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Original Research Article

Comparison of Surgical Outcomes of Total Neoadjuvant Therapy and Standard Long Course Chemoradiation in Rectal Cancer: A Prospective Cohort Study from a Tertiary Care Centre in Eastern India

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Abstract

Background: Total Neoadjuvant Therapy (TNT) is increasingly adopted for locally advanced rectal cancer (LARC) to improve systemic control and treatment compliance. However, concerns remain regarding its impact on surgical outcomes, especially in resource-constrained settings.

Objective: To prospectively compare surgical outcomes and pathological responses between TNT and standard Long-Course Chemoradiation (LCRT) in LARC patients at a tertiary centre in Eastern India.

Design: Prospective cohort study.

Setting: Department of Surgical Oncology, Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Eastern India.

Patients: 80 patients with histologically confirmed LARC (cT3-4/any T + cN+), enrolled from December 2023 to December 2024. 36 received TNT and 44 underwent LCRT.

Outcome Measures: Primary outcomes included major postoperative complications (Clavien-Dindo grade ≥III), operative time, Total Mesorectal Excision (TME) quality, R0 resection rate, circumferential resection margin positivity, and sphincter preservation rate. Secondary outcome: disease progression during neoadjuvant therapy.

Results: Baseline characteristics were comparable between groups. TNT resulted in significantly longer operative time (215 vs. 190 min; p=0.002), higher breached TME rates (22.2% vs. 4.5%; p=0.04), and greater blood loss (325 vs. 270 ml; p=0.008). Major complications were similar (TNT 16.7% vs. LCRT 15.9%). R0 resection rates (88.8% vs. 90.9%; p=0.78), pCR rates (13.9% vs. 15.9%; p=0.82), and sphincter preservation (72.2% vs. 75%; p=0.78) were comparable. Disease progression to unresectable disease was low in both groups.

Limitations: Single-centre study with a small sample size and short follow-up, lacking long-term oncologic outcomes.

Conclusions: TNT and LCRT yield comparable oncological outcomes and complication rates. However, TNT is associated with increased surgical complexity. Careful patient selection and surgical expertise are essential when implementing TNT, particularly in resource-constrained settings.

Keyword: Neoadjuvant Therapy, Chemoradiation, Rectal Cancer.

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Introduction

Rectal cancer is a significant global health concern, accounting for a large proportion of cancer-related morbidity and mortality worldwide. It is the eighth most common cancer globally, with over 700,000 new cases diagnosed annually [1]. The standard management of locally advanced rectal cancer (LARC), typically classified as cT3-T4 or node-positive disease, has evolved considerably over the past few decades. Historically, treatment involved long-course chemoradiation therapy (LCRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy, a regimen designed to

optimize local control and reduce recurrence [2,3]. Despite improvements in surgical techniques and radiotherapy, LCRT has limitations. Notably, compliance with postoperative chemotherapy remains suboptimal, with reports suggesting that fewer than 50% of patients complete the intended course of adjuvant therapy due to postoperative complications and poor tolerance [4,5]. Additionally, distant metastasis continues to be a leading cause of failure in rectal cancer management, underscoring the need for improved systemic control [6].

Total Neoadjuvant Therapy (TNT) has emerged as a promising alternative that seeks to address these limitations. TNT entails the delivery of all systemic chemotherapy and radiotherapy prior to surgery. This approach aims to increase patient compliance, enhance tumor downstaging, and potentially improve disease-free and overall survival [7,8,9]. Multiple large randomized controlled trials such as RAPIDO, PRODIGE 23, and OPRA have demonstrated that TNT can lead to higher rates of pathological complete response (pCR), reduced distant metastases, and potentially allow for non-operative management in select patients [10,11,12].

However, TNT is not without its challenges. Some studies13 have raised concerns about increased fibrosis and operative difficulty following intensive neoadjuvant regimens, potentially affecting surgical outcomes such as TME quality and margin status [14,15]. There is a paucity of data from developing countries, including India, on how these protocols translate into surgical practice in resource-constrained environments.

In this context, our study provides valuable prospective data from a tertiary academic cancer centre in eastern India. We aim to compare the surgical outcomes, including operative metrics and pathological results, between patients treated with TNT and those receiving the conventional LCRT approach. Our goal is to assess whether TNT confers additional surgical risks or compromises oncologic quality in an Indian cohort.

Objective : This study aims to prospectively compare the surgical outcomes, pathological responses of TNT and LCRT in patients with LARC.

