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Website: Kjar.spu.edu.iq | Email: kjar@spu.edu.iq

The effect of ileostomy closure timing on low anterior resection syndrome in patient who underwent low anterior resection for rectal cancer

Hemn Hussain kaka Ali
Kurdistan Center for
Gastroenterology &Hepatology
Sulaimani, Kurdistan, Iraq.
hemnhkaka@gmail.com

Qalandar Hussein Abdulkarim
High qualty Anwar shexa hospital, Zagros Str, Sulaimani
, Kurdistan,Iraq
qalandaar@gmail.com

Karzan Seerwan Abdulla
Department of surgery
College of medicine
Faculty of Medical Sciences University of Sulaimani, Sulaimani, Kurdistan, Iraq
.Karzan.Abdulla@univsul.edu.iq

Barham M .M .Salih
Department of surgery
College of medicine
Faculty of Medical Sciences University of Sulaimani, Sulaimani, Kurdistan, Iraq.
Barham.muhammed@univsul.edu.iq

Omar H Ghalib Hawramy
1. Smart Health Tower, Madam Mitterrand Str, Sulaimani, Kurdistan, Iraq.
2. Kurdistan Center for
Gastroenterology &Hepatology
Sulaimani, Kurdistan, Iraq.

Dara Ahmed Mohammed
Department of surgery
College of medicine
Faculty of Medical Sciences University of Sulaimani, Sulaimani, Kurdistan, Iraq.
Dara.marif@univsul.edu.iq

Syamand Orhaman Ahmed
Kurdistan Center for
Gastroenterology &Hepatology
Sulaimani, Kurdistan, Iraq.
syamandahmed@gmail.com

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ABSTRACT

This is a multi-center retrospective study in patients, in whom low anterior resection had been done for rectal cancer, there ileostomy had been done to protect low lying colo-rectal anastomosis, closure of the ileostomy had been delayed in some patients due to patient own will, surgical complications (anastomotic leak) or course of chemotherapy. The aim of this study is to evaluate the effect of temporary ileostomy on post-operative bowel dyfunction which is named Low anterior resection syndrome (LARS) which is includes; defecation urgency, bowel evacuation difficulty, and loss of control for feces

Keywords:

Stoma closure, cancer of rectum, colon cancer, anterior resection, low anterior resection syndrome, radiotherapy

and flatus. A total of 50 patients evaluated in the current study, the age of the participants was between 19 to 80 years old and the mean age was 51.96 years. The total number of males was (33, %66). Majority of patients were overweight (21, 42%). The distant between tumors and anal orifice were less than 10 cm in (31,62%). The mean duration of fecal diversion was 7.17 months. Loop ileostomy were closed before six months in (27,54%). The mean duration of diversion of patients had no LARS was 6.87 months which is shorter than those of developed LARS (7.31). Lower BMI patients were more prone to develop LARS, while Obese patients are more susceptible to develop major LARS. Nineteen cases developed LARS among those patient's ileostomies closed before six months, and 15 cases developed LARS in whom ileostomies closed after six months.

1. INTRODUCTION

Colo-rectal cancer (CRC) is the third most occurring lethal cancers in both genders in developed countries, followed by prostatic cancer in male, breast cancer in females, and lung cancer in both genders, which all have a similar tendency in cancer-specific mortality [1,2]. CRC is one of the most occurring malignancies in European countries, with Rectal cancer (RC) accounting for about 30% of cases and an annual incidence of 15-25 per 100,000 [3]. Total mesolectal excision (TME) with a colo-rectal anastomosis near the pelvic floor is considered as a standard surgical care for RC [4]. The rate of RC survival has dramatically improved as the result of improvement in screening, surgery and chemoradiotherapy. More than 80% of patients with RC underwent low anterior resection (LAR) procedure [5]. According to the data of National Bowel Cancer Audit's (NBOCA), stoma is formed in more than 77% of low lying rectal malignant tumors patients, and in up to 27% of patients the stoma persists beyond 18 months after the surgery [6]. Low anterior resection syndrome (LARS) is defined as a subsequent change in the bowel habits following LAR, resulting in a reduction in quality of life [7]. Incidence of LARS is about 90% in patients who are undergoing LAR with sphincter preservation for low lying cancer of rectum [8]. ILARS has been used to describe a broad range of symptoms such as evacuatory dysfunction, fecal urgency, and fecal incontinence [9]. LARS has been evaluated in a variety of ways, and incontinence is the most focusing symptom in the majority of reports compared to other symptoms such as frequency of defecation, clustering of feces, incomplete bowel evacuation, and quality of life.

