

Early ileostomy closure in patients with rectal cancer. Primary results of the randomized controlled multicenter trial

© E.A. GALLYAMOV¹, M.A. AGAPOV², O.E. LUTSEVICH³, V.A. KUBYSHKIN², V.V. KAKOTKIN², M.P. TOLSTYKH³

¹Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia;

²Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russia;

³Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia

ABSTRACT

Aim — to evaluate safety of early closure of ileostomy in patients with rectal cancer after primary surgery.

Material and methods. The trial included patients from several medical centers without signs of anastomotic leakage. CT-proctography or rectoscopy were performed in 8 days after primary surgery to confirm integrity of the anastomoses. Exclusion criteria were factors affecting normal tissue regeneration (diabetes mellitus, steroid drugs prescription, etc.). Patients with intact anastomoses and no exclusion criteria were randomized into 2 groups: group 1 (n=31) with early closure of ileostomy (in 8—13 days after surgery) and group 2 (n=34) with delayed closure (after 12 weeks). All data were analyzed.

Results. Postoperative morbidity was similar in both groups (6.45% vs. 5.88%, p=0.08). However, less duration of reconstructive surgery was noted in group 1 (50 (27—126) min vs. 71 min (31—134)). This value was 1.42 times less in the main group (95% CI 1.30—1.52; p=0.02).

Conclusion. Early closure of ileostomy in patients after surgery for rectal cancer is feasible and does not result increased postoperative morbidity. This approach may be considered as an alternative to delayed closure. However, further researches devoted to analysis of ileostomy-associated complications and quality of life are necessary.

Keywords: colorectal cancer, total, partial mesorectumectomy, ileostomy, early closure.

INFORMATION ABOUT THE AUTHOR:

Gallyamov E.A. — <https://orcid.org/0000-0002-1904-2660>

Agapov M.A. — <https://orcid.org/0000-0002-6569-7078>

Lutsevich O.E. — <https://orcid.org/0000-0002-8092-0573>

Kubyshekin V.A. — <https://orcid.org/0000-0002-9400-1826>

Kakotkin V.V. — <https://orcid.org/0000-0003-0352-2317>

Tolstykh M.P. — <https://orcid.org/0000-0002-9227-1136>

Corresponding author: Tolstykh M.P. — e-mail: tolstykh@mediasphera.ru

TO CITE THIS ARTICLE:

Gallyamov EA, Agapov MA, Lutsevich OE, Kubyshekin VA, Kakotkin VV, Tolstykh MP. Early ileostomy closure in patients with rectal cancer. Primary results of the randomized controlled multicenter trial. *Khirurgiya. Zhurnal im. N.I. Pirogova*. 2019;6:35-40. (In Russ.).
<https://doi.org/10.17116/hirurgia201906135>

Currently, colorectal cancer occupies the third position in the world among other malignancies. Prevalence of this disease is annually increased. Thus, according to the Russian Center for Information Technologies and Epidemiological Researches in Oncology, incidence of colorectal cancer was 138.3 (direct — 105.6) cases per 100,000 [1]. Radical surgery for colorectal cancer significantly increased 5-year survival. However, it was followed by occurrence of new condition presented in ICD-10 — ileo- or colostomy. There were near 180,000 patients with ileo- or colostomy in our country by 2013 [2]. The concept of stoma was earlier more typical for obstructive colon resection (Hartmann's procedure). Currently, ileo- or colostomy is often temporary measure after radical treatment of colorectal cancer aimed at reducing the likelihood of complications associated anastomotic leakage [3]. Neverthe-

less, ileo- and colostomy may also be associated with certain complications: skin maceration, inflammation, bleeding from the stoma, stenosis and many others [4, 5]. According to some authors, incidence of major complications varies from 0 to 7—9%, minor — from 4—5 to 30% [6]. It is worth to note that almost 13% of patients have initially temporary stomy becoming permanent in future that significantly worsens quality of life. Various recent trials are devoted to the question of early closure of ileostomy after advanced rectal surgery in order to prevent complications and to improve quality of life [7]. There were adequate conditions for such analysis in our clinics. Therefore, it was decided to use the protocol of randomized controlled trial from Denmark and Sweden [8]. We have assessed potential benefits of early ileostomy closure in patients with rectal cancer in our country.

