Cancer Management and Research

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of the Timing of Protective Stoma Reversal on Survival in Rectal Cancer Patients Undergoing Postoperative Adjuvant Chemotherapy: A Retrospective Single Center Study

Jiwei Wang*, Xiaoyun Lu*, Yanan Xu, Yin Wu, Tao Zhang, Jianguo Li

Department of General Surgery, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jianguo Li, Department of General Surgery, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Huichuan District, Zunyi, Guizhou, People's Republic of China, Tel +86-13017410630, Email jianguo_zmu@163.com

Background: Postoperative adjuvant chemotherapy used in patients with stage II/III rectal cancer, is usually administered for 3 to 6 months. However, the optimal timing of protective stoma reversal remains controversial. This study aimed to investigate the effect of stoma closure before or after adjuvant chemotherapy on survival and stoma-related complications.

Methods: A retrospective analysis was conducted on 144 patients who underwent radical rectal cancer surgery, prophylactic ileostomy and adjuvant chemotherapy from June 2018 to June 2021. 104 had their stoma reversal before adjuvant chemotherapy completion (Before group) and 40 after adjuvant chemotherapy completion (After group).

Results: There were no significant differences between the groups regarding demographics, clinical characteristics, perioperative complications, OS, or DFS. Pathologic T-stage [HR = 2.620 (1.291–5.320), $P = 0.008$ vs HR = 2.793 (1.297–6.017), $P = 0.009$] and N-stage [HR = 2.204 (1.168–4.157), $P = 0.015$ vs HR = 2.068 (1.125–3.789), $P = 0.019$] were identified as independent risk factors for OS and DFS. Stoma reversal after completing chemotherapy [OR = 39.979 (3.964–403.188), $P = 0.002$] and comorbidity [OR = 33.395 (5.931–188.033), $P < 0.001$] were independent risk factors for stoma-related complications. In high-risk stage III patients with T4 or N2, the 3-year OS rate was significantly lower in Before group than in After group (70.3% vs 92.6%, $P = 0.01$), as was the 3-year DFS rate (60.94% vs 74.07%, $P = 0.02$). Prolonged stoma duration [HR = 0.991 (0.982–1.000), $P = 0.048$] was an OS protective factor. Stoma reversal after chemotherapy [HR = 0.370 (0.141–0.972), $P = 0.044$] and cumulative 5-FU dosage [HR = 0.991 (0.985–0.997), $P = 0.003$] were DFS protective factors.

Conclusion: In high-risk stage III patients, delayed stoma reversal after adjuvant chemotherapy may improve survival, but it may also lead to more stoma-related complications.

Keywords: rectal cancer, protective ileostomy, adjuvant chemotherapy, survival, stoma-related complications

Introduction

Low rectal cancer resection often requires a protective ileostomy aimed at reducing anastomotic tension and bacterial contamination by diverting the faecal flow. This protective measure helps safeguard the anastomosis, reducing the risk of anastomotic leakage and its associated complications, such as abdominal infections and abscesses.[1,2] Typically, protective ileostomies are temporary, with stoma reversal performed once the patient's condition improves, including resolution of bowel oedema and improvement of adhesions around the intestine. However, current guidelines and expert consensus do not clearly define the optimal timing for stoma reversal. While most surgeons prefer stoma reversal 2–3 months after rectal cancer resection, some studies suggest earlier reversal within one month postoperatively or even ultra-early reversal within 10–12 days.[3] Elsner et al[4] compared the safety of stoma reversal performed early (2 weeks post-operatively) versus late (12 weeks postoperatively). However, the early reversal group was discontinued due to severe

Received: 30 December 2024
Accepted: 3 April 2025
Published: 15 April 2025

postoperative complications. Tramontano et al[5] compared perioperative and postoperative complications between patients who underwent stoma reversal within 4 weeks and those who had it after 4 weeks. The results showed that the timing of stoma reversal was not a factor influencing postoperative complications. For patients with stage II–III rectal cancer who require postoperative adjuvant chemotherapy, some scholars believe that stoma reversal can be performed after the completion of adjuvant chemotherapy, but this approach is also subject to debate.[6]

Postoperative adjuvant chemotherapy is an essential component of the comprehensive treatment for rectal cancer. For patients with high-risk stage II and stage III rectal cancer based on postoperative pathological staging, guidelines recommend adjuvant chemotherapy for 3 to 6 months.[7] Adjuvant chemotherapy aims to eradicate residual tumour cells using chemotherapeutic agents, thereby reducing the likelihood of tumour recurrence or metastasis. Standard regimens typically include fluoropyrimidine-based therapies such as CapeOx or FOLFOX or monotherapies like 5-FU/LV or capecitabine.[8] The optimal timing for stoma reversal in these patients has not yet been determined. During adjuvant chemotherapy, chemotherapy-related side effects, such as physical deterioration, weakened immunity, and overall debility, may increase the perioperative risks of stoma reversal.[9] Cheng et al found that the use of bevacizumab in chemotherapy is one of the independent risk factors for major complications after stoma reversal.[10] Furthermore, stoma-related complications occur in 20–80% of patients and include stenosis, retraction, prolapse, parastomal hernia, and stoma malignancy.[11–13] These complications are partly due to faecal diversion, which alters normal intestinal anatomy and physiology, potentially causing distal bowel inflammation and increasing the psychological and social burdens on patients.

For patients undergoing rectal cancer resection with protective stoma formation, the timing of stoma reversal must take into account multiple factors, including postoperative adjuvant chemotherapy, stoma-related complications, and the social, psychological, and economic impacts. Reversing the stoma before completing adjuvant chemotherapy may increase perioperative complications, prolong hospital stays, and delay postoperative recovery, potentially leading to chemotherapy delays or interruptions. Furthermore, the impact of early stoma reversal on patient survival before the completion of adjuvant chemotherapy remains unclear. On the other hand, whether delaying stoma reversal until after the completion of chemotherapy might prolong the stoma reversal timeline, increase stoma-related complications, and result in adverse clinical outcomes is also uncertain.

This study aims to investigate whether early stoma reversal, before the completion of adjuvant chemotherapy, affects survival and to explore whether the timing of stoma reversal influences the incidence of stoma-related complications.

Materials and Methods

This retrospective cohort study included patients who underwent rectal cancer resection with protective ileostomy between June 2018 and June 2021 at the Department of Gastrointestinal Surgery, Zunyi Medical University Affiliated Hospital. Demographic and clinical data were collected. The study was approved by the Ethics Committee of Zunyi Medical University (Ethics Approval No. KLLY-2023-075) and was conducted in accordance with the Declaration of Helsinki.