The post-operative bowel dysfunctions can be assessed by the unique international scoring system which is evolved to evaluate the bowel function and it is called LARS score [5]. The LARS scoring system is short and it has more clinical value because it allows patients to be quickly classified into no LARS, minor LARS, and major LARS groups, LARS scoring system was publicized for the first time in 2012 and translated versions have been used among different nations [10].

This study aimed to evaluate the effect of ileostomy closure timing on LARS in patients in whom LAR had been done for low lying rectal cancer.

2. METHOD AND MATERIALS

2.1 *Study design*

This is a multi-centre retrospective study of patient in whom RC resection had been done from (2013 - 2020). The socio-demographic and clinical data were retrieved from the patients' medical records and hospital data base.

2.2 *Inclusion criteria*
Patients who were diagnosed as RC and underwent sphincter preserving LAR are included in this study.

2.3 *Exclusion criteria*
We exclude from our study any patient without diverting stoma, patient with local recurrent and patient with anal sphincter damage due to a previous surgery.

2.4 *Preoperative assessment*
Patients who were diagnosed as RC underwent assessment by multidisciplinary team (MDT) for rectal cancer before the operation. Decision of operation alone or neo-adjuvant treatment had been done according to the stage of the disease. After confirmation by tissue diagnosis. all patients underwent local and systemic assessment to determine the stage of their disease by colonoscopy, computed tomography (CT) scan of abdomen and chest, magnetic resonance imaging (MRI) or EUS and/or positron emission tomography (PET) scan. Most of the patients were undergone down-staging with pelvic radiation therapy.

2.5 *Surgical intervention*
Operation had been done by qualified surgeon in multiple centers where TME had been done with an acceptable safety margin. Colo-rectal anastomoses had been done by circular stapler, diverting temporary ileostomy had been done to protect the anastomoses. The stoma were been closed after considerable time interval ranging from 1 month to 20 months. Ileostomy closure had been delayed in some patients due to patient own will, surgical complications (anastomotic leak) or coarse of chemotherapy.

2.6 *Post-operative follow-up*
Follow up have been done periodically with clinical examination, blood investigations including carcino-embryonic antigen (CEA), colonoscopy and abdominal CT-scan.

2.7 *Statistical analysis*
The data were recorded using an excel sheet, later, they were transferred to the statistical package for the social science (SPSS) version 24 after coding. The descriptive analysis was calculated in form of percentage, mean, range and standard deviation (SD).

3. RESULT

A total of 50 patients participated in the current study, the age of them were between 19 to 80 years old with a mean age of 51.96 years at time of follow up. The total number of male patients were 33 (%66). Majority of patients were overweight (21, 42%). The tumor was away from anal verge by less than 100 mm in 31 (62%) cases. The mean duration of fecal diversion was 7.17 months. Loop ileostomy were closed before six months in 27 (54%) cases. Four of 50 patients had a stoma closure beyond 18 months. Early closure of the stoma was more in female compared to male. Adjuvant chemotherapies were given to 37 (74%) cases. Neoadjuvant long course radiotherapies were received by 26 (52%) cases and neoadjuvant short course radiotherapy by 28 (56%).
Overall, major LARS developed in 24 (48%) cases, 10 (20%) patients reported minor LARS, and 16 (32%) reported no LARS. The prevalence of LARS, both major or minor, was 19 of 27 and 15 of 23 in the early and late closure groups. Table 1.

Table 1: Characteristic and demographic data of participants

Variable	N (%)
No. of the patients	50
Male	33(66)
Female	17(34)
Age at the time of follow up, mean (SD)	51.96(13.51)
Duration of diversion mean (SD)	7.17(5.40)
Body mass index BMI	
Under weight	4(8)
Normal	11(22)
Over weight	21(42)
Obese	14(28)
T-stage	
T0-2	18(36)
T3-4	32(64)
N-stage	
N0	18(36)
N1	32(64)
N2	0
Distant of the cancer from anal verge	
≤ 10 cm	31(62)
≥ 10 cm	19(38)
The time of ileostomy closure	
Ileostomy closed > 6 months	27(54)
Ileostomy closed ≥ 6 months	23(46)
Patient received neoadjuvant radiotherapy	
Yes	31(62)
No	19(38)
Patient received neoadjuvant chemotherapy	
Yes	19(38)
No	31(62)
Patient received adjuvant radiotherapy	
Yes	7(14)
No	43(86)
Patient received neoadjuvant long course radiotherapy	
Yes	26(52)
No	24(48)
Patient received neoadjuvant short course radiotherapy	
Yes	28(56)
No	22(44)
NO LARS	
Yes	16(32)
No	34(68)
Minor LARS	
Yes	10(20)
No	40(80)
Major LARS	
Yes	24(48)
No	26(52)

