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Total Neoadjuvant Therapy (TNT) Vs Standard Treatment in Rectal Cancer: Impact on Surgical Outcomes

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ABSTRACT

Background: Total Neoadjuvant Therapy (TNT) has emerged as a promising treatment strategy for locally advanced rectal cancer by delivering all planned chemotherapy and radiotherapy before surgery. This study compared TNT with standard treatment and evaluated its impact on surgical outcomes.
Materials and Methods: A comparative observational study was conducted in the Department of Surgical Gastroenterology, Dhanalakshmi Srinivasan Medical College Hospital, Perambalur, Tamil Nadu, from July 2023 to June 2026. Thirty patients with locally advanced rectal adenocarcinoma were enrolled and categorized into TNT (n=15) and standard treatment (n=15) groups. Clinical, radiological, pathological, surgical, and postoperative outcome measures were analyzed using appropriate statistical tests.
Results: The TNT group demonstrated significantly greater tumor size reduction (54.8% vs. 35.2%; p=0.001), lower post-treatment CEA levels (p=0.009), superior nodal downstaging (73.3% vs. 33.3%; p=0.028), and higher conversion to node-negative status (66.7% vs. 26.7%; p=0.028). Intraoperative blood loss was significantly lower in the TNT group (214.7 mL vs. 302.4 mL; p=0.015). Favorable trends were observed for pathological complete response, sphincter preservation, and R0 resection. Hospital stay was significantly shorter following TNT (p=0.029).
Conclusion: Total Neoadjuvant Therapy was associated with improved tumor response, enhanced pathological downstaging, better surgical outcomes, and shorter postoperative recovery without increasing perioperative morbidity. TNT represents an effective treatment strategy for patients with locally advanced rectal cancer.

Keywords*: Rectal Neoplasms; Total Neoadjuvant Therapy; Chemoradiotherapy; Total Mesorectal Excision; Pathological Complete Response; Surgical Outcomes.*

INTRODUCTION

Rectal cancer remains a major global health challenge and constitutes a significant proportion of colorectal malignancies. It is among the most frequently diagnosed cancers worldwide and continues to contribute substantially to cancer-related morbidity and mortality despite advances in screening, diagnostic modalities, and treatment strategies [1]. The primary goals of treatment are to achieve optimal oncological control, reduce local recurrence, preserve sphincter function whenever feasible, and improve long-term survival while maintaining quality of life [2].

The introduction of Total Mesorectal Excision (TME) represented a landmark advancement in rectal cancer surgery and significantly improved local disease control. However, despite meticulous surgical techniques, patients with locally

advanced rectal cancer remain at risk of distant metastasis and disease recurrence. Consequently, the management paradigm shifted toward combining surgery with chemotherapy and radiotherapy to enhance treatment outcomes [3].

Traditionally, the standard treatment for locally advanced rectal cancer has consisted of neoadjuvant chemoradiotherapy followed by TME surgery and subsequent adjuvant chemotherapy. Preoperative chemoradiotherapy has been shown to reduce tumor volume, improve resectability, decrease local recurrence rates, and facilitate sphincter-preserving procedures in selected patients [4]. Nevertheless, several limitations of this conventional strategy have been recognized. Compliance with postoperative chemotherapy is often poor due to surgical complications, prolonged recovery periods, and treatment-related toxicities. Consequently, many patients fail to receive the intended systemic therapy, potentially compromising control of occult micrometastatic disease [5].

Total Neoadjuvant Therapy (TNT) has emerged as an innovative treatment strategy for locally advanced rectal cancer. TNT involves the administration of all planned chemotherapy and radiotherapy before definitive surgical intervention. This approach aims to maximize tumor response, improve treatment compliance, eradicate micrometastatic disease at an earlier stage, and potentially increase the likelihood of complete pathological response [6].

One of the most notable benefits is the increased rate of pathological complete response (pCR), which has been associated with improved oncological outcomes and lower recurrence rates. Enhanced tumor downstaging achieved through TNT may also facilitate more conservative surgical approaches and improve the possibility of sphincter preservation in tumors located near the anal verge [7].