Clinical data were collected for patients who met the inclusion and exclusion criteria. Inclusion criteria were: (1) age ≥18 years; (2) histopathologically confirmed diagnosis of rectal cancer, staged as stage II with high-risk factors (poor histological differentiation (grade III or IV), proficient mismatch repair (pMMR) or microsatellite stability (MSS), vascular or lymphatic invasion, preoperative bowel obstruction or perforation, insufficient lymph node retrieval in the specimen (<12 nodes), neural invasion, positive or indeterminate surgical margins), or stage III; (3) patients who underwent rectal cancer resection with protective ileostomy and received postoperative adjuvant chemotherapy; (4) Patients diagnosed with rectal cancer for the first time and underwent radical surgery. (5) Patients with neoadjuvant treatment duration ≤ 3 months (4 cycles of CapeOX, or 6 cycles of FOLOX), who have been assessed to have apparent tumor regression and are eligible for radical surgery. Exclusion criteria included: (1) missing clinical or pathological data; (2) no ileostomy reversal within one year after surgery; (3) The stoma has not been reversed within one year after surgery due to tumor recurrence and metastasis, physical condition or other reasons. (4) Except for the first chemotherapy cycle after the ileostomy, other cycles have been delayed for more than 7 days beyond the specified time window. Follow-up continued until June 2024.

Given the differing pathological stages of rectal cancer, patients were assigned to receive 3 to 6 months of adjuvant chemotherapy. According to the NCCN Colorectal Cancer Guidelines, standard chemotherapy regimens were defined as four cycles of CapeOX or six cycles of FOLFOX for high-risk stage II or low-risk stage III patients. High-risk stage III patients (defined as T4 or N2) received eight cycles of CapeOX or 12 cycles of FOLFOX. We defined chemotherapy treatment delay as an adjuvant chemotherapy delay for more than 7 days beyond the specified time window. The chemotherapy regimen and duration were chosen based on postoperative pathological staging and the evaluation by the surgeon or oncologist. The final chemotherapy cycle was administered at least three weeks before stoma reversal surgery, and chemotherapy was resumed at least two weeks after stoma reversal. Stoma reversal during chemotherapy was defined as the "Before group" (reversal before chemotherapy completion), and stoma reversal after chemotherapy completion was defined as the "After group" (reversal after chemotherapy completion). The demographic characteristics, adjuvant chemotherapy regimens (including protocol, dosage, and timing), stoma-related complications, and survival analysis were compared between the two groups.

Prior to stoma reversal surgery, the anastomosis site was assessed through rectal examination, gastrointestinal contrast imaging, or colonoscopy to ensure the absence of leakage, stenosis, or other anastomotic issues. All the surgeons in our study have extensive surgical experience and hold at least the title of associate chief physician.

Data Collection

General patient data were collected, including age, sex, body mass index (BMI), comorbidities (hypertension, diabetes, and respiratory diseases), American Society of Anesthesiologists (ASA) physical status classification, postoperative pathological staging, tumour location, duration of stoma use, and details of neoadjuvant therapy. Information on adjuvant chemotherapy was also gathered, including whether neoadjuvant therapy was administered and the chemotherapy regimen and dosage. Perioperative data for stoma reversal included duration of surgery, length of hospital stay, intraoperative blood loss, complications associated with stoma reversal (infection, postoperative bowel obstruction, fistula, incisional hernia), 30-day postoperative mortality, and reoperation rates. Stoma-related complications were recorded, including parastomal hernia, stoma prolapse, peristomal skin irritation, stoma retraction, stoma stenosis, and stoma malignancy.

Outcome Measures

The primary endpoint of this study is OS, defined as the time interval from the date of surgery to the date of death or the date of the last follow-up (June 30, 2024).

The secondary endpoint is DFS, defined as the time from the date of surgery to the occurrence of disease recurrence or death from any cause.

The occurrence of stoma-related complications was recorded throughout the follow-up period. Perioperative complications related to stoma reversal were defined as complications occurring during the surgery or within one month postoperatively that were related to the surgical procedure. Stoma-related complications (Clavien-Dindo grade II or higher) were defined as a series of complications associated with the stoma, including stoma retraction, ischemic necrosis, stoma oedema, peristomal dermatitis, parastomal hernia, stoma stenosis, stoma prolapse, and stoma malignancy.

Statistical Methods

Statistical analysis was performed using SPSS version 29.0. Normally distributed quantitative data were described as mean ± standard deviation (x±s) and analyzed using the *t*-test. Non-normally distributed quantitative data were described by the median and interquartile range and analyzed using the nonparametric rank-sum test. Count data were presented as n (%), and comparisons were made using the chi-square test or Fisher's exact test. Kaplan-Meier survival curves were generated for both groups, and differences were compared using the Log rank test. Cox regression analysis was conducted to explore independent risk factors affecting OS and DFS. Binary logistic regression analysis was used to identify independent risk factors for stoma-related complications. A p-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 213 patients were initially enrolled in this study. After screening by inclusion and exclusion criteria, 144 patients were included and divided into two groups based on the timing of protective stoma reversal. The "Before" group consisted of 104 patients who underwent stoma reversal before completing adjuvant chemotherapy (ie, these patients had not completed the full chemotherapy regimen). The "After" group included 40 patients who underwent stoma reversal after completing all chemotherapy cycles (Figure 1). There were no significant differences between the two groups in age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, tumour location, pathological stage, or the presence of comorbidities such as hypertension, diabetes, and respiratory diseases (Table 1). Similarly, no significant differences were observed in neoadjuvant therapy, total doses of Oxaliplatin, or 5-fluorouracil (5-FU) between the two groups (Table 2). When comparing perioperative indicators for stoma reversal, including surgical duration, intraoperative blood loss, and length of hospital stay, no significant differences were found between the two groups (Table 3). Furthermore, neither group experienced surgical complications or unplanned reoperations during the perioperative period or within 30 days after stoma reversal.

Survival Outcomes

As of the last follow-up on June 30, 2024, the 3-year OS rate for the Before group and After group was 81.7% and 90%, respectively (P=0.18) (Figure 2). The 3-year DFS rate for the two groups was 74.04% and 82.5%, respectively (P=0.091) (Figure 2). No statistically significant differences in survival outcomes were observed between the two groups.

