

RESEARCH ARTICLE

Editorial Process: Submission:11/09/2021 Acceptance:03/06/2022

The Effect of 5-Fluorouracil on the Adhesion Process in Patients Operated on for Colorectal Cancer

Serik Zhakipbekov^{1*}, Muratbek Osombaev², Serik Irimbetov³

Abstract

Objective: The aim of this study was to improve the direct results of reconstructive surgery in patients operated on for complicated forms of colorectal cancer, by using 5-fluorouracil in the postoperative period. **Methods:** The study involved 126 patients (they were divided into 2 groups) with colorectal cancer, who underwent reconstructive surgery. They underwent a standard clinical examination and a mandatory examination program. **Results:** The use of 5-fluorouracil in adjuvant treatment in patients with colorectal cancer significantly reduces the number of subjective clinical manifestations (positional tests) in the main group – 17%, and in the control group – 54.3%, as well as objective clinical manifestations (instrumental research methods) in Group I – 13%, and Group II – 89.5%, respectively. The study shows that in re-operated patients with colorectal cancer who received 5-fluorouracil, abdominal adhesions are characterized by a low content of collagen and fibroblasts, low vascularization and a high content of polymerized fibrin strands. It was also found that re-operated patients with colorectal cancer who did not receive 5-fluorouracil, abdominal adhesions are characterized by a high collagen content, a large number of fibroblasts, and severe angiogenesis. **Conclusion:** It was found that the prolonged administration of 5-fluorouracil statistically significantly reduces the risk of adhesions, thereby showing the effectiveness of preventing adhesive disease of the abdominal organs. It was shown that the prolonged administration of 5-fluorouracil significantly reduces the number of subjective and objective signs of adhesive disease of the abdominal organs, as well as significantly decreases intraoperative and postoperative complications, the duration of the operation, and the amount of blood loss. In the postoperative period, it reduces the length of hospital stay and improves the quality of life of patients.

Keywords: Colorectal cancer- obstructive colon resection- colon continuity restoration- adhesion process-5-fluorouracil

Asian Pac J Cancer Prev, 23 (3), 995-1003

Introduction

About 1.4 million cases of colorectal cancer are diagnosed in the world each year, with annual deaths from this disease exceeding 50% of people. In terms of incidence, colorectal cancer ranks third among malignant tumors in both men and women, and comes second as the cause of death from malignant neoplasms (American Cancer Society, 2015; Ferlay et al., 2015; Shpitz, 2009).

Despite the development of modern diagnostic methods, there is no decrease in the number of patients with a complicated course of malignant colon diseases. The complicated course of colorectal cancer determines the need to start treatment with radical surgery to eliminate the pathological substrate and determine the possibility of a one- or multi-stage restoration of colonic continuity (Shurkalin et al., 2008; Barsukov, 2009). Currently, practitioners have no well-developed algorithm of surgical measures on this issue. Emergency care for the category of patients with a stenotic colon tumor in most institutions

is provided by general surgeons, and, according to the literature data, in most emergency cases, the operation of choice for left-sided tumor localization is obstructive resection, which usually requires the use of a multi-stage surgical treatment (Sprangers et al., 1995; Miziyeve et al., 2006).

Currently, the restoration of colonic continuity during colostomy is one of the urgent tasks of abdominal surgery, the sole purpose of which is to improve the quality of life of patients (Lyhman, 2015; Totikov and Totikov, 2014). This intervention is a technically complex operation associated with adhesive disease of the abdominal cavity. Sometimes it outweighs the primary operation and is characterized by a relatively high incidence of complications, which is more associated with the development of adhesive disease. Moreover, the adhesion process often leads to significant technical difficulties when performing repeated operations on the abdominal organs, while increasing the number of surgical complications (Lutsevich et al., 2007; Shchaeva, 2017; Banerjee et al., 2005; Dalgic et al., 2015).

¹Nur-Sultan Multidisciplinary Medical Center of Akimat, Nur-Sultan, Kazakhstan. ²Kyrgyz State Medical Institute for Retraining and Qualification named after S.B. Daniyarov, Bishkek, Kyrgyzstan. ³Astana Medical University, Nur-Sultan, Kazakhstan.

*For Correspondence: serikjakipbekov@gmail.com

According to various sources, the adhesion process of varying severity develops in 55-100% of patients after surgical interventions. In 40-75% of cases, intestinal obstruction is associated with peritoneum adhesions, and mortality in acute adhesive intestinal obstruction remains at a high level (6-10%) and has no tendency to decrease (Zhenchevsky, 1989; Holmdahl et al., 1998; Jacobi et al., 2001).

For the prevention of adhesions in the abdominal cavity, all modern methods used are ineffective. When performing reconstructive surgery, it is the adhesion process that complicates the course of the operation, prolongs its duration and increases the incidence of intraoperative and postoperative complications (Gorskiy et al., 2014; Krook et al., 1991; Krukowski, 2008; Menzies and Ellis, 1991).

An essential condition after radical surgery for colorectal cancer is the use of adjuvant chemotherapy for the antitumor purpose. The main drug for colon cancer is fluoropyrimidine – 5-fluorouracil. The antitumor mechanism of this medication has been sufficiently examined, but the role of 5-fluorouracil in preventing the development of the postoperative adhesion process in the abdominal cavity has not been studied. In our long-term practice, when performing reconstructive surgery, we observed the absence or low severity of the adhesion process of the abdominal cavity in patients who received chemotherapy with 5-fluorouracil in the postoperative period. In patients who did not receive this drug, the adhesion process was extensive (Rodel et al., 2012; Chen et al., 2012).

Therefore, there is a need to develop new methods and tools for the prevention of adhesive disease of the abdominal cavity after surgical interventions for colorectal cancer.

