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ORIGINAL ARTICLE

Impact of chemotherapy on surgical outcomes in ileostomy reversal: a propensity score matching study from a single centre

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Abstract

Purpose In patients with chemotherapy, there is no consensus on the timing of ileostomy closure. Ileostomy reversal could improve the quality of life and minimise the long-term adverse events of delayed closure. In this study, we evaluated the impact of chemotherapy on ileostomy closure and searched for the predictive factors for complications.

Methods We retrospectively analysed 212 patients with rectal cancer who underwent ileostomy closure surgery during and without chemotherapy and were consecutively enrolled between 2010 and 2016. As a result of the heterogeneity of the two groups, propensity score matching (PSM) was performed with a 1:1 PSM cohort.

Results A total of 162 patients were included in the analysis. The overall stoma closure-related complications (12.4% vs. 11.1%, $p = 1.00$) and major complications (2.5% vs. 6.2%, $p = 0.44$) were not significantly different between the two groups. Multivariate analysis demonstrated that chronic kidney disease and bevacizumab use are risk factors for major complications.

Conclusion Patients with oral or intravenous chemotherapy can safely have ileostomy closure with an adequate time delay from chemotherapy. When patients use bevacizumab, major complications related to ileostomy closure should still be cautioned.

Keywords Rectal cancer · Adjuvant chemotherapy · Target therapy · Ileostomy · Stoma · Morbidity · Complication

Introduction

The use of protective ileostomy is effective in safeguarding rectal anastomosis and reducing the incidence of anastomotic leakage and related adverse effects on patient survival [1–3]. However, it is important to consider that the use of stomas can have a significant impact on patients' quality of life, including negative effects on self-image, sexual intimacy, and psychological well-being such as anxiety and depression [4–7]. While clinicians tend to prioritize cancer treatment, patients often have high expectations for stoma closure following cancer treatment. Surgeons typically perform stoma closure at 8–12 weeks post-stoma creation for patients who do not receive chemotherapy, and at the end of the chemotherapy cycle for those who do [8–10]. Adjuvant chemotherapy may cause delays in stoma closure, which has been associated with an increased risk of low anterior resection syndrome and gastrointestinal toxicity, potentially leading to reduced treatment compliance [11–15].

Prior research has yielded conflicting results regarding the impact of chemotherapy on ileostomy closure, with some studies suggesting that closure during chemotherapy can increase complications. To further clarify this issue, the present study aimed to investigate the potential influence of different chemotherapy regimens and determine the optimal interval between completion of chemotherapy and ileostomy closure.

The results of this study have not been submitted for publication elsewhere nor reported at society meetings orconferences.

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Materials and methods

Patients

This retrospective study was approved by the local institutional review board (IRB number CE18031B). All patients who underwent rectal cancer operations and diversion ileostomy between January 2010 and December 2016 were included in our analysis. We divided our patients into two groups: patients who underwent ileostomy closure without chemotherapy (group A) and those who underwent ileostomy closure during chemotherapy (group B). In group B, ileostomy closure was scheduled between two consecutive cycles. The interval between the latest chemotherapy and ileostomy closure was planned for 2 weeks. This study aims to examine the impact of chemotherapy and target therapy on perioperative morbidity during stoma reversal. To accomplish this, we excluded patients with a prolonged interval between their last chemotherapy or target therapy treatment and stoma reversal. For patients who received oral or intravenous chemotherapy, those with an interval greater than 4 weeks between their last chemotherapy cycle and ileostomy closure were excluded from the study. Similarly, for patients who received intravenous chemotherapy in combination with target therapy, those with an interval greater than 6 weeks between their last treatment and stoma reversal were excluded from the study. The purpose of these exclusion criteria was to maximise the potential influence of recent chemotherapy or target therapy on perioperative outcomes. Exclusion criteria were colon cancer, benign diseases (including diverticulitis and ischaemic colitis), emergent operation, malignancy other than adenocarcinoma, gynaecological cancer with colorectal invasion, primary rectal cancer resection in other hospitals, and reversal of ileostomy with concurrent colorectal resection.

Perioperative setting of ileostomy closure

Neoadjuvant chemoradiotherapy was defined as radiotherapy of 50 Gy delivered in 25 fractions of 2 Gy, one fraction per day, and five fractions per week for 5 weeks. Preoperative clinical stage II and III patients had concurrent use of orally administered tegafur 350 mg/m^2 daily. Stage IV patients had concurrent use of oxaliplatin 55 mg/m^2 on day 1 and tegafur 350 mg/m^2 daily every 2 weeks.

