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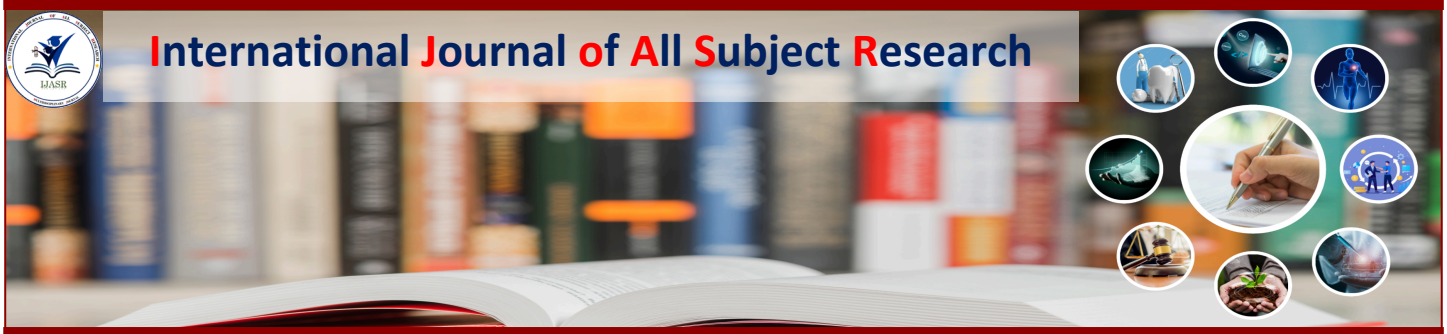

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Total Neoadjuvant Therapy in Rectal Cancer: Single Institution Experience

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Abstract

Total neoadjuvant treatment (TNT) is a more recent development in the treatment of rectal cancer. With new information on its effectiveness, the concept of delivering complete chemotherapy regimens that include capecitabine and oxaliplatin (CAPEOX) or modified 5 fluorouracil and oxaliplatin (mFOLFOX6) upfront with radiation in the preoperative setting is becoming more and more common. The main goal of this study was to determine the complete pathological response.

Materials and Methods: The present Retrospective study was conducted at a tertiary care centre between January 2022 to June 2024, among 50 Patients who were diagnosed with locally advanced (Ct3/4 or Ct2- N +) Rectal Cancer. The Patients Received 6 Cycles of Capeox Or 6-8 Cycles of Folfox followed by a Short Course of Radiation Therapy or Long Course Radiation Therapy and then surgery.

Results: A total of 50 patients were included for the study. About 25(50%) patients were in T3 stage and 33(66%) patients were in N1 stage. About 41(82%) patients received full dose TNT regimen CAPEOX. The majority of patients 29(58%) received Short Course Radiotherapy (SCRT). About 35(70%) patients underwent surgery between 1-2 months post radiotherapy and Laparoscopic Abdominoperineal resection was the commonest surgery performed among 28(56%) patients. About 18(36%) patients didn't complete TNT regimen due to various reasons like diarrhoea, bleeding, non-responsive to chemotherapy, and vomiting. Pathological complete response was observed among 18(36%) patients and Lymphovascular invasion (LVI) was positive among 08(16%) patients.

Conclusion: TNT represents a transformative approach in rectal cancer management, offering improved systemic control, higher compliance, and potential for organ preservation. While challenges remain, ongoing research and advancements in precision oncology hold promise for further refining TNT and expanding its benefits to a broader patient population.

Keywords: Total neoadjuvant treatment (TNT), rectal cancer, chemotherapy etc.

Introduction

Over the past few decades, there has been a significant change in the way rectal cancer is treated. Heald *et al.*'s introduction of whole mesorectal excision [1] reduced local recurrence rates from roughly 20% [2-5] to ≤5% [6-8].

The use of preoperative magnetic resonance imaging (MRI) evaluation and the introduction of neoadjuvant chemoradiation brought to additional significant advancement [9]. Total neoadjuvant treatment (TNT) is a more recent development in the treatment of rectal cancer. With new information on its effectiveness, the concept of delivering complete chemotherapy regimens that include capecitabine and oxaliplatin (CAPEOX) or modified 5 fluorouracil and oxaliplatin (mFOLFOX6) upfront with radiation in the preoperative setting is becoming more and more common [10-11]. These suggestions are supported by several randomized trials that show preoperative CRT is superior to postoperative CRT in terms of tumor control and treatment toxicity.

