PRELIMINARY RESULTS OF TOTAL NEOADJUVANT THERAPY IN STAGE II-III RECTAL CANCER: REAL-WORLD DATA FROM K HOSPITAL

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ABSTRACT

Background: Total Neoadjuvant Therapy (TNT) has recently emerged as a promising approach in the management of locally advanced rectal cancer. However, real-world evidence on its effectiveness and safety in Vietnam remains limited.

Methods: We retrospectively analyzed 148 patients with stage II–III rectal cancer of the middle or lower rectum treated with TNT at K Hospital. TNT regimens included chemotherapy combined with either short-course or long-course chemoradiation therapy. Surgery was performed 4–8 weeks after completion of TNT. Treatment outcomes, pathological response, sphincter preservation, and adverse events were assessed.

Results: The mean age was 57.2 years, with a male-to-female ratio of 1.96:1. Tumor downstaging was achieved in 68.9% of patients with a pathological complete response (pCR) rate of 25.7% and sphincter preservation rate of 71.6%. Peripheral neuropathy and elevated AST were the most common adverse events. Grade 3–4 toxicities most frequently included neutropenia (8.1%) and diarrhea (4.1%). Multivariate analysis revealed that earlier tumor stage and the use of triplet chemotherapy regimens were significantly associated with higher pCR rates.

Conclusions: Total neoadjuvant therapy (TNT) was well tolerated in this cohort and was associated with favorable pathological response in patients with stage II–III rectal cancer. Further prospective studies are warranted to confirm these findings and optimize treatment strategies in the Vietnamese setting.

Keywords: Rectal cancer; Total neoadjuvant therapy (TNT); pathological complete response (pCR).

1. INTRODUCTION

Rectal cancer is one of the most common malignancies of the gastrointestinal tract. According to GLOBOCAN 2022, there are approximately 784,139 new cases and 365,852 deaths from rectal cancer worldwide each year[1]. In Vietnam, colorectal cancer ranks fourth in incidence and fifth in cancer-related mortality[1].

Over recent decades, significant advances in treatment have contributed to improved prognosis for patients with rectal cancer. Notably, these include total mesorectal excision (TME), preoperative concurrent chemoradiotherapy, and more recently, Total Neoadjuvant Therapy (TNT) has emerged as an alternative to the standard preoperative chemoradiotherapy regimen, aiming to achieve tumor downstaging, increase sphincter

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preservation rates, reduce distant metastasis and recurrence, prolong survival, and improve patients' quality of life.

The efficacy of TNT has been demonstrated in phase III randomized controlled trials such as RAPIDO[2] and PRODIGE-23[3], which reported higher pathological complete response (pCR) rates, improved disease-free survival, and acceptable toxicity profiles. Consequently, TNT is increasingly recognized as a global treatment paradigm. However, most large-scale studies have been conducted in Western populations, which may not fully reflect the clinical characteristics of Asian patients in general and Vietnamese patients in particular.

In Vietnam, TNT has been implemented in several oncology centers, including K Hospital. Preliminary studies have reported pCR rates ranging from 19.4% to 33.3%[4–7] and high rates of sphincter preservation, with treatment-related toxicities generally limited to mild-to-moderate severity. Nevertheless, these studies are limited by small sample sizes and often evaluate only a single TNT sequence, without comparing different TNT strategies in real-world clinical practice in Vietnam.

Based on this context, we conducted this study to evaluate the efficacy and toxicity of various TNT regimens at K Hospital during the period 2021–2025, and to analyze factors associated with pathological complete response as well as selected treatment-related toxicities.

2. MATERIALS AND METHODS

2.1. Subjects

A total of 148 patients with stage II–III mid and low rectal cancer who received Total Neoadjuvant Therapy (TNT) at K Hospital between January 2021 and May 2025 were included in this study.

Inclusion Criteria

- Patients diagnosed with mid to low-rectal cancer with histopathological confirmation of adenocarcinoma based on endoscopic biopsy.

- Tumors staged as stage II or III (cT3-4 and/or cN+ M0) according to the UICC/AJCC 8th edition (2017).

- Availability of complete medical records.

Exclusion Criteria:

- Prior treatment for rectal cancer.

- Presence of other malignancies within the past 5 years.

- Previous pelvic radiotherapy or chemotherapy.

- Pregnant or breastfeeding women.