The adjuvant chemotherapy started 4–6 weeks after the primary tumour resection. Regimens included tegafur (300–350 mg/m^2/day), capecitabine (1000 mg/m^2, BID), FOLFOX (oxaliplatin, 85 mg/m^2; leucovorin, 400 mg/m^2 for 2 days; 5-FU, 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 over 46 h, continuous infusion, every 2 weeks), FOLFIRI (irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2 on day 1; 5-FU, 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 over 46 h, continuous infusion, every 2 weeks), Xelox (oxaliplatin 85 mg/m^2 on day 1, every 2 weeks, plus capecitabine 850–1000 mg/m^2 twice daily), Xeliri (irinotecan, 140–180 mg/m^2 on day 1, every 2 weeks, plus capecitabine 850–1000 mg/m^2 twice daily 10 days), bevacizumab (5 mg/kg, every 2 weeks) and cetuximab (500 mg/m^2, every 2 weeks).

Before ileostomy closure, the patient underwent either contrast studies or colonoscopy to check the intact anastomosis. The timing of ileostomy closure was decided by the surgeon's preference and according to the patient's general condition. If the patient had no adjuvant chemotherapy, the patient would have ileostomy closure 8–12 weeks after the tumour resection surgery. If the patient had adjuvant chemotherapy, the patient would have ileostomy closure 2–6 weeks after the last chemotherapy (depending on whether bevacizumab was used or not). We performed the anastomosis in the antiperistalsis side-to-side technique with staples.

Outcome measures

Data were extracted retrospectively from the surgical database. Patient demographics, tumour characteristics, pathological results, perioperative morbidity, outcomes, chemotherapy regimen, and chemotherapy duration were collected. We analysed the incidence of complications and classified them by the Clavien–Dindo classification during primary tumour resection and ileostomy closure. Major complications were defined as Clavien–Dindo > 2. Anastomotic stenosis was defined as narrowing of the anastomosis discovered by endoscopy or CT image and patients with either of the following symptoms: obstipation, abdominal fullness, bloating and vomiting. Surgical site infection (SSI) was defined according to the WHO classification. Anastomotic leakage was defined as free gas or fluid from the anastomosis in images. Postoperative ileus is defined as a temporary impairment in gastrointestinal motility following surgery and lasts more than 3 days. Stoma-related complications included stoma prolapse, stenosis, dehydration, peristomal dermatitis, bleeding and infection. Stoma output greater than 1500 ml daily was defined as high.

Statistics

Propensity scores for both the primary and control cohorts were calculated with a multivariate logistic regression model, including sex, age, American Society of Anaesthesiologists status (ASA), body mass index (BMI) and surgical approach. Patients in the two cohorts were matched 1:1 with a maximum difference between propensity scores

of 0.1. Continuous variables were expressed as the median and interquartile range (IQR) and compared using the Mann–Whitney test or Kruskal–Wallis test. Dichotomous data were compared using the chi-square test or Fisher's exact test and reported as absolute numbers and percentages (%). Receiver operating characteristic (ROC) curves are used to determine the optimal interval cut-off value. $P < 0.05$ was considered significant. Logistic regression was used to explore the relationship between the risk factors and post-stoma reversal complications. Potential confounders were those that showed a univariate relationship with the outcome at $p \leq 0.1$. These factors were included in the multivariate logistic regression. All calculated p values were two-sided, and p values < 0.05 were considered statistically significant. The results were reported as odds ratios (ORs) and 95% confidence intervals (95% CIs). Statistical analysis was performed using MedCalc Statistical Software version 15.8 (MedCalc Software, Ostend, Belgium).

Results

A total of 212 consecutive patients underwent loop colostomy or loop ileostomy closure during the study period. Of these, 113 patients (53.3%) had ileostomy closure without chemotherapy, and 99 patients (46.7%) had ileostomy closure during chemotherapy. The median follow-up was 40.2 months. After propensity score matching, there were 81 patients in each group for analysis. There was no significant difference between the two groups in sex, age, ASA classification, BMI, surgical approach or underlying disease. Group B had higher carcinoembryonic antigen (CEA) levels and increased advanced clinical and pathological TNM stage (Table 1). Twenty-eight (34.6%) and ten patients (12.3%) in groups A and B received neoadjuvant chemoradiotherapy. Ten of 28 patients in group A had a complete pathological response. Five (6.2%) and one (1.2%) patients in groups A and B had loop ileostomy following rectal anastomotic leakage. Eleven patients in group A and two patients in group B (13.6% vs. 2.5%, $p = 0.02$) experienced stoma-related complications, including high output (3.7%), bleeding (0.6%), peristomal dermatitis (2.5%) and stenosis (1.2%) (Table 2).

