Is better early closure compared to late closure of temporary ileostomy in rectal cancer? A randomized controlled trial study

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Abstract

Purpose

A temporary loop ileostomy is one of the most common methods for the prevention of anastomotic leakage in rectal cancer patients who underwent low anterior resection. However, the optimal timing of loop ileostomy reversal remains unknown. The main purpose of this study is to assess the suitable time for a reversal of temporary loop ileostomy in rectal cancer patients.

Methods

We conducted a prospective, randomized trial at Sina Hospital, Tehran, Iran from 2020 to 2021 to determine the appropriate time for closure of temporary loop ileostomy in rectal cancer patients who underwent low anterior resection.

Results

The results of this prospective randomized controlled trial are as shown: significantly difference in body mass index, the time interval between creation and closure of stoma, and distance from last chemotherapy. No significant difference was found between the two groups in terms of complications based on the Clavien-Dindo classification. As well as, there is no significant difference in perioperative outcomes, such as blood loss, operative time, re-admission, and re-operation. Also, statistically significant differences had reported between patients' quality of life and LARS score.

Conclusion

In summary, it seems that early closure of ileostomy is generally effective and safe in reducing the risk of complications and improving quality of life in patients with rectal cancer following low anterior resection and chemotherapy (neoadjuvant and adjuvant).

Trial registration number and date of registration:

IRCT20201113049373N1 (January 2,2021)

Introduction

Definitive treatment in patients with stage two or higher non-metastatic rectal cancer or involving perirectal fat or lymph node is neo-adjuvant (chemotherapy-radiation) and then surgery [1, 2]. The choice of surgical procedure is low anterior resection (LAR) [1]. A very serious problem after rectal cancer surgery

and radiation is anastomotic leakage, which is prevented by a temporary protective loop ileostomy [1]. A loop ileostomy is one of the most common techniques used to divert fecal and protect the anastomosis, however, ileostomy affects the patient's performance both mentally and physically and affects various aspects of life including: social, cultural, religious, sexual and can lead to depression in patients it over-shadows the quality of life (QOL) of patients [3, 4]. Therefore, it is important to close it soon [5]. On the other hand, it does have complications ranging from 14–79%. Complications of ileostomy include two main categories: early and late [3]. Early complications occurred within three months of stoma creation, including abscess formation, wound infection, bleeding, stomal necrosis, stomal retraction, mucocutaneous separation, and peristomal skin breakdown [6]. Late complications that occurred after three months include stomal stenosis, prolapse, parastomal herniation, fistula formation, and negative psychological effects [6].

Based on mentioned points and negative effects on patients' quality of life, a quicker reversal can be beneficial and lead to patients more satisfied [6, 7]. The optimal timing of loop ileostomy reversal remains largely unknown, but delayed ileostomy closure may increase postoperative complications. Few studies have evaluated the QOL of patients who reversed ileostomy several months after primary surgery [6]. We assessed QOL based on a questionnaire (sf-36) [4]. No study evaluates the effect of early or late closure of ileostomy on LARS score. We prospectively assessed the QOL patients, LARS score and its relation to early or late closure of the ileostomy. Thus, this study aimed to determine the appropriate time for ileostomy closure with minimal complications and the most satisfaction, in which compared early and late closure.

Methods

We designed a prospective, randomized controlled trial study from a single colorectal institution, a university-affiliated teaching hospital in Tehran, the public sector between 2021. Patients with stage two or three non-metastatic rectal adenocarcinoma that undergone neoadjuvant radiotherapy followed by LAR and total mesorectal excision (TME), then adjuvant chemotherapy were enrolled.

All operations were performed by an experienced surgical team, using a uniform technique. This study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS). The ethics code is IR.TUMS.MEDICINE.REC.1396.3145. It should also be noted that this study is recorded in the Iranian register of controlled trials (IRCT) which the IRCT code is IRCT20201113049373N1. Patients entered the study with informed consent, without coercion and voluntarily.

The eligibility criteria included: 1) confirmed diagnosis of stage two or three non-metastatic rectal adenocarcinomas; 2) patients undergoing neo-adjuvant radiotherapy, followed by LAR and loop ileostomy; 3) complete patients data. The exclusion criteria included patients with a history of inflammatory bowel disease (IBD), contraindication to adjuvant chemotherapy, uncompleted chemo/radiotherapy, advanced disease stage 4 under neo-adjuvant chemo/radiotherapy, and immunocompromised patients

In total, 104 patients with rectal cancer that had undergone neo-adjuvant radiotherapy, followed by LAR and temporary protective loop ileostomy and received adjuvant chemotherapy (FOLFOX protocol) after surgery were included in this study. Patients received 25 courses of neo-adjuvant radiotherapy over 5 weeks (45Gy), then underwent surgery after (6–8) weeks. The surgical method is LAR and TME, then loop ileostomy is inserted. FOLFOX is a chemotherapy regimen for the treatment of colorectal cancer, consisting of the drugs Folinic acid (leucovorin) "FOL", Fluorouracil (5-FU) "F", and Oxaliplatin (Eloxatin) "OX. After surgery, all the patients underwent ERAS protocols that include: pain control with non-opioid analgesics, early onset of fluids, and early out of bed. In fact, in the post of date (POD) 1, semi-solid regimen and POD2, a regular regimen is begun.