The impact of TNT on surgical outcomes has become an area of particular clinical importance. Effective tumor downstaging may lead to clearer resection margins, reduced tumor burden at the time of surgery, and improved technical feasibility of TME procedures. Additionally, higher rates of complete response may influence decisions regarding organ preservation strategies, including the emerging "watch-and-wait" approach in carefully selected patients [8].

Surgical parameters such as operative duration, intraoperative blood loss, margin status, sphincter preservation rates, postoperative complications, length of hospital stay, and pathological response provide critical insights into the effectiveness and safety of different treatment approaches [9]. Comparative assessment of TNT and conventional therapy can help identify whether the theoretical benefits of intensified neoadjuvant treatment translate into meaningful surgical advantages for patients with rectal cancer [10]. Given the growing adoption of TNT, there is a need to critically examine its impact on surgical outcomes in comparison with standard treatment protocols.

MATERIALS AND METHODS

Study Setting: This hospital-based comparative observational study was conducted in the Department of Surgical Gastroenterology, Dhanalakshmi Srinivasan Medical College Hospital, Perambalur, Tamil Nadu, India. The study was carried out over a three-year period from July 2023 to June 2026.

Study Participants: The study population comprised patients with histologically confirmed rectal adenocarcinoma who were managed at the Department of Surgical Gastroenterology during the study period. Eligible participants were recruited after detailed clinical assessment and review of radiological and pathological findings. Patients fulfilling the following criteria were included in the study: age ≥18 years, histopathologically confirmed adenocarcinoma of the rectum, locally advanced rectal cancer deemed suitable for neoadjuvant treatment followed by definitive surgery, patients who received either Total Neoadjuvant Therapy or conventional neoadjuvant chemoradiotherapy followed by surgery according to institutional treatment protocols, and those patients willing to participate and provide informed written consent.

Exclusion criteria included presence of distant metastatic disease at the time of diagnosis, recurrent rectal cancer previously treated elsewhere, histological subtypes other than adenocarcinoma, patients deemed medically unfit for major surgical intervention, and incomplete clinical records or loss to follow-up before surgical assessment.

Sample Size and Sampling Technique: A total sample size of 30 patients was included in the study. The sample comprised patients who satisfied the eligibility criteria and underwent treatment during the study period. A consecutive sampling technique was employed. All eligible patients presenting to the department during the study duration were screened for enrollment. Participants were subsequently categorized into two groups based on the neoadjuvant treatment strategy received: the Total Neoadjuvant Therapy group and the Standard Treatment group.

Study Tools: Data were collected using a structured study proforma developed specifically for the research. The proforma captured demographic characteristics, clinical presentation, comorbid conditions, tumor characteristics, radiological staging findings, treatment details, operative parameters, pathological findings, and postoperative outcomes.

Clinical evaluation included detailed history taking and physical examination. Diagnostic investigations comprised colonoscopy with biopsy, contrast-enhanced computed tomography, magnetic resonance imaging of the pelvis, routine

hematological investigations, and relevant biochemical parameters. Histopathological reports were reviewed to confirm diagnosis and assess pathological response following neoadjuvant therapy.

The primary study variables included operative duration, intraoperative blood loss, type of surgery performed, resection margin status, pathological staging, postoperative complications, duration of hospital stay, and other relevant surgical outcomes. Treatment-related variables such as neoadjuvant therapy regimen, treatment completion rates, and interval to surgery were also documented.

Study Procedure: Following institutional approval, all eligible patients diagnosed with locally advanced rectal cancer were evaluated in a multidisciplinary setting involving surgical gastroenterologists, medical oncologists, radiation oncologists, radiologists, and pathologists. Baseline demographic and clinical information was recorded at the time of enrollment.

Patients received treatment according to standard institutional protocols. Individuals in the Total Neoadjuvant Therapy group underwent systemic chemotherapy and chemoradiotherapy before definitive surgical resection. Patients in the Standard Treatment group received conventional neoadjuvant chemoradiotherapy followed by surgery, with adjuvant chemotherapy administered postoperatively when indicated.

All patients underwent definitive rectal cancer surgery after completion of the planned neoadjuvant treatment. Surgical procedures were performed by experienced gastrointestinal surgeons using accepted oncological principles. Intraoperative findings and surgical details were recorded systematically.