The purpose of the study is to improve the direct results of reconstructive surgery in patients operated on for complicated forms of colorectal cancer, by using 5-fluorouracil in the postoperative period.

Materials and Methods

Patient recruitment

The study involved 126 patients with colorectal cancer, who underwent reconstructive surgery in the Department of Intestinal Tumors at the National Center of Oncology in Bishkek from 2000 to 2015. A retrospective and prospective analysis of the study was conducted.

Table 1. Distribution of Patients Depending on the Tumor Location

Location	Number of patients	
	abs	%
Rectum	36	28.6
Rectosigmoid region	11	8.7
Sigmoid colon	54	42.8
Descending colon	23	18.8
Transverse colon	2	1.6
Total	126	100.0

All patients were divided into two groups:

1. Group I (main) consisting of 69 (54.7%) patients who underwent a postoperative course of adjuvant chemotherapy with 5-fluorouracil after the first stage of the operation;

2. Group II (control) consisting of 57 (45.3%) patients who did not receive a course of adjuvant chemotherapy with 5-fluorouracil after the first stage of the operation.

All patients underwent a standard clinical examination: medical history, assessment of the objective status of patients, multifunctional clinico-diagnostic examination, including the use of laboratory methods. The mandatory examination program, which was the basis for establishing the clinical stage of the disease, included conducting a digital rectal examination, video colonoscopy, irrigoscopy, CT of the abdominal and thoracic segments, MRI of the pelvic organs, as well as determination of CEA and CA19-9 levels.

The diagnosis and surgical indications were determined on the basis of medical history, clinical findings and diagnostic data. When collecting medical history, attention was paid to the age of patients, their social status, previous operations, and somatic diseases. By age, patients in the main and control groups did not differ significantly. The average age of patients was 57.07 ± 1.8 years in the control group and 54.78 ± 1.4 years in the main group. In terms of gender, there were two times more women than men. The number of men in the first group was 30 (43.4%), in the second group – 18 (31.5%), while that of women – 39 (56.6%) and 39 (68.5%), respectively. In total, there were 48 men (38.1%) and 78 women (61.9%).

Ethics approval

All patients provided their written informed consent for treatment. All diagnostic methods, tools and equipment were state registered.

Results

The distribution of patients depending on the location of the primary tumor is presented in Table 1. Of 126 patients (see Table 1), 54 (42.8%) patients had sigmoid colon cancer, 36 (28.6%) patients – rectal cancer, and the fewest number of patients (2 patients) had a transverse colon tumor. Table 2 shows the frequency of complicated forms of colon cancer.

Most often, in more than 86.5% of cases, patients, who were admitted to hospital (during initial presentation), had intestinal obstruction, while 11% of patients had perifocal tumor abscess and profuse bleeding. Tumor perforation

Table 2. Distribution of Patients by Type of Complications

Complicated forms	Number of patients	
	Abs	%
Intestinal obstruction	109	86.5
Perifocal abscess	7	5.5
Tumor bleeding	7	5.5
Tumor decay and perforation	3	2.5
Total	126	100.0

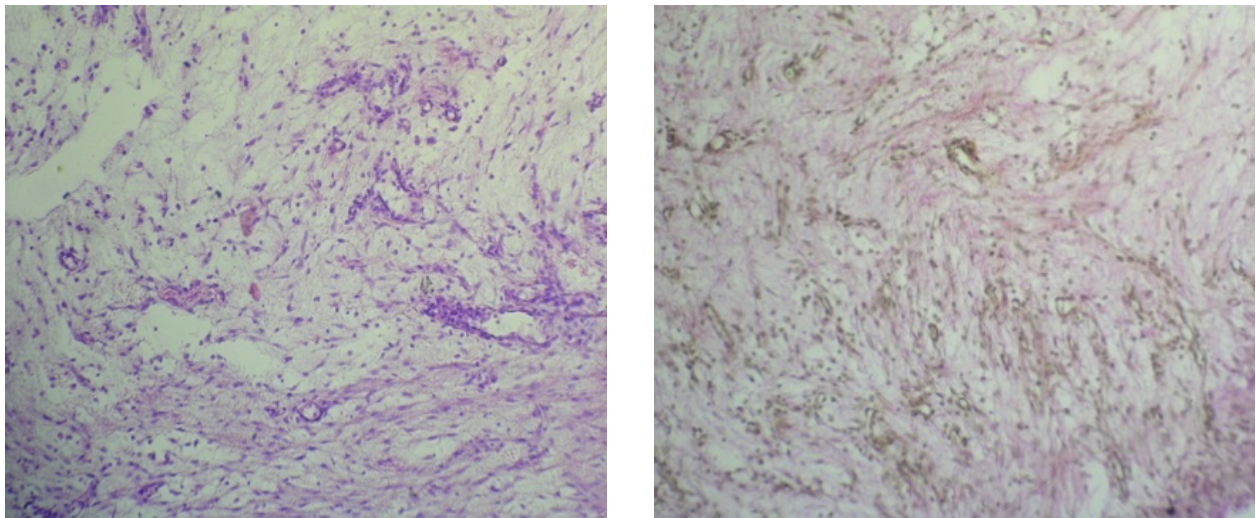


Figure 1. Samples of Loose Connective Tissue (Hematoxylin and Eosin Staining, Van Gieson Staining X100)

Table 3. Distribution of Patients by Performed Primary Surgical Interventions

Primary surgery volume	Group I		Group II	
	abs number	%	abs number	%
Obstructive rectal resection	26	37.7	18	31.6
Obstructive sigma resection	32	46.4	24	42.1
Obstructive left hemicolectomy	10	14.5	14	24.5
Obstructive resection of the transverse colon	1	1.4	1	1.8
Total	69	100.0	57	100.0

was observed in only three patients. Most of the surgical interventions were performed in various parts of the colon (see Table 3).