The patients were randomly divided into 54 (51.92%) in the control group (late closure of loop ileostomy) and 50 (48.07%) in the case group (early closure of loop ileostomy).

All patient's data were obtained prospectively. In early closure of loop ileostomy, reverse 2–3 weeks after receiving two courses of adjuvant chemotherapy [8], while in late closure, ileostomy returns 2–3 weeks after the end of adjuvant chemotherapy. All patients underwent a gastrografin enema and CT scan before the second surgery to reverse the ileostomy. The method of closure is similar in both groups and is as follows: by an elliptical incision around of ostoma, and the small bowel loop is released, then the side to side anastomosis is established by a linear cutter Ethicon stapler 75. Patients of the case group will continue adjuvant chemotherapy after (2–3) weeks of second surgery (clousre).

It is noted that the surgical team, courses of neoadjuvant and adjuvant chemotherapy, method of ileostomy's closure, pre-operative and post-operative care (ERAS protocol) are similar in both groups. Also, all the patients receive preoperative prophylactic antibiotics.

Patients were evaluated for postoperative complications in two groups based on a clivian-Dindo classification [10], QOL (36-sf questionnaire) [11], LARS score, mortality and recurrence rate over one year after surgery.

Statistical analysis

The statistical results were compared using the x_2-test or Fisher exact test and the comparative value of the data was considered significant with $P < 0.05$. In this study, independent t and chi-square tests were used. In judging the results of statistical tests, the quorum of the first type of error to accept the relationship or statistically significant difference was less than 5% alpha and in some cases, As required, a 95% confidence interval for the statistics has been calculated and reported.

Results

Out of 104 patients with rectal cancer were included in this study, 54 (51.92%) of whom were in the control group (late closure), whereas 50 (48.07%) were in the case group (early closure).

Demographic data of patients

Of the 104 patients, 62 (59.61%) were males and 42 (40.38%) were female, who were similarly distributed in the two groups (P = 0.451). The age of the participants ranged from 35 to 83 in the control group and from 27 to 81 in the case group and their mean age of patients was 63.18 ± 1.49 and 63.2 ± 1.70, respectively; but there was no significant difference (P = 0.757). Two groups only have a significant difference in BMI (P = 0.030), distance from last chemotherapy (P < 0.001) and interval time between creation and closure of stoma (P < 0.001). No significant differences were observed in other items between the two groups. Lower rectum tumors were more common in the control group, although no difference was in tumor's location between the two groups (P = 0.251). The patient's demographic data are summarized in Table 1.

Table 1
Demographic and clinical data of patients.

		Control group (N = 54)	Case group (N = 50)	P-value
Age (mean ± SD)		**63.18 ± 1.49**	63.2 ± 1.70	0.757
Gender	Female: 42 Male: 62	Female: 21 (38.9%) Male: 33 (61.1%)	21 (42%) 29 (58%)	0.451
BMI (mean ± SD)		23.79 ± 0.35	23.11 ± 0.41	0.030
Habitual history	Smoke: 48 Opium: 19 No: 37	24 (44.4%) 11 (20.4%) 19 (35.2%)	24 (48%) 8 (16%) 18 (36%)	0.895
ASA class	ASA1: 45 ASA2: 43 ASA3: 16	23 (42.6%) 23 (42.6%) 8 (14.8%)	22 (44%) 20 (40%) 8 (16%)	0.987
Distance of tumor from the anal verge (cm) (mean ± SD)		5.84 ± 0.31	6.37 ± 0.33	0.172
Location of tumor	Upper rectum: Mid rectum: Lower rectum:	4 (7.4%) 26 (48.1%) 24 (44.4%)	5 (10%) 30 (60%) 15 (30%)	0.251
T	T2: 7 T3: 84 T4: 13	4 (7.4%) 44 (81.5%) 6 (11.1%)	3 (6%) 40 (80%) 7 (14%)	0.616
N	N0: 42 N1: 62	22 (40.75%) 32 (59.25%)	20 (40%) 30 (60%)	0.79
Stage of disease	Stage 2:29 Stage 3:75	15 (27.8%) 39 (72.2%)	14 (28%) 36 (72%)	0.576
Type of surgery	Open: Laparoscopy:	42 (77.8%) 12 (22.2%)	35 (70%) 15 (30%)	0.248

