Comparison of Neoadjuvant Chemoradiotherapy With versus Without Consolidation FOLFOX in Locally Advanced Rectal Cancer: A Retrospective Cohort Study

Warut Boonnithi, MD[1]

[1] Department of Surgery, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand

Abstract

Background: Total neoadjuvant therapy (TNT), including consolidation chemotherapy after chemoradiotherapy (CCRT), has emerged as a promising strategy for locally advanced rectal cancer (LARC). However, real-world data from Thailand remain limited.

Objective: To compare pathological and oncologic outcomes between neoadjuvant CCRT alone and CCRT followed by consolidation FOLFOX in patients with LARC.

Materials and Methods: This retrospective cohort study was conducted at Maharat Nakhon Ratchasima Hospital between January 2017 and December 2024. Patients with histologically confirmed locally advanced middle and lower rectal adenocarcinoma (T3-T4 and/or N+) who underwent neoadjuvant treatment followed by curative-intent surgery were included. Patients were divided into two groups: CCRT alone and CCRT followed by consolidation FOLFOX. The primary outcome was pathologic complete response (pCR). Secondary outcomes included 5-year disease-free survival (DFS), overall survival (OS), and local recurrence rate.

Results: A total of 201 patients were included, with 184 in the CCRT group and 17 in the CCRT plus consolidation group. The consolidation group demonstrated a significantly higher pCR rate compared to the CCRT group (52.9% vs. 9.8%, p<0.001). The interval from CCRT to surgery was significantly longer in the consolidation group (131.7±56.9 vs. 76.5±29.1 days, p=0.001). There were no significant differences in postoperative complications between groups. After a median follow-up of 49 (35.9-60.8) months in the CCRT group and 29.8 (23.8-37.8) months in the consolidation group (p=0.003), the 5-year OS rates were 91.7% and 83.4% (p=0.622), and the 5-year DFS rates were 93.7% and 65.9% (p=0.112), respectively. The 5-year local recurrence rate was lower in the consolidation group (0% vs. 14.5%, p=0.191).

Conclusion: Consolidation FOLFOX following neoadjuvant CCRT was associated with a significantly higher pCR rate without increasing perioperative morbidity. Although survival differences were not statistically significant, favorable trends were observed. Further prospective studies are needed to confirm these findings.

Keywords: Rectal cancer; Neoadjuvant therapy; FOLFOX; Pathologic complete response; Total neoadjuvant therapy

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For locally advanced rectal cancer (T3-T4 and/or N+ disease), the standard treatment protocol is neoadjuvant long-course chemoradiotherapy (CCRT) followed by surgical resection with total mesorectal excision (TME). This approach improves local control and increases tumor downstaging; however, the rate of pathologic complete response (pCR), a key surrogate marker associated with improved long-term outcomes, remains relatively low, typically around 10% to 15%[1-6]. In recent years, a new approach called "total neoadjuvant therapy (TNT)" has gained attention as a strategy to enhance tumor response and improve survival outcomes[3,4,7]. Several

What is already known about this topic?

Neoadjuvant CCRT is the standard treatment for locally advanced rectal cancer, but relatively low pCR rates. TNT, including consolidation chemotherapy, has been shown in clinical trials to increase pCR rates to around 30% to 35%. However, real-world data remain limited.

What does this study add?

This study provides real-world evidence from a tertiary care center in Thailand demonstrating that the addition of consolidation FOLFOX after neoadjuvant CCRT significantly increases the pCR rate in patients with locally advanced rectal cancer. Favorable trends in survival outcomes were also observed.

Correspondence to:

Boonnithi W.

Department of surgery, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000, Thailand.

Phone: +66-86-9802436

Email: bank_ashura@hotmail.com

ORCID: 0000-0002-6854-3322

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studies have demonstrated that this strategy can significantly increase pCR rates, with some reports showing rates up to 30% to 35%[2-4,8]. This approach varies in chemotherapy regimens and sequencing but generally involves administering both radiation and full systemic chemotherapy (instead of a radio-sensitizing chemoradiation dose) prior to surgery. Despite promising results from randomized trials and prospective studies, the implementation of TNT strategies varies across institutions, and real-world data remain limited.

This study aimed to evaluate and compare the oncologic outcomes between patients treated with neoadjuvant CCRT alone and those receiving neoadjuvant CCRT followed by consolidation FOLFOX prior to curative-intent surgery. The primary outcome was the pCR rate, and secondary outcomes included disease-free survival (DFS) and overall survival (OS), providing real-world evidence from a tertiary care center in Thailand.