Cox Regression Analysis of OS-Related Risk Factors

Univariate Cox regression analysis revealed that pathological staging, specifically T stage [HR = 2.620 (1.291–5.320), P = 0.008] and N stage [HR = 2.204 (1.168–4.157), P = 0.015], receipt of neoadjuvant therapy [HR = 0.098

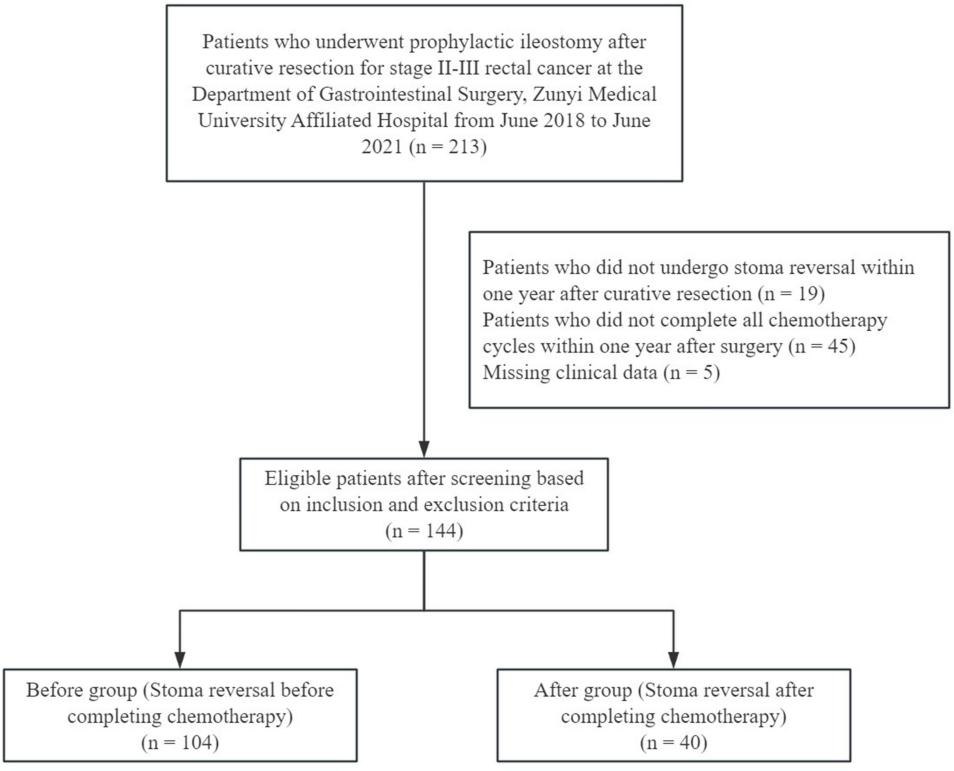

Figure 1 Study flowchart.

Table 1 Demographic and Clinical Characteristics of the Two Groups

	Before Group	After Group	t/X²/Z	P
	n=104	n=40		
Age (years)	60.32±13.196	63.70±9.146	−1.488	0.139[a]
Sex				
Male	60(77.9%)	44(65.7%)	2.680	0.102[b]
Female	17(22.1%)	23(34.3%)		
BMI (kg/m^2)	23.53(22.43,24.69)	24.54(23.28,25.32)	−1.926	0.054[c]
ASA*			4.532	0.870[b]
I	55(52.9%)	15(37%)		
II	45(43.3%)	25(62.5%)		
Comorbidities				
Hypertension	7(6.7%)	7(17.5%)	3.817	0.063[b]
Diabetes	5(4.8%)	3(7.5%)	0.399	0.685[b]
Respiratory diseases	12(11.5%)	9(22.5%)	2.787	0.115[b]
Tumour Location				
Low (≤5 cm)	79(76.0%)	30(75.0%)	0.015	0.904[b]
Middle/High (>5 cm)	25(24.0%)	10(25.0%)		
pTNM				
T T2	15(14.4%)	3(7.5%)	4.986	0.080[b]
T3	60(57.7%)	18(45.0%)		
T4	29(27.9%)	19(47.5%)		
N N0	26(25.0%)	11(27.5%)	0.338	0.884[b]
N1	23(22.1%)	10(25.0%)		
N2	55(52.9%)	19(47.5%)		

Notes: [a]*t*-test; [b]Chi-square test or Fisher's exact test; [c]Non-parametric rank-sum test.
Abbreviation: ASA, American Society of Anesthesiologists classification for physical status.

Table 2 Adjuvant Therapy-Related Data for the Two Groups

	Before Group	After Group	t/X²	P
	n=104	n=40		
Receipt of Neoadjuvant Therapy			3.614	0.066[b]
Yes	25(24.0%)	16(40.0%)		
No	79(76.0%)	24(60.0%)		
Cumulative Dose of Oxaliplatin (g)	1.41±0.44	1.35±0.48	0.662	0.509[a]
Cumulative Dose of 5-FU (g)	134.78±88.71	128.49±93.88	0.375	0.708[a]

Notes: [a]*t*-test; [b]Chi-square test or Fisher's exact test.

(0.013–0.723), $P = 0.023$], and cumulative 5-FU dose [HR = 0.993 (0.986–0.999), $P = 0.029$], were factors influencing OS ($P < 0.05$). Multivariate regression analysis showed that T stage [HR = 2.793 (1.297–6.017), $P = 0.009$], N stage [HR = 2.068 (1.125–3.789), $P = 0.019$], and receipt of neoadjuvant therapy [HR = 0.061 (0.008–0.459), $P = 0.007$] were factors influencing OS (Table 4 and Table 5).

Cox Regression Analysis of DFS-Related Risk Factors

Univariate Cox regression analysis revealed that pathological staging, specifically T stage [HR = 2.407 (1.360–4.259), $P = 0.003$], N stage [HR = 2.235 (1.336–3.738), $P = 0.002$], receipt of neoadjuvant therapy [HR = 0.371 (0.144–0.995),

Table 3 Perioperative Data for Stoma Reversal Surgery in the Two Groups

	Before Group	After Group	Z	P
	n=104	n=40		
Surgical Duration (minutes)	80(64.25,100)	85(62,103.75)	−0.552	0.581[a]
Length of Hospital Stay (days)	12(10,16.75)	14(10,19)	−0.964	0.335[a]
Intraoperative Blood Loss (mL)	15(10,15)	15(10,20)	−0.653	0.514[a]

Note: [a]Non-parametric rank-sum test.

$P = 0.040$], and cumulative 5-FU dose [HR = 0.994 (0.989–0.999), $P = 0.012$], were factors influencing DFS ($P < 0.05$). Multivariate regression analysis demonstrated that pathological staging, specifically T stage [HR = 2.302 (1.239–4.277), $P = 0.008$], N stage [HR = 2.105 (1.276–3.555), $P = 0.004$], and receipt of neoadjuvant therapy [HR = 0.252 (0.079-–0.791), $P = 0.006$] were factors affecting DFS (Table 6 and Table 7).

Survival Outcomes in High-Risk Stage III Rectal Cancer

Cox regression analysis identified T and N stages as independent risk factors for both OS and DFS. Therefore, a subgroup analysis was conducted for high-risk stage III rectal cancer patients, defined as those with T 4 or N 2. Of the 144 patients, 91 had high-risk stage III disease, with 64 in the Before group and 27 in the After group. In this subgroup, the 3-year OS rate for the Before group and After group was 70.3% and 92.6%, respectively ($P = 0.01$), and the 3-year DFS rate was 60.94% and 74.07%, respectively ($P = 0.02$) (Figure 3). These results suggest that patients in the After group had significantly better survival outcomes compared to those in the Before group.