Objective — to analyze safety of early ileostomy closure in patients with rectal cancer after primary intervention via the comparison of immediate outcomes and postoperative morbidity in two homogeneous groups of patients, to compare our data with those obtained in recent years by Western colleagues.

Material and methods

Design: randomized controlled multicenter trial involving several clinical centers of the Lomonosov Moscow State University, Evdokimov Moscow State University of Medicine and Dentistry and Sechenov First Moscow State Medical University. Participants were searched for and selected among patients who underwent total or partial mesorectumectomy for colorectal cancer followed by primary anastomosis and temporary ileostomy.

Participants — patients were examined by the surgeon 4–5 days postoperatively in order to identify clinical signs of anastomotic leakage in small pelvis. Patients without clinical symptoms of this complication were included in the trial as soon as informed consent has been signed. CT-proctoscopy with a water-soluble contrast administered through the rectum and/or rectoscopy with a flexible endoscope depending on certain center were performed after 8 days postoperatively in order to assess anastomoses. Both procedures were performed without general anesthesia. Patients were examined for the other contraindications to inclusion in the study according to the protocol proposed by European colleagues if signs of anastomotic failure were absent [9]. Exclusion criteria: diabetes mellitus, steroid drugs intake, expected low adherence to treatment, inability of long-term follow-up. All patients who were undesirable for the study were informed in certain form.

Randomization: patients were divided into 2 groups — early (within 8–13 days after surgery) and delayed closure of the ileostomy (over 12 weeks after surgery). Randomization was performed by using of random number generator. Randomization was carried out directly in clinical centers as soon as CT or rectoscopy have been made. Blinding at the stage of surgery was impossible.

Technical aspects: technique of ileostomy closure was determined by surgeon depending on clinical situation. Intestinal integrity was repaired by 2 techniques: manual suture and mechanical suture (linear stapling devices). Surgeons recorded time of surgery and intraoperative blood loss immediately after surgery. Postoperative period was analyzed considering the following important variables: gas output time, time to complete recovery of enteral nutrition, ICU-stay, postoperative hospital-stay. Clavien—Dindo classification was used to assess postoperative complications [10, 11]. Each complicated case was registered by using of official form described in EASY-protocol [9]. Severity of complication (from grade I meaning any deviation from the normal postoperative period without need for additional treatment or examination to grade

V meaning death of patient) was assigned by the expert during analysis of medical records rather attending physician.

Statistical analysis: detailed statistical processing was developed before trial onset. Negative binomial distribution was used to evaluate early postoperative outcomes. Data are presented as geometric mean, confidence intervals (CI 95%) and p-values for null hypothesis reliability testing.

Outcomes: the primary purpose was to estimate postoperative morbidity after closure of ileostomy in both groups and to compare time of surgery, intraoperative blood loss and all other above-mentioned variables. Long-term outcomes are currently being analyzed and cannot be presented in this report. None of the participants were excluded from the study for any reason.

Results

Overall results: a total of 76 patients were considered as potential participants in the study. Clinical signs of anastomotic failure were diagnosed in 6 patients at the first stage of selection; other clinical contraindications for inclusion into the trial were noted in 4 cases and 1 patient refused to be included into the study (**Fig. 1**). Sixty-five patients were randomized. Early ileostomy closure group consisted of 31 patients, delayed closure group — 34 patients (**Fig. 1**).

The main demographic data are presented in Table 1. Men were predominant in group 2. Other characteristics were similar in both groups. Radiotherapy was previously applied in 27.7% (n=18) of patients; these patients were equivalently randomized between both groups (**Table 1**). Mean age of patients was 62 and 67 years in groups 1 and 2, respectively. There is certain heterogeneity of groups in relation to UICC staging system. Thus, stage I was noted in 22% of the first group and in 33% of patients in group of delayed ileostomy closure. At the same time, inverse pattern was noted for patients with rectal cancer stage II: 38 and 23%, respectively. Some experts suggested to use ECOG-WHO scale additionally for comparison. This indicator was not used in original EASY-protocol. ECOG-scale was not applied in this study since we did not analyze effect of early ileostomy closure on the quality of life [9].

