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Original Article

Does the timing of protective ileostomy closure post-low anterior resection have an impact on the outcome? A retrospective study

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SUMMARY

Background: The optimal timing for ileostomy closure remains controversial, most of the surgeons are closing ileostomy after two to three months, although ileostomy closure considered a simple procedure, it can cause significant morbidity; this study aims to clarify any relation between the post-closure complications rate and the time from its creation to the repair.
Method: From January 2010 to December 2017, data retrieved for a 405 patients who had protective ileostomy closure after rectal cancer surgery, our sample has been enrolled into two arms, the first arm includes whose ileostomies closed at or before three months, and the second arm involved whose ileostomies closed after three months from the index surgery, statistical analysis was performed and compared in both arms,
Result: The overall post-closure complications in our hospital was 23.7%, there was no significant difference between the overall complications rate for both early and late closure groups (26.8% and 22.7%) respectively (P = 0.499), The majority of the complications were intestinal obstruction, and superficial surgical site infection, there was no significant association between the interval to ileostomy reversal and the intestinal obstruction although it was higher in the late closure group, in the other hand the surgical site infection complication found to be significantly higher in the early closure group than the late closure group (15.4% Vs 5.1%) with (P = 0.002).
Conclusion: The duration between the creation of protective ileostomy and its reversal was not a significant independent predictor of post-closure complications rate.

1. Introduction

The protective loop ileostomy, commonly performed during rectal cancer surgery as one of the most reliable methods to reduce the sequelae of pelvic sepsis caused by anastomotic leakage if occurred.[1–3] However, to date, the timing of ileostomy closure varies across hospitals as there is no consensus regarding the best time for its reversal.[4,5] Limited evidence is available regarding the optimal time for ileostomy closure,[6] most surgeons close ileostomy two to three months after its creation (for benign and malignant conditions), depending on a clinical base, closing the ileostomy after two months to allow the full recovery of the patient from the index surgery, and allows for the resolution of the edema around the ileostomy site. And for easier management of adhesion and to avoid higher psychological effect on the patients; ileostomy closure is generally not performed after three months.[7,8]

In previous studies, the safety of the early repair of ileostomy within two weeks of its creation was assessed[9,10]; however, most surgeons emphasize that this issue needs further assessment. Several studies revealed that the time to closure of the ileostomy was longer than that planned initially, which may be attributed to many factors including prolonged recovery period following initial surgery, development of complications in index surgery, and the

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requirement for adjuvant treatment.[7,11,12]

Protective ileostomy repair is a relatively simple surgical technique[13]; however, it can be associated with significant morbidity. The following two types of complications are associated with an ileostomy: complications associated with the presence of stoma itself (pre-closure complications), wherein dehydration, electrolytes imbalance, and psychological effects are commonly noted, and complications associated with ileostomy closure operation (post-closure complications), among which superficial surgical site infection (SSI) and intestinal obstruction are common.

Recent systematic reviews reported morbidity rates of (17.3–33.0%) associated with the post-ileostomy repair,[13–15] while for both pre-closure and post-closure complications of up to (40–70%) were reported.[7,16]

Essentially a longer duration between ileostomy creation and reversal exposes the patient to a higher incidence of pre-closure complications which was evidenced previously.[7]

To the best of our knowledge, the evidence on the effect of the timing to closure on the post-closure complications is limited. Therefore, our study aimed to evaluate the effect of the time interval between ileostomy creation and takedown after low anterior resection on the post-closure complications and to identify the risk factors for these complications.

2. Methods

2.1. Patients

As shown in Fig. 1 (926) patients underwent protective ileostomy concurrent with low anterior resection for rectal cancer at Severance hospital, Yonsei university, Seoul, the Republic of Korea, between January 2010 to December 2017. We excluded (407) cases according to our exclusion criteria (stage IV rectal cancer, ileostomy performed again due to late anastomotic leakage, concurrent surgery during ileostomy reversal, ileostomy not closed due to anastomosis leak, or ileostomy closed at a different hospital). All patients' data were retrieved from electronic medical records (EMR), subsequently another (114) patient were excluded due to incomplete data. Finally, we included (405) patients in our retrospective study and distributed them into the following two groups: a group comprising (97) patients in whom the ileostomy was closed at or before three months (early closure group), and the other group comprising (308) patients in whom ileostomy was closed more than three months after the index surgery (late closure group). This definition was dependent on the preference of the surgeons who mostly prefer to repair the ileostomy between two to three months after its creation[7,8]. Subsequently the demographic data, perioperative characteristic, and complication rate of both groups were compared.

