The THAI Journal of SURGERY 2025;46(4):184-191.
Official Publication of The Royal College of Surgeons of Thailand

Original Article

Efficacy of Total Neoadjuvant Therapy (TNT) Versus Concurrent Neoadjuvant Chemoradiotherapy (CCRT) Alone for Locally Advanced Rectal Cancer in Rajavithi Hospital: A Retrospective Study

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Abstract

Background: Conventional therapy for locally advanced rectal cancer included concurrent chemoradiotherapy (CCRT) followed by surgery and adjuvant chemotherapy. An alternative strategy known as total neoadjuvant therapy (TNT) involves the administration of neoadjuvant chemotherapy plus CCRT before surgery. The studies before suggest that TNT is a promising strategy in locally advanced rectal cancer with a superior rate of PCR compared with conventional therapy. The purpose of this study is to compare the rate of PCR using these 2 approaches in patients at Rajavithi Hospital.

Objective: To determine the differences in rates of pathologic complete response (PCR), R0 resection, and 30-day mortality between patients receiving TNT vs conventional CCRT.

Materials and Methods: We performed a retrospective study of patients with clinical stage II/III rectal cancer within Rajavithi Hospital. All patients who received TNT and conventional CCRT were collected between 2019 and 2024, and the rates of pathological complete response (pCR) were compared between the two arms.

Results: Of the 135 patients in the cohort, 102 (76%) received conventional treatment and 33 (24%) received TNT. At baseline, patients in both groups were more likely to have clinical Stage 3 disease. There were 5 (15.2%) TNT patients who achieved pCR after surgery, compared to 8 (7.8%) conventional CCRT patients ($P = 0.305$), with no significant difference. There were no significant differences in the rate of positive margins after surgery (3% vs. 8.8%, $P = 0.45$). Only one patient in the standard arm has mortality within 30 days.

Conclusion: In the TNT group, PCR was found to be higher than the standard group (15.2% vs 7.8%, $p = 0.305$), although PCR was not significantly different, the real pCR rate was consistent with previous studies that suggest TNT is a promising strategy in locally advanced rectal cancer, with superior rates of PCR compared to standard CCRT.

Keywords: Total neoadjuvant chemotherapy (TNT), Concurrent chemoradiotherapy (CCRT), Locally advanced rectal cancer (LARC), Pathological complete response (PCR)

Received for publication 2 May 2025; Revised 21 August 2025; Accepted 1 September 2025

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https://doi.org/10.64387/tjs.2025.275196

Introduction

Rectal cancer has been increasingly diagnosed over the years in Thailand, with an incidence of 14.1 per 100,000 in men and 10 per 100,000 in women.[1] In 2018, there were 17,534 new cases of rectal cancer, accounting for 10.3% of all newly diagnosed cancers in Thailand.[2] For patients with locally advanced rectal cancer (LARC), locoregional recurrence rates have declined in recent years due to advances in surgical techniques and the adoption of neoadjuvant chemoradiation. As a result, the most common cause of death is now distant metastasis.[3,4] This risk can be reduced through the use of systemic chemotherapy.

However, the optimal timing for administering systemic chemotherapy in these patients remains unclear. Historically, patients with LARC have undergone neoadjuvant chemoradiation and surgery, followed by adjuvant chemotherapy. Nevertheless, intolerance to chemotherapy following surgery leads to poor compliance, with only 40%-50% of patients completing the adjuvant treatment course in clinical trials.[5,6]

In recent years, a new treatment strategy known as total neoadjuvant therapy (TNT) has emerged. In this approach, patients receive both systemic chemotherapy and chemoradiation prior to definitive surgical resection.[7] TNT is theoretically associated with improved treatment compliance, higher rates of R0 resection, and increased pathologic complete response (pCR) rates.

