 (1.4%)	2 (2.7%)	0
Immune-related AEs				
Immune-related rash	0	0	2 (2.7%)	0

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Immune-related pruritus	0	0	1 (1.3%)	0
Immune-related enteritis	0	0	2 (2.7%)	0
Immune-related Hypothyroidism	0	0	3 (4.0%)	0
Reactive cutaneous capillary endothelial proliferation	0	0	19 (25.3%)	0
Postoperative complications				
Anastomotic leakage	0	0	1 (1.3%)	0
Anastomotic stenosis	3 (4.2%)	0	1 (1.3%)	0
Intestinal perforation	0	0	1 (1.3%)	0

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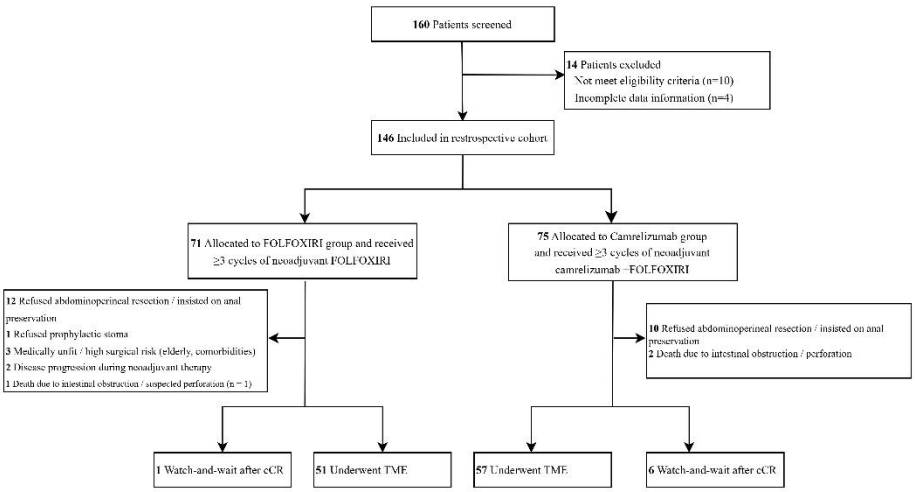

Figure 1. Study flowchart.

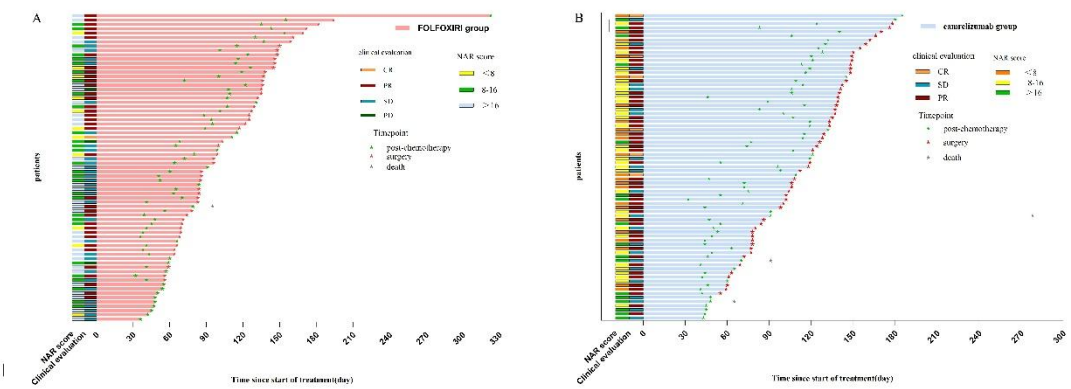

Figure 2. Swimmer plot of the patients' clinical treatment process. (A). Treatment process for patients in the FOLFOXIRI group. (B). Treatment process for patients in the camrelizumab group. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. NAR score, neoadjuvant rectal score.

