

Clinical and Pathological Response in Rectal Cancer to Total Neoadjuvant Therapy (TNT) Using Long-Course Chemoradiation Therapy (LCCRT)

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ABSTRACT

Objective: To evaluate the clinical and pathological response rates to long-course Concurrent Chemoradiation therapy in rectal cancer patients, including the rate of conversion to resectable disease and tumor size reduction.

Study Design: Prospective Observational Study.

Place and Duration of Study: Department of Radiation Oncology, Combined Military Hospital, Rawalpindi Pakistan, from Sept 2024 to Feb 2025.

Methodology: A total of 44 biopsy-proven rectal adenocarcinoma patients received 4 cycles of CAPOX chemotherapy, followed by concurrent chemoradiotherapy (CCRT) with 45 Gy in 25 fractions with an optional 5.4 Gy boost, and oral Capecitabine on radiation days. Post-CCRT evaluation was done 4–6 weeks later using MRI, CT scan, digital rectal examination, and sigmoidoscopy. Clinical response was assessed per RECIST 1.1. Postoperative pathology determined treatment response, and data was recorded on a structured proforma. Data was collected and analyzed using SPSS v.25.

Results: Complete clinical response was seen in 16(36.4%) patients, partial response in 21(47.7%) patients. 4(9.1%) showed stable disease and 3(6.8%) of the patients showed progressive disease. Pathological stage was ypT0N0 (pCR; pathological complete response) in 9(20.5%), ypT1–T2N0 in 13(29.5%), and ypT3–T4 and/or N+ in 22(50.0%). Low anterior resection was done in 27(61.4%), and abdominoperineal resection in 17(38.6%), with negative margins in 36(81.8%). Lymph node involvement was negative in 26(59.1%) and positive in 18(40.9%).

Conclusion: TNT with LCCRT is an effective treatment for rectal cancer, producing favorable pathological and clinical responses. A notable pCR rate was achieved, and many patients had complete or partial clinical responses.

Keywords: Long-course Chemoradiation Therapy (LCCRT), Pathological Response, Rectal Cancer, Total Neoadjuvant Therapy (TNT).

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INTRODUCTION

Colon cancer is now the second most frequent cancer in Pakistan according to new statistics from the National Cancer Registry, highlighting its significant influence on the local populace.¹ Rectal cancer represents a significant oncological challenge, particularly in locally advanced stages.¹⁻³ According to the World Health Organization, colorectal cancer ranks second in women and third in men across the world as per GLOBOCAN database organization.⁴

Recently, the standard of care for locally advanced rectal cancer (LARC) has changed to include more people using total neoadjuvant therapy (TNT), which involves upfront induction chemotherapy followed by either a short-course preoperative radiotherapy (SCPRT) or long-course chemoradiation (LCCRT) platform. With increases in disease-free

survival (DFS), pivotal phase 3 trials evaluating the effects of TNT have achieved their main goal 2 and disease-related treatment failure (DRTF).³ Total neoadjuvant therapy has increased the rates of both clinical and pathologic complete responses,²⁻⁴ thereby enhancing options for non-operative management. It is a new paradigm in the treatment of rectal cancer.

It involves delivering the adjuvant phase of chemotherapy before concurrent chemoradiotherapy. This strategy aims to minimize the risk of metastatic spread while simultaneously providing maximum downstaging in cases where the primary tumor is either unresectable or only marginally resectable. Because there would be a gap between radiotherapy and surgery, there would be a chance for improved treatment adherence, early intervention for micrometastatic illness, and increased rates of complete pathological responses (pCR). Clinical trials have evaluated several TNT methods in recent years. While PRODIGE-23¹⁰ has investigated induction chemotherapy (iCT) followed by CRT in comparison

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to standard CRT, RAPIDO,⁶ Polish-II,⁸ and STELLAR,⁹ have used SCRT followed by consolidation chemotherapy (cCT). When compared to historical controls treated with chemoradiotherapy, TME, and post-operative chemotherapy, OPRA, a multicenter, open-label, phase 3 randomized controlled trial finished in 2023, demonstrated that organ preservation is possible in half of the patients treated with TNT without a significant reduction in survival.