At the time of ileostomy closure, group A had a shorter time from ileostomy creation to closure (95 vs. 119 days, $p < 0.01$) (Table 3). There was no significant difference in the time to resumption of a soft diet and postoperative hospital stay between the two groups. There was no 30-day surgical mortality. The total incidence of postoperative complications in groups A and B was 12.4% and 11.1%, respectively ($p = 1.00$). The incidence of major postoperative complications (a Clavien–Dindo score > 2) in groups A and B was 2.5% and 6.2%, respectively ($p = 0.44$). There was one case of anastomotic leakage in each group; in group A, the patient

Table 1 Patient characteristics and demographics

	No chemotherapy (group A) ($n = 81$)		During chemotherapy (group B) ($n = 81$)		p
Gender					0.87
Male	53	65.4%	51	63.0%	
Female	28	34.6%	30	37.0%	
Age	62.7	52.8–75.0	60.3	51.8–68.0	0.24
BMI	23.9	21.5–25.9	23.9	21.8–25.8	0.98
ASA score > 2					0.54
No	64	79.0%	68	84.0%	
Yes	17	21.0%	13	16.0%	
Tumour location (above anal verge)	6	5.0–7.0	6	5.0–9.3	0.26
CEA levels > 5					< 0.01
No	58	71.6%	40	49.4%	
Yes	23	28.4%	41	50.6%	
Neoadjuvant therapy					< 0.01
No	53	65.4%	71	87.7%	
CCRT	28	34.6%	10	12.3%	
Clinical stage					< 0.01
0	10	12.3%	0	0.0%	
1	8	9.9%	2	2.5%	
2	33	40.7%	10	12.3%	
3	27	33.3%	55	67.9%	
4	3	3.7%	14	17.3%	
Pathological stage					< 0.01
0	15	18.5%	0	0.0%	
1	19	23.5%	3	3.7%	
2	24	29.6%	13	16.0%	
3	20	24.7%	51	63.0%	
4	3	3.7%	14	17.3%	
Primary tumour approach					0.74
Laparoscopy	54	66.7%	57	70.4%	
Open	27	33.3%	24	29.6%	
HTN					1.00
No	54	66.7%	55	67.9%	
Yes	27	33.3%	26	32.1%	
DM					0.40
No	72	88.9%	76	93.8%	
Yes	9	11.1%	5	6.2%	
CKD					1.00
No	79	97.5%	80	98.8%	
Yes	2	2.5%	1	1.2%	
CAD					0.68
No	78	96.3%	78	96.3%	
Yes	3	3.7%	3	3.7%	
Arrhythmia					1.00
No	80	98.8%	79	97.5%	
Yes	1	1.2%	2	2.5%	

BMI body mass index, *ASA* American Society of Anaesthesiologists, *CCRT* concurrent chemoradiotherapy, *CEA* carcinoembryonic antigen, *HTN* hypertension, *DM* diabetes mellitus, *CKD* chronic kidney diseases, *CAD* coronary artery disease

Table 2 Stoma-related complications

	No chemotherapy (group A) ($n=81$)		During chemotherapy (group B) ($n=81$)		p
Stoma complication	11	13.6%	2	2.5%	0.02
High output	5		1		
Stoma bleeding	1		0		
Peristomal dermatitis	3		1		
Stoma stenosis	2		0		

had reoperation of ileocaecal resection to reconstruct the anastomosis on postoperative day 4; in group B, the patient had reoperation of bypass and drainage of intra-abdominal abscess on postoperative day 8. Four patients in group B experienced anastomotic stenosis. Three of them had segmental resection of the small bowel, and one of them had ileocaecal resection. The median interval to reoperation of these four patients was 16.5 days. Six and nine patients in groups A and B had readmission within 30 days. In group A, the cause of readmission included three cases of ileus (2), frequent bowel movements with electrolyte imbalance (3) and cholecystitis (1). In group B, the cause of readmission included three cases of ileus (3), poor wound healing (2), pneumonia (1), urinary tract infection (1) and frequent bowel movement with electrolyte imbalance. Incidence of late morbidity (> 90 days) was 6.2% and 9.9% ($p=0.77$) in groups A and B, respectively.