Cox Regression Analysis of OS-Related Risk Factors in High-Risk Stage III Rectal Cancer

Univariate Cox regression analysis in the subgroup revealed that stoma duration [HR = 0.991 (0.982–1.000), $P = 0.048$], stoma reversal after completing chemotherapy [HR = 0.200 (0.047–0.858), $P = 0.030$], and cumulative 5-FU dose [HR = 0.992 (0.985–0.999), $P = 0.021$] were factors influencing OS ($P < 0.05$). Multivariate Cox regression analysis showed that stoma duration [HR = 0.991 (0.982–1.000), $P = 0.048$] and cumulative 5-FU dose [HR = 0.992 (0.985–0.999), $P = 0.032$] were factors influencing OS (Table 8 and Table 9).

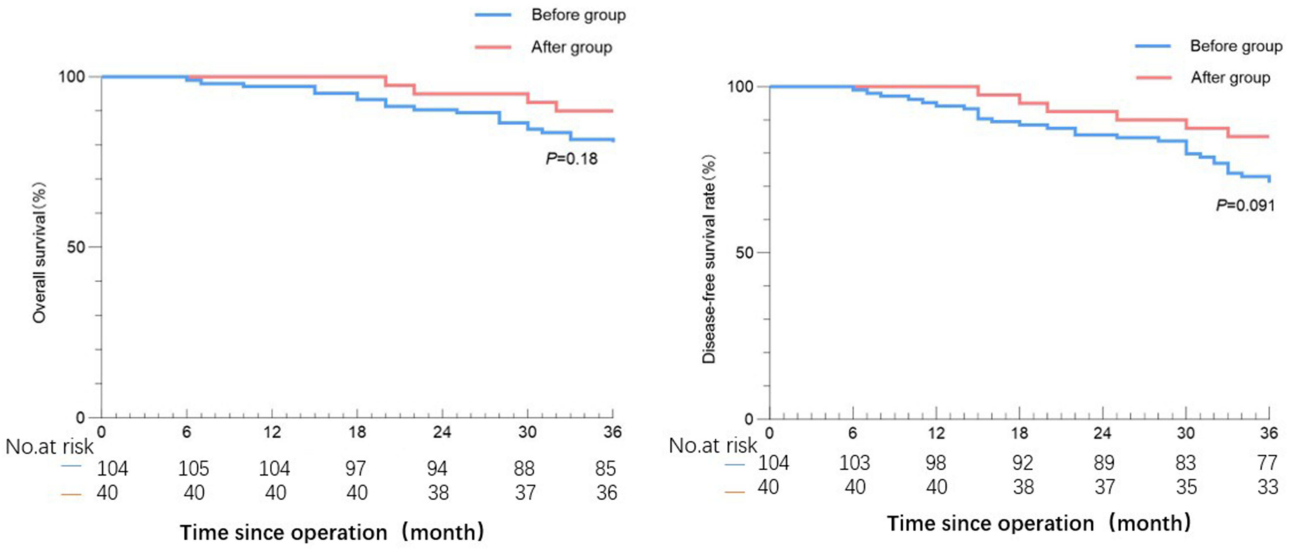

Figure 2 OS and DFS survival curves between the two groups in the entire cohort.

Table 4 Univariate Analysis of OS in Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	P	HR	95% CI for HR	
						Lower Limit	Upper Limit
Age	0.015	0.018	0.750	0.387	1.015	0.981	1.051
Sex (Male vs Female)	0.121	0.455	0.071	0.790	1.129	0.462	2.756
BMI	0.071	0.095	0.563	0.453	1.107	0.891	1.389
ASA	0.712	0.442	2.598	0.107	2.308	0.857	4.844
Tumour Location (≤5 cm vs >5 cm)	−0.517	0.548	1.606	0.205	0.446	0.128	1.555
Pathological Staging							
T	0.963	0.361	7.110	0.008*	2.620	1.291	5.320
N	0.790	0.324	5.962	0.015*	2.204	1.169	4.157
Surgical Duration	−0.005	0.008	0.331	0.565	0.995	0.980	1.011
Length of Hospital Stay	−0.055	0.041	1.762	0.184	0.947	0.874	1.026
Intraoperative Blood Loss	−0.017	0.035	0.234	0.629	0.983	0.917	1.053
Duration of Stoma Use	−0.004	0.004	1.122	0.289	0.996	0.989	1.003
Receipt of Neoadjuvant Therapy	2.327	1.022	5.189	0.023*	0.098	0.013	0.723
Completion of chemotherapy before fistula closure	−0.715	0.548	1.706	0.192	0.489	0.167	1.431
Stoma-Related Complications	−1.065	1.022	1.088	0.297	0.345	0.047	2.552
Cumulative Oxaliplatin Dose	0.339	0.464	0.740	0.390	1.491	0.600	3.701
Cumulative 5-FU Dose	−0.007	0.003	4.771	0.029*	0.993	0.986	0.999

Note: *P<0.05.

Table 5 Multivariate Analysis of OS in Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Pathological Staging							
T	1.027	0.391	6.887	0.009*	2.793	1.297	6.017
N	0.726	0.310	5.480	0.019*	2.068	1.125	3.798
Receipt of Neoadjuvant Therapy	−2.798	1.030	7.375	0.007*	0.061	0.008	0.459
Cumulative 5-FU Dose	−0.005	0.004	2.238	0.135	0.135	0.988	1.002

Note:*P<0.05.

Table 6 Univariate Analysis of DFS in Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Age	0.003	0.014	0.043	0.837	1.003	0.976	1.031
Sex (Male vs Female)	0.046	0.334	0.019	0.890	1.047	0.554	2.014
BMI	0.025	0.079	0.097	0.755	1.025	0.878	1.197
ASA	−0.037	0.300	0.015	0.901	0.963	0.535	1.734
Tumour Location (≤5 cm vs >5 cm)	−0.353	0.421	0.704	0.401	0.702	0.308	1.603
Pathological Staging							
T	0.878	0.291	9.103	0.003*	2.407	1.360	4.259
N	0.804	0.262	9.394	0.002*	2.235	1.336	3.738
Surgical Duration	−0.005	0.007	0.698	0.403	0.995	0.982	1.007

(*Continued*)

https://doi.org/10.2147/CMAR.S511962

Table 6 (Continued).

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Length of Hospital Stay	−0.045	0.032	1.951	0.162	0.956	0.897	1.018
Intraoperative Blood Loss	−0.036	0.035	1.037	0.309	0.965	0.901	1.034
Duration of Stoma Use	−0.003	0.003	1.127	0.288	0.997	0.991	1.003
Receipt of Neoadjuvant Therapy	−0.991	0.482	4.224	0.040*	0.371	0.144	0.995
Completion of chemotherapy before fistula closure	−0.734	0.447	2.691	0.101	0.480	0.200	1.154
Stoma-Related Complications	−1.522	1.014	2.252	0.133	0.218	0.030	1.593
Cumulative Oxaliplatin Dose	−0.022	0.368	0.004	0.951	0.978	0.476	2.010
Cumulative 5-FU Dose	−0.006	0.003	6.304	0.012*	0.994	0.989	0.999

Note: *P<0.05.