Materials and Methods

After obtaining approval from the Institutional Review Board of Maharat Nakhon Ratchasima Hospital (IRB No. 033/2025, Study code 68022), we conducted a retrospective cohort study of patients diagnosed with locally advanced middle and lower rectal cancer who underwent neoadjuvant treatment followed by curative-intent surgery between January 1, 2017, and December 31, 2024. Patient data, including demographic characteristics, preoperative carcinoembryonic antigen (CEA) levels, and tumor location, were retrieved from the electronic medical records database. Clinical staging at diagnosis was determined based on magnetic resonance imaging (MRI) and/or computed tomography (CT) imaging findings. Inclusion criteria consisted of: a histologically confirmed diagnosis of adenocarcinoma of the middle and lower rectum with locally advanced disease (T3-T4 and/or N+ disease) according to the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual[9], age >18 years, treatment with neoadjuvant CCRT alone or neoadjuvant CCRT followed by consolidation FOLFOX prior to curative-intent surgery, and availability of complete clinical, pathological, and follow-up data. Exclusion criteria included metastatic disease at diagnosis, incomplete treatment or follow-up records, or a history of malignancy within the previous five years.

Sample Size Calculation

To compare the pCR rates between patients receiving neoadjuvant CCRT alone and those receiving neoadjuvant CCRT followed by consolidation FOLFOX, pCR was used as the primary outcome measure. Based on prior clinical evidence[2-4,8] and our institutional experience, we assumed a pCR rate of 10% in the CCRT-alone group and 35% in the CCRT plus consolidation FOLFOX group. We hypothesized that there would be a significant difference in pCR rates between the two treatment strategies.

Using a two-sided significance level of 5% and a statistical power of 80%, the estimated sample size required to detect this difference was approximately 20 patients in the CCRT plus consolidation FOLFOX group and 150 patients in the CCRT-alone group, reflecting the expected unequal group distribution in our retrospective database.

Given the retrospective nature of the study and the possibility of incomplete medical records or missing pathological data, we allowed for a margin of approximately 10% to 15% of potentially ineligible or incomplete cases. Therefore, all eligible patients within the study period were included to ensure adequate statistical power for detecting the anticipated difference in pCR rates between the two groups.

Statistical Analysis

Data analysis was carried out using Stata Statistical Software, version 17 (StataCorp LLC, College Station, TX, USA). Descriptive statistics were used to summarize baseline characteristics. Continuous variables were reported as mean ± standard deviation for normally distributed data or median with interquartile range (IQR) for skewed data. Group comparisons for continuous variables were conducted using Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Categorical variables were presented as frequencies and percentages and analyzed using Pearson's chi-square test or Fisher's exact test, depending on the data distribution. To assess survival outcomes, Kaplan-Meier analysis was used to estimate 5-year DFS, OS, and local recurrence rate, with statistical significance defined as p-value less than 0.05.

Results

Patients

A total of 201 patients were included in this study, of whom 184 received neoadjuvant CCRT alone and 17 received neoadjuvant CCRT followed by consolidation FOLFOX. Baseline demographic data of both groups are summarized in Table 1. There

Table 1. Baseline demographic data

	CCRT (n=184)	CCRT + consolidate (n=17)	p-value
Sex; n (%)			0.843
Male	102 (55.4)	9 (52.9)	
Female	82(44.6)	8 (47.1)	
Age (years); mean±SD	60.5±10.9	57.3±10.1	0.221
From AV; mean±SD	6.8±2.9	6±2.6	0.216
Cell type; n (%)			0.093
Well diff.	114 (61.9)	15 (88.2)	
Moderately diff.	64 (34.8)	2 (11.8)	
Poorly diff.	6 (3.3)	0 (0.0)	
cT staging; n (%)			0.219
T2	6 (3.3)	2 (11.8)	
T3	159 (86.4)	13 (76.4)	
T4	19 (10.3)	2 (11.8)	
cN staging; n (%)			0.859
N0	31 (16.9)	2 (11.8)	
N1	134 (72.8)	13 (76.4)	
N2	19 (10.3)	2 (11.8)	
CEA at diagnosis; median (IQR)	2.7 (1.7 to 5.8)	2.8 (2.1 to 7.8)	0.564
Pre-neoadjuvant diversion; n (%)	61 (33.2)	7 (41.2)	0.503
Treat with colorectal surgeon; n (%)	66 (35.9)	14 (82.4)	<0.001