Many trials of TNT have been previously studied,[8-16] demonstrating excellent compliance rates and tolerability. However, the unclear result of the pathological complete response rate. One small phase 2 trial directly compared neoadjuvant CAPOX (TNT) to adjuvant CAPOX and found no difference in pCR after surgery.[12] Recently, a single institution retrospective study found that TNT increased rates of pCR.[17]

In the COVID-19 ERA, due to limited access to surgical facilities, we initiated total neoadjuvant therapy (TNT) as a treatment strategy for LARC patients at Rajavithi Hospital. We performed a single retrospective study at Rajavithi Hospital to examine whether the TNT approach is associated with improved pathological complete response (pCR) to conventional historical CCRT.

Materials and Methods

A retrospective study was conducted at Rajavithi Hospital, focusing on the period from January 2019 to June 2024. The initial query included all adult patients diagnosed with rectal cancer who received chemotherapy between 2019 and 2024 (N = 567). Patients with clinical stage 1 or 4, who have undergone no definitive surgery, upfront surgery, received post-op RT, and who have received an incomplete dose of chemotherapy were excluded.

The study included patients diagnosed with rectal cancer at American Joint Committee on Cancer (AJCC) clinical stage II or III who received all three of the following treatments: (1) systemic chemotherapy, (2) neoadjuvant chemoradiotherapy, and (3) surgery.

Data were obtained from the Rajavithi Hospital database, including patient age, gender, ASA score, tumor characteristics (both clinical and pathological AJCC TNM stage), chemotherapy regimen, surgical margin status, surgical approach and type, pathological complete response (pCR), and 30-day postoperative mortality.

Patients in the conventional arm were defined as those who received concurrent chemoradiation (CCRT) prior to surgery. TNT patients were defined as those who received neoadjuvant chemotherapy either before or after chemoradiation, followed by surgery. The exclusion criteria were clinical I or IV, the patient did not undergo definitive surgery, an incomplete course of chemotherapy, the patient underwent upfront surgery, or the patient received postoperative radiotherapy. The definition of incomplete course chemotherapy is failure to receive the planned full course of systemic chemotherapy, either due to premature discontinuation, dose omission, or early termination before completing the scheduled cycles.

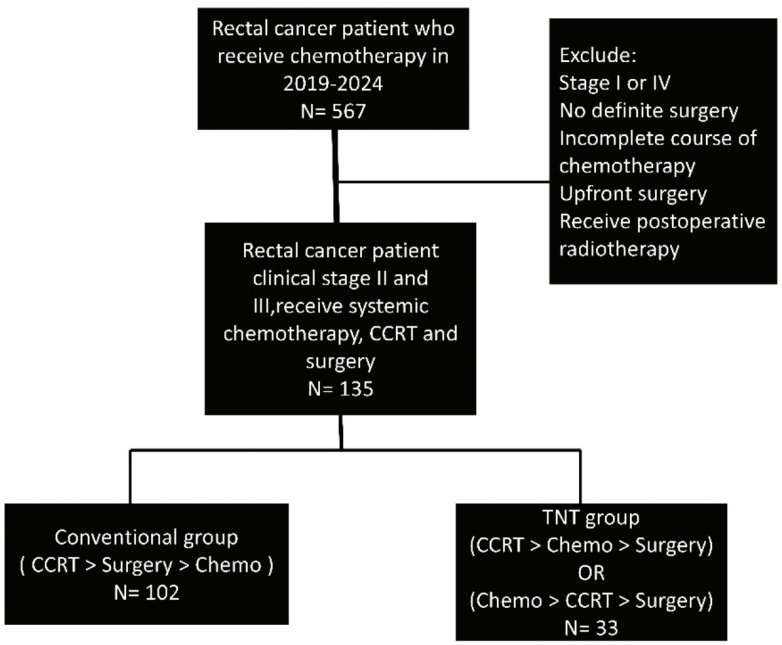

Figure 1

The primary outcome was to determine the difference rate of pathological complete response (pCR) between patients receiving total neoadjuvant therapy (TNT) and those receiving conventional concurrent chemoradiation (CCRT). pCR was defined based on pathological T and N staging.

The secondary outcomes were to compare the rates of R0 resection and 30-day postoperative mortality between the two treatment groups.

Statistical analysis

Data were analyzed using SPSS version 26.0. Univariate analysis was performed using the $\chi 2$ test for dichotomous variables and the Student's *t*-test or Wilcoxon rank sum test for normal and non-normal continuous variables, respectively, with a *p*-value of less than 0.05 defined as statistically significant.