Characteristics of surgical interventions and complications are presented in **Table 2**. Mean time to closure of ileostomy was 11 and 148 days in both groups, respectively. Intraoperative blood loss (blood loss ratio in both groups 1.00, 95% CI 0.96–1.05; p=0.03), postoperative morbidity were similar in the main and control groups (6.45% vs. 5.88%; p=0.08). There was one case of redo surgery in the control group due to small intestine obstruction. Mean time of surgery was significantly lower in early closure group than in the control group (50 min (27–126) vs. 71 min (31–134)). This value was 1.42 times lower in the 1st group on the average (95% CI 1.30–1.52; p=0.02). Mean hospital-stay was 4 days in each group

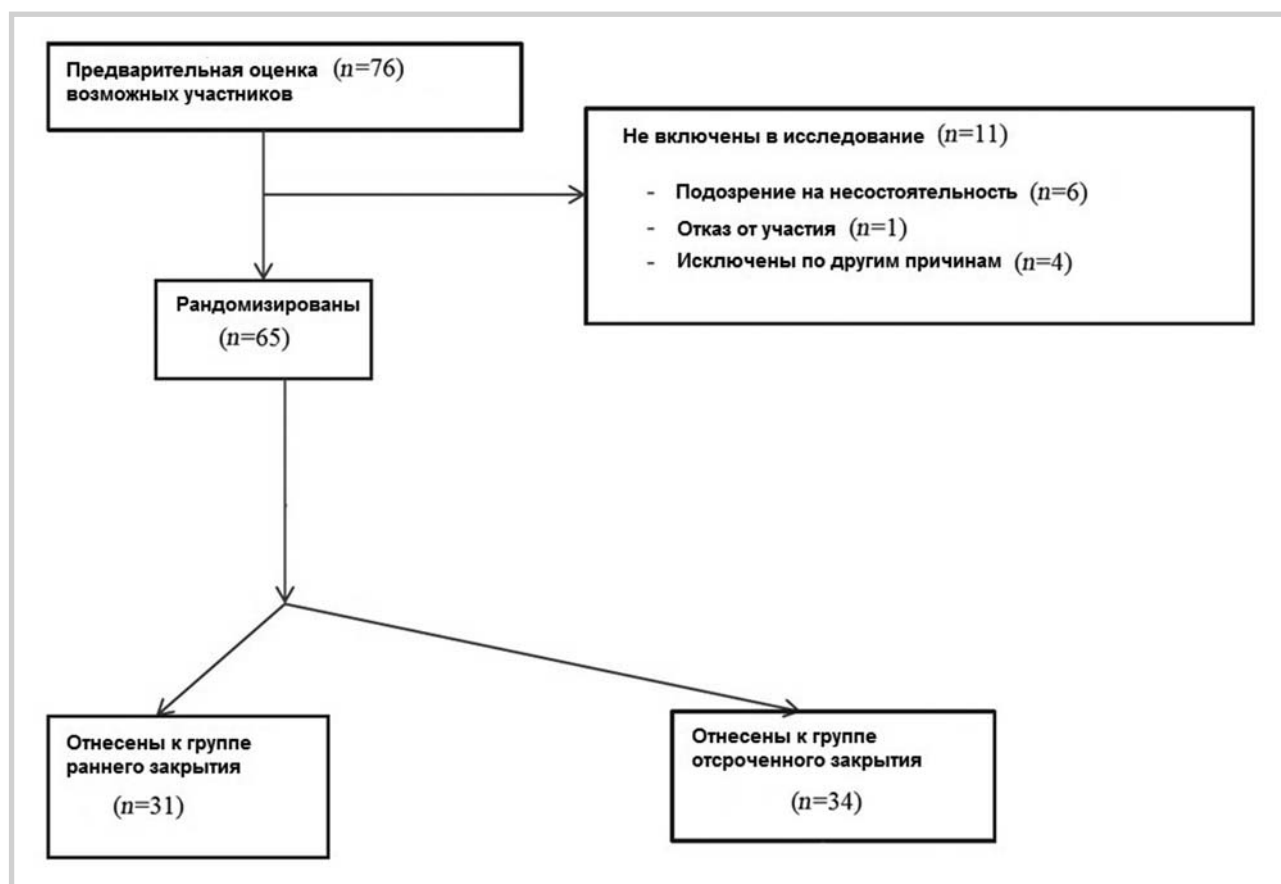


Fig. 1. Scheme of selection and distribution of patients into the groups.

Table 1. Main characteristics and preoperative variables of patients

	Randomized groups	
	Early closure	Delayed closure
Number of patients	31	34
Age, years	62 (32–78)	67 (35–77)
Sex, female/male	17 (56%)/14 (44%)	13 (37%)/21 (63%)
Body mass index (kg/m ²)	24 (17–33)	23 (18–35)
Patients with multiple comorbidities, n (%)	13 (42)	15 (42)
Previous radiotherapy	9 (29%)	9 (28%)
Inferior border of the tumor (cm from pectinate line)		
5–9	15 (49%)	14 (42%)
10–15	15 (49%)	20 (58%)
>15	1 (2%)	0
UICC stage		
I	7 (22%)	12 (33%)
II	12 (38%)	8 (23%)
III	10 (33%)	13 (35%)
IV	2 (5%)	1 (2%)
Method for evaluating anastomosis		
CT	8 (25%)	12 (33%)
Rectoscopy	8 (25%)	6 (18%)
Both methods	15 (49%)	16 (49%)

Table 2. Characteristics of surgical interventions and early postoperative outcomes in both groups

	Randomized groups	
	Early closure	Early closure
Number of patients	31	34
Mean time to closure, days	11 (8–21)	148 (64–265)
Intraoperative blood loss, ml	5 (0–160)	5 (0–130)
Time of surgery, min	50 (27–126)	71 (31–134)
Manual suture (number of operations), abs. (%)	6 (18)	10 (30)
Stapling device (number of operations), abs. (%)	25 (82)	34 (70)
Epidural anesthesia/ abs. (%)	1 (2)	1 (2)
Time of gas discharge, days	1 (0–6)	2 (0–8)
Time to complete enteral nutrition, days	1 (0–8)	2 (0–20)
Hospital-stay after closure	4 (2–21)	4 (2–28)