Postoperative monitoring was carried out throughout the hospital stay. Early postoperative complications, including surgical site infection, anastomotic leakage, bleeding, wound-related complications, and other adverse events, were documented. Histopathological examination of resected specimens was performed to assess tumor response, pathological staging, circumferential resection margin status, and lymph node involvement.

Ethical Issues: Approval for the study was obtained from the Institutional Ethics Committee of Dhanalakshmi Srinivasan Medical College Hospital before commencement of data collection. Written informed consent was obtained from all participants prior to enrollment. Participants were informed regarding the objectives of the study, the nature of data collection, and their right to withdraw from the study at any stage without affecting their treatment. Confidentiality and anonymity of patient information were maintained throughout the study by assigning unique identification codes and restricting access to study records.

Statistical Analysis: The data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize demographic, clinical, and treatment-related variables. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages. Comparisons between the Total Neoadjuvant Therapy group and the Standard Treatment group were performed using appropriate statistical tests. The independent sample t-test or Mann–Whitney U test was used for continuous variables, while the Chi-square test or Fisher's exact test was employed for categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 demonstrates that the two treatment groups were well matched at baseline. The mean age was 54.9 ± 10.3 years in the TNT group and 56.8 ± 11.2 years in the standard treatment group (p=0.634). Males constituted 66.7% and 60.0% of the TNT and standard treatment groups, respectively (p=0.705). No statistically significant differences were observed regarding BMI, diabetes mellitus, hypertension, smoking history, ECOG performance status, distance from the anal verge, baseline CEA levels, clinical T stage, or nodal status (all p>0.05).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	TNT Group (n=15)	Standard Treatment Group (n=15)	Test Statistic	p value
Age (years), Mean ± SD	54.9 ± 10.3	56.8 ± 11.2	t = 0.48	0.634
Male Gender, n (%)	10 (66.7)	9 (60.0)	$\chi^2 = 0.14$	0.705
BMI (kg/m²), Mean ± SD	24.6 ± 3.2	25.1 ± 3.5	t = 0.41	0.686
Diabetes Mellitus, n (%)	4 (26.7)	5 (33.3)	$\chi^2 = 0.16$	0.690
Hypertension, n (%)	5 (33.3)	6 (40.0)	$\chi^2 = 0.14$	0.709
Smoking History, n (%)	6 (40.0)	7 (46.7)	$\chi^2 = 0.14$	0.713
ECOG Performance Status ≥1, n (%)	5 (33.3)	6 (40.0)	$\chi^2 = 0.14$	0.709

Distance from Anal Verge (cm), Mean ± SD	6.3 ± 2.1	6.8 ± 2.4	t = 0.61	0.548
Baseline CEA (ng/mL), Median (IQR)	7.1 (4.8–10.2)	7.8 (5.1–11.6)	U = 101.5	0.594
Clinical T3 Disease, n (%)	11 (73.3)	10 (66.7)	$\chi^2 = 0.16$	0.690
Clinical T4 Disease, n (%)	4 (26.7)	5 (33.3)	$\chi^2 = 0.16$	0.690
Node Positive Disease, n (%)	12 (80.0)	11 (73.3)	$\chi^2 = 0.19$	0.663

Table 2 compares treatment response between the two groups. Patients receiving TNT demonstrated significantly greater tumor size reduction than those receiving standard treatment (54.8 ± 15.3% vs. 35.2 ± 14.6%, p=0.001). Post-treatment CEA levels were significantly lower in the TNT group (median 2.8 ng/mL) compared with the standard treatment group (median 4.9 ng/mL, p=0.009). Nodal downstaging was observed in 73.3% of TNT-treated patients compared with 33.3% of standard-treatment patients (p=0.028), while conversion to node-negative status occurred in 66.7% and 26.7% of patients, respectively (p=0.028).