TNT administration before surgery eliminates the requirement for postoperative adjuvant therapy, which is sometimes postponed due to stoma presence and/or postoperative problems. On the other hand, a longer time between neoadjuvant treatment and surgery raises the rates of full pathological response, which has been linked to improved disease-free survival [12].

The patient may have the best chance of obtaining a full recovery with this combination of chemotherapy and radiation treatment. Rectal resections may therefore be avoided in certain patients who exhibit full clinical response and may instead be treated using a "watch-and-wait" approach [13].

Materials and Methods

The present Retrospective study was conducted at a tertiary care centre between January 2022 to June 2024, among 50 Patients who were diagnosed with locally advanced (Ct3/4 or Ct2- N +) Rectal Cancer. Institutional ethics committee approval was obtained for this study. In addition to surgical and pathological reports, patient demographic data was evaluated, including physical examination details, chemotherapy regimens, and pre- and posttreatment MRIs.

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The main goal of this study was to determine the complete pathological response, which was defined as the absence of any tumor in the final surgical pathology specimen. The complete and incomplete pathologic response populations were compared in terms of demographic data, such as surgical and pathological factors, as well as pre- and posttreatment staging.

The Patients Received 6 Cycles of Capeox Or 6-8 Cycles of Folfox followed by a Short Course of Radiation Therapy or Long Course Radiation Therapy and then surgery. They Were Assessed for Pathological Complete Response, Patient Compliance to Chemotherapy.

Results

A total of 50 patients were included for the study. Table 1 shows that most patients were in the age group 41-50 years and 51-60 years with 14(28%) patients in each age group. The maximum number of patients 35(70%) were males and 15(30%) patients were females. About 31(62%) patients were in Eastern Cooperative Oncology Group (ECOG) Grade 0 who were fully active and could carry on all pre-disease performance without restriction. About 25(50%) patients were in T3 stage and 33(66%) patients were in N1 stage.

Table 1: Demographic and tumor-related factors among patients

Demographic factors	No. (%)
Age (Years)	
≤30	01(2.0)
31-40	07(14.0)
41-50	14(28.0)
51-60	14(28.0)
61-70	11(22.0)
71-80	03(6.0)
Gender	
Male	35(70.0)
Female	15(30.0)
Tumour Related Factors	
ECOG Status	
Grade 0	31(62.0)
Grade 1	19(38.0)
T Staging	
T2	11(22.0)
T3	25(50.0)
T4	14(28.0)
N Staging	
N0	02(4.0)
N1	33(66.0)
N2	15(30.0)

Table 2: Treatment-related factors among study participants

Treatment-related Factors	No. (%)
TNT Regimen	
Full Dose	
#6 CAPEOX	32 (64.0)
#5 CAPEOX	09 (18.0)
Reduced Dose	
#4 CAPEOX	07 (14.0)
#2 CAPEOX	02 (4.0)
Type of Radiotherapy	
SCRT	29 (58.0)
LCCRT	21 (42.0)
Surgery	
Interval for Surgery (Days)	
<30	07 (14.0)
30-60	35 (70.0)
>60	08 (16.0)
Type of Surgery	
LAP APR	28 (56.0)

Open APR	02 (4.0)
LAP LAR	12 (24.0)
Open LAR	03 (6.0)
Robotic APR	02 (4.0)
Robotic LAR	02 (4.0)
LAP ULAR	01 (2.0)

Table 2 shows treatment-related factors among study participants. About 41(82%) patients received full dose TNT regimen CAPEOX. The majority of patients 29(58%) received Short Course Radiotherapy (SCRT). About 35(70%) patients underwent surgery between 1-2 months post radiotherapy and Laparoscopic Abdominoperineal resection was the commonest surgery performed among 28(56%) patients.

Table 3: Compliance rates to chemotherapy and Pathological Complete Response (PCR) rates among patients

Compliance to the TNT Regimen	**No. (%)**
Completed	32 (64.0)
Incomplete	18 (36.0)
Reason for not Completing the Regimen	
Diarrhoea	07 (14.0)
Bleeding	04 (8.0)
No response to chemotherapy	04 (8.0)
Vomiting, weakness	01 (2.0)
Pathology Factors	
No response	05 (10.0)
Pathological poor response	15 (30.0)
Partial response	12 (24.0)
Pathological complete response	18 (36.0)
LVI (+) Post-treatment	08 (16.0)

Table 3 shows that the majority of patients 32(64%) had completed TNT regimen showing good compliance. About 18(36%) patients didn't complete TNT regimen due to various reasons like diarrhoea, bleeding, non-responsive to chemotherapy, and vomiting.