Postoperative complications (patients), Clavien-Dindo classification (grade I–V), abs. (%)	2 (6.45)	2 (5.58)
Grade I	1	0
Grade II	0	1
Grade IIIb	1	1
Cause of redo surgery after ileostomy closure	0	Small intestine obstruction (n=1)

(ratio of the main and control groups 1.00, 95% CI 0.94–1.08; $p < 0.05$).

Discussion

The results of our trial confirm safety of early closure of ileostomy in patients with colorectal cancer after total and partial mesorectumectomy. The study included patients without early failure of the anastomosis regardless previous preoperative radiotherapy or severe somatic and nutritional status. Exclusion criteria prevented the influence of some factors aggravating normal tissue regeneration (diabetes mellitus, steroid drugs intake). In this study, there were no objectives to assess quality of life in patients with ileostomy prior to their closure or to analyze ileostomy-associated complications in the control group. Our goal was to determine the response of patients after total and partial mesorectumectomy on early redo surgery. Moreover, we assessed the influence of tissue changes around ileostomy on the time of surgery and intraoperative blood loss. Postoperative morbidity, intraoperative blood loss, length of hospital-stay and ICU-stay were similar in both groups. There was one complication in each group which required redo surgery. Postoperative bleeding occurred in 1 patient after early closure of ileostomy. Bleeding was caused by small vein in aponeurosis. Bleeding was localized within subcutaneous tissue. In the control group, single case of complication grade IIIb was associated with small intestine obstruction near the anastomosis due to its edema. Anastomosis de novo was formed

again. In both cases, the patients were discharged from the hospital without further complications. We also believe that complication in the control group cannot be considered as a direct consequence of treatment strategy or drawback of delayed closure of ileostomy. Incidence and severity of postoperative complications according to Clavien–Dindo classification were similar in both groups (2 in the main group and 2 in the control group).