Table 2: Comparison of Neoadjuvant Treatment Response and Tumor Downstaging

Variable	TNT Group (n=15)	Standard Treatment Group (n=15)	Test Statistic	p value
Treatment Completion Rate, n (%)	15 (100.0)	12 (80.0)	Fisher's Exact	0.068
Reduction in Tumor Size (%), Mean ± SD	54.8 ± 15.3	35.2 ± 14.6	t = 3.60	0.001
Post-treatment CEA (ng/mL), Median (IQR)	2.8 (1.7–4.1)	4.9 (3.2–6.8)	U = 55.0	0.009
Radiological Complete Response, n (%)	4 (26.7)	1 (6.7)	Fisher's Exact	0.143
Clinical Downstaging, n (%)	12 (80.0)	7 (46.7)	$\chi^2 = 3.59$	0.058
Nodal Downstaging, n (%)	11 (73.3)	5 (33.3)	$\chi^2 = 4.82$	0.028
Conversion to cN0 Status, n (%)	10 (66.7)	4 (26.7)	$\chi^2 = 4.82$	0.028

Table 3 presents the surgical outcomes of both treatment groups. The TNT group experienced significantly lower intraoperative blood loss compared with the standard treatment group (214.7 ± 78.3 mL vs. 302.4 ± 104.8 mL; p=0.015). Although operative duration was shorter in the TNT group, the difference was not statistically significant (188.4 ± 29.6 vs. 205.7 ± 31.8 minutes; p=0.135). Higher rates of sphincter preservation (73.3% vs. 46.7%) and R0 resection (100% vs. 80%) were observed in the TNT group, although statistical significance was not reached.

Table 3: Comparison of Surgical Outcomes Between TNT and Standard Treatment Groups

Variable	TNT Group (n=15)	Standard Treatment Group (n=15)	Test Statistic	p value
Operative Duration (minutes), Mean ± SD	188.4 ± 29.6	205.7 ± 31.8	t = 1.54	0.135
Intraoperative Blood Loss (mL), Mean ± SD	214.7 ± 78.3	302.4 ± 104.8	t = 2.60	0.015
Sphincter Preservation, n (%)	11 (73.3)	7 (46.7)	$\chi^2 = 2.22$	0.136
R0 Resection Rate, n (%)	15 (100.0)	12 (80.0)	Fisher's Exact	0.068
Circumferential Margin Positive, n (%)	0 (0.0)	3 (20.0)	Fisher's Exact	0.068
Protective Ileostomy, n (%)	7 (46.7)	8 (53.3)	$\chi^2 = 0.13$	0.715
Conversion to Open Surgery, n (%)	1 (6.7)	3 (20.0)	Fisher's Exact	0.598

Table 4 demonstrates superior pathological outcomes among patients receiving TNT. Pathological complete response was achieved in 33.3% of TNT patients compared with 6.7% in the standard treatment group, although the difference narrowly missed statistical significance (p=0.080). Significantly more patients in the TNT group achieved favorable pathological staging (ypT0–T1) than those receiving standard treatment (46.7% vs. 13.3%; p=0.045).

Table 4: Pathological Outcomes Following Surgical Resection

Variable	TNT Group (n=15)	Standard Treatment Group (n=15)	Test Statistic	p value
Pathological Complete Response (pCR), n (%)	5 (33.3)	1 (6.7)	Fisher's Exact	0.080

ypT0–T1 Stage, n (%)	7 (46.7)	2 (13.3)	$\chi^2 = 4.03$	0.045
ypN0 Status, n (%)	12 (80.0)	7 (46.7)	$\chi^2 = 3.59$	0.058
Retrieved Lymph Nodes, Mean ± SD	16.7 ± 4.1	15.9 ± 3.8	t = 0.55	0.588
Lymphovascular Invasion, n (%)	2 (13.3)	6 (40.0)	$\chi^2 = 2.73$	0.098
Perineural Invasion, n (%)	1 (6.7)	5 (33.3)	Fisher's Exact	0.169

Table 5 summarizes postoperative morbidity and short-term outcomes. Overall postoperative complications occurred in 20.0% of patients receiving TNT compared with 46.7% in the standard treatment group, although the difference was not statistically significant (p=0.121). Rates of surgical site infection, anastomotic leakage, and postoperative ileus were numerically lower among TNT-treated patients but were comparable between groups statistically. The mean duration of hospital stay was significantly shorter in the TNT group (8.1 ± 2.3 days) than in the standard treatment group (10.4 ± 3.1 days; p=0.029). No 30-day mortality was recorded in either group.