As can be seen from Table 3, obstructive resection of the sigmoid colon was performed more often both in the main group (32, or 46.4%, patients) and in the control group (24, or 42.1%, patients). According to the data of our study, Hartmann's operation comes second in terms of performed primary surgical interventions both in the main group (26, or 37.7%, patients) and in the control group (18, or 31.6%, patients). In one case, obstructive resection of the transverse colon was performed. Due to the local

prevalence of the tumor process, 15 patients underwent combined operations with resection or extirpation of the adjacent organs (see Table 4).

As can be seen from the above Table 4, 15 combined operations were performed in the study groups: 7 in the main group (10.1%) and 8 in the control group (14%). Postoperative histology in both groups with the dominant morphological variant was moderately differentiated adenocarcinoma, which amounted to 78 (67.2%) cases, and poorly differentiated adenocarcinoma – 12 (10.3%) cases. In one case (0.8%), hemangiopericytoma was detected in the control group. The indicated distribution of patients

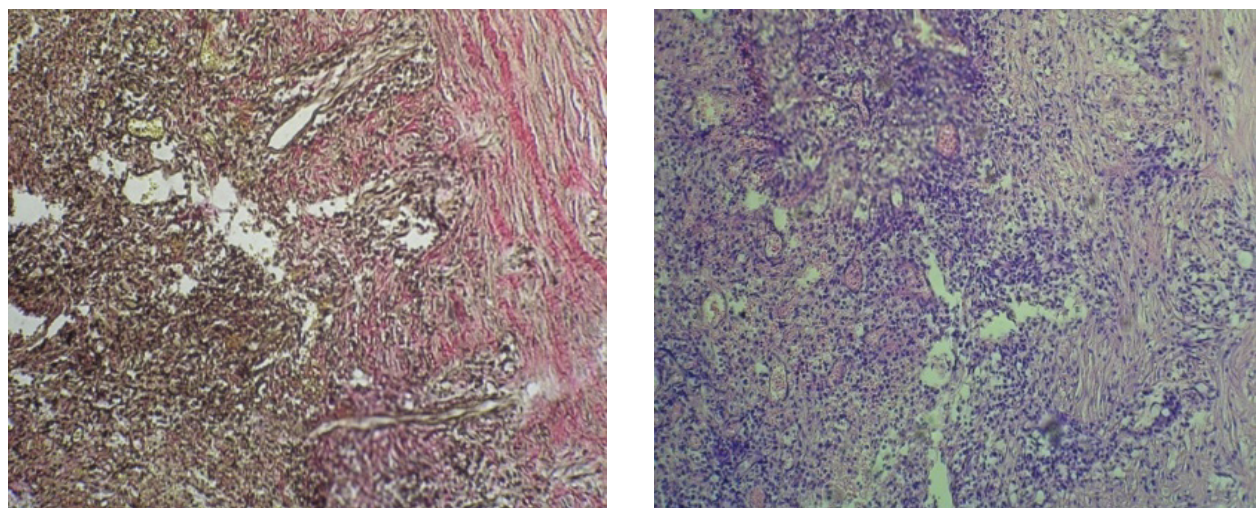


Figure 2. Samples of Granulation Tissue (Hematoxylin and Eosin Staining, Van Gieson Staining X100)

Table 4. Types of Combined Operations

Combined operations	Group I	Group II
Combined obstructive operation of the colon with extirpation of the uterus with appendages	3	4
Combined obstructive operation of the colon with resection of the bladder and ureter	2	2
Combined obstructive resection of the colon with resection of the small intestine	2	1
Combined obstructive resection of the transverse colon with stomach resection	-	1
Total	7 (10,1%)	8 (14%)

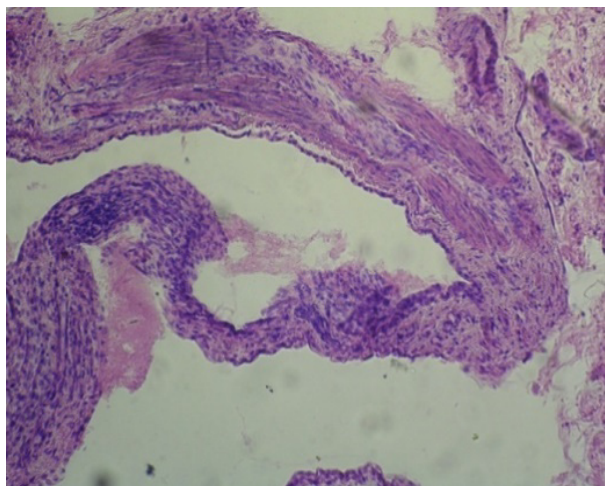


Figure 3. Restored Mesothelial Cover (Hematoxylin and Eosin Staining X100, X400)

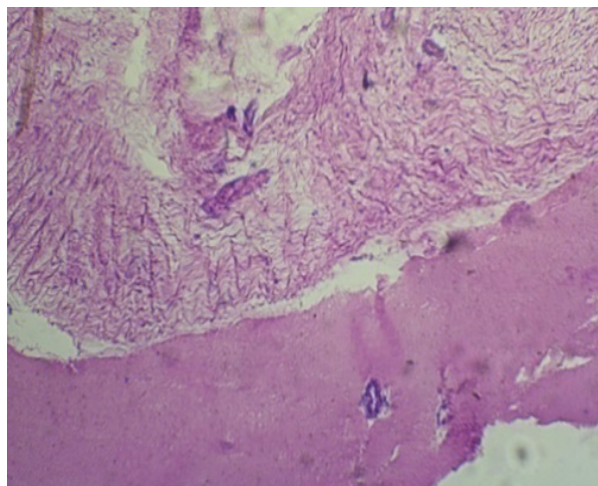


Figure 4. Proliferation of Mesotheliocytes (Hematoxylin and Eosin Staining X100, X400)

by morphological forms was carried out according to the criteria and terminology of the International Histological Classification of Tumors.