We should also consider such variable as mean time of surgery. This value was almost 1.5 times lower in the main group than in the control group. These differences may be due to objective reasons. Advanced cicatricial processes around ileostomy develop after 12 weeks in the control group that greatly complicates following closure.

It can be concluded that patients after radical rectal surgery followed by ileostomy can safely undergo early closure of ileostomy after 8–13 days without risk of postoperative complications if clinical, X-ray and endoscopic signs of anastomotic failure are absent. This approach gradually spreads throughout the world and needs further study. Our further objectives are comparison of long-term results and quality of life after early closure of ileostomy. It is very important since the last variable has been recently considered as one of the essential factors in choosing surgical strategy for many diseases. Our second goal will be analysis of the effect of early ileostomy closure on the cost expenditures to maintain adequate function of ileostomy by using of specialized devices.

Authors declare no conflict of interests.

REFERENCES

1. Каприн А.Д., Старинский В.В. *Состояние онкологической помощи населению России в 2016 г.* МНИОИ им. П.А. Герцена — филиал ФГБУ «НМИРЦ» Минздрава России. М. 2017.
Kaprin AD, Starinski VV. *The state of oncological medical services for Russian population in 2016.* P.A. Gertsen MSROI — the filial of FSBI NMR-CR of the Ministry of Health of Russia Federation. М. 2017. (In Russ.).
2. Ассоциация колопроктологов России. *Клинические рекомендации по ведению взрослых пациентов с кишечной стомой.* Министерство здравоохранения Российской Федерации. М. 2013.
The Russian Association of Coloproctologists. *Clinical recommendations for management of adult patients with o-stomy.* The Ministry of Health of Russia Federation. М. 2017. (In Russ.).
3. Salamone G, Licari L, Agrusa A, Romano G, Cocorullo G. Usefulness of ileostomy defunctioning stoma after anterior resection of rectum on prevention of anastomotic leakage A retrospective analysis. *Ann Ital Chir.* 2016;87:155-160.
4. Wong NY, Eu KW. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. *Dis colon rectum.* 2005 Nov;48(11):2076-2079.
<https://doi.org/10.1007/s10350-005-0146-1>
5. Umesh Jayarajah, Asuramuni MP Samarasekara. A study of long-term complications associated with enteral ostomy and their contributory factors. *BMC Res Notes.* 2016;9:500.
<https://doi.org/10.1186/s13104-016-2304-z>
6. Hindenburg T, Rosenberg J. Closing a temporary ileostomy within two weeks. *Dan Med Bul.* 2010;57:1-5.
7. Farag S, Rehman S, Sains P, Baig MK, Sajid MS. Early vs delayed closure of loop defunctioning ileostomy in patients undergoing distal colorectal resections: an integrated systematic review and metaanalysis of published randomized controlled trials. *Colorectal Dis.* 2017 Dec;19(12):1050-1057.
<https://doi.org/10.1111/codi.13922>
8. Danielsen AK, Jansen JE, Bock D, Skullman S. Early closure of a temporary ileostomy in patients with rectal cancer. A multicenter randomized controlled trial. *Annals of surgery.* 2017 Feb;265:284-290.
9. Danielsen AK, Correa-Marinez A, Angenete E et al. Early closure of temporary ileostomy — the EASY trial: protocol of randomized controlled trial. *BMJ Open.* 2011;1:1-7.
10. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann surg.* 2009;250:187-196.
11. Dindo D, Demartines M, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of survey. *Ann surg.* 2004;240:205-213.

Received 04.10.2018
Accepted 18.12.2018