2.2. Clinical variables

Data of the patients retrieved from EMR included the demographic characteristics, comorbidities, the American Society of Anesthesiologists classification for operative risk (ASA) index scores, body mass index (BMI), the time interval between stoma creation and its reversal.

2.3. Operative management

According to our hospital's treatment policy, the stoma takedown usually performed two to three months from its creation, the reversal operation proceeded by gastrografin radiological study for confirmation of an intact anastomosis. If it revealed no signs of leakage and the patients' general condition was fit for surgery, an ileostomy takedown was perform, in circumstances where signs of leakage were present or the patient required chemotherapy, the takedown was delayed.

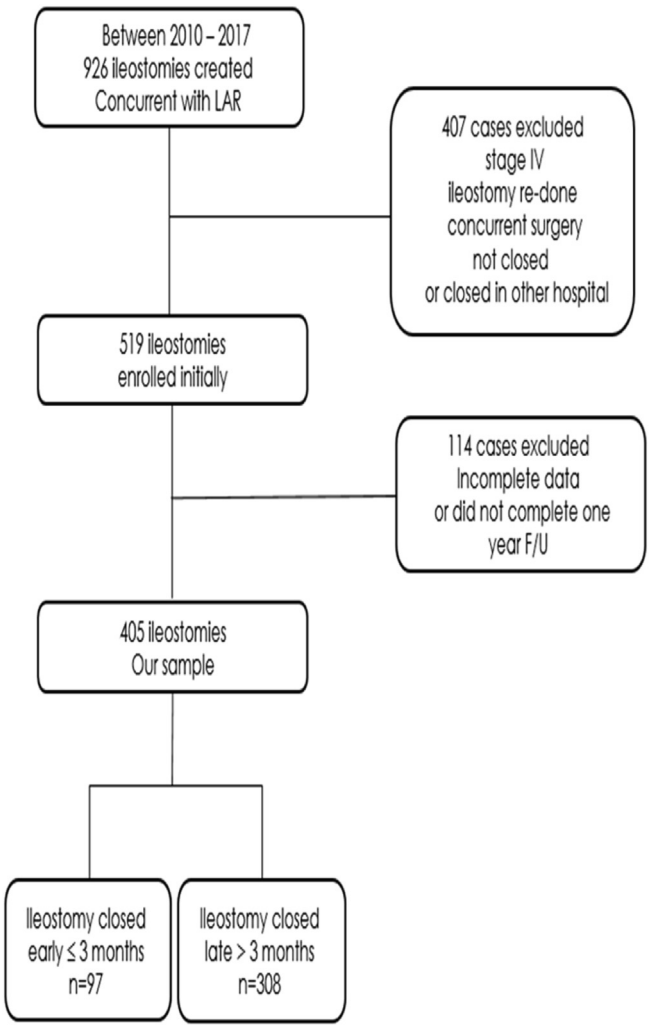

Fig. 1. The study design.

The only exception for that if the patient show significant early complication secondary to ileostomy creation (which is rare), in this situation we usually close it as early as possible; sometime even within a month from its creations.

We also retrieved the perioperative characteristics of the ileostomy repair surgery from the EMR, including the operation time, and the blood loss, anastomotic technique used (hand-sewn end-to-end anastomosis, hand-sewn closure of the enterotomy (fold-over) or a stapled side to side anastomosis). The skin closure was either by staple, interrupted sutures or rarely purstring.

2.4. Post-operative outcomes

The data for the first bowel movement, first feeding, and length of hospital stay and the outpatient department follow-up notes for up to one year, A diagnosis of post-operative intestinal obstruction was considered when the bowel function did not restart within five or more days post-operatively or reinsertion of a nasogastric tube required after the oral feeding was started,14,17.

Superficial SSI defined as an infection occurring within 30 days postoperatively, involving only the skin or subcuticular tissue of the

incision, with at least one of the following signs, purulent discharge from the superficial incision, organism isolated from a culture fluid or tissue from the superficial incision, having at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat.[18]

The complications retrieved and stratified according to Calvin–dendo classification.[19]

2.5. Statistical analysis

We performed all statistical analyzed using SPSS version 25 (IBM Co., Armonk, NY, USA). We analyzed categorical variables using the chi-square or Fisher exact t-test, and the continuous variables were analyzed using Student t-test or Mann Whitney U-test. Univariate and multivariate analysis were performed and the $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic data

The demographic data for the patients are listed in Table 1, the median age of the patients in the early closure group was significantly higher than that of those in the late closure group (61 years vs. 59 years, $p = 0.04$). The number of men was higher in both groups. There were no differences between the groups with respect to sex, smoking, alcohol consumption, ASA score and comorbidities.

