Laparoscopic surgical treatment for ulcerative colitis

Ph.D. Thesis

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CONTENTS

LIST OF PAPERS

This doctoral thesis is based on the following publications:

I. **Tajti J Jr**, Simonka Z, Paszt A, Abraham S, Farkas K, Szepes Z, Molnar T, Nagy F, Lazar G. Role of laparoscopic surgery in the treatment of ulcerative colitis; short- and mid-term results. *Scand J Gastroenterol.* 2015; 50: 406-412. *IF: 2.199*

II. **Tajti J Jr**, Simonka Zs, Paszt A, Ábrahám Sz, Farkas K, Szepes Z, Molnár T, Nagy F, Lázár Gy. [Minimally invasive surgical treatment of ulcerative colitis – long-term results] [Article in Hungarian] *Orv Hetil.* 2015; 156(39): 1585-1592. *IF: 0.291*

III. **Tajti J Jr.**, Látos M, Farkas K, Ábrahám S, Simonka Z, Paszt A, Molnár T, Lázár G. Effect of Laparoscopic Surgery on Quality of Life in Ulcerative Colitis. *J Laparoendosc Adv Surg Tech A.* 2018; 28(7):833-838. *IF (2017): 1.257*

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II. **Tajti J Jr**, Pieler J, Simonka Z, Paszt A, Lázár G. [Treatment of pregnancy-associated breast cancer]. [Article in Hungarian] *Magy Seb.* 2014; 67(4): 268-70.

III. Simonka Z, Paszt A, Géczi T, Ábrahám S, Tóth I, Horváth Z, Pieler J, **Tajti J**, Varga A, Tiszlavicz L, Németh I, Izbéki F, Rosztóczy A, Wittmann T, Lázár G. [Comparison of surgical patients with gastroesophageal reflux disease and Barrett's esophagus] [Article in Hungarian] *Magy Seb.* 2014; 67(5): 287-296.

IV. Farkas K, Saródi Z, Bálint A, Földesi I, Tiszlavicz L, Szűcs M, Nyári T, **Tajti J**, Nagy F, Szepes Z, Bor R, Annaházi A, Róka R, Molnár T. The diagnostic value of a new fecal marker, matrix metalloprotease-9, in different types of inflammatory bowel diseases. *J Crohns Colitis*. 2015; 9(3): 231-7. *IF: 6.585*

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LIST OF ABBREVIATIONS

ASA	Anesthesiologists Physical Status
BIPQ	Brief Illness Perception Questionnaire
BMI	Body Mass Index
CRP	C-Reactive Protein
GIQLI	Gastrointestinal Quality of Life Index
Hgb	Hemoglobin
Htc	Hematocrit
ICU	Intensive Care Unit
IBD	Inflammatory Bowel Diseases
IPAA	Ileal Pouch–Anal Anastomosis
MRSA	Methicillin-resistant Staphylococcus aureus
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
UC	Ulcerative Colitis
WBC	White Blood Cell

1. INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease affecting the whole large intestine. The epidemiological data reveal that the incidence of UC is constantly rising, primarily as a consequence of the spreading of the "western" lifestyle and urbanization [1].The incidence of inflammatory bowel diseases (IBD) is 11.3/100,000 in Eastern Europe, 14.0/100,000 in Western Europe, and it is estimated to be 24/100,000 in Hungary [2]. In 2010, the IBD registry of five Hungarian centres included 1390 patients, 539 of whom had UC, but since the estimated prevalence of IBD in Hungary is 25,000, these data relate only to the more severe cases [3]. The two varieties of IBD are UC and Crohn's disease. Crohn's disease affects the entire gastrointestinal tract, while UC affects the colon and rectum. The exact pathogenesis of IBD is still unknown, but environmental, genetic and immunological impacts and interactions are postulated [1, 4]. UC is characterized by inflammation and ulcers of the colon and rectum, and destruction of the intestinal wall, which appear firstly in the recto-sigmoid colon. Thanks to the broad-spectrum medical and biological therapy, the disease can generally be controlled for a long time with conservative treatment, but unresponsive cases with frequent relapses and complicated cases require surgical intervention. An estimated 25-45% of patients with UC need surgery at some time [1, 5, 6]. The purpose of the surgical intervention is to remove the affected bowel segment, which can be achieved with either the conventional, open or the laparoscopic technique. The first minimally invasive colon resection, a right hemicolectomy was performed by *Moise Jacobs* in 1990 [7]. Currently, the generally accepted procedure, which has become the gold standard for the surgical treatment of UC, is total proctocolectomy with the creation of an ileal pouch–anal anastomosis (IPAA) [8, 9]. This procedure was first performed with a laparoscopic approach by *Peters* in 1992 [10]. A number of studies have shown that laparoscopic surgery has numerous advantages, such as less postoperative pain, shorter hospital stay, less time required for recovery of the bowel function, and better cosmetic results [11]. The importance of surgical treatment is supported by studies that show that patients treated with conservative methods experienced a worse long-term quality of life compared to those receiving surgical treatment [12, 13]. As a result, it can be concluded that surgery provides successful treatment for UC in the long term and it is therefore important to inform the patients about it. Rather limited experience is available, however, as regards the long-term results of laparoscopic surgery. Limited data are available on quality of life in patients with UC undergoing surgery as well. Laparoscopic technique for the surgical

intervention of UC was initiated in the Department of Surgery, University of Szeged in 2005, since then our working group gained the greatest experience in this field in Hungary.

2. AIMS

(i) Compare the short- and mid-term follow-up results on patients treated for UC with the conventional and the minimally invasive surgical method (Study I.).

(ii) Compare the long-term follow-up results on patients treated for UC with the conventional and the minimally invasive surgical method (Study II.).

(iii) Evaluate quality of life after surgery for UC by investigating the connection between gastroenterological and psychological conditions, daily activities (Study III.).

3. PATIENTS AND METHODS

3.1. Patients

Patients who had undergone operation for UC between 1 January 2005 and 1 March 2016 were involved in our investigation.

Study I. The first follow-up period - from 1 January 2005 to 31 May 2013, mean follow-up of 38 (1-92) months - was defined as short- and mid-term follow-up, with a total of 45 patients (n=27 women, n=18 men). The mean age of the patients was 42.29±14.37 years in the laparoscopy group and 38.91±12.58 years in the open surgery group.

Study II. The second period - from 1 January 2005 to 31 December 2014, mean follow-up of 47,84 (3-111) months - was defined as long-term follow-up, with 56 patients (n=31 women, n=25 men). The mean age of the patients was 45.09±14.49 years in the laparoscopy group and 38.26±12.68 years in the open surgery group.

Study III. At the third period between 1 January 2005 and 1 March 2016, surgery was performed for UC in a total of 75 patients. The mean duration of the follow-up was 46 (1-124) months. Our examinations were performed in 58 cases (n=29 women, n=29 men). The mean age of the patients was 46.98±13.38 years in the laparoscopy group and 45.47±12.59 years in the open surgery group.

3.2. Surgery

Strategy for the surgical treatment of UC is determined by the general status of the patients and the type of the surgical indication.

The indication for emergency surgery was the presence of a severe, toxic condition, which was accompanied by bleeding, perforation or severe malnutrition. In case of emergency surgical indication or patients with weak general status three-stage surgical strategy (*i.* total colectomy, mucous fistula and end ileostomy, *ii.* J-pouch creation and ileostomy, *iii.* ileostomy closure) was needed.

The elective interventions were performed because of a condition that could not be controlled with conservative treatment. In an elective case patients with good general status were undergone a two-stage surgical procedure (*i.* proctocolectomy, IPAA and ileostomy, *ii.* closure of ileostomy).