Table 7 Multivariate Analysis of DFS in Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Pathological Staging							
T	0.834	0.316	6.953	0.008*	2.302	1.239	4.277
N	0.744	0.255	8.502	0.004*	2.105	1.276	3.555
Receipt of Neoadjuvant Therapy	−1.378	0.497	7.700	0.006*	0.252	0.079	3.471
Cumulative 5-FU Dose	−0.005	0.003	3.528	0.060*	0.995	0.990	1.000

Note: *P<0.05.

Cox Regression Analysis of DFS-Related Risk Factors in High-Risk Stage III Rectal Cancer

Univariate Cox regression analysis in the subgroup revealed that stoma reversal after completing chemotherapy [HR = 0.349 (0.134–0.906), P = 0.031] and cumulative 5-FU dose [HR = 0.991 (0.985–0.997), P = 0.002] were factors

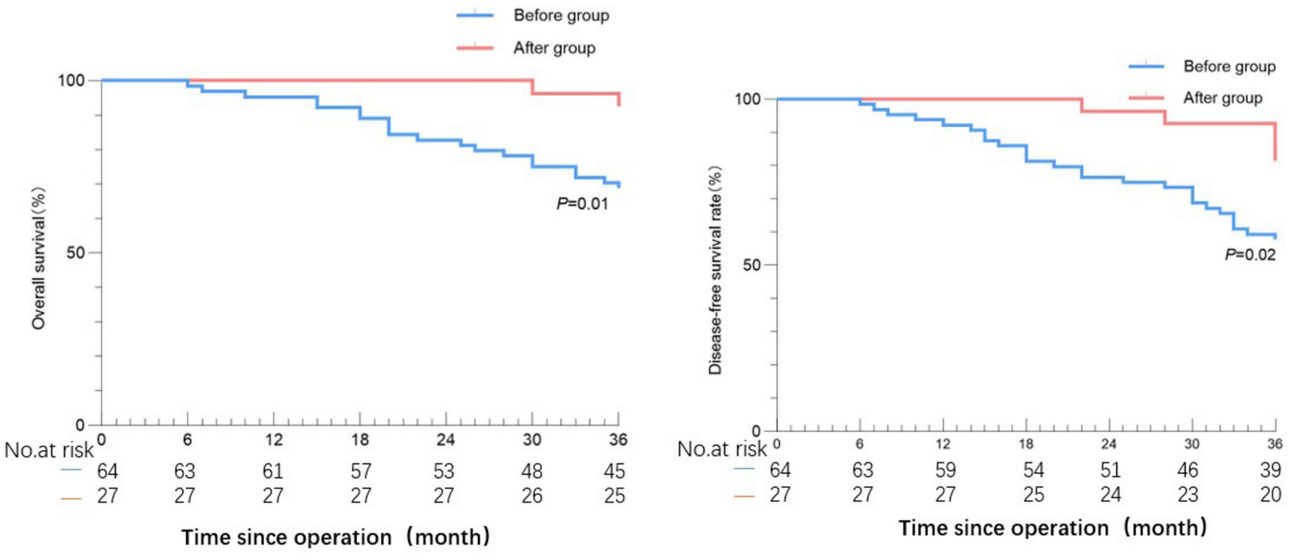

Figure 3 OS and DFS survival curves between the two groups in high-risk stage III rectal cancer.

Table 8 Univariate Analysis of OS in High-Risk Stage III Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Age	−0.014	0.019	0.547	0.459	0.986	0.951	1.023
Sex (Male vs Female)	−0.13	0.428	0.093	0.761	0.878	0.379	2.032
BMI	0.043	0.105	0.171	0.679	1.044	0.851	1.282
ASA	0.068	0.411	0.027	0.869	1.070	0.478	12.395
Tumour Location (≤5 cm vs >5 cm)	−0.700	0.621	1.268	0.260	0.497	0.147	1.679
Surgical Duration	−0.007	0.008	0.747	0.387	0.993	0.977	1.009
Length of Hospital Stay	−0.055	0.041	1.809	0.179	0.946	0.873	1.026
Intraoperative Blood Loss	−0.007	0.048	0.032	0.889	0.993	0.903	1.092
Duration of Stoma Use	−0.009	0.005	3.925	0.048*	0.991	0.982	1.000
Completion of chemotherapy before fistula closure	−1.608	0.742	4.695	0.030*	0.200	0.047	0.858
Stoma-Related Complications	−1.399	1.024	1.867	0.172	0.247	0.033	1.836
Cumulative Oxaliplatin Dose	0.287	0.479	0.358	0.549	1.332	0.521	23.405
Cumulative 5-FU Dose	−0.008	0.003	5.319	0.021*	0.992	0.985	0.999

Note: *P<0.05.

Table 9 Multivariate Analysis of OS in High-Risk Stage III Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Duration of Stoma Use	−0.001	0.006	0.053	0.048*	0.991	0.982	1.000
Completion of chemotherapy before fistula closure	−1.318	0.910	2.101	0.147	0.268	0.045	1.591
Cumulative 5-FU Dose	−0.008	0.004	4.579	0.032*	0.992	0.985	0.999

Note: *P<0.05.

influencing disease-free survival (DFS) ($P < 0.05$). Multivariate Cox regression analysis confirmed that stoma reversal after completing chemotherapy [HR = 0.370 (0.141–0.972), $P = 0.044$] and cumulative 5-FU dose [HR = 0.991 (0.985–0.997), $P = 0.003$] remained factors influencing DFS (Table 10 and Table 11).

Table 10 Univariate Analysis of DFS in High-Risk Stage III Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Age	−0.018	0.016	1.160	0.282	0.983	0.952	1.014
Sex (Male vs Female)	0.018	0.354	0.003	0.960	1.018	0.509	2.036
BMI	0.045	0.091	0.259	0.617	0.956	0.799	1.142
ASA	0.010	0.339	0.001	0.978	0.990	0.510	1.924
Tumour Location (≤5 cm vs >5 cm)	−0.128	0.428	0.090	0.764	0.880	0.380	2.034
Surgical Duration	−0.008	0.007	1.448	0.229	0.992	0.979	1.005
Length of Hospital Stay	−0.048	0.033	2.101	0.147	0.954	0.894	1.017
Intraoperative Blood Loss	−0.028	0.041	0.456	0.499	0.973	0.897	1.064
Duration of Stoma Use	−0.005	0.003	2.323	0.127	0.995	0.989	1.001
Completion of chemotherapy before fistula closure	−1.054	0.487	4.675	0.031*	0.349	0.134	0.906

(*Continued*)

Table 10 (Continued).