Most patients in the early closure group were classified as ASA grade I, while the most common grade in the late group was ASA grade II. The mean BMI in both groups was 23 KG/M2. There was a significant difference between the two groups regarding the rate of stage III of the rectal cancer in the index surgery and the rate of adjuvant chemotherapy in favor of the late closure group $p = 0.001$ for both.

3.2. Perioperative characteristics

Table 2 shows that the median hospitalization period was six days for both groups; the median operation time for the total cohort was 100 min, and the median blood loss for the cohort was 30 ml. The operation time and the blood loss volume were significantly higher in the late closure group ($p = 0.001$). The median time to the first gas passage in both groups was four days and the groups showed no difference in the median time for consumption of the first soft diet; four days for each group. The side-to-side stapling method was the most commonly used anastomosis repair method in both groups, as well as the skin stapler method as a method for skin closure was the most commonly used in both groups (in 95.8% of early and in 83.1% of late closure group), Purstring as a method for skin closure is not popular in our hospital it has been used only in 3.6% in the late and not used in the early closure group.

3.3. Complication rates

According to Table 3, 105 complications occurred in our patient cohort in a total of 96 patients because more than one complication was noted in some patients. The morbidity rate was 23.7%; the rate of patients with complications was higher in the early closure group than in the late closure group, and the difference was not statically significant (26.8% vs. 22.7%, $p = 0.44$). In total, 10 complication types occurred across both groups, of which, intestinal obstruction and superficial SSI were the most frequent, occurring in 11.3% and 7.7% of the patients respectively.

The number of intestinal obstruction cases were non-significantly higher in the late group, while the number of SSI cases were significantly higher in the early closure group ($p = 0.002$). Most complications in our patient cohort were of Clavien–Dindo class I and II (14.56% and 4.93% respectively), and there were no cases of class IV complications and mortality, Regarding the rate of Clavien-Dindo class III complications, it was

Table 1
Demographic data.

	Early closure ≤ 3 M[a)] (N = 97), %	Late closure > 3 M[a)] (N = 308), %	P value
Age in years (range)	61 (35–88)	59 (28–89)	0.04*
Sex			0.59
Male	70 72.2%	220 71.4%	
Female	27 27.8%	88 28.6%	
ASA			0.21
I	44 45.4%	124 40.3%	
II	39 40.2%	135 43.9%	
III	14 14.4%	49 15.8%	
BMI, (SD)	23.3 ± 2.5	23.6 ± 3.1	0.14
Diabetes	19 19.6%	63 20.4%	0.90
Hypertension	38 39%	116 37.7%	0.64
Cardiac	1 1%	11 3.6%	0.08
Smoker	40 41.2%	125 40.6%	0.71
Alcoholic	40 41.2%	131 42.5%	0.86
P Stage		0.001*	
0 (no residual tumor)	18 18.5%	10 3.2%	
I	36 37.1%	69 22.4%	
II	20 20.6%	89 28.9%	
III	23 23.8	140 45.5%	
Adjuvant Chemotherapy received			0.001*
not received	40 41.2%	235 76.3%	
	57 58.8%	73 23.7%	

[a)] Months from the ileostomy creation,ASA: American Society of anesthesia score, BMI: Body mass index, M: months, N: number, SD: Standard deviation, P stage: pathological stage.
* Statistically significant value.

Table 2
Peri operative characteristics.

	Early closure ≤ 3 M[a)] (N = 97)	Late closure > 3 M[a)] (N = 308)	P value
Hospital stay, days, (range)	6 (4–21)	6 (3–29)	0.14
Operation time, minutes, (range)	87.5 (40–175)	105 (45–265)	0.001*
Blood loss in ML (range in ML)	10 (0–150)	25 (0–120)	0.001*
Time to first gas passage days, (range)	4 (1–8)	4 (1–14)	0.31
Time to first soft diet days (range)	4 (2–10)	4 (1–18)	0.18
Method of ileostomy closure			0.37
stapler side to side, percentage	78 80.5%	231 75%	
hand sewn end to end, percentage	18 18.5%	64 20.8%	
fold over, percentage	1 1%	13 4.2%	
Method of skin closure			0.014*
skin stapler, percentage	93 95.8%	256 83.1%	
interrupted suture, percentage	4 4.2%	41 13.3%	
purstring, percentage	0 0	11 3.6%	

[a)] Months from the ileostomy creation,M: Months, ML: Milliliter, N: Number.
* Statistically significant value.