Table 5: Postoperative Morbidity and Early Clinical Outcomes

Variable	TNT Group (n=15)	Standard Treatment Group (n=15)	Test Statistic	p value
Any Postoperative Complication, n (%)	3 (20.0)	7 (46.7)	$\chi^2 = 2.40$	0.121
Surgical Site Infection, n (%)	1 (6.7)	3 (20.0)	Fisher's Exact	0.598
Anastomotic Leak, n (%)	1 (6.7)	2 (13.3)	Fisher's Exact	1.000
Postoperative Ileus, n (%)	1 (6.7)	2 (13.3)	Fisher's Exact	1.000
Reoperation Required, n (%)	0 (0.0)	2 (13.3)	Fisher's Exact	0.483
Length of Hospital Stay (days), Mean ± SD	8.1 ± 2.3	10.4 ± 3.1	t = 2.30	0.029

The study results suggest that Total Neoadjuvant Therapy was associated with significantly improved tumor regression, superior nodal downstaging, reduced intraoperative blood loss, better pathological downstaging, and shorter postoperative hospitalization compared with conventional treatment. Trends toward higher pathological complete response rates, improved sphincter preservation, greater R0 resection rates, and fewer postoperative complications were also observed.

DISCUSSION

The management of locally advanced rectal cancer has undergone substantial evolution over the past decade with increasing emphasis on multimodal treatment strategies aimed at improving both oncological and surgical outcomes. Total Neoadjuvant Therapy (TNT), which involves administration of all planned chemotherapy and radiotherapy before surgery, has emerged as a promising approach to enhance tumor regression, improve compliance with systemic therapy, and reduce the risk of disease recurrence [11].

One of the most important findings of the present study was the significantly greater reduction in tumor size among patients receiving TNT compared with those receiving standard treatment (54.8% vs. 35.2%; p=0.001). In addition, post-treatment carcinoembryonic antigen levels were significantly lower in the TNT group. These findings indicate superior tumor regression following intensified neoadjuvant treatment. The RAPIDO trial demonstrated that TNT substantially improved disease-related treatment outcomes and enhanced tumor response rates compared with conventional chemoradiotherapy followed by surgery [11].

The PRODIGE 23 trial reported improved pathological and radiological responses among patients treated with induction chemotherapy before chemoradiotherapy and surgery [12]. The greater degree of tumor shrinkage observed in the present study may be attributed to earlier delivery of systemic chemotherapy, which facilitates eradication of both locoregional and microscopic disease.

An equally important observation was the significant improvement in nodal downstaging in the TNT group. Nodal downstaging occurred in 73.3% of patients receiving TNT compared with 33.3% in the standard treatment group (p=0.028), while conversion to node-negative status was achieved in 66.7% and 26.7% of patients, respectively. Nodal response has emerged as a critical predictor of long-term outcomes in rectal cancer because persistent nodal disease is associated with increased recurrence and reduced survival. The findings of the present study are consistent with the OPRA trial, which demonstrated enhanced tumor regression and improved treatment response following TNT-based protocols [13].

The influence of TNT on surgical outcomes represents one of the most clinically relevant aspects of this study. Although operative duration did not differ significantly between groups, intraoperative blood loss was significantly lower among patients receiving TNT. Reduced blood loss may be attributable to improved tumor shrinkage and clearer tissue planes

resulting from more effective tumor regression. Similar observations have been reported in several institutional studies evaluating TNT, where enhanced tumor downstaging facilitated technically less demanding resections [14].

The TNT group also demonstrated higher rates of sphincter preservation and R0 resection. Although these differences did not achieve statistical significance, likely due to the limited sample size, the observed trends remain clinically meaningful. Preservation of sphincter function is a major therapeutic goal in rectal cancer management because it directly influences postoperative quality of life. The increased rate of sphincter-preserving surgery observed in the TNT group likely reflects more effective reduction in tumor bulk and improved distance from critical anatomical structures [13,14].

The pathological findings further support the benefits of TNT. Pathological complete response (pCR) was achieved in 33.3% of patients receiving TNT compared with only 6.7% in the standard treatment group. Although statistical significance was narrowly missed ($p=0.080$), the magnitude of the difference is noteworthy and aligns closely with contemporary literature. The PRODIGE 23 trial reported significantly higher pathological complete response rates among patients treated with TNT compared with conventional therapy [12]. Similarly, long-term analyses from RAPIDO and OPRA have demonstrated improved pathological regression with TNT-based treatment strategies [11,13].