Nevertheless, none of the published studies from this region have particularly examined patients receiving Total Neoadjuvant Therapy treatment with LCCRT, despite the growing body of research on the treatment of rectal cancer worldwide.

Our study, which attempts to thoroughly assess individuals treated with TNT using LCCRT, is planned in response to this gap in the literature. This study investigates the clinical and pathological response of patients with rectal cancer treated with TNT using LCCRT and shed light on the potential benefits of this therapy modality in terms of response rates, tumor down staging, and surgical outcomes.

METHODOLOGY

This Prospective observational Study was conducted at the Department of Radiation Oncology, CMH Rawalpindi, Pakistan from September 2024 to February 2025, after obtaining ERC approval (ERC N0. 916 dated Aug 6th, 2024). Non-probability Convenience sampling was used for the recruitment of patients. The sample size for the study was determined using the WHO sample size calculator, considering an absolute precision of 10%, a 95% confidence level, and an anticipated population proportion of 87.5%¹¹ resulting in a sample size of 44 patients.

Inclusion Criteria: Patients with Stage II/III rectal adenocarcinomas as defined by the AJCC classification 8th edition, who were suitable for surgical resection following total neoadjuvant treatment, aged 18 years or older, with an ECOG performance status of 0-2 indicating satisfactory physical functioning were included.

Exclusion Criteria: Patients with history of previous pelvic radiotherapy, history of inflammatory bowel disease, MMR (Mismatch Repair) deficient rectal adenocarcinomas, comorbidities contraindicating chemotherapy or radiotherapy (such as severe cardiac, pulmonary, or renal disease), those who underwent upfront resection, inability to comply with the study

protocol or follow-up visits, known hypersensitivity to chemotherapy components or other contraindications to proposed treatments, recurrent disease, medical contraindications to MRI, or a second primary malignancy.

All patient information was treated with the strict confidentiality. A thorough history, a physical and digital rectal examination, a performance status evaluation, a complete blood count, electrolytes, serum creatinine, liver function tests, albumin, magnesium, serum calcium, and imaging with contrast-enhanced pelvic MRI and chest, abdomen, and pelvic CT scan were all part of it. Additionally, baseline serum levels of the carcinoembryonic antigen (CEA) were noted.

Patients received 4 cycles of CAPOX, comprising Oxaliplatin 130 mg/m² IV on day 1 and oral Capecitabine 1000 mg/m² twice daily for 14 days, followed by a one-week break every three weeks. This was followed by concurrent chemoradiotherapy (CCRT), for which a planning CT simulation scan with IV contrast was performed after bowel and bladder preparation using Aquilion LB CT Simulator. Concurrent Chemoradiotherapy (CCRT) consisted of 45 Gy in 25 fractions over 5 weeks with an optional 5.4 Gy boost, along with oral Capecitabine 825 mg/m² twice daily on radiation days using CT-planned IMRT/VMAT via VITAL BEAM or CLINAC DHX dual-energy LINAC. Target volumes and organs-at-risk (OARs) were contoured per RTOG and ICRU guidelines. Inverse planning was done on the Eclipse Treatment Planning System using 6 MV photons, aiming to cover 95% of the PTV with the 95% isodose line. All contours and treatment plans were finalized after peer review by another radiation oncologist. An MRI pelvis was performed 4–6 weeks after CCRT completion to assess clinical response per RECIST criteria 1.1. Patients also underwent digital rectal examination, CT chest/abdomen/pelvis, and sigmoidoscopy. Each case was reviewed in a multidisciplinary team (MDT) meeting for surgical planning. Postoperative histopathology was obtained to assess pathological response, and all data was recorded in a structured proforma.

The collected data were entered and analyzed using Statistical Package for Social Sciences (Version 25.0). Age and tumor size demonstrated normal distribution. Descriptive statistics included Mean ± Standard Deviation (SD) for continuous variables (age, tumor size) and frequencies with percentages for

categorical variables including Stage, lymph node (LN) involvement, Types of surgery, margin status, clinical response and pathological response.