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Stoma-Related Complications	−1.873	1.016	3.398	0.065	0.154	0.021	1.126
Cumulative Oxaliplatin Dose	0.177	0.394	0.201	0.654	1.193	0.551	2.583
Cumulative 5-FU Dose	−0.009	0.003	9.687	0.002*	0.991	0.985	0.997

Note: *P<0.05.

Table 11 Multivariate Analysis of DFS in High-Risk Stage III Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	HR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Completion of chemotherapy before fistula closure	−0.995	0.493	4.068	0.044*	0.370	0.141	0.972
Cumulative 5-FU Dose	−0.009	0.003	8.745	0.003*	0.991	0.985	0.997

Note: *P<0.05.

Logistic Regression Analysis of Risk Factors for Stoma-Related Complications

A total of 15 patients developed stoma-related complications: 2 in the Before group (2 with peristomal dermatitis) and 13 in the After group (3 with parastomal hernia, 9 with peristomal dermatitis, 1 with stoma prolapse, 1 with stoma stenosis). Univariate logistic regression analysis was performed to investigate whether the timing of stoma reversal was associated with stoma-related complications. The results showed that stoma duration [OR = 1.009 (1.003–1.016), $P = 0.006$], stoma reversal after completing chemotherapy [OR = 24.556 (5.223–115.456), $P < 0.001$], and comorbidities such as hypertension, diabetes, and respiratory diseases [OR = 40.083 (8.341–192.626), $P = 0.000$] were factors influencing stoma-related complications ($P < 0.05$). Multivariate regression analysis confirmed that stoma reversal after completing chemotherapy [OR = 39.979 (3.964–403.188), $P = 0.002$] and comorbidities such as hypertension, diabetes, and respiratory diseases [OR = 33.395 (5.931–188.033), $P < 0.001$] were risk factors for stoma-related complications (Table 12 and Table 13). The results suggest that stoma reversal after completing chemotherapy may increase the incidence of stoma-related complications.

Table 12 Univariate Logistic Regression Analysis of Stoma-Related Complications in Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	0R	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Age	0.006	0.023	0.073	0.786	1.006	0.963	1.052
Sex (Male vs Female)	−0.297	0.556	0.285	0.593	0.743	0.250	2.209
BMI	0.103	0.128	0.065	0.420	1.108	0.863	1.181
ASA	0.450	0.487	0.851	0.356	1.568	0.603	4.073
Tumour Location (≤5 cm vs >5 cm)	−0.277	0.677	1.168	0.682	0.758	0.201	2.856
Pathological Staging							
T	0.748	0.463	2.611	0.106	2.112	0.853	5.230
N	−2.314	0.333	0.138	0.710	1.132	0.589	2.174
Surgical Duration	−0.011	0.011	1.045	0.307	0.989	0.967	1.010
Length of Hospital Stay	−0.001	0.046	0.000	0.984	0.999	0.921	1.038
Intraoperative Blood Loss	−0.049	0.060	0.681	0.409	0.952	0.847	1.070
Duration of Stoma Use	0.009	0.003	7.695	0.006*	1.009	1.003	1.016
Completion of chemotherapy before fistula closure	3.201	0.790	16.426	0.000*	24.556	5.223	115.456
With comorbidities	3.691	0.801	21.237	0.000*	40.083	8.341	192.626

Note: *P<0.05.

Table 13 Multivariate Logistic Regression Analysis of Stoma-Related Complications in Rectal Cancer Patients Undergoing Protective Ileostomy After Curative Resection

Factor	B	SE	Wals	*P*	OR	95% Confidence Interval for EXP(B)	
						Lower Limit	Upper Limit
Duration of Stoma Use	−0.006	0.006	0.906	0.341	0.994	1.003	1.006
Completion of chemotherapy before fistula closure	3.508	1.179	9.785	0.002*	39.979	3.964	403.188
With comorbidities	3.508	0.882	15.832	<0.001*	33.395	5.931	188.033

Note: *P<0.05.

Discussion

Patients with high-risk stage II and III rectal cancer typically require postoperative adjuvant chemotherapy to reduce the likelihood of recurrence and metastasis. The duration of adjuvant chemotherapy is associated with pathological staging. This study initially examined survival outcomes between the two groups based on the timing of stoma reversal relative to the completion of chemotherapy. We observed that there was no significant differences of the 3-year OS rate and the 3-year DFS rate between the two groups. However, further Cox regression analysis identified pathological T and N stages as risk factors for both OS and DFS. Compared to low-risk stage II and III patients, high-risk stage III patients may require higher doses of adjuvant chemotherapy. Higher doses of adjuvant chemotherapy require longer treatment courses, which result in a longer duration of stoma use for patients who undergo stoma reversal after completing chemotherapy. Additionally, high-risk stage III patients have poorer survival compared to stage II and low-risk stage III patients. Therefore, this study focused on patients with T4 or N2 to explore the influencing factors. The results indicated that longer stoma duration and higher cumulative 5-FU dose were protective factors for OS. Completion of the full chemotherapy regimen before stoma reversal and the cumulative 5-FU dose were identified as protective factors for DFS. A Japanese study examining the relationship between protective ileostomy and adjuvant chemotherapy in rectal cancer patients concluded that the presence of a stoma within 12 months after rectal resection did not affect the chemotherapy drug dose, but it could delay the initiation of chemotherapy. Additionally, patients who underwent later stoma reversal were able to receive higher chemotherapy doses.[14,15]

In the subgroup analysis, the cumulative 5-FU dose was identified as a protective factor for OS as part of the foundation for adjuvant chemotherapy. The mechanism of action of fluorouracil involves its conversion in the body to 5-fluoro-2-deoxyuridine monophosphate, which inhibits thymidylate synthase and blocks the conversion of deoxyribonucleotides to deoxythymidine monophosphate, thereby inhibiting DNA synthesis. Additionally, it prevents the incorporation of uracil and Orotic Acid into RNA, thereby inhibiting RNA synthesis.[3] As one of the most important antitumour agents, the dose of 5-FU may influence patient survival. In this study, fluorouracil was identified as a protective factor, with patients in the group (who underwent stoma reversal after completing chemotherapy) receiving higher doses of treatment. While postoperative adjuvant chemotherapy is generally indicated in patients with protective ileostomy, the timing of stoma reversal must be carefully considered. The timing of stoma reversal can affect the ability to complete adjuvant chemotherapy, as some patients may experience severe perioperative complications that delay or interrupt the chemotherapy regimen. In our subgroup analysis, stoma reversal after completing chemotherapy was identified as a protective factor for survival. This may be related to the fact that stoma reversal was not considered during the chemotherapy course, allowing for a complete and uninterrupted treatment regimen.[16,17]