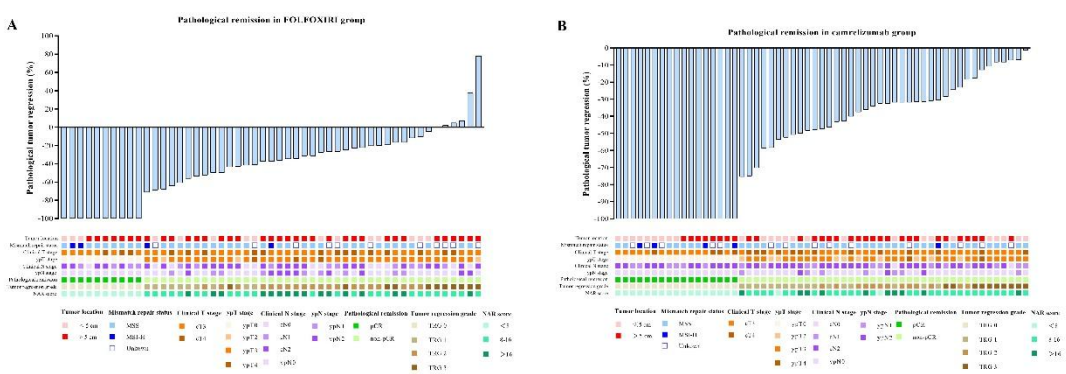

Figure 3. Pathological tumor regression percentage and patient disease characteristics. (A). Pathological tumor regression percentage and patient disease characteristics in the FOLFOXIRI group. (B) Pathological tumor regression percentage and patient disease characteristics

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in the camrelizumab group. MSS, microsatellite stable; MSI-H, microsatellite instability-high; cT/cN, clinical T stage/N stage at baseline; ypT/ypN, pathological T stage/N stage after neoadjuvant therapy; pCR, pathological complete response rate; TRG, tumor regression grade; NAR score, neoadjuvant rectal score.

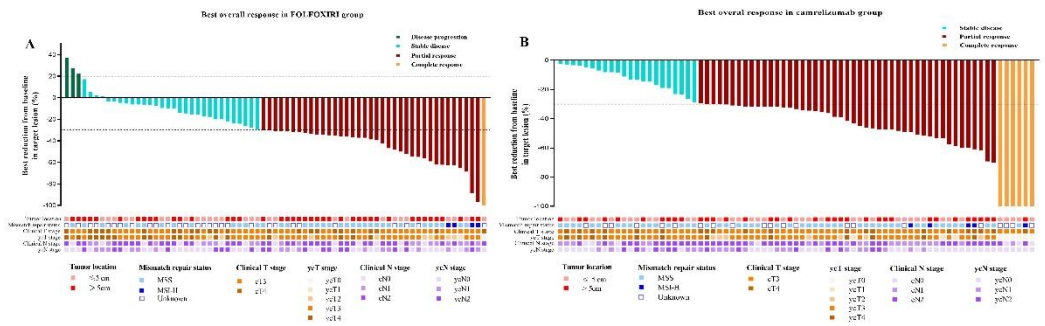

Figure 4. Imaging efficacy evaluation and disease characteristics of patients. (A). Evaluation of radiographic efficacy and characteristics of patients in FOLFOXIRI group. (B). Evaluation of radiographic efficacy and characteristics of patients in camrelizumab group. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. cT/cN, clinical T stage/N stage at baseline; ycT/ycN, clinical T stage/N stage after neoadjuvant therapy.

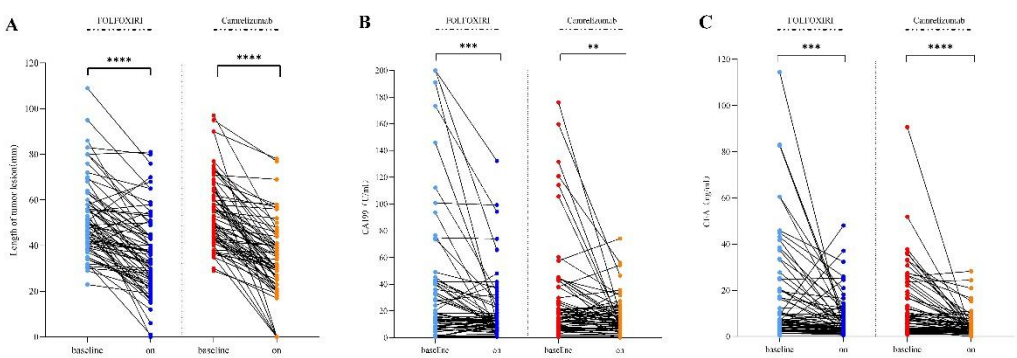

Figure 5. Changes in tumor length, CA199, and CEA levels between baseline and after neoadjuvant therapy. (A). Changes in tumor length in FOLFOXIRI group and camrelizumab group between baseline and after neoadjuvant therapy. (B). Changes in CA199 in the FOLFOXIRI group and camrelizumab group between baseline and after neoadjuvant therapy. (C). Changes in CEA in the FOLFOXIRI group and camrelizumab group between baseline and after neoadjuvant therapy.