Comparing the different chemotherapy regimens, 44 patients (54.3%) received intravenous (IV) chemotherapy, 12 (14.8%) received intravenous chemotherapy plus targeted therapy and 25 (30.1%) received oral chemotherapy. The detailed regimens are shown in Table 4. The time between ileostomy creation and ileostomy reversal in patients with IV chemotherapy and IV chemotherapy plus targeted therapy was significantly delayed compared to those without chemotherapy (126 vs. 208 vs. 95 days, $p<0.01$). The time from the last chemotherapy was shorter in the oral chemotherapy group than in the IV chemotherapy and chemotherapy plus target therapy groups (4 vs. 18 vs. 25 days, $p<0.01$). There was no difference in the postoperative complications in each group (12.0% vs. 9.1% vs. 16.7%, $p=0.75$). IV plus targeted therapy resulted in more major complications (16.7%) than the other two groups, but the difference was not significant. The percentage of patients who resumed treatment after ileostomy closure was 72.0%, 86.4%, and 83.3% in each group ($p=0.10$). A higher proportion of patients (28.0%) who received oral chemotherapy did not continue the future treatment. There was no difference in the time from ileostomy closure to the resumption of chemotherapy (27 vs. 27 vs. 25 days, $p=0.75$).

We created a receiver operating characteristic (ROC) curve by using the interval periods between the latest

Table 3 Postoperative outcomes of ileostomy reversal

	No chemotherapy (group A) ($n=81$)		During chemotherapy (group B) ($n=81$)		p
Stoma creation to closure (days)	95	77–120	119	91–146	< 0.01
Postoperative hospital stay (days)	7	6–8	7	6–8	0.58
Stoma reversal to resume soft diet (days)	5	5–7	5	5–6	0.37
Postoperative complication	10	12.4%	9	11.1%	1.00
Postoperative ileus	4		2		0.68
Superficial SSI	2		1		
Anastomosis leakage	1		1		
Anastomosis stenosis	0		4		
Urinary tract infection	2		0		
Pneumonia	1		2		
Reoperation	1	1.2%	5	6.2%	0.21
Major complications*	2	2.5%	5	6.2%	0.44
Readmission within 30 days	6	7.4%	9	11.1%	0.59
Late morbidity (> 90 days)	5	6.2%	6	9.9%	0.77
Ileus	2		1		
Delayed leakage	1		0		
Incisional hernia	2		4		
Anastomosis stenosis	0		1		

SSI surgical site infection

*Major complications: Clavien-Dindo score > 2

Table 4 Relationship between different regimens and perioperative outcomes

	Oral 5-FU ($n=25$)		Intravenous ($n=44$)		Intravenous + target ($n=12$)		p
Regimen	Tegafur = 20 Capecitabine = 5		FOLFOX/Xelox = 42/2 Xeliri = 2		FOLFOX/FOLFIRI = 1:11 Cetuximab/bevacizumab = 2:10		
Median cycle	6 weeks	4.0–6.5	6.0	4.0–6.8	7.0	5.5–12.0	
Stoma creation to closure (days)	85	68–94	126	107–147	208	126–282	< 0.01
Last chemotherapy to closure (days)	4	2–8	18	12–20	25	15–32	< 0.01
Postoperative complication	3	12.0%	4	9.1%	2	16.7%	0.75
Major complications*	0	0.0%	3	6.8%	2	16.7%	0.14
Post-stoma reversal chemotherapy							0.10
Yes	18	72.0%	38	86.4%	10	83.3%	
No (chemotherapy intolerance)	7	28.0%	3	6.8%	1	8.3%	
No (treatment completed)	0	0.0%	3	6.8%	1	8.3%	
Discharge to resume chemotherapy (days)	27	12–37	27	21–38	25	17–29	0.75

FOLFOX leucovorin, 5-FU, and oxaliplatin, *FOLFIRI* leucovorin, 5-FU, and irinotecan, *Xelox* capecitabine and oxaliplatin, *Xeliri* capecitabine and irinotecan

*Major complications: Clavien-Dindo score > 2

chemotherapy and ileostomy closure and the absence of complications as the test variable in the different regimens.

In oral chemotherapy, the cut-off point was 3 days with an area under the curve of 0.50 ($p=1.00$, sensitivity 33%, specificity 45%). In IV chemotherapy, the cut-off point was 22 days with an area under the curve of 0.57 ($p=0.70$, sensitivity 100%, specificity 22%). In IV chemotherapy plus targeted therapy, the cut-off point was 33 days with an area under the curve of 0.85 ($p=0.70$, sensitivity 100%, specificity (80%) (Fig. 1).