Pathological complete response was observed among 18(36%) patients and Lymphovascular invasion (LVI) was positive among 08(16%) patients.

Discussion

Numerous studies have shown that the introduction of TNT for individuals with locally advanced rectal cancer offers tremendous promise. As a result, the most recent National Comprehensive Cancer Network guidelines have included it as a therapy option [14]. Nonetheless, there are differences among these patients with locally advanced rectal cancer (stage II–III). As a result, not every patient would benefit from the same therapeutic approach. For these patients, a risk-adapted treatment approach is more suitable when thinking about neoadjuvant therapy. It has been demonstrated that patients with T4b disease, extensive involvement lymph nodes, MRF+, EMVI+, and positive lateral lymph nodes are more likely to experience relapses [15]. For these high-risk patients, intensified and tailored neoadjuvant chemoradiotherapy may improve the prognosis.

Total neoadjuvant treatment has garnered more attention recently and is probably a superior option for those with high risk factors for rectal cancer. Additionally, TNT offers the benefits of eliminating adjuvant chemotherapy, which is still debatable [16], and initiating systemic chemotherapy three to four months sooner than normal neoadjuvant concurrent CRT, which may improve long-term survival [17]. Nevertheless, there is still uncertainty regarding the best order for induction chemotherapy, concurrent CRT and consolidation chemotherapy, the proper time between concurrent chemoradiotherapy and surgery completion, and the best chemotherapy regimens.

In our series out of 32 patients (64%) who completed TNT regimen, 18(56%) had pathological complete response, which is higher than the rate with traditional chemoradiation therapy. With a high rate of minimally invasive procedures, TNT administration had no detrimental effects on surgical results. The reason for not completing the TNT regimen in our series was 14% had Diarrhoea, 8% had bleeding and 2% had Vomiting and generalized tiredness.

In contrast, Wang *et al*.'s study revealed that leukopenia (10.6%) and radiation dermatitis (6.4%) were the most frequent grade 3 adverse events. There were no grade 4 or higher neoadjuvant therapy problems noted. According to Julio *et al*., neutropenia (6%) was the most frequent grade 3 or above adverse event were 4% had lymphopenia [18]. Bujko *et al*. contrasted normal CRT with short-term radiation therapy + consolidation chemotherapy [19]. Additionally, it was noted that in two groups, the percentage of grade 3 and grade 4 acute toxicities was 23% and 21%, respectively.

TNT has been shown to be effective in improving outcomes for people with rectal cancer in a number of significant clinical trials and retrospective investigations. TNT (short-course radiation followed by six cycles of CAPOX or nine cycles of FOLFOX) was compared to the conventional strategy of CRT followed by TME and optional adjuvant chemotherapy in the RAPIDO study. TNT considerably decreased the disease-related treatment failure rate (23.7% vs. 30.4%) and distant metastases (20% vs. 26.8%) [20]. Patients in the PRODIGE 23 study were randomized to either standard CRT and TME or neoadjuvant FOLFIRINOX followed by CRT and TME. TNT improved three-year disease-free survival (76% vs. 69%), decreased metastatic recurrence, and increased pathological complete response (pCR) rates (28% vs. 12%) [21].

According to a pooled investigation by Maas *et al*., TNT can have a pCR rate of up to 25%, while traditional CRT can only achieve a rate of 10-15% [22]. Additionally, retrospective studies indicate that TNT improves sphincter preservation, decreases recurrence rates, and promotes tumor regression in low rectal tumors [23-24].

Rectal cancer treatment has evolved significantly over the past few decades, with a focus on improving both oncologic outcomes and quality of life. The concept of total neoadjuvant therapy (TNT) represents a major shift in the management of locally advanced rectal cancer. TNT involves delivering all systemic chemotherapy and radiation therapy before surgical resection, departing from the traditional approach of surgery followed by adjuvant therapy. This review summarizes the

rationale, clinical evidence, advantages, challenges, and future directions of TNT in rectal cancer management.

Despite its advantages, TNT is not without challenges. Extended exposure to systemic chemotherapy and CRT can lead to cumulative toxicity, impacting patient quality of life and treatment adherence. Identifying patients who will benefit most from TNT remains a challenge. Factors such as tumor stage, molecular profile, and patient comorbidities must be considered. Lack of Universal Protocols is also another drawback.