The optimal timing for stoma reversal after protective ileostomy remains controversial in current studies. In the Chinese expert consensus on protective ileostomy for middle and low rectal cancer surgery,[18] some scholars recommend that patients requiring adjuvant chemotherapy may wait until the completion of chemotherapy before undergoing stoma reversal. However, stoma formation during chemotherapy may increase the risk of high-volume output, which could lead to dehydration, electrolyte imbalances, and even renal failure. Prolonged chemotherapy can also affect patients' overall physical condition, including a decrease in wound healing capacity.[19,20] Zhen et al[21] compared stoma reversal before, during, and after adjuvant chemotherapy. The conclusion was that stoma reversal at any stage—before, during, or after adjuvant chemotherapy—could achieve similar clinical and oncological safety outcomes. However, stoma reversal during

chemotherapy may be associated with serious complications that lead to delays or interruptions in chemotherapy.[22] Tulchinsky et al[23] compared survival outcomes between patients who underwent stoma reversal during adjuvant chemotherapy and those who had it after completing chemotherapy. The conclusion was that the timing of stoma reversal did not alter short-term or long-term oncological outcomes. However, the study had some limitations, as the group that underwent stoma reversal during chemotherapy had earlier staging. Tsai et al[22] explored the clinical and oncological outcomes of stoma reversal before and after adjuvant chemotherapy and concluded that patients experiencing major complications requiring reoperation within 30 days of stoma reversal had poorer long-term survival. A prospective randomized controlled study from Germany examined the optimal timing for stoma reversal in rectal cancer patients, concluding that early stoma reversal can reduce the occurrence of stoma-related complications and is overall safe and effective in improving quality of life.[3,24] Similarly, He et al[25] studied stoma reversal after the completion of chemotherapy and concluded that early stoma reversal does not affect surgical complications or oncological outcomes and that delaying stoma reversal to accommodate chemotherapy should not be recommended. In contrast, our study's findings suggest that in high-risk stage III rectal cancer patients, stoma reversal after completing chemotherapy is associated with improved survival. We considered the reasons behind might be: 1) Firstly, earlier stoma reversal (before chemotherapy) developed stoma-related complications and further led to subsequent chemotherapy delays, thereby affecting the patient's chemotherapy regimen and ultimately impacting survival; 2) Secondly, due to the trauma of the surgery and other induced stress, there existed differences in postoperative patients on perspectives of bodily function recovery after surgery, chemotherapy tolerance, and quality of life. All of above factors might affect the results of OS and DFS. For the first reason, we minimized the influence by excluding patients with more than 7 days of treatment delay. For the second reason, especially quality-of-life related factors, we did not explore much in our work due to very limited patients' data. We hope to dig out the reasons more in future prospective studies.

Regarding perioperative complications of stoma reversal, no severe complications were observed within 30 days postoperatively in this study. However, some studies suggest that early stoma reversal may lead to more serious complications. Yin et al[26] examined perioperative complications in patients undergoing rectal cancer resection with concomitant chemoradiotherapy and found that early stoma reversal was associated with a higher incidence of perioperative complications. Additionally, stoma reversal within 109 days was identified as an independent risk factor for perioperative complications. Previous studies have also reported that severe complications after stoma reversal led to the termination of certain trials.[4] In comparison to delayed stoma reversal, some researchers still consider early stoma reversal as a feasible approach.[10,24] However, the lack of perioperative complications in our study may be attributed to the relatively small sample size, and further investigation with larger sample sizes is needed to better understand whether these findings are independent risk factors for stoma-related complications. A multicenter randomized trial comparing early versus late stoma reversal demonstrated that the incidence of stoma-related complications, including parastomal hernia, was higher in the late reversal group. The study also confirmed that early stoma reversal in rectal cancer patients was safe and effective in reducing complication risks and improving quality of life.[22] Consistent with the findings of our study, the incidence of stoma-related complications increased as the duration of stoma use was prolonged. Furthermore, our study also confirmed that in high-risk stage III rectal cancer patients, stoma reversal after completing chemotherapy was associated with longer survival. Therefore, while striving to extend survival, stoma-related complications are an unavoidable consequence. The timing of stoma reversal should be carefully selected based on individual patient factors.

This study has several limitations. First, the definition of the chemotherapy regimen may change as clinical guidelines evolve. The chemotherapy regimen used in this study was based on the 2018 NCCN colorectal cancer guidelines, and there are some differences from the current adjuvant therapy protocols for rectal cancer due to continuous updates in the guidelines. Second, this study is a retrospective observational study with a relatively small sample size, particularly in the After group, which underwent stoma reversal after completing chemotherapy. This may be influenced by early surgeons' perspectives on the timing of stoma reversal and patient preferences. Therefore, larger prospective studies are needed to confirm these findings further. The optimal timing for protective ileostomy reversal is a topic that warrants further investigation, particularly since most rectal cancer patients undergoing curative resection require scheduled adjuvant chemotherapy within a specific time frame. It is crucial to avoid other factors that may negatively affect patient survival, providing guidance for clinical practice.

Conclusion

Reversing the stoma before completing chemotherapy does not have a significant impact on overall survival in the general population of patients with stage II–III rectal cancer. However, it may negatively affect survival in high-risk stage III patients. Stoma reversal after the completion of adjuvant chemotherapy is associated with improved survival outcomes, but the prolonged duration of stoma use may lead to an increased incidence of stoma-related complications. Therefore, for high-risk stage III patients, stoma reversal after completing chemotherapy may be considered, but careful management of stoma-related complications is essential. Prospective randomized controlled trials are needed to further confirm these findings, particularly for this subset of patients.

Data Sharing Statement

Data is available on reasonable request. The data supporting the study's conclusions are accessible from the corresponding author upon reasonable request. (Jianguo Li, Email: jianguo_zmu@163.com).