The significantly higher proportion of patients achieving ypT0-T1 staging in the TNT group further emphasizes the enhanced pathological response associated with this treatment approach. Downstaging of the primary tumor is clinically important because it is associated with improved resectability, lower recurrence rates, and potentially improved survival outcomes. The present findings reinforce the growing body of evidence suggesting that TNT produces more profound tumor regression than conventional treatment pathways [12,13].

Another notable finding was the lower frequency of adverse pathological features such as lymphovascular invasion and perineural invasion in the TNT group. Although these differences were not statistically significant, they suggest a favorable biological response to intensified neoadjuvant therapy. Both lymphovascular invasion and perineural invasion are recognized prognostic indicators associated with increased recurrence risk and poorer survival outcomes.

The present study demonstrated that TNT did not adversely affect postoperative recovery. The incidence of overall postoperative complications was lower in the TNT group (20.0%) than in the standard treatment group (46.7%), although this difference did not reach statistical significance. Rates of surgical site infection, anastomotic leakage, and postoperative ileus were also comparable between groups. These findings are consistent with those of the RAPIDO and STELLAR trials, which demonstrated that TNT does not substantially increase postoperative morbidity despite intensification of neoadjuvant treatment [11,15]. Similar conclusions have been reported in several meta-analyses that evaluated the safety profile of TNT and found no increase in perioperative mortality or major surgical complications [16].

An additional advantage observed in the present study was the significantly shorter duration of hospital stay among patients receiving TNT. The mean hospital stay was reduced by more than two days in the TNT group compared with the standard treatment group. Shorter hospitalization may reflect lower complication rates, improved recovery, and more favorable postoperative physiology. Reduced hospital stay also carries important implications for healthcare resource utilization and treatment costs, particularly in resource-constrained settings.

The findings of this study should be interpreted with few limitations. The relatively small sample size may have limited the ability to detect statistically significant differences in several clinically important outcomes, including pathological complete response, R0 resection rates, and postoperative complications. The single-center design may also affect the generalizability of the findings.

CONCLUSION

The present study supports the use of Total Neoadjuvant Therapy in locally advanced rectal cancer. TNT was associated with superior tumor regression, improved nodal downstaging, reduced intraoperative blood loss, enhanced pathological response, and shorter postoperative hospitalization without increasing surgical morbidity.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.
2. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl 4):iv22-iv40.
3. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? Br J Surg. 1982;69(10):613-616.
4. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731-1740.

5. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114-1123.
6. Cercek A, Roxburgh CS, Strombom P, Smith JJ, Temple LK, Nash GM, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol. 2018;4(6):e180071.
7. Fokas E, Schlenska-Siemens A, Ghadimi M, Sprenger T, Grothe W, Hochhaus A, et al. Pathological complete response after neoadjuvant chemoradiotherapy in rectal cancer: long-term results of the CAO/ARO/AIO-04 randomized phase III trial. J Clin Oncol. 2022;40(31):3589-3599.
8. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711-717.
9. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryj M, et al. Long-course oxaliplatin-based chemoradiotherapy versus 5 × 5 Gy radiation and consolidation chemotherapy for cT3 or cT4 rectal cancer: pathological response in the Polish II randomized trial. Radiother Oncol. 2016;119(2):270-275.
10. Kasi A, Abbasi S, Handa S, Al-Rajabi R, Saeed A, Baranda J, et al. Total neoadjuvant therapy vs standard neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(12):e2030097.
11. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CA, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):29-42.
12. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(5):702-715.
13. Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol. 2022;40(23):2546-2556.
14. Perez RO, Habr-Gama A, Lynn PB, Sao Juliao GP, Bianchi R, Proscurshim I, et al. Transanal endoscopic microsurgery for residual rectal cancer after neoadjuvant chemoradiation therapy is associated with high local recurrence rates. Ann Surg. 2011;254(5):745-750.
15. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N, et al. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). J Clin Oncol. 2022;40(15):1681-1692.
16. Petrelli F, Trevisan F, Cabiddu M, Sgroi G, Lonati V, Vavassori I, et al. Total neoadjuvant therapy in locally advanced rectal cancer: a systematic review and meta-analysis of individual patient data. Ann Surg. 2020;271(5):820-828.