All patients of the main group received adjuvant chemotherapy according to the scheme: 5-fluorouracil 500 mg/m², 4 cycles, 4 courses, every 3 weeks.

In all patients who underwent primary surgery, colorectal cancer proceeded with complications, such as intestinal obstruction, perifocal abscess, etc. In 15 (12%) patients, primary surgical interventions were combined, with resection or removal of the adjacent organs, which indicates the prevalence of surgical traumatic effects.

When analyzing the nature of complaints in the long

term of the postoperative period, it was revealed that most often patients had alternating chronic constipation, flatulence and abdominal pain. Moreover, a larger percentage of cases was observed among patients of Group II. Abdominal pain occurring during physical exertion more often than other was also noted in patients of Group II. Table 5 presents the frequency of pain symptoms from positional tests.

The analysis of the positional test data revealed that the frequency of positive symptoms is three-fold higher in the control group in comparison with the main group.

Table 6 presents the frequency of detecting the adhesion process of the abdominal cavity by instrumental

Table 5. Distribution of Patients According to the Results of Positional Tests

Positive positional tests	Group I		Group II	
	abs number	%	abs number	%
Knoch positive symptom	3	4.3	10	17.5
Pain with body being bent forward (Blinov's symptom)	4	5.8	14	24.5
Pain with traction over the scar area (Bondarenko's symptom)	5	7.2	7	12.3
Total	12	17.3	31	54.3

Table 6. Instrumental Research Methods

Diagnostic methods	Group I		Group II	
	abs number	%	abs number	%
Ultrasound (abdominal cavity)	6	8.7	28	49.1
Colonoscopy (irrigoscopy)	3	4.3	17	29.8
Plain abdominal radiography	-	-	6	10.6
Total	9	13.0	51	89.5

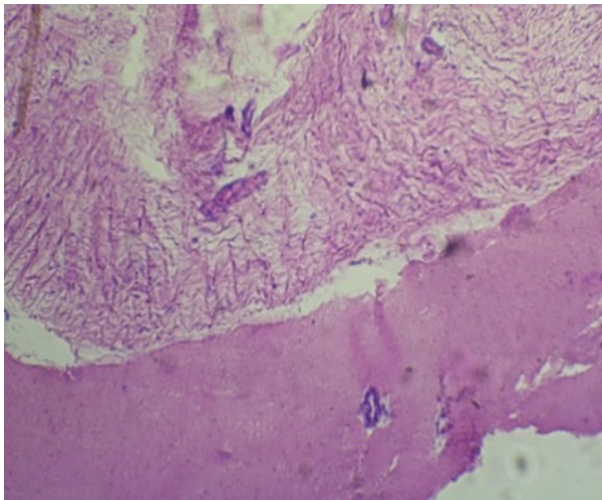


Figure 5. Polymerized Fibrin Strands (Hematoxylin and Eosin Staining X200)

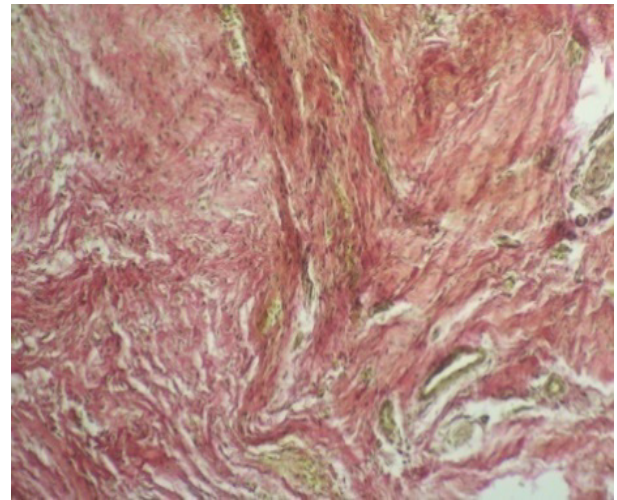


Figure 6. Coarse Fibrous Connective Tissue

methods.

Table 6 shows that during the transabdominal ultrasound examination of the abdominal organs, there were signs of the adhesion process, usually in the form of viscero-parietal fusion and thickening of the peritoneal areas, in 6 (8.7%) patients of Group I (main) and 28 (49.1%) patients of Group II (control). When performing colonoscopy, indirect signs of adhesive disease of the abdominal organs were manifested primarily in the form of pain syndrome during the study, as well as difficulties in the apparatus passing through the intestines; changes in the intestinal contour were detected in 3 (4.35%) patients of Group I (main) and 17 (29.8%) patients of Group II. Intestinal obstruction during the observational fluoroscopy of the abdominal organs was suspected in 6 (10.5%) patients of Group II, but was not observed in the main group. Against the background of conservative measures, obstruction phenomena were resolved for one patient of Group II, while the rest were operated on for adhesive intestinal obstruction on an emergency basis.

All of the above methods for examining patients with the aim of identifying the adhesion process are indirect signs. It became possible to objectively determine the effectiveness of 5-fluorouracil for the prevention of adhesion processes during reconstructive surgery.