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Zunyi Medical University (Ethics Approval No. KLLY-2023-075). Informed consent from the participants was waived by the institutional review board. According to China's Measures for Ethical Review of Life Science and Medical Research Involving Human Beings, this study was conducted by retrospectively observing while not interfering with data generated by patients' behaviors, and the information kept by the investigators would not identify patients, which is in line with exemptions from ethical review described in the Measures.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was funded by the National Natural Science Foundation of China (81960105), Medical Research Union Found for High-quality health development of Guizhou Province (2024GZYXKYJJXM0155), and the Training Plan for Clinical Famous Doctors of Zunyi Medical University (RC220230405).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Lee BC, Lim SB, Lee JL, et al. Defunctioning protective stoma can reduce the rate of anastomotic leakage after low anterior resection in rectal cancer patients. *Ann Coloproctol*. 2020;36(3):192–197. doi:10.3393/ac.2019.11.19.1
2. Wang FG, Yan WM, Yan M, et al. Comparison of anastomotic leakage rate and reoperation rate between transanal tube placement and defunctioning stoma after anterior resection: a network meta-analysis of clinical data. *Eur J Surg Oncol*. 2019;45(8):1301–1309. doi:10.1016/j.ejso.2019.01.182
3. Keane C, Park J, Oberg S, et al. Functional outcomes from a randomized trial of early closure of temporary ileostomy after rectal excision for cancer. *Br J Surg*. 2019;106(5):645–652. doi:10.1002/bjs.11092
4. Elsner AT, Brosi P, Walensi M, et al. Closure of temporary ileostomy 2 versus 12 weeks after rectal resection for cancer: a word of caution from a prospective, randomized controlled multicenter trial. *Dis Colon Rectum*. 2021;64(11):1398–1406. doi:10.1097/DCR.0000000000002182
5. Tramontano S, Sarno G, Iacone B, et al. Early versus late closure of protective loop ileostomy: functional significant results in a preliminary analysis. *Minerva Surg*. 2024;79(4):435–442. doi:10.23736/S2724-5691.24.10305-X
6. Bausys A, Kuliavas J, Dulskas A, et al. Early versus standard closure of temporary ileostomy in patients with rectal cancer: a randomized controlled trial. *J Surg Oncol*. 2019;120(2):294–299. doi:10.1002/jso.25488
7. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022;20(10):1139–1167. doi:10.6004/jnccn.2022.0051
8. China N H C O T P S R O. Chinese protocol of diagnosis and treatment of colorectal cancer (2023 edition). *Chin J Dig Surg*. 2023;22(6):667–698.
9. Panis Y. Early stoma closure after rectal resection for cancer: still a matter of debate? *Dis Colon Rectum*. 2021;64(11):1303–1304. doi:10.1097/DCR.0000000000002231

10. Cheng HH, Shao YC, Lin CY, et al. Impact of chemotherapy on surgical outcomes in ileostomy reversal: a propensity score matching study from a single centre. *Tech Coloproctol*. 2023;27(12):1227–1234. doi:10.1007/s10151-023-02790-6
11. Malik T, Lee MJ, Harikrishnan AB. The incidence of stoma related morbidity - a systematic review of randomised controlled trials. *Ann R Coll Surg Engl*. 2018;100(7):501–508. doi:10.1308/rcsann.2018.0126
12. Taneja C, Netsch D, Rolstad BS, et al. Risk and economic burden of peristomal skin complications following ostomy surgery. *J Wound Ostomy Continence Nurs*. 2019;46(2):143–149. doi:10.1097/WON.0000000000000509
13. Voegeli DK, Eddes EH, Hansen HD, Zeeberg R, Håkan-Bloch J, Hedegaard CJ. Factors influencing the incidence of peristomal skin complications: evidence from a multinational survey on living with a stoma. *Gastrointest Nurs*. 2020;18(Sup4):S31–S38. doi:10.12968/gasn.2020.18.Sup4.S31
14. Hoshino N, Hida K, Fukui Y, et al. Relationship between diverting stoma and adjuvant chemotherapy in patients with rectal cancer: a nationwide study using the national database of health insurance claims and specific health checkups of Japan. *Int J Clin Oncol*. 2022;27(3):545–552. doi:10.1007/s10147-021-02079-4
15. Zhen L, Wang Y, Zhang Z, et al. Effectiveness between early and late temporary ileostomy closure in patients with rectal cancer: a prospective study. *Curr Probl Cancer*. 2017;41(3):231–240. doi:10.1016/j.currproblcancer.2017.02.007
16. Herrle F, Sandra-Petrescu F, Weiss C, et al. Quality of life and timing of stoma closure in patients with rectal cancer undergoing low anterior resection with diverting stoma. *Dis Colon Rectum*. 2016;59(4):281–290. doi:10.1097/DCR.0000000000000545
17. Massucco P, Fontana A, Mineccia M, et al. Prospective, randomised, multicentre, open-label trial, designed to evaluate the best timing of closure of the temporary ileostomy (early versus late) in patients who underwent rectal cancer resection and with indication for adjuvant chemotherapy: the STOMAD (STOMa closure before or after ADjuvant therapy) randomised controlled trial. *BMJ Open*. 2021;11(2):e044692. doi:10.1136/bmjopen-2020-044692
18. Stoma Committee Of Chinese Physicians Association C P A, Colorectal Surgery Group Of Chinese Medical Association, Chinese Association Of Anorectal Physicians, Chinese Medical Association. Chinese expert consensus on protective ostomy for mid-low rectal cancer (version 2022). *Chin J Gastrointest Surg*. 2022;25(6):471–478. doi:10.3760/cma.j.cn441530-20220421-00169
19. Hajibandeh S, Hajibandeh S, Sarma DR, et al. Meta-analysis of temporary loop ileostomy closure during or after adjuvant chemotherapy following rectal cancer resection: the dilemma remains. *Int J Colorectal Dis*. 2019;34(7):1151–1159. doi:10.1007/s00384-019-03321-2
20. Davis BR, Valente MA, Goldberg JE, et al. The American society of colon and rectal surgeons clinical practice guidelines for ostomy surgery. *Dis Colon Rectum*. 2022;65(10):1173–1190. doi:10.1097/DCR.0000000000002498
21. Sun Z, Zhao Y, Liu L, et al. Clinical outcomes of ileostomy closure before adjuvant chemotherapy after rectal cancer surgery: an observational study from a Chinese center. *Gastroenterol Res Pract*. 2021;2021:5592721. doi:10.1155/2021/5592721
22. Tsai KY, You JF, Huang SH, et al. Comparison of clinical outcomes of stoma reversal during versus after chemotherapy for rectal cancer patients. *Langenbecks Arch Surg*. 2023;408(1):274. doi:10.1007/s00423-023-03014-z
23. Tulchinsky H, Shacham-Shmueli E, Klausner JM, et al. Should a loop ileostomy closure in rectal cancer patients be done during or after adjuvant chemotherapy? *J Surg Oncol*. 2014;109(3):266–269. doi:10.1002/jso.23493
24. Ahmadi-Amoli H, Rahimi M, Abedi-Kichi R, et al. Early closure compared to late closure of temporary ileostomy in rectal cancer: a randomized controlled trial study. *Langenbecks Arch Surg*. 2023;408(1):234. doi:10.1007/s00423-023-02934-0
25. He F, Yang F, Tang C, et al. Clinical outcomes of ileostomy closure during versus after adjuvant chemotherapy in patients with rectal cancer. *Can J Gastroenterol Hepatol*. 2024;2024:2410643. doi:10.1155/2024/2410643
26. Yin TC, Tsai HL, Yang PF, et al. Early closure of defunctioning stoma increases complications related to stoma closure after concurrent chemoradiotherapy and low anterior resection in patients with rectal cancer. *World J Surg Oncol*. 2017;15(1):80. doi:10.1186/s12957-017-1149-9