- Patients with severe acute or chronic comorbid conditions.

2.2. Study Methods

- Study design: Retrospective observational study.

- Sample size and sampling method: Total sampling.

- Study setting and period: K Hospital, from January 2021 to May 2025.

2.3. Study Procedure

Step 1: Patient selection and pretreatment evaluation.

Step 2: Treatment according to Total Neoadjuvant Therapy (TNT) protocols:

1. Short-course radiotherapy → consolidation chemotherapy → surgery

2. Long-course chemoradiotherapy→ consolidation chemotherapy → surgery

3. Induction chemotherapy → long-course chemoradiotherapy → surgery

In this real-world cohort, the selection and sequencing of Total Neoadjuvant Therapy were not protocol-mandated and were based on multidisciplinary team discussions, physician experience and patient- and disease-related factors.

- Radiotherapy:

+ Target volume delineation: Defined according to the 2016 international consensus guidelines

+ Radiation dose: Long-course chemoradiotherapy: Total dose of 50.4 Gy delivered in 28 fractions, with concurrent Capecitabine 825 mg/m² administered twice daily on radiotherapy days (5 days/week); Short-course radiotherapy: Total dose of 25 Gy delivered in 5 fractions.

- Chemotherapy: Consolidation/induction chemotherapy regimens included mFOLFIRINOX, mFOLFOX6, or CAPEOX administered over 12-16 weeks.

Step 3: Monitoring and recording all treatment-related adverse events during and after therapy.

Step 4: Assessment of clinical and paraclinical response before surgery.

Step 5: Surgery is performed 4-8 weeks after completion of neoadjuvant treatment.

Step 6: Postoperative evaluation and consideration of adjuvant therapy.

Step 7: Postoperative follow-up.

Treatment completion was defined as the receipt of all planned radiotherapy dose and all planned cycles of chemotherapy without premature discontinuation.

**** Study Variables and Outcomes:***

- Patient characteristics (age, gender, tumor stage).

- Treatment response (pathological complete response [pCR], resection margin status, downstaging rate).

- Treatment-related toxicities.

**** Research Instruments and Data Collection Methods:***

- Medical records of all eligible rectal cancer patients meeting inclusion and exclusion criteria were collected, organized by patient, and chronologically.

- Patient data were extracted from medical records using a standardized data collection form (case report form).

**** Statistical Analysis:***

Data were analyzed using SPSS version 26.

Baseline characteristics between treatment groups were compared using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. The primary endpoint was pathological complete response (pCR). Factors associated with pCR were initially evaluated using univariable logistic regression analysis. Multivariable logistic regression was then performed to identify independent factors associated with pCR. Variables included in the multivariable model were selected a priori based on clinical relevance, including treatment strategy and key tumor characteristics. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided p-value < 0.05 was considered statistically significant.

2.4. Ethical Considerations

The study protocol was approved by the Institutional Review Board of K Hospital on April 22, 2025. All collected data were kept confidential and used solely for research purposes.

3. RESULTS

A total of 148 patients with stage II–III rectal cancer who received Total Neoadjuvant Therapy (TNT) at three facilities of K Hospital between January 2021 and May 2025 were included in this study.

The mean age of the study population was 57.2 ± 11.4 years, with a male-to-female ratio of 1.96:1. Overall, the majority of patients presented with cT3–T4 disease (94.4%), and 85.1% had clinically suspected nodal metastases.

Three TNT regimens were implemented at K Hospital. The most commonly used regimen was

long-course concurrent chemoradiotherapy followed by consolidation chemotherapy (60.8%), followed by induction chemotherapy combined with long-course chemoradiotherapy (22.9%), and short-course radiotherapy followed by consolidation chemotherapy (18.2%).

The most frequently utilized radiotherapy technique was three-dimensional conformal radiotherapy (3D-CRT) (66.2%), while intensity-modulated radiotherapy/volumetric modulated arc therapy (IMRT/VMAT) accounted for 33.1%.