Discussion

In the period from 6 to 8 months after primary surgery,

69 (54.7%) patients of Group I and 57 (45.3%) patients of Group II underwent reconstructive colon surgery. During the operation, the quantitative and qualitative nature of adhesion formation was evaluated. For this purpose, the developed scale of objective and instrumental indicators based on the classification by Diamond (1987) and Antsupov (2006) was used. The severity of adhesion processes was evaluated on the following basis: less than 6 points were regarded as the absence of adhesions; 7-12 points – slightly pronounced; 13-24 points – moderately pronounced; 25-37 points – a strongly pronounced adhesion process.

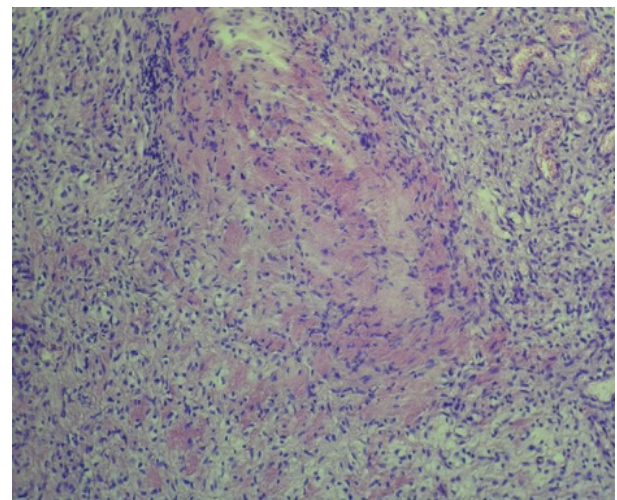


Figure 7. Hyalinosis Area in Coarse Fibrous Connective Tissue

Table 7. Diamond's Scale for Patient Distribution

No	Scale	Group I (n=69)	Group II (n=57)	P
1	Severity of the adhesion process of the abdominal organs	1.49±0.07	3.11±0.07	=0.001
2	Adhesion process of the pelvic organs	1.54±0.13	3.37±0.08	=0.001
3	Adhesion type	1.25±0.05	3.26±0.19	=0.001
4	Topographic anatomical location	2.62±0.1	5.75±0.33	=0.001
5	Presence of a vascular adhesion component	1.17±0.06	3.74±0.12	=0.001
6	Adhesion density	1.25±0.08	4.86±0.11	=0.001
7	Deformation or involvement of the intestinal mesentery in the adhesion process	0.22±0.94	2.89±0.74	>0.05

Table 8. Degree of Severity of the Adhesion Process

Severity of the adhesion process during repeated surgery	Group I with the use of 5-fluorouracil		Group II without the use of 5-fluorouracil	
	abs number	%	abs number	%
Absence of adhesions	16	48.5	-	-
Slightly pronounced	10	30.3	2	6.5
Moderately pronounced	4	12.1	9	29
Strongly pronounced	3	9.1	20	64.5

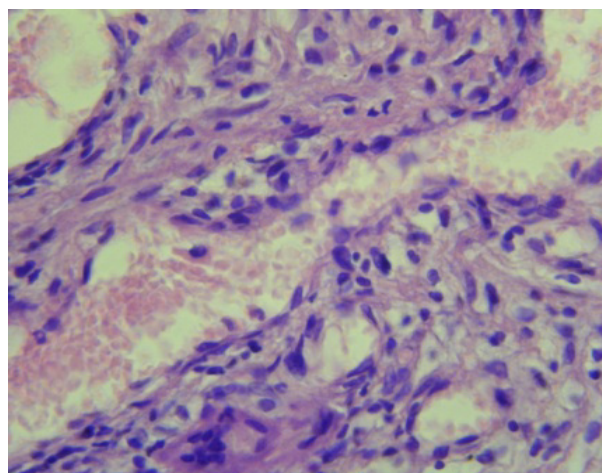
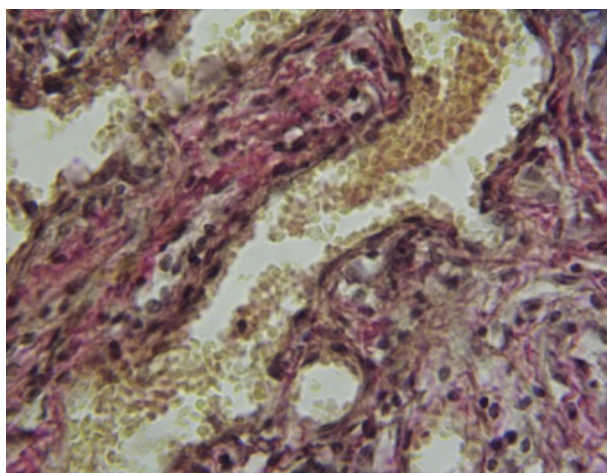


Figure 8. Blood Vessels of Various Calibers (Hematoxylin and Eosin Staining X400, Van Gieson staining X400)

On a point scale, the severity of adhesion processes ranged from 18 to 34 points, a larger number corresponded to a moderate and pronounced adhesion process (see Table 7).