Results

Patient Demographics and Clinical Characteristics (Table 1)

A total of 135 patients were included in the study, with 102 patients receiving conventional concurrent chemoradiation therapy (CCRT) and 33 patients receiving total neoadjuvant therapy (TNT). The participants consisted of 63% males and 37% females, with a mean age of 55.48 years. The majority of patients were classified as ASA class II (59.3%), followed by class I (38.5%) and class III (2.2%).

Regarding tumor characteristics, 80% of patients had AJCC clinical stage III disease, and 20% had stage II disease. The most common clinical T stages were cT3 (65.2%) and cT4 (28.9%). Clinically positive lymph nodes (cN+) were present in 79.3% of patients, while 20.7% were cN0. Pathological T stage was mostly ypT3 (47.4%) and ypT4 (25.9%), and pathological N stage was mostly ypN0 (62.2%).

The overall pathological complete response rate was 9.6%, R0 resection was achieved in 92.6% of patients, and only 1 patient died (0.7%) within 30 days postoperatively. Among the TNT group, the most commonly used chemotherapy regimen was FOLFOX (73%), followed by CAPOX (27%).

Table 1 Demographic and Clinical Characteristics between TNT gr and conventional gr.

Characteristics	Group		*p*-value
	TNT patients n (%) = 33	Conventional patients n (%) = 102	
Gender			0.357
Male	23 (69.7)	62 (60.8)	
Female	10 (30.3)	40 (39.2)	
Age (year)			0.893
Mean ± SD	55.85 ± 11.23	55.36 ± 11.02	
ASA score			0.666
I	38 (37.3)	14 (42.4)	
II	62 (60.8)	18 (54.5)	
III	2 (2)	1 (3)	
Tumor characteristics			
AJCC clinical staging			0.089
Stage 2	10 (30.3)	17 (16.7)	
Stage 3	23 (69.7)	85 (83.3)	
Clinical T classification			0.828
cT1	0	1 (1)	
cT2	1 (3)	6 (5.9)	
cT3	23 (69.7)	65 (63.7)	
cT4	9 (27.3)	30 (29.4)	
Clinical N classification			0.119
cN0	10 (30.3)	18 (17.6)	
cN+	23 (69.7)	84 (82.4)	
Pathological T classification			0.72
ypT0	5 (15.2)	8 (7.8)	
ypT1	0	1 (1)	
ypT2	5 (15.2)	17 (16.7)	
ypT3	14 (42.4)	50 (49)	
ypT4	9 (27.3)	26 (25.5)	
Pathological N classification			< 0.001
ypN0	30 (90.9)	54 (52.9)	
ypN1	3 (9.1)	36 (35.3)	
ypN2	0	12 (11.8)	
Pathological complete response (pCR)			0.305
Yes	5 (15.2)	8 (7.8)	
No	28 (84.8)	94 (92.2)	
Chemotherapy Regimen			
CAPEOX	9 (27)	-	
FOLFOX	24 (73)	-	
Surgical approach			1.0
Open	16 (48.5)	48 (47.1)	
Laparoscopic	16 (48.5)	50 (49)	
Lap convert to open	1 (3)	4 (3.9)	
Surgical type			0.695
AR/LAR/ISR	21 (63.6)	61 (59.8)	
APR/Hartman/Pelvic ex	12 (36.4)	41 (40.2)	
R0 resection margin			0.45
Yes	32 (97)	93 (91.2)	
No	1 (3)	9 (8.8)	

Values were represented as n (%), mean ± SD, and median (min-max). The p-value from the student *t*-test and chi-square test * significant at $p < 0.05$

Comparison of TNT vs. Conventional CCRT

Compared to patients who received conventional therapy, patients in both the TNT and conventional groups were likely to have non-different clinical stage III disease. The mean age was comparable between the TNT and the conventional group, as were sex distribution, ASA score, clinical T stage (cT), and clinical N stage (cN).