Table 1: Baseline Characteristics of the Study Patients

Characteristics		n (%)
Age		57.2±11.4
Gender	Female	50 (33.8%)
	Male	98 (66.2%)
Stage T	cT2	8 (5.4%)
	cT3	114 (77.0)
	cT4	26 (17.6)
Stage N	cN0	22 (14.9)
	cN1	56 (37.8)
	cN2	70 (47.3)
MRF	(+)	48 (32.4)
	(-)	96 (64.9)
	Missing	4 (2.7)
EMVI	(+)	31 (20.9)
	(-)	113 (76.4)
	Missing	4 (2.7)
Position Tumor	Middle rectum	61 (41.2)
	Lower rectum	87 (58.8)
Treatment Regimens	Induction CT + LCRT	31 (21.0)
	LCRT + Consolidation CT	90 (60.8)
	SCRT + Consolidation CT	27 (18.2)
Chemotherapy regimens	mFOLFIRINOX	29 (19.6)
	mFOLFOX6/ XELOX	119 (80.4)
Radiotherapy techniques	3D	98 (66.2)
	IMRT	27 (18.2)
	VMAT	22 (14.9)
	Missing	1 (0.7)
Treatment completion	Radiationtherapy Completed	148 (100)
	Incompleted	0 (0)
	Chemotherapy Completed	115 (77.7)
	Incompleted	33 (22.3)

Among the study population, the majority of patients achieved R0 resection (98.6%). In addition, the sphincter preservation rate was 71.6%. Following treatment, tumor downstaging was observed in 68.9% of patients, and 25.7% achieved a pathological complete response (pCR).

Table 2: Response Evaluation

Characteristics		n (%)
Interval between treatment completion and surgery		43±14 days
Resection margin status	R0	146 (98.6)
	R1	1 (0.7)
	R2	1 (0.7)
Sphincter preservation	Yes	106 (71.6)
	No	42 (28.4)
ypT	ypT0	39 (26.3)
	ypT1	8 (5.4)
	ypT2	43 (29.1)
	ypT3	49 (33.1)
	ypT4	9 (6.1)

Characteristics		n (%)
ypN	ypN0	120 (81.1)
	ypN1	26 (17.6)
	ypN2	2 (1.3)
pCR	Complete response	38 (25.7)
	Incomplete response	110 (74.3)
Tumor downstaging	Yes	102 (68.9)
	No	46 (31.1)
Nodal downstaging	Yes	135 (91.2)
	No	13 (8.8)

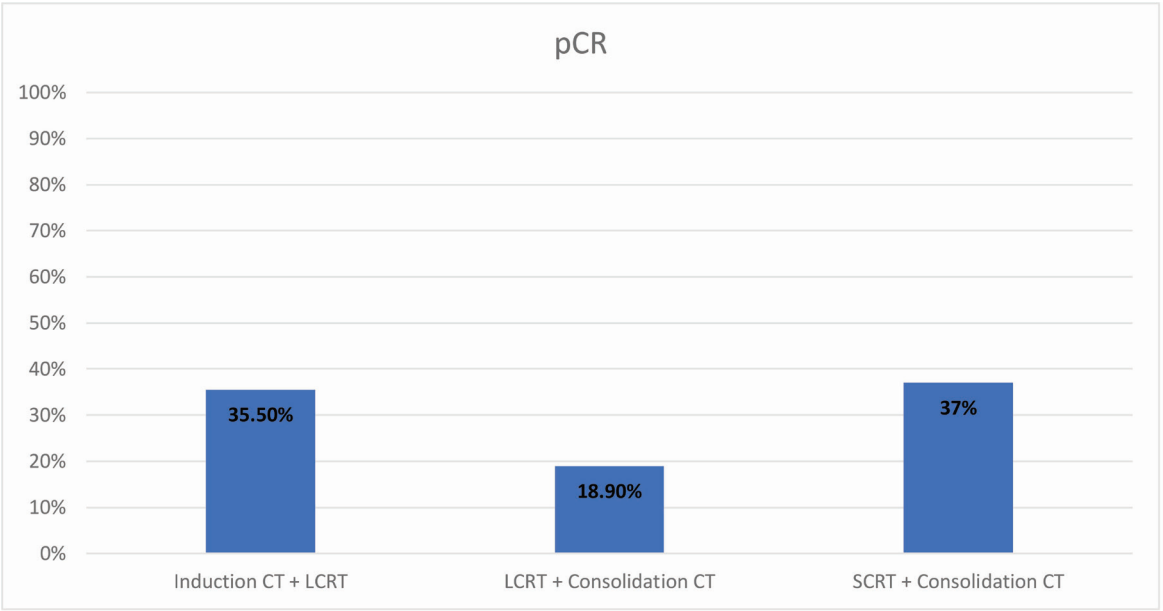

Chart 1: Pathological complete response (pCR) rates among the three Total Neoadjuvant Therapy (TNT) regimens

Analysis of Factors Associated with Pathological Complete Response (pCR): Multivariable logistic regression analysis demonstrated that:

- The mFOLFIRINOX regimen was associated with a 2.8-fold increase in the likelihood of achieving pathological complete response (pCR) compared to doublet chemotherapy regimens (OR = 2.795; p = 0.033).