The mean duration of ileostomy in patients had no LARS was 6.87 months which was shorter than those who developed LARS (7.31) months, and 7.52 months in patient who developed major LARS which was longer compared to those not developed LARS (6.85). Table 2:

Table 2: Duration of ileostomy and development of LARS

Variable	Duration of diversion Mean±SD	P value
No LARS		
Yes	6.87±3.66	0.058
No	7.31±6.10	
Minor LARS		
Yes	6.81±4.85	0.423
No	7.26±5.59	
Major LARS		
Yes	7.52±6.63	0.010
No	6.85±4.07	

The mean age of those patients who developed LARS was 54.3 years, which was older than those developed had no LARS 47.68 years. Out of 17 females 14 (82%) developed LARS, while only 38.7% of the male patients developed LARS. Out of 4 patients who BMI were lower than 18.5 kg/m2, 3 patients developed LARS, while obese patients were more susceptible to develop major LARS. Neoadjuvant short and long course radiotherapy had a higher effect on developing major LARS. Table 3

Table 3; characteristics and demographic effect on LARS

Variable	No LARS	Minor LARS	Major LARS	P value
Age (Mean±SD)	47.68±15.70	55.10±14.88	53.5±11.04	<0.001
Sex No (%)				
Male	13(81.3)	8(80)	12(50)	<0.001
Female	3(18.8)	2(20)	12(50)	
BMI No (%)				
<18.5	1(6.3)	2(20)	1(4.2)	
18.5-24.9	4(25)	1(10)	6(25)	<0.001
25-29.9	6(37.5)	6(60)	9(37.5)	
>30	5(31.3)	1(10)	8(33.3)	
Neoadjuvant short course radiotherapy				<0.001
Yes	4(50)	2(33.3)	10(71.4)	
No	4(50)	4(66.6)	4(28.6)	
Neoadjuvant long course radiotherapy				<0.001
Yes	4(50)	3(42.9)	8(72.7)	
No	4(50)	4(57.1)	3(27.3)	
Adjuvant chemotherapy				<0.001
Yes	12(75)	7(70)	18(75)	
No	4(25)	3(30)	6(25)	
Adjuvant radiotherapy				<0.001
Yes	2(12.5)	2(20)	3(12.5)	
No	14(87.5)	8 (80)	21(87.5)	

Nineteen cases developed LARS among those patient ileostomies closed before six months, and 15 cases developed LARS in those ileostomies closed after six months. This means that early closure has a higher risk of developing LARS with statistically significant difference. Table 4

Table 4: Effect of ileostomy closure timing on LARS

time of ileostomy closure	No LARS	Minor LARS	Major LARS	P value
Ileostomy closed ≤ 6 months, no(percentage)	8(50)	4(40)	15(62.5)	<0.001
Ileostomy closed ≥ 6 months, no(percentage)	8(50)	6(60)	9(37.5)	

4. DISCUSSION

Loop ileostomy is the most common procedure performed in patient with lower RC aimed to prevent complications related to ileoanal and coloanal anastomosis [11]. Although it is an essential choice for fecal diversion with the aim of minimizing clinical significance of anastomotic leakage, it is related with serious morbidity, declining life quality which may progress to an irreversible damage [12]. Still there is controversy on the effect of temporary diverting stoma on the incidence of functional bowel alteration following LAR [13]. There are a broad variety of potential disadvantages associated with stoma such as the need of reoperation, long hospital stays and dehydration [8]. Other complications are skin problems, obstruction, bleeding, parastomal hernia, and rarely stoma stenosis [14]. In addition, loop ileostomy formation and closure have a considerable morbidity and increased costs [15]. The overall incidence of leakage and reoperation rates have been shown to be equal in both groups with or without stoma [16], therefore, the decision of making a is even more challenging and further study is needed [17].