Table 7 shows that the severity of the adhesion process of the abdominal organs in the main group amounted to

1.49 ± 0.07 , and in the control group – to 3.11 ± 0.07 . The adhesion process of the small pelvis in the main group was 1.54 ± 0.13 , in the control group – 3.37 ± 0.08 . On the third scale for the adhesion type, in the main group it was 1.25 ± 0.05 , in the control group – 3.26 ± 0.19 . On the fourth scale for the topographic anatomical location,

Table 9. Intraoperative Complications

Complications	Group I		Group II	
	abs number	%	abs number	%
DesORIZATION of hollow organs	7	10.2	35	61.4
Enterotomy	2	2.8	14	24.6
Bleeding	1	1.5	4	7
Intestinal resection due to multiple desORIZATION	-		4	7

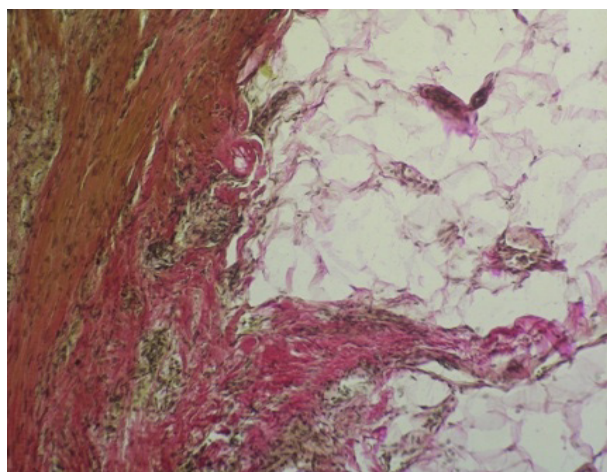


Figure 9. Adhesion Represented by Fibrous and Adipose Tissue (Van Gieson Staining X100)

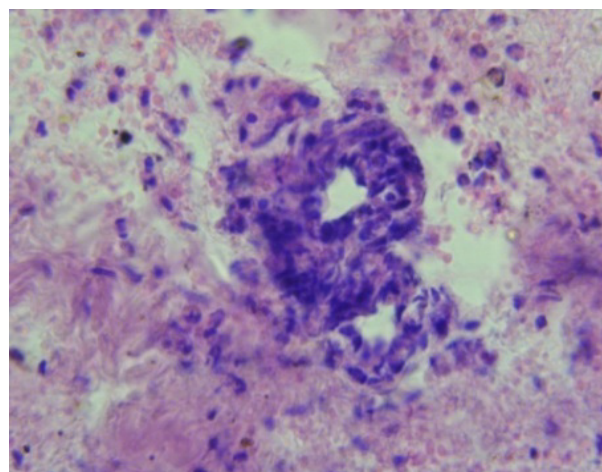


Figure 10. Productive Vasculitis (Hematoxylin and Eosin Staining X400)

Table 10. Distribution of Patients According to the Duration of the Operation, the Volume of Blood Loss, and the Length of Hospital Stay

Group	Group I	Group II
Duration of the operation (min)	117.4±3.3	175.7±7.8
Volume of blood loss (ml)	381.1±24.5	653.5 ± 31.3
Length of hospital sta	15.8±0.3	21.6 ± 0.8

in the main group it was 2.62 ± 0.1 , in the control group – 5.75 ± 0.33 . On the fifth scale for the presence of a vascular adhesion component, in the main group it was 1.17 ± 0.06 , and in the control group – 3.74 ± 0.12 . On the sixth scale for the adhesion density, in the main group it amounted to 1.25 ± 0.08 , in the control group – 4.86 ± 0.11 . On the seventh scale for the deformation and involvement of the mesentery in the adhesion process, in the main group it was 0.22 ± 0.94 , and in the control group – 2.89 ± 0.74 . Based on the foregoing, the average amount of the main group was 9.6 ± 0.51 , and that of the control group – 27.1 ± 0.65 . The result is statistically significant $p=0.001$.

During the operation and in the early postoperative period, the following criteria were used to analyze and compare the nature of clinical manifestations in the studied groups: the prevalence of adhesions, intraoperative and postoperative complications, the duration of the operation, the amount of blood loss, the length of hospital stay, and the severity of pain.

When performing reconstructive surgery in patients with colorectal cancer, the degree of severity of the adhesion process in the abdominal cavity was evaluated intraoperatively (see Table 8).

No adhesions were intraoperatively detected in 16 (48.5%) patients of the main group. A slightly pronounced adhesion process was observed in 10 (30.3%) patients of Group I and in 2 (6.5%) patients of Group II. A moderately pronounced adhesion process was detected in 4 (12.1%) patients of the main group and in 9 (29%) – of the control group. A strongly pronounced adhesion process was detected in 3 (9.1%) patients of the main group and in 20 (64.5%) patients of the control group. In 2 patients of the control group, during the second stage of the operation, reconstructive surgery was not possible due to the pronounced cicatricial adhesions. In patients of Group II, the adhesion process of varying severity was intraoperatively detected in 100% of cases.

As can be seen from Table 9, complications were dominated by desorption in the control group – 35 (61.4%) patients, and in the main group it was observed in 7 (10.2%) patients. In 4 (7%) patients of the control group, due to multiple desorption during adhesiolysis, intestinal resection was needed to be performed, but in the main group such cases were not observed. Enterotomy in patients of the main group was observed in 2 (2.8%) cases, and in the control group – 14 (24.6%). Bleeding was detected in 4 (7%) cases in the control group and in only 1 case in the main group.

Table 10 presents the volume of blood loss, the duration of the operation, and the length of hospital stay in the study groups.

As can be seen from the above table, the average

Table 11. Incidence and Types of Postoperative Complications

Complications	Group I		Group II	
	abs number	%	abs number	%
Adhesive intestinal obstruction	-	-	6	10.6
Eventration	2	2.9	2	3.5
Anastomotic leakage	2	2.9	3	5.3
Wound abscess	2	2.9	1	1.8
Total	6	8.7	12	21.2

duration of the operation varied in Group I in the interval 117 ± 3.3 minutes (1 hour 57 minutes), and in Group II – 175.7 ± 7.8 minutes (2 hours 55 minutes), which indicates the severity of the adhesion process and its complications. Blood loss in Group I amounted to 381.1 ± 24.5 ml and in Group II – to 653.5 ± 31.3 , which was primarily associated with the severity of the adhesion process with the involvement of organs. The average length of hospital stay in Group I was 15.8 ± 0.3 days and in Group II – 21.6 ± 0.8 days. Table 11 presents postoperative complications.