RESULTS

An analysis was conducted on 44 patients who had rectal cancer. The clinical and pathological response were assessed as outcomes. The mean age of patients was 54.57 ± 9.00 years, with most falling within the 41–60 years age group, 26 patients (59.1%), followed by those greater than 60 years, 16 patients (36.4%) and a small proportion aged 20–40 years, 2 patients (4.5%). The majority was male, 29 patients (65.9%), while females constituted 15 patients (34.1%) of the sample. ECOG performance status was 0 in 16(36.4%) patients, 1 in 20(45.5%), and 2 in 8(18.2%) patients. All 44(100%) patients had a histologically confirmed diagnosis of rectal adenocarcinoma. Tumor location was most commonly in the middle rectum 21(47.7%), followed by the lower rectum 14(31.8%) and upper rectum 9(20.5%). The mean tumor size was 4.34 ± 0.68 cm. Tumor staging revealed 7(15.9%) with cT2N1, 12(27.3%) with cT3N0, 16(36.4%) with cT3N1, and 9(20.5%) with cT4N1 disease (Table-I).

Table-I: Demographic and Tumor Characteristics of the Study Population (n=44)

Variable(s)	Values
Age	54.57±9.00
Age Groups	
20-40 years	2(4.5%)
41-60 years	26(59.1%)
>60 years	16(36.4%)
Gender	
Male	29(65.9%)
Female	15(34.1%)
ECOG Performance Status	
0	16(36.4%)
1	20(45.5%)
2	8(18.2%)
Histological Diagnosis	44(100.0%)
Tumor Location	
Upper Rectum	9(20.5%)
Middle Rectum	21(47.7%)
Lower Rectum	14(31.8%)
Tumor Stage	
cT2N1	7(15.9%)
cT3N0	12(27.3%)
cT3N1	16(36.4%)
cT4N1	9(20.5%)

ECOG: Eastern Cooperative Oncology Group, T: Tumor, N:Node

In terms of clinical response, 16(36.4%) of patients achieved a complete response, 21(47.7%) had a partial response, 4(9.1%) exhibited stable disease, and 3(6.8%) showed progressive disease. The pathological stage (ypTNM) distribution revealed that 9 patients (20.5%) had ypT0N0 (pathological complete response, pCR),

13 patients (29.5%) had ypT1–T2N0, and 22 patients (50.0%) had ypT3–T4 and/or N+. Among surgical procedures, 27(61.4%) underwent low anterior resection, while 17(38.6%) had abdominoperineal resection. Surgical margins were negative in 36(81.8%) of cases, positive in 5(11.4%), and close (<1 mm) in 3(6.8%) patients. Lymph node involvement (ypN) was negative in 26(59.1%) and positive in 18(40.9%) of cases (Table-II).

Table-II: Clinical and Pathological Outcomes in Patients (n=44)

Clinical Response	n(%)
Complete Response	16(36.4%)
Partial Response	21(47.7%)
Stable Disease	4(9.1%)
Progressive Disease	3(6.8%)
Pathological Response	
Pathological Stage (ypTNM)	
ypT0N0 (pCR)	9(20.5%)
ypT1–T2N0	13(29.5%)
ypT3–T4 and/or N+	22(50.0%)
Type of Surgery Performed	
Low Anterior Resection	27(61.4%)
Abdominoperineal Resection	17(38.6%)
Surgical Margins	
Negative	36(81.8%)
Positive	5(11.4%)
Close (<1mm)	3(6.8%)
Lymph Node Involvement (ypN)	
Positive	18(40.9%)
Negative	26(59.1%)

T: Tumor, N: Node, M:Metastasis

DISCUSSION

The introduction of total neoadjuvant therapy (TNT) has significantly advanced the management of locally advanced rectal cancer (LARC). Our single-center experience with 44 patients demonstrated a pathological complete response (pCR) rate of 20.5% and a clinical complete response (cCR) rate of 36.4%, aligning with major randomized trials while providing unique insights compared to other institutional studies.

The RAPIDO trial⁶ (28% pCR) and STELLAR trial⁹ (22.5% pCR) both utilized short-course radiotherapy (SCRT)-based TNT, closely matching our pCR rate (20.5%). However, these trials exclusively enrolled high-risk patients (cT4/N2), whereas our study included intermediate-stage disease (63.7% cT3N0/N1), suggesting comparable efficacy in less advanced tumors.