- Patients with cT2–3 tumors had a 4.7-fold higher likelihood of achieving pCR compared to those with cT4 tumors (OR = 0.213; p = 0.048).

The use of triplet chemotherapy and tumor stage were identified as independent predictive factors associated with pathological complete response.

Table 3: Treatment-Related Adverse Events

Treatment-Related Adverse Events		Grade 1-2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic toxicities	Anemia	38.5	0.7	
	Leukopenia	50.0	2.0	0.7
	Neutropenia	41.9	6.1	2.0
	Thrombocytopenia	59.4	2.7	0.7
Hepatic and renal toxicities	Elevated AST	70.3	2.0	0
	Elevated ALT	56.7	1.4	0
	Elevated urea	4.7	0	0
	Elevated creatinine	3.4	0	0
Clinical toxicities	Diarrhea	43.3	4.1	0
	Proctitis	21.0	0.7	0
	Cystitis	9.0	0	0
	Peripheral neuropathy	87.0	2.7	0
	Nausea	37.2	0.7	0
	Vomiting	13.5	0	0

Analysis of Factors Associated with Treatment Toxicity:

Neutropenia: Univariate logistic regression analysis showed that the use of the mFOLFIRINOX regimen was associated with a 4.75-fold increased risk of neutropenia compared with other regimens (OR = 4.750; p = 0.020).

Diarrhea: When stratified by radiotherapy technique, the short-course radiotherapy group had a significantly higher rate of severe diarrhea (Grade 3-4) compared to the long-course radiotherapy group (18.5% vs. 0.8%; p = 0.001).

4. DISCUSSION

Total Neoadjuvant Therapy (TNT) has recently emerged as a novel treatment strategy for locally advanced rectal cancer. Phase III randomized controlled trials, such as RAPIDO[2] and PRODIGE-23[3], have demonstrated that TNT increases pathological complete response (pCR) rates and reduces the risk of distant metastasis, thereby influencing treatment guidelines worldwide, including in Vietnam. In Vietnam, TNT has been implemented in recent years across multiple oncology centers. Preliminary studies suggest that TNT is a feasible, effective, and safe approach for Vietnamese patients.

Our study included 148 patients with a mean age of 57 years and a male-to-female ratio of approximately 2:1. The epidemiological characteristics of this cohort are generally consistent with both domestic and international reports on rectal cancer, with most patients aged between 50 and 70 years and a higher prevalence in males[8, 9]. Regarding disease characteristics, a substantial proportion of patients presented with high-risk features: cT4 accounted for 17.6%, cN2 for 47.3%, 32.4% had suspected mesorectal fascia (MRF) involvement, and 20.9% had suspected vascular invasion. These rates are higher than those reported in some studies, such as PRODIGE-23[3], which documented 21% MRF involvement and 26% N2 disease. This discrepancy may be explained by the initial

implementation phase, during which TNT was preferentially applied to high-risk patients to ensure cautious translation from Western clinical trials into Vietnamese practice.

At K Hospital, the most commonly used TNT sequence was long-course chemoradiotherapy followed by consolidation chemotherapy (60.8%), predominantly using doublet chemotherapy regimens. This choice reflects the favorable tolerability profile of doublet regimens in Vietnamese patients. Additionally, long-course chemoradiotherapy remains more routinely utilized than short-course radiotherapy due to greater clinical experience at the institution.

The study results demonstrated an R0 resection rate of 98.6%, with 71.6% of patients achieving sphincter preservation. Tumor downstaging occurred in 68.9% of patients, and the pCR rate was 25.7%. These findings are comparable to large international trials such as PRODIGE-23[3] and RAPIDO[2] (pCR ~28%, R0 rate 90–95%). The pCR rate in our study is also consistent with domestic reports, such as Nguyen Van Dang[6] (2025) reporting 21.2% and Nguyen Hai Hoang[4] reporting 23.6%.