According to the data presented in Table 11, adhesive intestinal obstruction was observed only in the control group – 6 (10.5%) patients. Such formidable complications as anastomotic leakage in the main group amounted to 2.9%, and in the control group – 5.3%.

In order to eliminate complications associated with anastomotic leakage and eventration, appropriate emergency surgical interventions were performed in Group I in 4 (5.8%) patients and in Group II in 5 (8.8%) patients. The largest number of postoperative complications was observed in the control group – 21%, and in the main group – 9%.

Morphological characteristic of adhesions

A study was conducted of the prospective histological material obtained during the second stage of the operation. First of all, the mesothelial cover of the peritoneum as well as the underlying tissues were examined using optical microscopy methods. Primary biopsy (flaps of the intact peritoneum up to 2-3 cm) was taken in patients of both groups during reconstructive surgery, from the zone of previous destruction of the peritoneum. After the biopsy study, the analysis and comparison of the obtained data was performed.

The mesothelial cover of the visceral and parietal peritoneum was studied in the intact and repaired zone using microscopy. The material for morphological examination was taken according to standard requirements for the manufacture of histological preparations. Histological sections 3 to 5 μ m thick were stained with hematoxylin and eosin, as well as picrofuxin according to van Gieson's method. The preparations were studied under Nikon 50i microscope (Japan), and the photographing of the micropreparations was carried out using a digital camera.

Morphological characteristics of adhesions in re-operated patients with colorectal cancer who received 5-fluorouracil

During histological examination in the main group, it was noted that in all patients, adhesions were represented by loose connective tissue with a small number of fibroblasts and fibrocytes. There are small areas where the mesothelium is saturated with fibrin. Diffuse leukocyte infiltration is absent. There are a few spindle-shaped fibroblasts and mitotic figures. There are fibroblasts with dystrophic changes. The number of cellular elements is significantly smaller than in the comparison group. There are a few lymphocytes and plasma cells (see Figure 1).

In five cases, maturing granulation tissue was determined (Figure 2).

A morphological study of the restored peritoneal zone revealed the restoration of the mesothelial cover with small cell infiltration of the underlying connective tissue plate and with moderate proliferation of the mesothelium. Changes in the structure of mesotheliocytes after chemotherapy with 5-fluorouracil consisted in the fact that the cells had the most diverse number of contacts in shape and size from giant to very small. An analysis of the distribution of the mesothelial cells lining the restored peritoneal zone in terms of the degree of connectivity showed that these differences are limited to the interval 3-9. In the repaired mesothelium, an almost complete absence of milky spots was observed. In some areas, cell stratification was detected with the creation of a multi-row epithelium, some cells of which had fragmented cytoplasmic membranes (see Figures 3 and 4).

The study of the vascular bed showed that neoangiogenesis was less pronounced in patients who received 5-fluorouracil compared with those who did not. In some patients, polymerized fibrin seed strands were determined on the surface of soft, loose connective tissue (see Figure 5).

This indicates a moderate inflammatory reaction in adhesions, which leads to a sluggish fibrin transudation and a self-sustaining course of adhesion formation.

Thus, our study shows that in re-operated patients with colorectal cancer who received 5-fluorouracil, abdominal adhesions are characterized by a low content of collagen and fibroblasts, low vascularization and a high content of polymerized fibrin strands.

Morphological characteristics of abdominal adhesions in re-operated patients with colorectal cancer who did not receive 5-fluorouracil

Histological examination revealed that in the majority of patients, adhesions were represented by coarse fibrous connective tissue (see Figure 6). At the site of damage, there is an already formed granulation tissue consisting of capillaries, cellular elements and collagen fibrils. Dense fibrous connective tissue is found, which is represented mainly by collagen fibers as well as fibroblasts and fibrocytes located between them. In dense connective tissue, collagen fibers are oriented longitudinally, slightly curved. The phenomena of hyalinosis are also observed (see Figure 7).

The development of such an adhesion process of a

fibro-hyalinous nature was accompanied by the formation of blood vessels of various calibers. A large number of capillaries lined with a single layer of the endothelial cells located on a thin basement membrane is determined in granulation tissue. In addition, the capillaries are formed by the endothelialization of gaps between fibrin strands. The capillary loops are dilated and full-blooded. In the lumen of some of them, erythrocyte aggregation and stasis are observed. An increase in the permeability of capillary walls is noted, which led to tissue edema as well as erythrocyte and leukocyte diapedesis. Some capillary branches have a vertical orientation. There are numerous cellular elements of granulation tissue between the capillaries: fibroblasts, macrophages, plasma cells, and lymphocytes (see Figure 8).

In some cases, in addition to fibrous tissue, adipose tissue was also detected (see Figure 9). The adhesion process is represented by a combined focal-diffuse or fragmentary substitution of connective and adipose tissue with the presence of lymphocyte and fibroblast infiltration.

Tissue reorganization and modification in the form of multiple sprouting neurovascular bundles in the thickness of the fusion was also noted. In three cases, productive vasculitis was found on the periphery of adhesions (see Figure 10).

Therefore, histological examination data show that in re-operated patients with colorectal cancer who did not receive 5-fluorouracil, abdominal adhesions are characterized by a high collagen content, a large number of fibroblasts, and severe angiogenesis.

The study found that the prolonged administration of 5-fluorouracil statistically significantly reduces the risk of adhesions, thereby showing the effectiveness of preventing adhesive disease of the abdominal organs. It was shown that the prolonged administration of 5-fluorouracil in patients operated on for colorectal cancer significantly reduces the number of subjective and objective signs of adhesive disease of the abdominal organs, as well as significantly decreases intraoperative and postoperative complications, the duration of the operation, and the amount of blood loss. In the postoperative period, it reduces the length of hospital stay and improves the quality of life of patients.