The PRODIGE-23 trial¹⁰ (28% pCR with FOLFIRINOX induction) and OPRA trial¹² (48% cCR) demonstrated superior responses, likely attributable to intensified chemotherapy and stringent selection

criteria. Our results confirm that TNT achieves meaningful tumor regression across risk groups.

Our study demonstrated a 61.4% low anterior resection (LAR) rate and 38.6% abdominoperineal resection (APR) rate, with no cases of local excision or non-operative management (NOM). In OPRA trial,¹² the rates were 58% LAR, 32% APR, 4% local excision, and 41% NOM in clinical complete responders (cCR). In RAPIDO Trial⁶, these were 65% LAR, 28% APR, and only 9% NOM despite 28% achieving pCR, reflecting its protocol-mandated surgery. Our higher APR rate (38.6%) suggests either more distal tumors (31.8% lower rectum in our study) or less aggressive pursuit of sphincter preservation or NOM pathway. Our cCR rate demonstrates that TNT enables organ preservation opportunities comparable to major centers. OPRA Trial reported 48% cCR rate with TNT, leading to 41% organ preservation at 3 years. But it used strict "watch-and-wait" criteria (digital exam, MRI, endoscopy) compared to our institutional protocol. It highlights that formal NOM pathways—with multidisciplinary response assessment and surveillance protocols are needed to translate this potential into clinical practice.¹³⁻¹⁵

Our R0 resection rate (81.8%) was lower than in RAPIDO (92%) and STELLAR (93%), possibly due to variations in surgical technique or tumor location. Nevertheless, the low rate of positive margins (11.4%) suggests that TNT effectively downsizes tumors, facilitating resection.¹⁶⁻¹⁸

The pCR rate observed in our study compares favorably with recent reports from major academic centers employing similar LCCRT-intensive regimens. For instance, MD Anderson's 2023 analysis of 150 LARC patients¹⁸ treated with LCCRT followed by consolidation chemotherapy demonstrated a 22% pCR rate, nearly identical to our findings. Similarly, Memorial Sloan Kettering's (MSKCC) 2024¹⁹ series of 98 patients receiving FOLFOX/LCCRT reported a 23.5% pCR rate, further validating our institutional outcomes. These consistent pCR rates across studies suggest that LCCRT-based TNT achieves reproducible tumor regression regardless of center-specific protocols.

However, our 36.4% clinical complete response (cCR) rate appears modest when compared to Johns Hopkins' 2023 data (42% cCR using similar LCCRT regimens), likely reflecting differences in response assessment criteria.²⁰ Where Hopkins employed rigorous endoscopic mucosal biopsy confirmation of

cCR, our study relied on a composite of imaging and clinical findings. This methodological variation underscores the need for standardized response evaluation protocols, particularly given that Hopkins achieved a 38% organ preservation rate in cCR patients.

Notably, our R0 resection rate of 81.8% falls slightly below the 87-92% rates reported in comparable single-institute studies.²¹ This discrepancy may stem from our inclusion of more advanced tumors (20.5% cT4N1 vs. typically <15% in comparator studies) or differences in surgical technique.

The consistency of pCR rates across institutions reinforces LCCRT-based TNT as a reliable backbone regimen, while observed variations in surgical and organ preservation outcomes highlight the critical impact of center-specific protocols and expertise. Future quality improvement initiatives should focus on adopting best practices from high-performing centers while maintaining our demonstrated strengths in pathological response rates.

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CONCLUSION

Total Neoadjuvant Therapy (TNT) using LCCRT is a successful treatment for rectal cancer, producing positive pathological and clinical results. A noteworthy rate of pathological complete response (pCR) was seen, with a substantial percentage of patients achieving complete or partial clinical responses. Good tumor down staging was demonstrated by the majority's sphincter-preserving surgery with negative surgical margins. In patients with locally advanced rectal cancer, these results support the notion that total neoadjuvant therapy using long course chemoradiotherapy (LCCRT) is a practical approach to enhance long-term disease control, refining surgical strategies, and improving treatment outcomes.

LIMITATION OF STUDY

It was a non-randomized, single institute study with a limited sample size. No disease-free survival or long-term results are available yet. Toxicity profile of chemoradiotherapy regimen was not included in this study.

Conflict of Interest: None.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SJ & SA: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZAA & TM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

WR & KF: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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