Following surgery, the pathological T0 stage (pT0) was observed in 15.2% of TNT patients and 7.8% of conventional neoadjuvant CCRT patients ($P = 0.72$), while the pathological N0 stage (pN0) was significantly higher in the TNT group (90.9% vs. 52.9%, $P < 0.001$). Notably, all patients with pT0 also achieved pathological complete response (pCR).

There was no statistically significant difference in the rate of positive surgical margins between the two groups (3.0% vs. 8.8%, $P = 0.45$). Thirty-day postoperative mortality occurred in only one patient, who was in the conventional group.

There was no significant difference in the type of surgical approach (laparoscopic vs. open) between the TNT and conventional group.

In the TNT group, the FOLFOX regimen was more commonly used than CAPOX (73% vs. 27%).

Pathological complete response

A total of 5 patients (15.2%) in the TNT group achieved pathological complete response (pCR) after surgery, compared to 8 patients (7.8%) in the conventional neoadjuvant CCRT group; this difference was not statistically significant ($P = 0.305$).

However, the nodal conversion rate from clinically positive nodes (cN+) to pathologically negative nodes (ypN0) was significantly higher in the TNT group compared to the conventional group (90.9% vs. 52.9%, $P < 0.001$).

Discussion

In the COVID-19 era, physicians at Rajavithi Hospital are increasingly using TNT in practice due to limitations in the operating room and this strategy has favorable tolerability profile, including a shorter ostomy duration, as demonstrated in previous studies.[8-13] Additionally, TNT has not been shown to negatively affect overall survival (OS), which supports its growing use as an alternative to conventional neoadjuvant therapy in LARC.[18,19]

In this retrospective cohort study conducted at Rajavithi Hospital, we compared the efficacy of total neoadjuvant therapy (TNT) versus conventional neoadjuvant concurrent chemoradiotherapy (CCRT) in patients with locally advanced rectal cancer (LARC). Our primary outcome was the rate of pathological complete response (pCR), with secondary outcomes including R0 resection rates and 30-day postoperative mortality. Among 135 patients, 33 received TNT and 102 received conventional neoadjuvant CCRT. The pCR rate was higher in the TNT group compared to the CCRT group, at 15.2% and 7.8%, respectively, but no statistically significant difference ($P = 0.305$). Notably, the nodal conversion rate was significantly higher in the TNT group, 90.9% and. 52.9%, $P < 0.001$. Rates of R0 resection and 30-day mortality were similar between two groups.

About the pCR rate, our study was concordant with previous reports in recent meta-analyses and randomized controlled trials (RCTs), which generally report pCR rates between 14% and 36% for TNT and 7–22% for conventional neoadjuvant CCRT.[20-24]

There are several factors that are associated with pathological complete response after TNT. Two studies demonstrate that the predictors of pCR are total neoadjuvant treatment.[25,26] Patient-related factors, such as young age (less than 60 years) and better performance status (ECOG 0-1), are associated with a higher pCR rate.[25,26] Tumor-related factors, including non-mucinous adenocarcinoma, are associated with a higher pCR rate; conversely, mucinous adenocarcinoma and signet-ring cell carcinoma are associated with a lower pCR rate.[25,26] Biological marker: CEA level < 5 ng/mL before treatment predicts a higher pCR rate, although the relationship between post-treatment CEA level and pCR remains unclear.[25] Receiving a complete course of chemotherapy without interruption and a longer interval between completion of neoadjuvant chemoradiotherapy (nCRT) and surgery shows an increased pCR rate.[26,27] But it should be noted that Yacoub H, etal, reported this study with total neoadjuvant treatment using short-course radiotherapy, commonly used in European countries.[26]

Although the pCR rate in our study was not statistically significant, this outcome remains clinically relevant. pCR is considered a surrogate marker for improved long-term survival, with previous studies showing better outcomes in patients who achieve pCR.[18] In our study, the pCR rate was higher in the TNT group compared to the conventional group (15.2% vs. 7.8%; $P = 0.305$), which is concordant with previous reports.[18-26] Kong et al. reported a pCR rate of 22.3% in the TNT group versus