Anastomotic leakage is a risk factor for developing major LARS [18], however, some studies showed no correlation between LARS and anastomotic leak [5,19, 20]. A study reported that there is two-fold rise in the incidence of post-operative bowel dysfunction in patients with a diverting stoma [21]. Loop ileostomy may alter microbiota and colonic environment [21], affecting the cell turnover of the epithelial lining of the intestine, and altering the structural and functional properties of the intestine [22]. Evidences suggested that bowel dysfunctioning after rectal resection is associated with decreased neorectal compliance occurring with lower anastomosis, so it is important to preserve residual rectum as much as possible without affecting adequate tumor clearance [13]. LARS may persist for many years after operation [23]. The best time for closure of stoma is 2 to 3 months [14]. Most surgeons try to close diversion within 2 to 4 months after primary operation, however the timing of ileostomy closure is different between centers [21, 24]. To date it is recommended that if stoma is created it should be closed before six months after initial operation, since the incidence of LARS is lower in that case [5]. There is a similar incidence of post-operative complications and anastomotic leakage between delayed closure and early closure of dyfunctioning stoma after surgery [25]. Shaw et al reported that there is a delay in stoma reversal beyond 18 months in up to 40% of patients [26]. In contrast to our study which only 8% of patient got closure after 18 months.

Many studies reported that diversion stoma is related with post-operative side effects in up to 29% and mortality in a small number of cases [14]. Adjuvant chemotherapy is considered as an important factor for delay of ileostomy reversal [27], however, Vogel et al reported that there is no reason explaining the delay in stoma closure and there is lack of guidance regarding ideal time of closure of stoma [21]. Surgeons think that chemotherapy has bad effect on surgical site regeneration after stoma reversal and recommended that ileostomy reversal better to be delayed till the end of chemotherapy [27]. Tulchinsky et al said that reversal of stoma at the time of

adjuvant chemotherapy didn't has bad effect on post-operative hospital time, percentage of reversal complications and death rate compared to those closed after chemotherapy [28]. Vrakas et al reported that the time between diversion creation and closure after LAR is significantly impacted by chemotherapy [29], however, Choi et al illustrated that stoma closure during and after chemotherapy are equally safe [27]. The current study demonstrated that the risk of developing LARS between patients with and without chemotherapy is nearly similar.

Factors such as age of patient, small body mass index, end ileostomy and irradiation are considered as risk factor for the non-reversal of stoma [30]. Current study also demonstrated that lower BMI patients are more at risk for developing LARS, but obese patients are more prone to have major LARS. One third of patient above 70 years undergo non-reversal [31]. The presenting study showed that older aged are at higher risk of developing LARS. Sun et al reported that preoperative radiotherapy decreased reversal rate [30], however, in another study they mentioned that preoperative radiotherapy doesn't associate with non-reversal [32]. Long coarse neoadjuvant radiotherapy, distance of anastomosis and loop ileostomy are considered as independent risk factors for the development of post-operative bowel dysfunction [20], however perioperative radiotherapy regarded as a risk factor for the loss of fecal controlling during the first six months after surgery, and different studies suggested that pre-operative radiation is a risk factor for developing post-operative bowel dysfunction [33]. Similarly, to the present study showed long and short courses neoadjuvant radiotherapy significantly associated with development of LARS.

Postoperative radiotherapy also has a risk of developing anal sphincter dysfunction [34]. Nevertheless, radiotherapy is significantly affective in improving overall survival and that's why the exclusion of this important line of management modality is not a good choice [35]. A study reported that tumor with short distance from anal orifice and tumor with bigger size are more related with LARS after surgery [18], however, Keane et al reported that longer distance is more associated with LARS [8].

Hughes et al reported that ileostomy reversal during the first 6 months after primary operation is associated with lower incidence of major LARS but reversal beyond one year is associated with higher incidence of major post-operative bowel dysfunction [5], however, Jiménez-Rodríguez et al reported that there is no association between timing of closure of stoma and LARS [36]. Several studies showed that longer time associated with increased risk of LARS without statically significant difference [13,18,19]. Keane et al reported that those experienced late stoma closure have a greater problem with soiling [8], however, in the current study early closure of the loop (< 6 months) is importantly related with the development of LARS. Vogel et al reported that cases with no post-operative bowel dysfunction had a mean duration of time of stoma reversal 10 weeks earlier than Patients with major LARS.

This study had some limitations: a retrospective data was used for the analysis, the times of assessment of patients after surgery were variable between the patients. It was also difficult to retrospectively to collect a detailed information about participants, which is necessary for more detailed analysis. Small sample size is another important limitation. The potential strength of this study is that only rectal cancer patients were involved, and there was no bias in this study due to included surgeries of patients with inflammatory bowel disease.

5. CONCLUSION

LARS represents a major concern of both survivors of malignant rectal tumor and the colorectal surgeons. The current study found that the incidence of LARS is about 68% among patients who had a loop ileostomy. Early reversal of diverting stoma is more associated with the development LARS. These results indicate that more potential studies are required to determine either early or late reversal of stoma is better to decrease the rate of LARS.

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