The primary objectives of the study are:

1. To evaluate the surgical outcomes of TNT and LCRT, including the completeness of TME and postoperative complications.
2. To assess the pathological responses to TNT and LCRT, including pCR rates and TRG.

Methods

Study Design and Setting: This prospective cohort study was conducted at the Department of Surgical Oncology, AHPGIC, a tertiary academic centre in Eastern India. Written informed consent was obtained from all participants. The study duration was from December 2023 to December 2024.

Patient Selection : A total of 80 patients with histologically confirmed locally advanced rectal cancer (cT3-4/any T + cN+) were enrolled in the study.

Patients were divided into two groups based on the treatment protocol: 36 patients received TNT, while 44 patients underwent standard LCRT. Convenience sampling was used for patient allocation.

Inclusion Criteria:

- Age ≥18 years
- Radiologically staged cT3-T4 and/or cN+ rectal adenocarcinoma
- ECOG performance status 0-2

Exclusion Criteria:

- Metastatic disease at presentation
- Previous pelvic radiotherapy
- Contraindications to chemotherapy or surgery

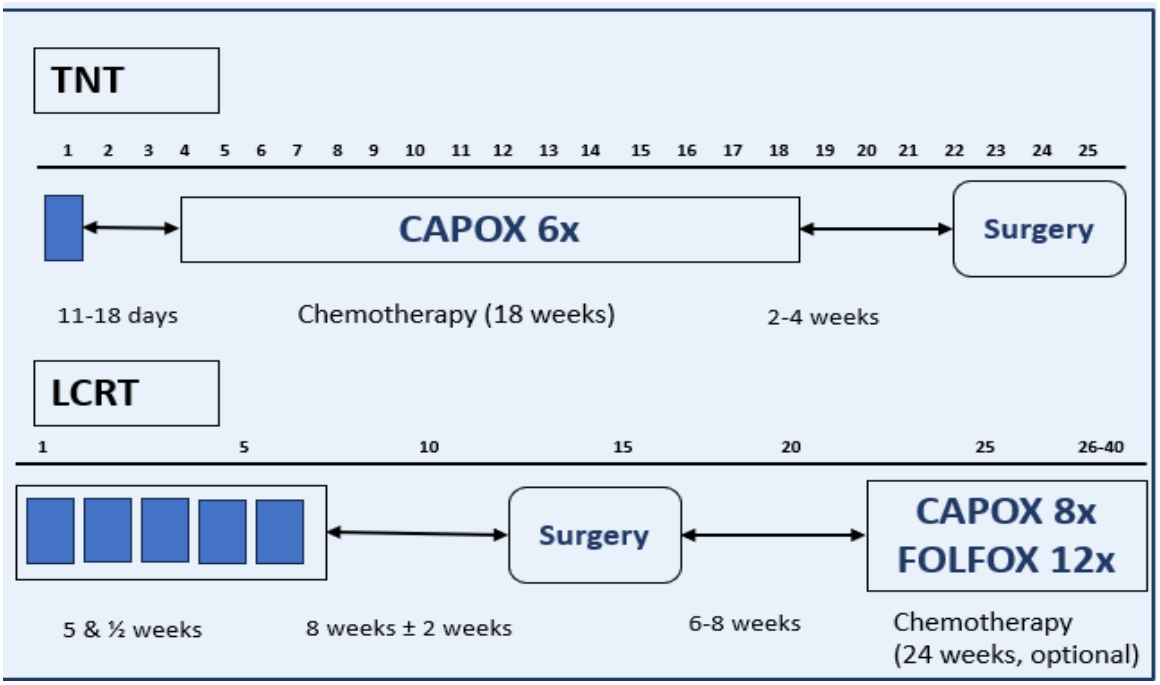

Figure 1: Treatment protocol showing Total Neo Adjuvant Therapy (TNT) group and Long Course Rdiotherapy (LCRT) group; TNT: short course Radio Therapy (RT) followed by consolidation chemotherapy followed by surgery; LCRT: Long Course Radio Therapy followed by surgery followed by adjuvant Chemotherapy.

1. Total Neoadjuvant Therapy (TNT) Group: Patients in this group received short-course radiotherapy (25 Gy in 5 fractions over 5 days) followed by consolidation chemotherapy (CAPOX 6 cycles) and subsequent TME. Adjuvant chemotherapy was administered based on the pathological findings.

2. Long-Course Chemoradiation (LCRT) Group: Patients in this group underwent standard long-course chemoradiation (50.4 Gy in 28 fractions over 5.5 weeks) with concurrent capecitabine, followed by TME and adjuvant chemotherapy (CAPOX 8 cycles or FOLFOX 12 cycles).