	Control group (N = 54)	Case group (N = 50)	P-value
CEA	Primary:1.47 ± 0.11 Third month: 0.39 ± 0.57 Six month:0.42 ± 0.58 One year after closure:0.45 ± 0.59	1.36 ± 0.12 0.308 ± 0.58 0.36 ± 0.057 0.402 ± 0.56	0.425 0.171 0.245 0.407
The time interval between creation and closure of stoma(week) (mean ± SD)	29.88 ± 0.26	9.14 ± 0.137	< 0.001
Distance from last chemotherapy(week) (mean ± SD)	3.53 ± 0.81	2.36 ± 0.48	< 0.001
Operative time(min) (mean ± SD)	53.72 ± 0.96	52.04 ± 0.96	0.159
Rate of blood loss during surgery(cc) (mean ± SD)	5.92 ± 0.56	6.64 ± 0.54	0.238
Duration of hospitalization(day) (mean ± SD)	4.46 ± 0.46	4.22 ± 0.49	0.335
Re-admission during the first 30 days(N)	1	2	
Re-operation(N)	2	0	
Interval for resuming the diet	1.07 ± 0.26	1.06 ± 0.23	
Next chemotherapy(day) (mean ± SD)	0	17.9 ± 2.63	

Perioperative outcomes of ileostomy closure

No significant differences were observed in preoperative outcomes of ileostomy closure, including operative time, blood loss, postoperative hospitalization, and interval for resuming diet. None of the patients with early closure did have re-admission or re-operation during the first 30 days after primary surgery; while re-admission and re-operation occurred in one and two patients with late closure, respectively. The related data are shown in Table 1.

Comparison of post-operation complication after ileostomy closure between two groups

We evaluated the complications into two groups and compared them between the two groups:

1. Post-operative complications: It should be noted that these complications were assessed based on the Clavien-Dindo classification, consisting of 7 grades (I, II, IIIa, IIIb, IVa, IVb and V) [10], (Table 2). Post-operative complications showed no significant difference in the case group compared to the control group (P = 0.294) (Table 2). According to the Clavien-Dindo classification, 10 (9.6% of all patients) of the complications were rated as Clavien I, 11 (10.57% of all) as Clavien II, 3 (2.88% of all) as Clavien IIIa, 2 (1.92% of all) as Clavien IIIb. No Clavien grade IVa, IVb, and V complications occurred over the period under investigation. The related data are summarized in Table 2.

Table 2
Frequency of Clavien-Dindo grades after ileostomy closure between two groups.

Grade	Control group (N = 54)	Case group (N = 50)	Total (N = 104)	P-value	Percentage overall (%; N = 104)	Of complications (%; N = 26)
None	36	40	76	0.294	73.07	-
I	6	4	10		9.61	38.46
II	7	4	11		10.57	42.30
IIIa	1	2	3		2.88	11.53
IIIb	2	0	2		1.92	7.69

Table 3 presents the most common complications and their treatment that these complications are based on the grading of the Clavien-Dindo questionnaire. Management of all complications in the early closure group was medical, but surgery was also used in the other group. Medical treatment was similar in both groups, which is as follows: Bedside wound drainage for superficial SSI; Bedside drainage associated antibiotic therapy for deep SSI due to cellulite; NPO, fluid and electrolyte management, and TPN for ileus; Drainage under ultrasound-guided along with antibiotic therapy and implanting drain for intra-abdominal abscess; Drainage under ultrasound-guided with implanting drain for hematoma. Leakage anastomotic and obstruction due to anastomotic stenosis, related to grade IIIb, were observed in the late closure group, that underwent surgical treatment. One patient also had leakage anastomotic related to grade II, which managed conservative and occurred in patients with late closure. In the control group, we had one re-admission and two re-operation that was due to anastomotic stenosis and leakage because of peritonitis.

Table 3
Most common complications and their treatment

Grade	Complication	Control group	Case group	Treatment
I	1. Superficial SSI	**5**	4	Bedside wound drainage
	2. Wound dehiscence	**1**	0	Conservative
II	1. Ileus	5	3	Conservative
	2. Anastomotic leakage	1	0	Conservative
	3. Deep SSI	1	1	Bedside drainage & Antibiotic
IIIa	1. Intra-abdominal abscess	1	1	Percutaneous drainage & Antibiotic
	2. Hematoma	0	1	Percutaneous drainage
IIIb	1. Anastomotic leakage	1	0	Surgery
	2. Obstruction due to leakage	1	0	Surgery

1. Complications associated with an ostomy after primary surgery that including Para-stomal hernia, stomal prolapse and stenosis, stomal retraction, para-stomal skin excoriation, high output acute kidney injury, and electrolyte disturbances (Table 4).