Notably, patients receiving induction chemotherapy followed by long-course chemoradiotherapy achieved a significantly higher pCR rate (35.5%) compared to those receiving consolidation chemotherapy (18.9%) ($p < 0.05$). One key explanation for this difference lies in the chemotherapy regimens used. In the induction group, up to 84% of patients received triplet chemotherapy (based on the PRODIGE-23 protocol), whereas only 5% in the consolidation group received such regimens ($p < 0.05$). Multivariable logistic regression confirmed that the use of triplet chemotherapy was an independent predictor of pCR, increasing the likelihood by 2.8-fold compared to doublet regimens ($p = 0.033$). This suggests that higher chemotherapy intensity, rather than TNT sequencing alone, plays a crucial role in improving treatment outcomes.

Additionally, the pCR rate in the short-course radiotherapy plus consolidation chemotherapy group was 37.0%, higher than that in the long-course chemoradiotherapy plus consolidation group (18.9%) ($p < 0.05$). However, this difference is largely attributable to baseline patient characteristics. Specifically, the long-course group had a significantly higher proportion of cT4 tumors (22.2%) compared to the short-course group (0%) ($p = 0.007$). This observation aligns with evolving clinical practice at K Hospital following updated 5-year results from the RAPIDO trial[10], which suggested superior local control with long-course chemoradiotherapy, particularly in patients at high risk of local recurrence. Logistic regression analysis in our study further confirmed tumor stage as an independent predictor of pCR, with cT2–3 tumors having a 4.7-fold higher likelihood of achieving pCR compared to cT4 tumors ($p = 0.048$). Therefore, differences in pCR between radiotherapy strategies in this study should primarily be interpreted as reflecting patient selection rather than intrinsic treatment efficacy.

Regarding toxicity, peripheral neuropathy and elevated AST were the most common adverse events, occurring in 89.7% and 72.3% of patients, respectively. However, these were predominantly low-grade and did not lead to treatment interruption. Grade 3–4 toxicities were mainly neutropenia (8.1%) and diarrhea (4.1%). The use of triplet chemotherapy increased the risk of grade 3–4 neutropenia by 4.8-fold compared to doublet regimens ($p = 0.02$); However, these events were manageable with granulocyte colony-stimulating factor (G-CSF) prophylaxis in subsequent cycles. Two patients (6.9%) required modification of chemotherapy due to toxicity.

In terms of gastrointestinal toxicity, the short-course radiotherapy group exhibited a higher rate

of diarrhea compared to the long-course group. This may be related to the fact that 85.2% of patients in the short-course group were treated using three-dimensional conformal radiotherapy (3D-CRT), as well as the higher dose per fraction and larger irradiated volumes, which may increase acute toxicity. Other adverse events were mostly grade 1-2 and showed no significant differences among the three TNT regimens.

Clinical T stage and chemotherapy regimen were significantly associated with pCR, consistent with findings from other international studies. Additional factors such as incomplete chemotherapy cycles, interval between radiotherapy and surgery, carcinoembryonic antigen (CEA) levels, and tumor length may also influence pCR rates, although further data are required to confirm these associations.

This study has several limitations. First, its retrospective design introduces potential information and selection biases. Second, the sample sizes of the short-course radiotherapy and induction chemotherapy groups were relatively small. Therefore, prospective, multicenter studies with larger sample sizes are needed to validate and expand upon these findings in the future.

5. CONCLUSION

This cohort study shows that Total Neoadjuvant Therapy (TNT) was associated with favorable rates of pathological complete response (pCR), R0 resection, and sphincter preservation in patients with locally advanced rectal cancer. Higher clinical T stage (cT) and the use of triplet chemotherapy (versus doublet) were associated with differences in pCR rates.

These findings further support the role of TNT in the management of rectal cancer in Vietnam and suggest that individualized selection of treatment sequence and chemotherapy regimen is essential to optimize efficacy while minimizing toxicity. However, due to the retrospective design and limited sample size, particularly in the short-course radiotherapy and induction chemotherapy groups, prospective, multicenter studies with larger cohorts are warranted to validate these results and strengthen the evidence base for clinical practice.

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