All were open surgeries and were done by surgeons with minimum experience of 50 rectal surgeries.

Outcome Measures

Primary outcomes:

- Major postoperative complications (Clavien-Dindo grade III or higher)
- Operative time
- TME quality (intact vs breached)
- R0 resection rate
- Circumferential resection margin (CRM) positivity
- Sphincter preservation rate

Secondary outcome: Disease progression to unresectable stage during neoadjuvant therapy

Data Collection and Analysis: Data on patient demographics, treatment details, surgical outcomes & pathological responses were collected prospectively. Continuous variables were presented as means or medians with standard deviations (SD) or interquartile ranges (IQR) and compared using t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were presented as percentages and compared using Fisher's exact test or the chi-square test. Results were reported with 95% confidence intervals (CI), and a p-value of <0.05 was considered statistically significant

Results

The demographic characteristics of the patients in both groups were compared in Table 1. The median age in the TNT group was 62.5 years (IQR: 55-69), while in the LCRT group, it was 60 years (IQR: 55-64). The gender distribution was also similar between the two groups, with a male predominance in both cohorts (TNT: 69.4% male; LCRT: 59.1% male). Other baseline characteristics, including tumour stage and location, were well-balanced between the two groups. All values are given in median (IQR), IQR: Interquartile Range, T/t: Treatment, RT: Radio Therapy, Sx: Surgery TNT: Total Neo Adjuvant Therapy, LCRT: Long Course Radio Therapy, *: p<0.005 is significant In Table 2 we can see that TNT is associated with a significantly longer overall treatment duration and operative time (median: 215 minutes vs. 190 minutes, p=0.002), but similar hospitalization durations, compared to LCRT. The prolonged

interval between treatment and surgery in the TNT group reflects the protocol design and may impact surgical complexity.

Table 1: Baseline Characteristics of Patients in TNT and LCRT group

Variables	TNT (n=36)	LCRT (n=44)	P value
Performance status (ECOG)			0.32
0-1	28 (77.8)	38 (86.4)	
2	8 (22.2)	6 (13.6)	
co-morbidity			0.11
+nt	9 (25)	5 (13.9)	
-nt	27 (75)	39 (88.6)	
Distance from anal verge			0.90
0-5 cm (lower)	15 (41.7)	18 (45.9)	
>5-10 cm (mid)	19 (52.8)	23 (52.3)	
>10-15 cm (upper)	2 (5.5)	3 (6.8)	
Mesorectal fascia			0.47
≤1 mm	28 (77.8)	37 (84.1)	
>1 mm	8 (22.2)	7 (15.9)	

All data are given as n (%). ECOG: Eastern Cooperative Oncology Group, TNT: Total Neo Adjuvant Therapy, LCRT: Long Course Radio Therapy, *: p<0.005 is significant

Table 2: Treatment Timeline in TNT and LCRT group

Variables	TNT (n=36)	LCRT (n=44)	P value
Start of T/t to Sx (wks)	**26 (24-27)**	**15.5 (14-17)**	
End of RT to Sx (wks)	**25 (23-26)**	**10.5 (9-12)**	
Operating Time (min)	**215 (200-225)**	**190 (170-220)**	**0.002***
Length of stay (days)	**9 (7-10)**	**8 (7-9)**	**0.14**

Table 3: Surgical Outcomes in TNT and LCRT group

Variables	TNT (n=36)	LCRT(n=44)	RR	P value
Breached TME (Incomplete)	8 (22.22)	2 (4.54)	4.89	0.04*
0-5 cm (lower rectum)	4 (11.1)	1 (2.3)		
5-10 cm (mid rectum	4 (11.1)	1 (2.3)		
10-15 cm (upper rectum)	0	0		
Sphincter Preservation Rates	26 (72.2)	33 (75)	0.96	0.78
Blood loss, ml, median (IQR)	325 (290-370)	270 (270-310)	1.83	0.008*
Post Op Complication				
Ileus	2 (5.6)	3 (6.8)	0.81	1.00
Pelvic infection	3 (8.3)	2 (4.5)	1.83	0.81
UTI	1 (2.8)	2 (4.5)	0.61	1.00
CD Grade			1.05	0.99
0-2	30 (83.3)	37 (84.1)		
3-4 (Major Morbidity)	6 (16.66)	7 (15.90)		

All data are given as n (%) or median (IQR). TME: Total Mesorectal Excision, IQR: Inter Quartile Range, UTI: Urinary Tract Infection, CD Grade: Clavien-Dindo grade. TNT: Total Neo Adjuvant Therapy, LCRT: Long Course Radio Therapy, *: p<0.005 is significant.