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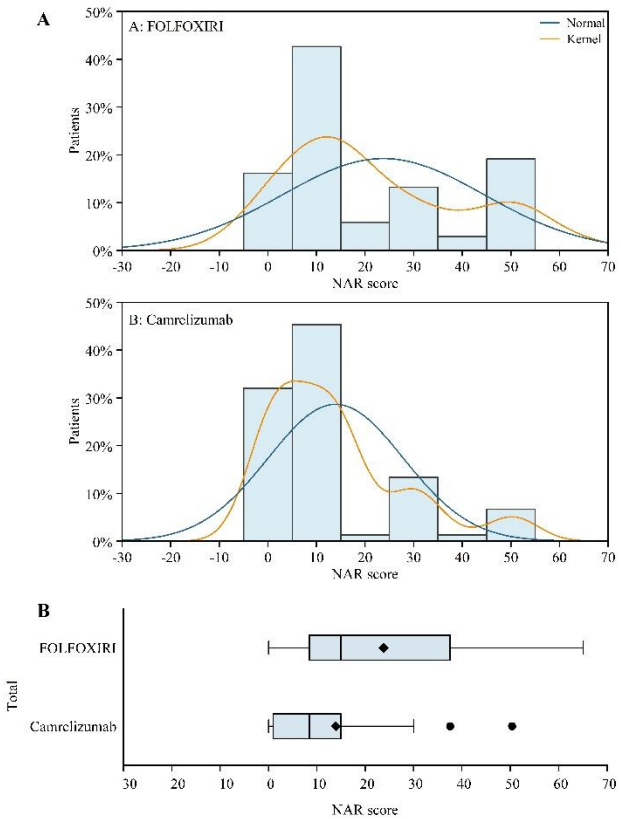

Figure 6. Distribution of NAR scores. (A). Best fit normal distribution (Gaussian distribution) in both groups. (B). Kernel (smooth nonparametric) distribution in both groups.

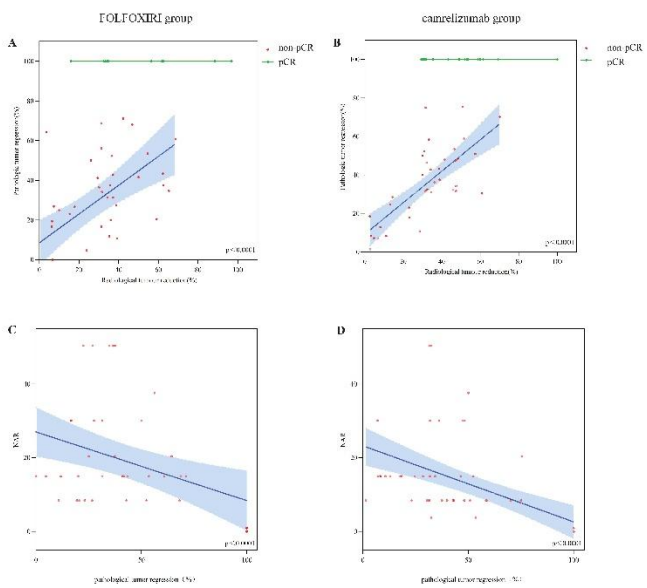

Figure 7. Correlation between pathological tumor regression and the degree of radiographic tumor regression or NAR score. (A.B). Correlation between pathological tumor regression and the degree of radiographic tumor regression. (C.D). Correlation between pathological tumor regression and NAR score.