Univariate and multivariate analyses were performed to identify risk factors for overall post-closure complications and major post-closure complications (Table 5). An ASA score > 2, DM history and major complications after primary tumour resection were associated with overall postoperative complications. In the multivariate analysis, an ASA score > 2 ($p=0.01$) and having major complications after primary tumour resection ($p=0.01$) were risk factors for overall post-closure complications.

BMI, diabetes mellitus (DM) history, chronic kidney disease (CKD) history and bevacizumab use were associated with major post-closure complications. In the multivariate analysis, CKD history ($p=0.03$) and bevacizumab use ($p=0.01$) were risk factors for major post-closure complications.

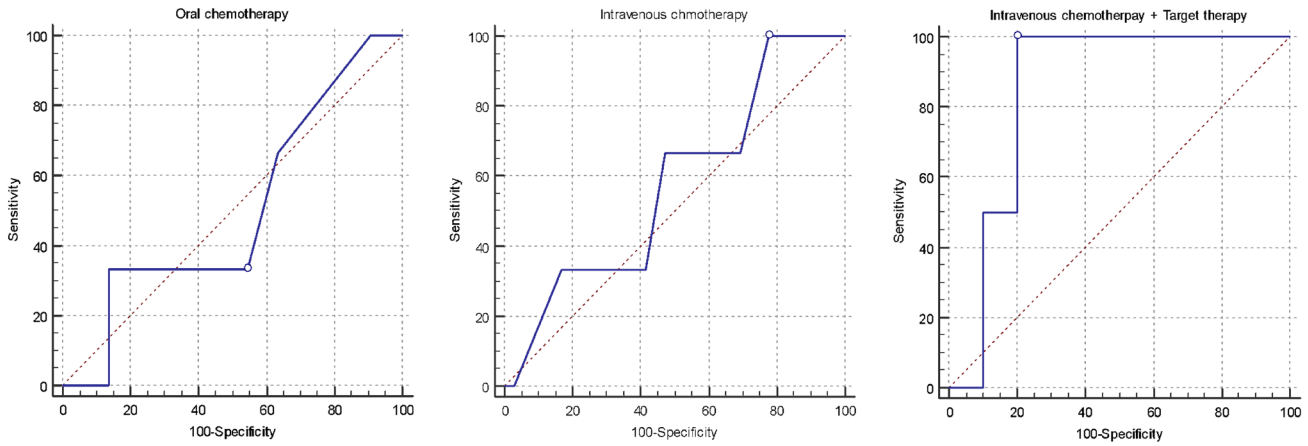

Fig. 1 Comparison of ROC curves correlating the time from the last round of chemotherapy to reversal with postoperative complications in the different regimens. When using intravenous chemotherapy with targeted therapy, intervals greater than 33 days were associated with an increased risk of postoperative complications (AUC 0.85, sensitivity 100%, specificity 80%, $P<0.01$)

Table 5 Univariate and multivariate analysis of factors associated with all complications and major complications

	Univariate			Multivariate		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Postoperative all complications						
ASA > 2	4.00	1.45–11.07	0.01	4.26	1.48–12.27	0.01
DM	3.55	0.99–12.71	0.05			
Major complication after tumour resection	4.75	1.42–15.87	0.01	5.18	1.46–18.38	0.01
Postoperative major complications						
BMI	1.21	1.00–1.47	0.06			
DM	4.77	0.83–27.22	0.08			
CKD	12.75	1.01–160.9	0.05	18.25	1.36–245.2	0.03
Bevacizumab use	8.46	1.39–51.50	0.02	10.43	1.62–66.93	0.01

ASA American Society of Anaesthesiologists, *DM* diabetes mellitus, *CKD* chronic kidney diseases, *BMI* body mass index

Discussion

In this study, we analysed the impact of chemotherapy regimens on ileostomy reversal. The study confirmed that the incidence of postoperative complications is not higher in ileostomy closure during chemotherapy. In addition, the study also identified bevacizumab as an independent risk factor for major post-reversal complications.