Table 4: Pathological Response in TNT and LCRT group

Variables	TNT (n=36)	LCRT (n=44)	RR	P value
T stage down staging	20 (55.6)	23 (52.3)		
N stage down staging	27 (75)	31 (70.5)		
Pathologic complete response,	5 (13.9)	7 (15.9)	0.87	0.82
Disease Progression	1 (2.8)	2 (4.5)	0.61	0.74

All data are given as n (%), TNT: Total Neo Adjuvant Therapy, LCRT: Long Course Radio Therapy, *: p<0.005 is significant.

The surgical outcomes and pathological response rates are summarized in Table 3 and Table 4 respectively. The TNT group had a higher rate of breached TME (22.22% vs. 4.54%, p=0.04) compared to the LCRT group, considering complete and nearly complete TME in Quirke's grading as Intact, and incomplete TME as Breached [16]. TNT group was associated with more blood

loss as compared to LCRT group (p= 0.008). There was no statistical significant between LCRT group vs TNT group regarding complete pathological response (pCR) (13.9% vs. 15.9%, p=0.82).

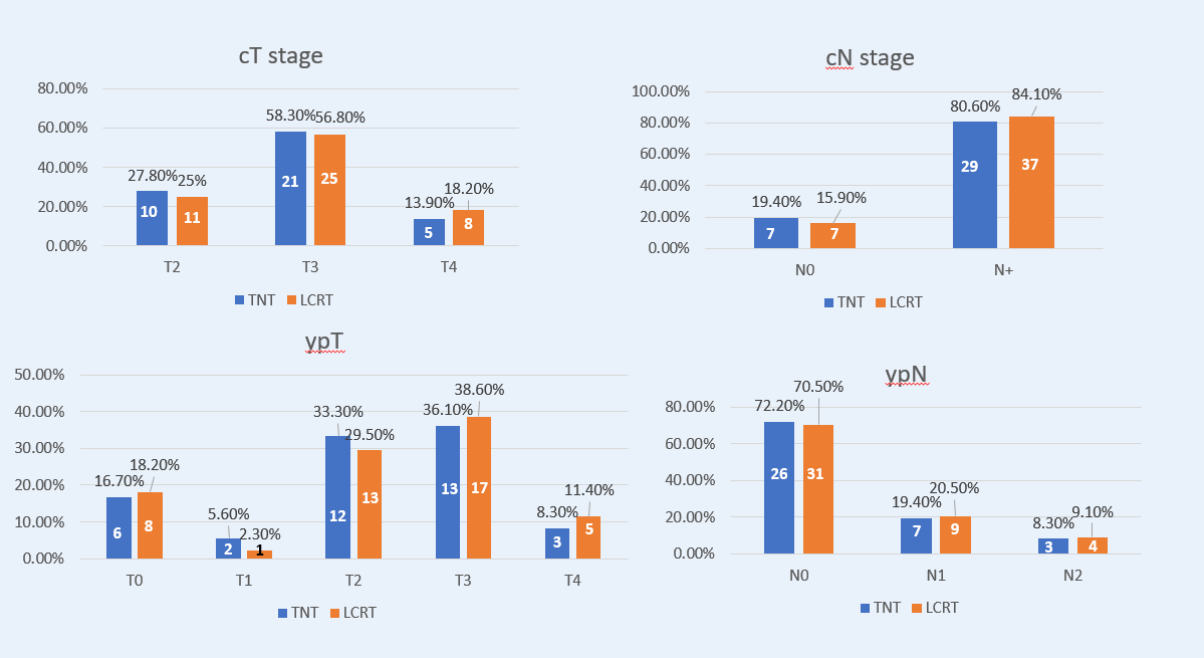

Figure 1: Proportion (%) of patients in each group—Total Neoadjuvant Therapy (TNT) and Long Course Radiotherapy (LCRT)—based on clinical (pre-treatment) and pathological (post-treatment) T and N staging. cT: clinical T stage, cN: clinical N stage; ypT: Pathological T stage, ypN: Pathological N stage

The rate of complete resection (R0) was similar in both groups (TNT: 88.8% vs. LCRT: 90.9%, p=0.78). The rate of partial response was also comparable between the two groups (TNT: 79.6% vs. LCRT: 83.3%, p=0.68) (Fig 2).