During our practice one-stage surgical procedures (rectum extirpation, proctocolectomy with end ileostomy, colectomy with ileorectostomy, total colectomy with ileostomy) were also performed, because of sphincter disorder.

Conversion from laparoscopy to open surgery was required, because of massive adhesions or because of the risk of bowel injury and perforation. These cases were excluded from the subsequent analyses.

All surgical procedures were carried out in general anaesthesia combined with epidural analgesia. During the procedures we used metronidazole and 2nd generation cephalosporin for antibiotic prophylaxis, while during emergency operations therapy was completed with 3rd generation cephalosporin or imipenem/cilastatin in cases of severe septico-toxic condition or peritonitis.

3.2.1. Laparoscopic technique

The laparoscopically assisted proctocolectomy + IPAA and the total colectomy + mucous fistula were performed with the use of 6 or 7 ports, depending on the auxiliary incision. The resection of the colon, and the creation of the anastomosis and the mucous fistula were performed from the cosmetically favourable Pfannenstiel incision. The J-pouch was created from the terminal ileum with a straight stapler(s), and a double stapler technique was used for the ileoanal anastomosis. The staple line was protected with a loop ileostomy in every case.

The pouch created as the second surgical step was also achieved from the Pfannenstiel incision.

3.2.2. Conventional technique

In the cases involving the conventional method, a midline laparotomy was performed to explore the abdominal cavity, in the lower recess of which the mucous fistula was created; the pouch and the ileoanal anastomosis were created in the same way as during the laparoscopic interventions.

3.3. Short-, mid- and long-term follow-up

3.3.1. Comparison of preoperative data

During the preoperative period general status of UC patients was examined, namely gender, Body Mass Index (BMI), Anesthesiologists physical status (ASA) class, age, inflammatory parameters, blood count, albumin level, number of stools daily. The time from the onset of UC to surgery, the use of biological therapy was described.

3.3.2. Comparison of operative/intraoperative data

Distribution and duration of the different types of surgical interventions were examined.

3.3.3. Comparison of postoperative data

The length of hospital stay, the number of days spent in the intensive care unit (ICU), the time to the recovery of the bowel function, and the need for transfusion were examined. Postoperative complications were classified as early (within 30 days) or late (after 30 days) with regard to their onset after primary surgery. Complications requiring and not requiring reoperation were investigated. From the aspect of the cosmetic result, the patients graded their satisfaction on a five-item scale (not at all satisfied – slightly satisfied– moderately satisfied – rather satisfied – very satisfied). The preoperative and postoperative general status of the patients were graded on a scale from 1 to 10, where 1 was the best, and 10 was the worst general status. Postoperative number of stools daily and body weight were registered and compared.

3.4. Quality of life

Quality of life was examined with questionnaires considering gastroenterological and psychological conditions, daily activities and headache. Results were analyzed in the laparoscopic group and in patients undergoing open surgery, in patient with or without a stoma, in case of acute and elective interventions, and regarding early and late complications.

3.4.1. Questionnaires

3.4.1.1. Testing gastroenterological conditions

3.4.1.1.1. Functional Scoring System

The functional scoring system is a questionnaire consisting of twelve questions on patients' bowel movements (number of bowel movements during the day and at night, urgency and perianal soreness), incontinence (during the day and at night and use of protective pads), diet, drug therapy and potential social disadvantages [14].

3.4.1.1.2. Gastrointestinal Quality of Life Index (GIQLI)

The GIQLI studies gastroenterological condition (abdominal pain, epigastric fullness, bloating, flatulence, eructation, increased bowel movements, urgency, diarrhoea, constipation, nausea, blood in the stool, heartburn and bowel incontinence), alimentation (appetite, eating speed and swallowing a bite), physical condition, daily activities, social activities and psychological condition for two weeks before completing the questionnaire [15].

3.4.1.1.3. Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The SIBDQ studies gastrointestinal symptoms and their effect on social and physical well-being for two weeks before completing the questionnaire based on ten questions [16].