Table 3
Postoperative complications types and rate.

Type	**Total sample (N), percentage**	Early closure ≤ 3 M[a)] (N) percentage	Late closure > 3 M[a)] (N), percentage	P Value
Total number of complications	105	29	76	
Total number of patients with complications				
	96 23.7%	26 26.8%	70 22.7%	0.44
Intestinal obstruction	47 11.3%	9 9.2%	38 12%	0.28
Superficial SSI	31 7.7%	15 15.4%	16 5.1%	0.002*
Melena	2 0.49%	2 2.06%	0 0	
Pneumonia	5 1.23%	1 1.03%	4 1.29%	
Atelectasis	6 1.48%	0 0	6 1.94%	
PMC	3 0.74%	0 0	3 0.97%	0.55
UTI	2 0.49%	0 0	2 0.64%	
Thrombi – embolic	2 0.49%	0 0	2 0.64%	
Incisional hernia	5 1.23%	2 2.06%	3 0.97%	
Bleeding	2 0.49%	0 0	2 0.64%	
Clavin-Dindo grade				0.29
I	59 14.56%	19 19.58%	40 12.98%	
II	20 4.93%	7 7.21%	13 4.22%	
III	17 4.19%	1 1.03%	16 5.19%	
IV	0 0	0 0	0 0	
V	0 0	0 0	0 0	

[a)] Months from ileostomy creation,M: months, N: number, PMC: Pseudomembranous colitis, SSI: Surgical site infection, UTI: Urinary tract infection.
* Statistically significant value.

non significantly higher in the late closure group (5.19% Vs 1.03%) and it was 4.19% in our total sample (17 patients), the total number of patients needed urgent re-operation were three, two of them were intestinal obstruction due to adhesive band and due to narrow lumen after the fold over closure (simple closure of enterotomy), and the third patient who developed bleeding in the mesentery after ileostomy repair where re operation needed to control it, the remaining patients of C-D III were three patients needed intervention radiologist, one with bleeding in the mesentery needed percutaneous drainage, two patients of thrombi – embolic needed inferior vena cava umbrella, another five patients needed endoscopy, three of them with Pseudomembranous colitis, and two with melena, five patients with Incisional hernia needed elective repair, and lastly one patient of atelectasis needed bronchoscope for lavage and to roll out other lung pathology.

3.4. Risk factors for the complications

By analyzing Table 4, three risk factors that were significant in univariate analysis were identified, namely, hypertension, older age, and hand-sewn anastomosis closure (p = 0.03, 0.04 and 0.03, respectively). However, in the multivariate analysis, only the hand-sewn anastomosis closure method was a significant risk factor (HR: 3.831, 95% CI: 1.947–7.538, p = 0.04).

4. Discussion

Generally, protective loop ileostomy is commonly performed concurrently with low anterior rectal cancer resection. However, the timing of ileostomy closure is a common concern for surgeons while discussing with patients in the surgical outpatient department; patients look forward to early closure of ileostomies while surgeons prolong the wait for to complete the adjuvant chemotherapy.

Although Perez et al reported that the complication rates were significantly associated with shorter time intervals between the index surgery and ileostomy closure; and they recommended that ileostomy closure must be performed more than two months after the creation.[17] Our study showed no significant differences in the rate of the postoperative complications between the early and the late closure groups (26.8% and 22.7% respectively, p = 0.44).

The most frequent complications in our patients were intestinal

Table 4
Risk factors for the overall post-operative complications.