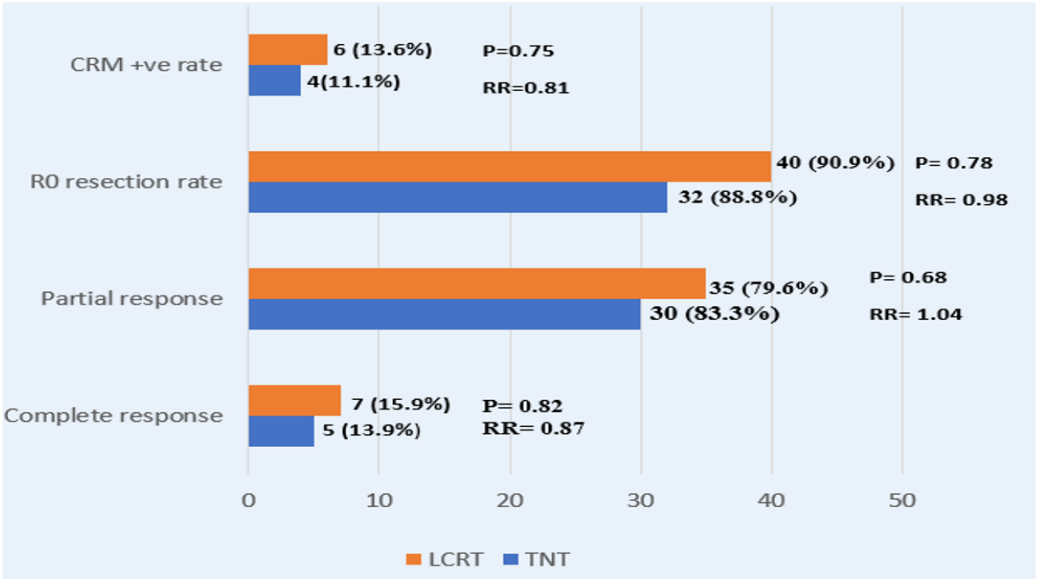

Figure 2: Proportion of patients (n, %) achieving key surgical and pathological outcomes in the Total Neoadjuvant Therapy (TNT) and Long Course Radiotherapy (LCRT) groups, along with corresponding p-values and risk ratios (RRs).

TNT: Total Neo Adjuvant Therapy, LCRT: Long Course Radio Therapy

Discussion

Our study demonstrates that TNT and LCRT offer comparable outcomes in terms of major complications, R0 resection, pCR and CRM positivity. However, the TNT group exhibited a significantly higher incidence of breached TME,

blood loss and longer operative time, findings consistent with previous studies suggesting increased surgical complexity after intensified neoadjuvant regimens [14,15,17].

The RAPIDO trial, a landmark randomized trial, reported improved disease-related treatment failure with TNT but also noted a slight increase in local recurrence at 5 years (10% vs 6%) [10]. This could be attributed to challenges in surgical planes due to fibrosis and scarring, which may alter the anatomical planes and make surgical dissection more difficult. Additionally, the intensified systemic chemotherapy in the TNT regimen may lead to increased tissue edema and inflammation, further complicating the surgical procedure. Similarly, the STELLAR trial also reported increased pelvic fibrosis following TNT, necessitating more experienced surgical handling [15].

Despite these challenges, TNT offers notable systemic advantages. Improved compliance with chemotherapy and early systemic exposure potentially reduce the risk of micrometastatic disease. PRODIGE 23 showed a significantly lower rate of distant metastasis in the TNT group [11]. In our cohort, fewer patients in the TNT group progressed to unresectable disease, although the difference was not statistically significant.

Organ preservation is another emerging goal in rectal cancer treatment18. Studies like OPRA have shown that TNT facilitates non-operative management in patients achieving clinical complete response [12]. While our study was not designed to evaluate non-operative management, the comparable sphincter preservation rates suggest that TNT does not compromise functional outcomes.

Limitations of our study include a small sample size, single-centre design, and lack of long-term oncological outcomes. However, the prospective nature and focus on real-world Indian clinical practice provide valuable insights.

Conclusion

In conclusion, this study provides valuable insights into the comparative efficacy and surgical outcomes of TNT and LCRT in patients with locally advanced rectal cancer. While both treatment strategies demonstrated comparable rates of complete resection and pathological response, TNT was associated with increased surgical complexity and a higher local recurrence rate. These findings highlight the importance of careful patient selection and optimization of surgical techniques to minimize the risks associated with TNT and improve long-term oncological outcomes. Further research is needed to identify patient subgroups that may benefit the most from TNT and to develop strategies to enhance the efficacy and safety of this treatment approach. Further research is needed to identify predictive biomarkers and optimize treatment protocols to maximize the benefits of TNT while minimizing its risks.

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