SD=standard deviation; IQR=interquartile range; CCRT=chemoradiotherapy; AV=anal verge; CEA=carcinoembryonic antigen

were no significant differences between the two groups in terms of sex distribution (male: 55.4% vs. 52.9%, p=0.843) or mean age (60.5±10.9 vs. 57.3±10.1 years, p=0.221). The distance from the anal verge was also comparable between groups (6.8±2.9 vs. 6.0±2.6 cm, p=0.216). Clinical T stage at diagnosis was similar between groups (p=0.219), with the majority of patients presenting with T3 disease. Likewise, no significant differences were observed in clinical N stage (p=0.859). Baseline CEA levels were comparable between the two groups (median 2.7 vs. 2.8 ng/mL, p=0.564). The proportion of patients undergoing pre-neoadjuvant diversion was also similar (33.2% vs. 41.2%, p=0.503). However, a significantly higher proportion of patients in the CCRT plus consolidation group were managed by colorectal surgeons compared to the CCRT-alone group (82.4% vs. 35.9%, p<0.001).

Neoadjuvant Treatment

Details of neoadjuvant treatment are summarized in Table 2. Among patients in the CCRT plus consolidation FOLFOX group, the number of chemotherapy cycles varied, with 47.1% receiving 3 cycles, 35.3% receiving 6 cycles, and 17.6% receiving 12 cycles. The interval from completion of CCRT to surgery was significantly longer in the CCRT plus consolidation group compared to the CCRT-alone group (131.7±56.9 vs. 76.5±29.1 days, p=0.001). Similarly, the time from diagnosis to surgery was also significantly prolonged in patients receiving consolidation chemotherapy (203.9±67.7 vs. 154.9±42.3 days, p=0.009).

Table 2. Neoadjuvant treatment

	CCRT (n=184)	CCRT + consolidate (n=17)	p-value
FOLFOX cycle; n (%)			
3	-	8 (47.1)	
6	-	6 (35.3)	
12	-	3 (17.6)	
From CCRT to surgery (days); mean±SD	76.5±29.1	131.7±56.9	0.001
From diagnosis to surgery (days); mean±SD	154.9±42.3	203.9±67.7	0.009

SD=standard deviation; CCRT=chemoradiotherapy

Table 3. Surgical aspects

	CCRT (n=184)	CCRT + consolidate (n=17)	p-value
Approach; n (%)			0.013
Open	121 (65.8)	6 (35.3)	
Laparoscopic	63 (34.2)	11 (64.7)	
Procedure; n (%)			0.138
LAR	145 (79.2)	16 (94.1)	
APR	38 (20.8)	1 (5.9)	
En bloc resection; n (%)			
Wedge vaginal wall	3 (1.6)	0 (0.0)	
Hysterectomy	13 (7.1)	2 (11.8)	
Total cystectomy	1 (0.5)	0 (0.0)	
Operative time (minutes); mean±SD	238.5±90.4	247.1±53.2	0.561
Blood loss (mL); mean±SD	314.8±344.6	229.4±265.6	0.231
Protective ostomy; n (%)	113 (61.4)	15 (88.2)	0.089
Complication; n (%)			
Postoperative ileus	14 (7.6)	2 (11.8)	0.545
Surgical site infection	6 (3.3)	0 (0.0)	0.450
Anastomosis leakage	4 (2.2)	0 (0.0)	0.539
Hospital stay (days); mean±SD	9.2±5.8	8±4.1	0.254

SD=standard deviation; CCRT=chemoradiotherapy; LAR=low anterior resection; APR=abdominoperineal resection

Surgical Aspects

Surgical aspects are summarized in Table 3. The laparoscopic approach was significantly more frequently performed in the CCRT plus consolidation group compared to the CCRT-alone group (64.7% vs. 34.2%, p=0.013). There was no significant difference in the type of surgical procedure between groups, although low anterior resection (LAR) was more commonly performed in the consolidation group

Table 4. Pathological outcomes

	CCRT (n=184)	CCRT + consolidate (n=17)	p-value
ypT; n (%)			
T0	19 (10.3)	10 (58.8)	
T1	16 (8.7)	0 (0.0)	
T2	63 (34.2)	2 (11.8)	
T3	76 (41.3)	4 (23.5)	
T4	10 (5.4)	1 (5.9)	
ypN; n (%)			
N0	128 (69.6)	12 (70.6)	
N1	44 (23.9)	5 (29.4)	
N2	12 (6.5)	0 (0.0)	
Nodal retrieval; mean±SD	10.3±4.6	9±4.9	0.330
Lymphovascular invasion; n (%)	32 (17.4)	4 (23.5)	0.528
Positive margin; n (%)	4 (2.2)	0 (0.0)	0.539
ypStage; n (%)			
Stage I	68 (37)	2 (11.8)	
Stage II	42 (22.8)	1 (5.9)	
Stage III	56 (30.4)	5 (29.4)	
pCR; n (%)	18 (9.8)	9 (52.9)	<0.001