In conclusion, the use of 5-fluorouracil in adjuvant treatment in patients with colorectal cancer significantly reduces the number of subjective clinical manifestations (positional tests) in the main group – 17%, and in the control group – 54.3%, as well as objective clinical manifestations (instrumental research methods) in Group I – 13%, and Group II – 89.5%, respectively.

The use of 5-fluorouracil significantly decreases the incidence of intraoperative and postoperative complications (9% in the main group, 21% in the control group), as well as reduces the duration of the operation by more than 60 minutes, the amount of blood loss during surgery by 2 times, and the length of hospital stay.

Based on pathomorphological studies, it can be argued that adjuvant chemotherapy with 5-fluorouracil is an effective method for the prevention and treatment of adhesive disease of the abdominal cavity in patients with colorectal cancer.

Author Contribution Statement

Serik Zhakipbekov - concept, design and control of the research; writing the text of the article; approval of the final version of the article. Muratbek Osombaev - collection and preparation of data; primary processing of the material and its verification; statistical processing and analysis of the material; writing the text of the article. Serik Irimbetov - primary processing of the material and its verification; statistical processing and analysis of the material; writing the text of the article. All authors approved the final version of the manuscript.

Acknowledgements

This study was not funded. It was part of Serik Zhakipbekov's PhD dissertation. The Ethical Committee of Kyrgyz-Russian Slavic University approved the research.

Conflict of interests

The authors declare that they have no competing interests; neither financial nor non-financial interests.

References

- American Cancer Society (2015). Global Cancer Facts & Figures 3rd Edition; 61.
- Banerjee S, Leather AGM, Rennie JA, et al (2005). Feasibility and morbidity of reversal of Hartmann's. *Colorectal Dis*, **7**, 454-9.
- Barsukov YuA (2009). The modern strategy for creating high-tech treatment programs in oncoproctology. Proceedings of the 3rd Russian Oncological Congress. Moscow, 2009, pp 455-6.
- Chen MJ, Chen TY, Cheng YM, Hsu YC (2012). The effect of postoperative hyperbaric oxygen treatment on intra-abdominal adhesions in rats. *Int J Mol Sci*, **13**, 12224-31.
- Dalgic T, Oymaci E, Bostanci EB, Cakir T (2015). Effects of carbon dioxide pneumoperitoneum on postoperative adhesion formation and oxidative stress in a rat cecal abrasion model. *Int J Surg*, **21**, 57-62.
- Ferlay J, Soerjomataram I, Dikshit R, et al (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, **136**, 359-86.
- Gorskiy VA, Agapov MA, Klimov AE, Andreev SS. The problem of consistency of intestinal seam. *Pract Med*, **5**, 33-6.
- Holmdahl L, Eriksson E, Eriksson BI, Risberg B (1998). Depression of peritoneal fibrinolysis during operation is a local response to trauma. *Surgery*, **123**, 539-44.
- Jacobi CA, Sterzel A, Halle A, et al (2001). The impact of conventional and laparoscopic colon resection(CO2 or helium) on intraperitoneal adhesion formation in a rat peritonitis model. *Surg Endosc*, **15**, 380-6.
- Krook JE, Moertel CG, Gunderson LL, et al (1991). Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med*, **324**, 709-15.
- Krukowski Z (2008). Prevention and treatment of complications in colonic surgery. Colorectal congress. Switzerland: St.Gallen; pp 102-3.
- Lutsevich OE, Gallamov EA, Tolstykh MP, et al (2007). Laparoscopic reconstructive interventions in coloproctology. Actual Issues of Coloproctology: Proceedings of the 2nd

- Congress of Coloproctologists of Russia. Ufa; pp 589-59.
- Lyhman VN (2015). Optimization of the outcomes of reconstructive-restorative operations for colon with regard to the prevention of purulent-septic complications. *World Med Biol*, **3**, 54-5.
- Menzies D, Ellis H (1991). The role of plasminogenactivator in adhesionprevention. *Surg Gynec Obstet*, **172**, 362-6.
- Miziyeve IA, Mischenko SF, Zhakhushev A (2006). The principles of surgical tactics in acute colonic obstruction. Proceedings of the 1st Congress of Surgeons. Rostov; pp 153.
- Rodel C, Trojan J, Bechstein WO, Woeste G (2012). Neoadjuvant short- or long-term radio(chemo) therapy for rectal cancer: How and Who Should Be Treated. *Dig Dis*, **30**, 102-8.
- Shchaeva SN (2017). Surgical treatment of complicated colorectal cancer: tactical aspects (a literature review). *Pelvic Surg Oncol*, **7**, 57-68.
- Shpitz ND, Bugaev B, Grancin N, et al (2009). Young-age onset of colorectal cancer in Israel. *Technique Coloproctol*, **2009**, 183-9.
- Shurkalin BK, Volenko AV, Gorskiy VA, et al (2008). Post-operative complications of surgical interventions on the colon and ways of their prevention in a general surgical clinic. Moscow; pp 46.
- Sprangers MA, Taal BG, Aaronson NK (1995). Quality of live in colorectal cancer: stoma versus nonstoma patients. *Dis Colon Rectum*, **38**, 361-9.
- Totikov ZV, Totikov VZ (2014). Surgical tactics in color cancer complicated by acute obstruction. *Koloproctologia (Coloproctology)*, **3**, 80-80a.
- Zhenchevsky RA (1989). Adhesive disease. Moscow: Meditsina; pp 191.



This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.