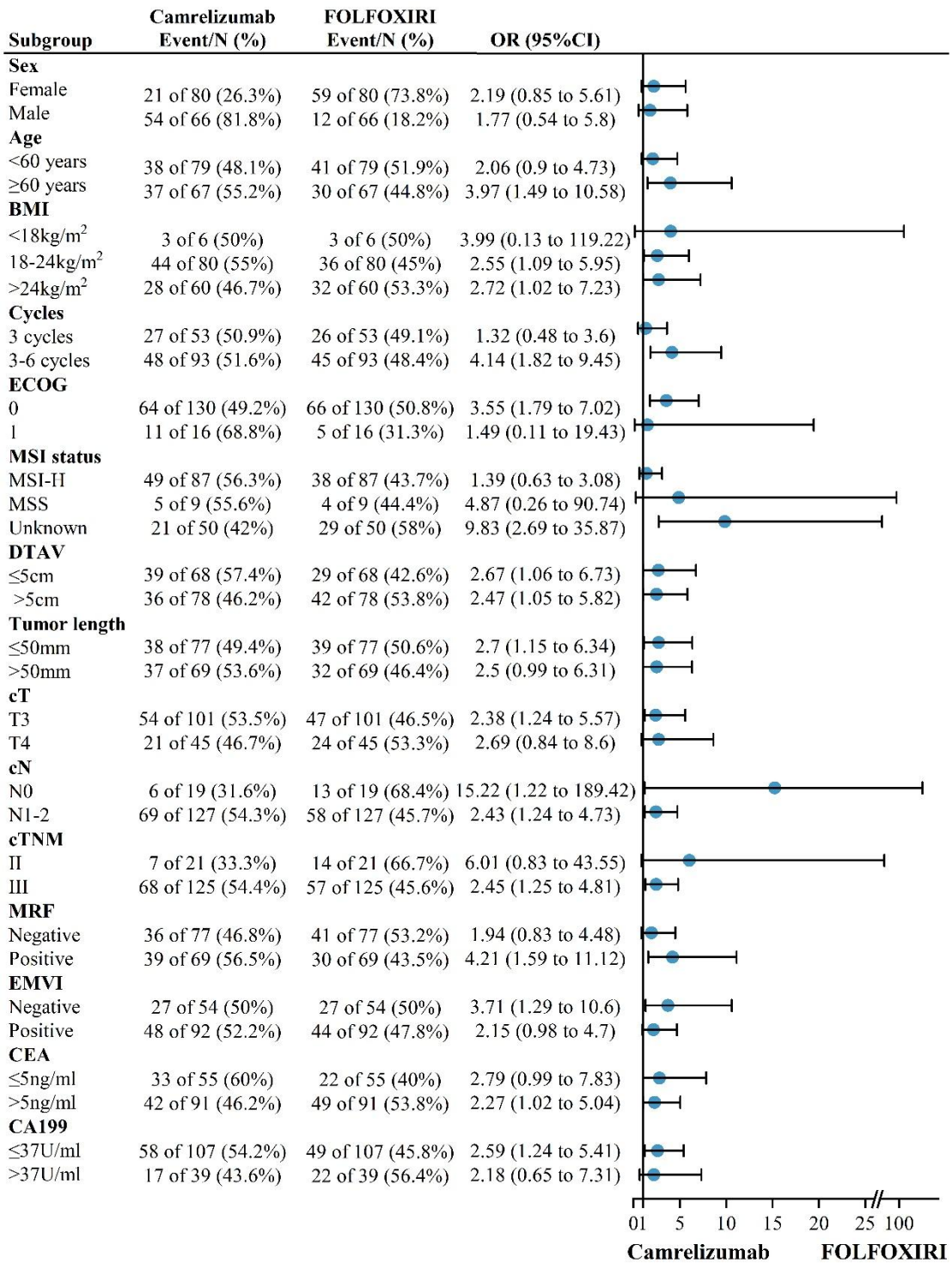

Figure 8. Subgroup analysis of patients' baseline characteristics.

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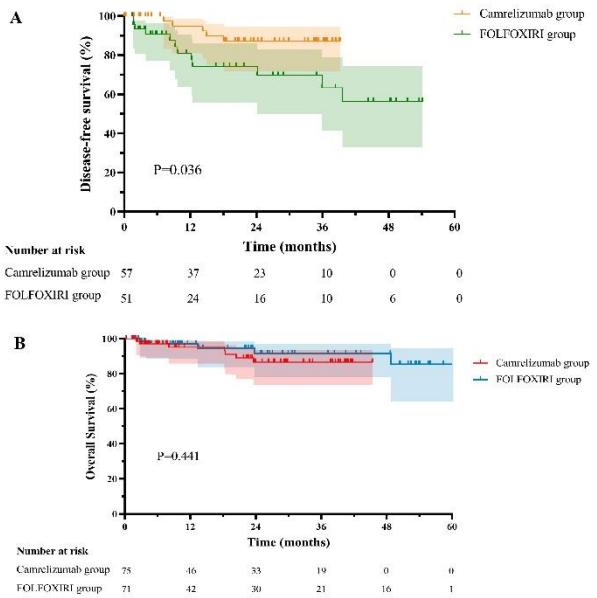

Figure 9. Survival Curve. (A) Disease-free survival for surgical patients in both groups; (B) Overall survival for all enrolled patients in both groups.

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