SD=standard deviation; CCRT=chemoradiotherapy; pCR=pathologic complete response

(94.1% vs. 79.2%, p=0.138). Operative outcomes, including operative time (247.1±53.2 vs. 238.5±90.4 minutes, p=0.561) and intraoperative blood loss (229.4±265.6 vs. 314.8±344.6 mL, p=0.231), were comparable between the two groups. The rate of protective ostomy tended to be higher in the consolidation group (88.2% vs. 61.4%, p=0.089). The incidence of postoperative ileus (11.8% vs. 7.6%, p=0.545), surgical site infection (0% vs. 3.3%, p=0.450), and anastomotic leakage (0% vs. 2.2%, p=0.539) did not differ significantly. Additionally, the length of hospital stay was comparable (8.0±4.1 vs. 9.2±5.8 days, p=0.254).

Pathological Outcomes

Pathological outcomes are summarized in Table 4. Patients in the CCRT plus consolidation FOLFOX group demonstrated significantly improved tumor response compared to those receiving CCRT alone. A higher proportion of patients in the consolidation group achieved pCR (52.9% vs. 9.8%, p<0.001). Consistent with this finding, the distribution of ypT stage showed a substantial shift toward earlier tumor stages in the consolidation group, with 58.8% of patients achieving ypT0 compared to 10.3% in the CCRT-alone group. Nodal status (ypN) was comparable between groups, with no statistically significant differences observed.

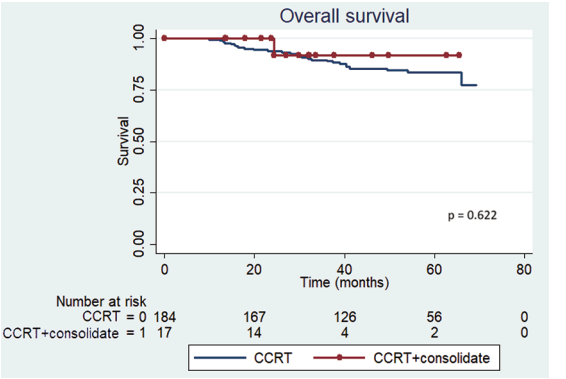

Figure 1. Overall survival.

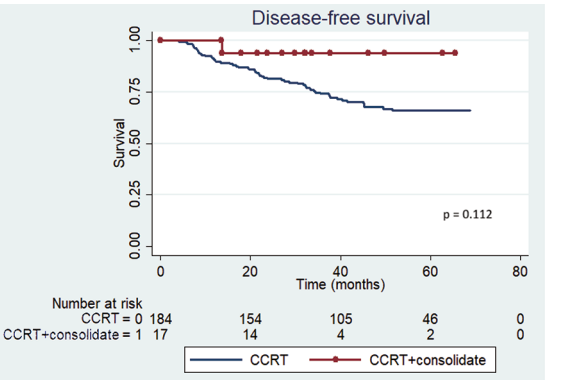

Figure 2. Disease-free survival.

The mean number of retrieved lymph nodes was also similar (9.0±4.9 vs. 10.3±4.6, p=0.330). Other pathological features, including lymphovascular invasion (23.5% vs. 17.4%, p=0.528) and positive resection margin (0% vs. 2.2%, p=0.539), did not differ significantly between the two groups.

Survival Outcomes

The median follow-up duration was significantly shorter in the CCRT plus consolidation group compared to the CCRT-alone group [49 (IQR 35.9-60.8) vs. 29.8 (IQR 23.8-37.8) months, p=0.003]. Kaplan-Meier analysis demonstrated no statistically significant difference in OS between the two groups (p=0.622), although a trend toward improved survival was observed in the consolidation group (Figure 1). The estimated 5-year OS rates were 91.7% in the CCRT plus consolidation group and 83.4% in the CCRT-alone group. Similarly, DFS showed a favorable trend in the consolidation group but did not reach statistical significance (p=0.112) (Figure 2). The 5-year DFS rates were 93.7% in the consolidation group compared to 65.9% in the CCRT-alone group. Regarding local