In previous studies, adjuvant chemotherapy was a risk factor for delayed stoma closure and non-closure [8, 16, 17]. Thalheimer et al. [18] first described the impact of chemotherapy on stoma closure, and they reported increased minor complications in the adjuvant chemotherapy groups (25.5% vs. 9.2%). Fok et al. [19] showed that adjuvant chemotherapy is associated with a higher risk of wound complications and incisional hernia. Several studies have reported that 5-FU and oxaliplatin negatively affect anastomotic integrity, adhesion formation and inflammatory reactions [20–24]. These studies were based on animal models. The administration route was intraperitoneal, and the animal was killed approximately 1 week later. As the protocol was different from the current practices in humans, those results could not be extrapolated to humans. Bevacizumab is an antiangiogenic and antimitotic agent that increases anastomotic leakage and surgical wound complications [25, 26]. The US Food and Drug Administration (FDA) suggested delaying surgery for 28 days after bevacizumab usage [27]. In our study, we provided new evidence in this biological era. The postoperative complication rates were 12.0%, 9.1% and 16.7% in the oral, IV and IV plus target therapy groups, respectively, and these results were comparable to the no chemotherapy group (12.4%).

The optimal interval between chemotherapy and ileostomy closure was an important issue.

The use of chemotherapy before surgery may reduce patients' general physical condition, and the toxicity from chemotherapeutic agents can induce an immunocompromised state. There was no recommendation for the interval. Several randomised trials have focused on neoadjuvant therapy in patients with metastatic colon cancer [28, 29]. In these studies, surgery could be carried out 3–4 weeks after neoadjuvant therapy without increasing surgical morbidity. In our study, the median interval of the IV chemotherapy group was 18 days, and it achieved a non-inferior complication rate compared with the no chemotherapy group. The complication rate in the oral chemotherapy group was higher than expected. This might contribute to shorter intervals between chemotherapy and surgery. The median interval of the IV chemotherapy plus targeted therapy group was 25 days. The incidence of complications is still high, especially for major complications. The ROC curve identified that 33 days might be a more suitable delay to decrease postoperative complications in the IV chemotherapy plus targeted therapy group. These patients should thoroughly know the benefits and harms of ileostomy closure and continuing chemotherapy. This study showed that 81.4% of patients were able to resume chemotherapy after the procedure. The interval between the discharge after stoma reversal and resumption of chemotherapy was approximately 1 month. This finding may suggest that the patients who underwent stoma reversal experienced fewer surgical complications, as evidenced by their ability to continue chemotherapy. This finding is particularly relevant as chemotherapy can increase the risk of surgical complications due to its effect on the immune system and wound healing. The study results suggest that stoma reversal may be a safe and viable option for patients undergoing chemotherapy, and that the procedure is associated with acceptable risks.

Recent studies compared stoma closure during and after chemotherapy [18, 30–34] and confirmed that the complication rate was similar in both groups. According to the meta-analysis by Hajibandeh et al. [35], in the group during

chemotherapy, the incidence of overall complications, anastomotic leakage, SSI and ileus was 19.5%, 1.9%, 8.8% and 6.3%, respectively, and the hospital stay was 6.9 days. In our study, the incidence of overall complications, anastomotic leakage, SSI and ileus was 11.1%, 1.2%, 1.2% and 2.5%, and the hospital stay was 7 days. The postoperative results and leakage rates are comparable. The low incidence rate of SSI may be attributed to ileostomy's low infection rate. Furthermore, we applied only loose nylon sutures to the skin layer, and fluid did not accumulate in the subcutaneous layer.

Limitations

The current study was limited by its retrospective nature with selection bias. Surgeons' preferences and the patient's desires influence the timing of the closure, and these could not be analysed in this study. In addition, the optimal number of cycles before stoma closure is unknown regarding oncological outcomes for the patient. Nutritional status evaluation before stoma reversal is not part of our current practices, so the actual nutritional status is unspecified. In our study, most patients had stoma closure during chemotherapy instead of at the end of treatment. We could not compare these two groups because of the small sample size. Future studies could provide better insight into this issue, including functional assessment with objective scoring systems and survival outcome comparisons.

Conclusion

In patients with rectal cancer undergoing chemotherapy, the incidence of stoma closure-related complications was not higher than in the non-chemotherapy group. Patients with oral or IV chemotherapy could undergo ileostomy closure safely with an adequate delay after chemotherapy. High-risk groups of major complications, including CKD history and bevacizumab usage, are often associated with reoperation or prolonged hospital stay, and these would potentially hinder future procedures. Ileostomy reversal is recommended at the end of treatment.

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Declarations

Conflict of interest All authors declare no conflicts of interest.

Ethical approval This study was approved by the local institutional review board (IRB number CE18031B).

Consent for publication Informed consent was not required for this retrospective cohort study.

Research involving human and animal participants The data that support the findings of this study are not available on request from the corresponding author (HHC). The data are not publicly available due to compromising the privacy of research participants.

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