14.2% in the conventional group ($P < 0.001$), and there was a significantly better 3-year disease-free survival and overall survival in the TNT compared to the conventional neoadjuvant CCRT group.[23] Similarly, Gabbani et al. conducted a meta-analysis of 14 randomized controlled trials and found a pCR rate of 23.6%, with 3- and 5-year overall survival rates of 93% and 81.6%, respectively.[24] A systematic review and meta-analysis by Kasi et al. in 2020 reported a pooled pCR rate of 29.9% (range, 17.2%–38.5%) in the TNT group versus 14.9% (range, 4.2%–21.3%) in the conventional group. The authors concluded that TNT is a promising strategy in LARC, associated with a significantly greater chance of achieving pCR (odds ratio [OR], 2.44; 95% CI, 1.99–2.98).[20]

The rationale for TNT is to reduce a patient's risk of distant metastasis, which is a major cause of death in rectal cancer. Early systemic chemotherapy can eradicate micrometastases before they become distant metastases and improve overall survival.[22] TNT consists of induction chemotherapy and consolidation chemotherapy. Both induction and consolidation chemotherapy improve pCR rate and disease control compared to CCRT. A recent meta-analysis does not show evidence that induction or consolidation is better.[21,22] The pCR rate for induction and consolidation is similar in the meta-analysis.[20,21,22] Induction chemotherapy may be better for early systemic control. Consolidation chemotherapy may maximize tumor shrinkage before surgery and better selection for the organ preservation strategy.[22]

Our study shows a significantly higher nodal conversion rate in the TNT group, at 90.9%, compared to 52.9% in the CCRT group ($P < 0.001$). This observation is consistent with the hypothesis that early and intensified systemic chemotherapy, as delivered in TNT, is more effective at eradicating micrometastatic disease and achieving nodal downstaging, aligning with results from the RAPIDO and PRODIGE-23 trials. Other studies have similarly reported that TNT increased nodal downstaging and reduced rates of distant metastasis.[18,22]

Systematic review and meta-analysis from Kong et al. showed that Patients who received TNT were less likely to have residual nodal disease on final pathology (pooled OR 0.87, 95% CI 0.73–1.03, $p = 0.122$, I 2 = 67.7%), sub meta-analysis showed that there is significantly nodal conversion in induction chemotherapy group (OR 0.56, 95% CI 0.41–0.77, $p < 0.001$, I 2 = 33.5%).[22] The author concluded that TNT is associated with downstaging of both the primary site and nodal basin, which also added benefit in the rate of anal preservation, distant recurrences, disease-free survival, and 3-year overall survival.[22]

Regarding the primary outcome, our study did not demonstrate a statistically significant difference in pCR rate between the TNT group and the conventional group. The pCR rate is consistent with previously published data.[8,10-14,17-26] The absence of statistical significance is likely attributable to the small sample size of the TNT arm (N = 33), which limited the statistical power to detect the differences.

Limitations

This study is limited by its retrospective design, which may introduce selection bias and confounding factors between the treatment groups. Although the sample size calculation for the TNT group indicated that at least 73 patients would be required to achieve adequate statistical power, only a small population of about 33 patients met the inclusion criteria during the study period at Rajavithi Hospital (January 2019 to June 2024). As a result, the study may have been underpowered to detect a statistically significant difference in outcomes between the groups.

Another limitation of our study is the exclusion rate between groups. Patients in the CCRT group were excluded more frequently than those in the TNT group due to lower compliance with completing the planned chemotherapy regimen. This may have introduced a selection bias.

Conclusion

In the TNT group, the pathological complete response (pCR) rate was no different compared with the conventional CCRT group (15.2% vs. 7.8%, $P = 0.305$). This may be attributed to the limited sample size in the TNT group at Rajavithi Hospital. A future multicenter study with a larger population is warranted to increase statistical power and validate these findings.

Additionally, significantly greater nodal downstaging was observed in the TNT group, which reflects patterns seen in larger trials and meta-analyses. These findings support the continued investigation and possible adoption of TNT as a conventional strategy for LARC, particularly in patients at high risk of systemic disease.

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