Risk factors	Univariate	Multivariate	
	P value	P value HR 95% CI	
Hand sewn as a method of ileostomy closure	0.001*	0.04*	3.83 (1.947–7.538)
Hypertension	0.03*	0.18	0.71 (0.436–1.178)
Old Age (≥ 65 Y)[a)]	0.04*	0.14	0.69 (0.421–1.141)
Early closure of ileostomy ≤ 3 M	0.49		
Diabetes	0.21		
Cardiac diseases	0.17		
BMI more than 25	0.23		
Smoking	0.98		
Alcoholic	0.13		
Gender	0.83		
ASA more than II	0.07		
Operation time > 100 min[b)]	0.81		
Blood loss more than 30 ML[c)]	0.08		
Adjuvant chemotherapy	0.94		

ASA: American Society of anesthesia score, BMI: Body mass index, CI: Confidence interval, HR: Hazard ratio, M: Months, ML: Milliliter, Y: Years.
[a] According to WHO definition for old age.
[b)] Our mean operative time.
[c)] Our mean blood loss in ileostomy reversal operations.
* Statistically significant value.

obstruction and superficial SSI (11.3% and 7.7%, respectively), the incidence of intestinal obstruction was non-significantly higher in the late closure group p = 0.28. Williams et al also reported intestinal obstruction as the most common complication following loop ileostomy repair, with an incidence reaching 29%.[20] Carlsen et al suggested that a more than six month duration until ileostomy closure can cause a higher incidence of intestinal obstructions, which they attributed to atrophy and reduction in the motility of the bypassed limb which has been demonstrated in patients with a diversion ileostomy.[21] In the present study, the hand-sewn anastomosis closure method was a significant risk factor for overall complications in which the intestinal obstruction was the most common. This can be explained by the wider anastomotic line in the stapled method, while the hand-sewn anastomosis line is narrower and consequently more liable to temporary obstruction secondary to postoperative edema.[7]

Superficial SSI, which was the second most frequent post-operative complication in our study, was significantly higher in the early closure group P = 0.002. This result was concurrent with the findings of other studies, which showed that early ileostomy reversal causes higher wound infection rates. Alves et al found that wound infections occurred at significantly higher rates in the early closure group (ileostomy closed eight days post its creation) than that in the late closure group (ileostomy closure at 60 days post creation) 19% vs. 5%, respectively, p = 0.007.[10] Moreover, Worni et al revealed that wound infection in the early closure group (median duration until closure = 49 days) was 7.5%, while in the late closure group (median duration until closure = 206 days) was 4.8% but with no significant difference.[6] The higher incidence of SSI in the patients whose ileostomy was closed early was explained according to Hensler et al by the immunity which possibly reduced in the immediate postoperative period, particularly because of the suppression of T-cell functions.[22] On the other hand, another study reported that SSI rates after early ileostomy closure (13 days after the index surgery) was near that after conventional ileostomy closure (two to three months after index operation),[9] this shows that the relation between SSI and early closure still debated.

Concerning the perioperative characteristics, we found that both operation time and blood loss was significantly higher (p = 0.001 for each) in the late group. This could have occurred by adhesion, which usually found more fibrous with longer intervals between ileostomy creation and reversal and so more tough adhesion need more dissection which needs more time and caused more blood loss.

The significant difference between the two groups regarding the adjuvant chemotherapy in favor of the late closure group in our study reflects our practices in closing the protective ileostomy after the end of adjuvant chemotherapy, usually 6 months after its creation.

Our study had several limitations to be considered, one being its retrospective design. Secondly, the ileostomy repair was conducted by several surgeons with different experience levels, and so we could not definitively conclude the complication rates and types. Hence, randomized control studies are warranted to confirm these result until we reach a consensus on the ileostomy closure timing. Nevertheless, this study discussed a simple yet important and controversial topic of ileostomy closure timing, which is till now considered as a debatable subject.

In conclusion, our study revealed that the duration between the creation of protective ileostomy and its reversal was not a significant independent predictor of post-closure complications rate.

Depending on whether a patient has mild pre-closure complications and appears tolerant of the psychological effect of his stoma, the ileostomy closure can be deferred safely for a real indication such as completing adjuvant chemotherapy without concern that the longer duration to closure will increase the post-operative complications rate.

We sincerely hope that our effort adds to the body of evidence until a consensus regarding the ileostomy closure timing is reached.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Abbreviations

(SSI) surgical site infection
(EMR) electronic medical records
(ASA) the American Society of anesthesia score
(BMI) Body mass index

(NAT) neoadjuvant therapy
(CCRT) concurrent chemoradiotherapy
(M) months
(ML) milliliter
(HR) hazard ratio
(CI) confidence interval
(SD) standard deviation
(N) number
(PMC) pseudomembranous colitis
(UTI) urinary tract infection.

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Ethical approval

The ethics committee of Yonsei University approved the design and protocol of the study (IRB approval number: 4-2019-1345).

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