Table 4
Comparison ostomy complications between groups

Complications	Control group	Case group	Total	P-value
Para-stomal hernia	2	-	2	0.555
Stomal stenosis	1	-	1	
Stomal prolapse	1	-	1	
Skin excoriation	2	3	5	
Electrolyte disturbances	1	2	3	

We followed the patients for a year and after a year we also examined the recurrence and mortality rates. During the one-year follow-up, despite that there was both a recurrence and mortality in the control group, there was no statistically significant difference between the two groups (P = 0.348).

Low anterior resection syndrome score

Overall, 27 patients reported major LARS (25.96%; 10 in the early group and 17 in the late group), 33 reported minor LARS (31.73%; 15 and 18 participants respectively) and 44 reported no LARS (42.30%; 22 and 22 participants respectively). The results were similar and don't show differences between groups (P = 0.356).

Quality of life

Patients' quality of life (QOL) was assessed based on the Persian version of questionnaire short form 36 [11]. The quality of life scores on sf-36 improved after ileostomy closure. SF-36 scores were significant differences in mental health before closure (Table 2).

To determine whether Lars affects patients' QOL, we assessed the association between them. All of the domains QOL of SF-36 had significant differences with LARS score between two groups (P < 0.05). In addition, we compared each score of LARS with two others, and its association with QOL. There was no significant difference only in the comparison of minor and major scores and their relationship with QOL (P > 0.05) (Table 5).

Table 5
SF-36 scores at primary surgery, before closure, 3, and 12 months after ileostomy closure

		Primary surgery	P-value	Before closure	P-value	3months after closure	P-value	12months after closure	P-value
Physical health	Early	63.14 ± 12.01	0.932	49.82 ± 10.32	0.235	59.34 ± 11.83	0.465	63.46 ± 12.72	0.092
	Late	62.51 ± 10.80		52.09 ± 10.97		57.61 ± 11.85		59.18 ± 12.74	
Mental health	Early	61.36 ± 11.72	0.693	48.40 ± 10.09	0.042	57.96 ± 11.82	0.799	61.80 ± 12.79	0.117
	Late	61.74 ± 10.56		51.88 ± 10.29		57.22 ± 11.49		57.96 ± 11.95	

Discussion

It seems that the implantation of diverting ileostomy is reliable for the prevention of complications of anastomotic leakage. Furthermore, stoma-related complications before closure negatively impact their QOL [1,3]. On the other hand, the length of time over which the stoma should persist is still uncertain. Thus, the main purpose of this prospective study was to determine the appropriate time to ileostomy closure in patients with rectal cancer because of the reduction of complications and improving QOL. The results of this prospective RCT is as follows: significantly difference in BMI, the time interval between creation and closure of stoma, and distance from last chemotherapy. No significant difference was found between the two groups in terms of complications based on the Clavien-Dindo classification [10]

(Table 2). As well as, there was no significant difference in perioperative outcomes, such as blood loss, operative time, re-admission, and re-operation as shown in Table 1.

C Kean et al [7], Benjamin Menahem et al [12], and Ahmed A. Aljorfi et al [3] have supported early closure of ileostomy to reduce stoma-related complications. Although, Krand et al [13], Danielsen et al [5], and Jennifer Parki et al [14], advocated early closure due to fewer complications, but should be done only in patients without anastomotic leakage; the findings of our study showed similar results that early closure is effective and safe. While a study by Li Wangi et al [15], demonstrated that late closure is more suitable compared to early closure. Similarly, another study also showed that early closure is not safe [9, 16].

In the present study, we also evaluated Lars score and its association with QOL, and the results were truly remarkable so that all domains of QOL according to SF-36 were better and showed a significant difference in the early closure. On the contrary, Andreas's study demonstrated that early stoma closure was associated with higher morbidity rather than late closure [17].

A study to evaluate the effectiveness of early closure versus late closure showed that timing of closure was not effective in reducing postoperative complications, while early closure improved patients' QOL. As in the study of Catalin Copaescu et al [18], early closure was better in reducing the postoperative complications in selected patients than in other patients.

In the present study, we assessed the LARS score between groups, which did not observe a significant difference. Also, we evaluated the effect of LARS score on patients' QOL which demonstrated statistically significant differences between them.

One of the strengths of our study is a randomized design. Also, this is the only study that simultaneously examines the timing of the closure, patients' QOL, and Lars score.

However, this study suffers from some limitations; for instance, the number of patients studied is low.

Conclusion

In summary, it seems that early closure of ileostomy is generally effective and safe in reducing the risk of complications and improving QOL in patients with rectal cancer following LAR and chemoradiation (neoadjuvant and adjuvant).

Declarations

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Ethics approval: This study was approved by the ethical committee of Tehran University of Medical Sciences.

Consent to Participate: Informed consent was obtained from all participants included in this study.

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