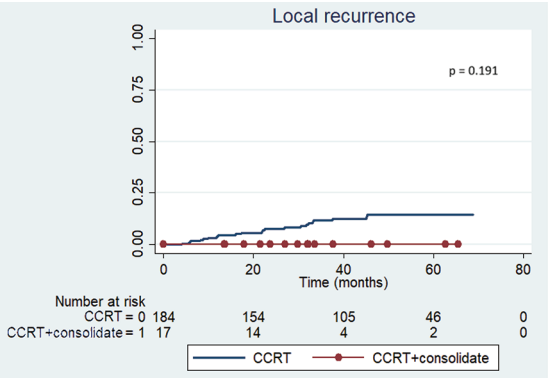

Figure 3. Local recurrence.

control, the 5-year local recurrence rate was lower in the consolidation group (0% vs 14.5%), although this difference was not statistically significant (p=0.191) (Figure 3).

Discussion

This study demonstrated that the addition of consolidation FOLFOX after neoadjuvant CCRT was associated with a higher pCR rate compared with CCRT alone (52.9% vs. 9.8%, p<0.001). Although no statistically significant differences were observed in 5-year OS, DFS, or local recurrence, consistent trends toward improved oncologic outcomes were noted in the consolidation group.

The pCR rate observed in our study (52.9%) is higher than those reported in randomized trials evaluating TNT. For example, the PRODIGE 23 trial reported a pCR rate of approximately 27.5% with intensified neoadjuvant treatment[4], while studies evaluating consolidation chemotherapy after CCRT have reported pCR rates in the range of 30% to 35%[2-4,8]. The higher pCR rate in our study may be explained by several factors. First, the significantly prolonged interval from completion of CCRT to surgery in the consolidation group (131.7 vs. 76.5 days, p=0.001) may have allowed for greater tumor regression. Second, the administration of additional systemic chemotherapy likely contributed to enhanced tumor response. Third, selection bias inherent to the retrospective cohort study design cannot be excluded, particularly given the small sample size of the consolidation group.

Despite the significant improvement in pCR, survival outcomes did not reach statistical significance. However, the observed trends toward improved 5-year OS (91.7% vs. 83.4%) and DFS (93.7% vs. 65.9%) suggest a potential clinical benefit. The lack of statistical significance is likely attributable to limited statistical power, the relatively small number of patients in the consolidation group (n=17), and the significantly shorter follow-up duration compared with the CCRT-alone group. These factors may have limited the ability to detect differences in long-term outcomes.

The addition of consolidation chemotherapy did not result in increased perioperative morbidity. Surgical outcomes, including operative time, blood loss, postoperative complications, and length of hospital stay, were comparable between the two groups. This finding supports the safety of this treatment strategy in real-world clinical practice. Additionally, the higher rate of laparoscopic surgery in the consolidation group may reflect improved tumor downstaging, which could also have contributed to favorable outcomes.

However, several limitations should be acknowledged. First, the retrospective design introduces the possibility of selection bias and unmeasured confounding factors. Second, the relatively small sample size, especially in the consolidation group, limits the statistical power of the study. Third, the imbalance in baseline characteristics, including a higher proportion of surgeries performed by colorectal surgeons in the consolidation group, may have influenced outcomes. Finally, the shorter follow-up duration in the consolidation group may underestimate long-term recurrence and survival outcomes.

Conclusion

The addition of consolidation FOLFOX following neoadjuvant CCRT was associated with a significantly higher pCR rate without increasing perioperative morbidity. Although survival benefits were not statistically significant, favorable trends were observed. Further prospective studies with larger sample sizes and longer follow-up are warranted to confirm these findings and to better define the role of consolidation chemotherapy in the management of locally advanced rectal cancer.

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Author Contributions

The author contributed to the study conception and design, data collection, data analysis and interpretation, drafting of the manuscript, and critical revision of the manuscript.

Conflicts of interest

The author declares no conflicts of interest.

Data Availability Statement

The datasets generated and/or analyzed during this study are not publicly available due to patient confidentiality and institutional regulations, but are available from the corresponding author on reasonable request and with permission from the Institutional Review Board of Maharat Nakhon Ratchasima Hospital.

Clinical Trial Registration

Not applicable. This study was a retrospective cohort study and was not registered as a clinical trial.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Maharat Nakhon Ratchasima Hospital (IRB No. 033/2025, Study code 68022). Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures were conducted in accordance with the ethical standards of the Institutional Research Committee.

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Use of Artificial Intelligence

The authors used ChatGPT (OpenAI, USA) to assist in English language editing and grammar checking. The author reviewed and approved all content and take full responsibility for the accuracy and integrity of the manuscript.

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