The primary limitation of our series is a single center study, and the second limitation is less sample size.

Conclusion

TNT represents a transformative approach in rectal cancer management, offering improved systemic control, higher compliance, and potential for organ preservation. While challenges remain, ongoing research and advancements in precision oncology hold promise for further refining TNT and expanding its benefits to a broader patient population

References

1. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery-the clue to pelvic recurrence? Br J Surg. 1982; 69:613-616.
2. Tonak J, Gall FP, Hermanek P, Hager TH. Incidence of local recurrence after curative operations for cancer of the rectum. ANZ J Surg. 1982; 52:23-27.
3. Vlasak JW, Wagner D, Passaro E Jr, Wilson SE. Local recurrence after curative resection of rectal cancer: A comparison of low anterior resection and abdominoperineal resection. *J Surg Oncol*. 1989; 41:236-239.
4. Arbman G, Nilsson E, Hallbo¨ok O, Sj ¨ odahl R. Local re- ¨ currence following total mesorectal excision for rectal cancer. Br J Surg. 1996; 83:375-379.
5. Swedish Rectal Cancer Trial. Local recurrence rate in a randomised multicentre trial of preoperative radiotherapy compared with operation alone in resectable rectal carcinoma. Swedish rectal cancer trial. *Eur J Surg.* 1996; 162:397-402.
6. MacFarlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. Lancet. 1993; 341:457-460.
7. Nissan A, Guillem JG, Paty PB, *et al*. Abdominoperineal resection for rectal cancer at a specialty center. Dis Colon Rectum. 2001; 44:27-35.
8. Law WL, Chu KW. Local recurrence following total mesorectal excision with double-stapling anastomosis for rectal cancers: Analysis of risk factors. *World J Surg*. 2002; 26:1272-1276.
9. Taylor FGM, Quirke P, Heald RJ, *et al*. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol*. 2014; 32:34-43.
10. Cercek A, Roxburgh CSD, Strombom P, *et al*. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol.* 2018; 4(6):e180071.
11. Petrelli F, Trevisan F, Cabiddu M, *et al*. Total neoadjuvant therapy in rectal cancer: A systematic review and meta-analysis of treatment outcomes. Ann Surg. 2020; 271(3):440-448.
12. Marco MR, Zhou L, Patil S, *et al*. Consolidation mFOLFOX6 chemotherapy after chemoradiotherapy improves survival in patients with locally advanced rectal cancer: Final results of a multicenter phase II trial. Dis Colon Rectum. 2018; 61(10):1146-1155.
13. Smith JJ, Strombom P, Chow OS, *et al*. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol. 2019; 5(4):e185896.
14. https://www.nccn.org/professionals rectal cancer, Version 1, 2020.
15. Chand M, Siddiqui MR, Swift I, Brown G. Systematic review of prognostic importance of extramural venous invasion in rectal cancer. *World Journal of Gastroenterology*. 2016; 22(4):1721–6.
16. Bosset JF, Calais G, Mineur L, *et al*. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014; 15:184–90.
17. Poulsen LØ, Qvortrup C, Pfeiffer P, *et al*. Review on adjuvant chemotherapy for rectal cancer – why do treatment guidelines differ so much? Acta Oncol 2015; 54:437–46.
18. Garciaaguilar J, Chow OS, Smith DD, *et al*. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015; 16:957–66
19. Bujko K, Wyrwicz L, Rutkowski A, *et al*. Long-course oxaliplatin-based preoperative chemoradiation versus 5-5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016; 27:834–42.
20. Bahadoer R *et al*. Short-course radiotherapy followed by chemotherapy before TME in rectal cancer. The Lancet Oncology. 2020; 21(6):834-844.
21. Conroy T *et al*. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative CRT in rectal cancer. The Lancet Oncology. 2021; 22(5):702-715.
22. Maas M *et al*. Pathologic response after CRT in rectal cancer. Journal of Clinical Oncology. 2011; 29(13):1754-1760.
23. Fernandez-Martos C *et al*. Sequential induction chemotherapy and CRT in rectal cancer. Annals of Oncology. 2015; 26(9):1823-1828.
24. Shi X *et al*. TNT vs. CRT for rectal cancer: A meta-analysis. Cancer Medicine. 2022; 11(5):1234-1244.