3.4.1.2. Considering psychological status

3.4.1.2.1. Spielberger's State-Trait Anxiety Questionnaire and the Beck Depression Inventory

Spielberger's State-Trait Anxiety Questionnaire and the Beck Depression Inventory were used to measure the level of anxiety and mood [17, 18].

3.4.1.2.2. Brief Illness Perception Questionnaire (BIPQ)

Illness perceptions and attitude towards healing were studied using the BIPQ, consisting of eight subscales (consequences, timeline, personal control, treatment control, identity, concern, coherence and emotional representation) [19].

3.4.1.3. Examining headache

3.4.1.3.1. Headache Questionnaire

The nature of the headache was evaluated with the 16-question Headache Questionnaire. It contains questions about frequency of headaches, laterality, localization, nature, severity, duration, accompanying symptoms, patients' opinions on the headache, therapy employed, efficacy of therapy and the effect of the headache on everyday life, based on the criteria of the International Classification of Headache Disorders, 3rd edition (beta version) [20].

3.5. Statistics

Patients were examined retrospectively, and statistical analysis was performed with the SPSS program (IBM SPSS Statistics, Version 20.0 2014, Chicago, IL, USA). Pearson and Spearman correlations were used to determine relationships between variables. The independent samples t-test, Mann–Whitney test, ANOVA and Chi-square test were used to compare the groups. Values were considered to be statistically significant if *P* was lower than 0.05.

4. RESULTS

4.1. Comparison of the conventional and the minimally invasive surgical method in treatment for UC, short- and mid-term result (Study I.)

4.1.1. Preoperative results

There was no significant difference in the time from the onset of UC to surgery between the laparoscopic group (8.71 years) and the open surgery group (8.63 years). In the preoperative period, 16 patients (35.55%) received biological therapy, with infliximab. The preoperative laboratory test results, revealed a significant difference between the two groups only in CRP (**Table 1**).

	Age (years)	ASA	BMI	WBC (G/L)	CRP (mg/L)	Hgb (g/L)	Htc (L/L)	Albumin (g/L)
Laparoscopy	41.29	2.19	24.03	8.33	16.79	105.43	33.81	37.79
Open surgery	38.91	2.14	22.88	9.06	47.66	109.13	33.96	33.01
		P=0.818	P=0.490	P=0.529	*P=0.028	P=0.471	P=0.920	P=0.108

Table 1. Mean age, American Society of Anesthesiologists physical status (ASA) class, Body Mass Index (BMI) and preoperative laboratory data in the laparoscopic and open surgery groups. *$P \leq 0.05$

WBC: White Blood Cell; CRP: C-Reactive Protein; Hgb: Hemoglobin; Htc: Hematocrit

On the other hand, the preoperative laboratory data for the patients who participated in emergency surgery indicated an increased inflammatory response. The hematocrit levels (31.31 vs. 35.31 L/L, P=0.007) and albumin levels (28.93 vs. 39.67 g/L, P<0.001) were significantly lower in the emergency group than in the elective group.

Before the surgical interventions, the mean number of stools daily was 10.78 and 9.64, respectively, in the two groups. The last colonoscopy report before surgery indicated 30 cases (66.67%) of pancolitis, 5 cases (11.11%) of left-sided involvement and 10 cases (22.22%) of distal involvement.

4.1.2. Surgical Procedures

Sixteen (35.5%) of the surgical interventions were emergency procedures, while 29 (64.5%) were elective interventions. The laparoscopic technique was used in 23 (51.1%) and the conventional method in 22 (48.9%) cases. Total proctocolectomy with the creation of a J-

pouch and protective loop ileostomy was carried out laparoscopically in 13 cases and with the open technique in 5 cases. Total colectomy with mucous fistula and end ileostomy was performed using the minimally invasive technique in 8 cases and the conventional method in 13 cases. Conversion from laparoscopy to open surgery was required in 3 cases (3/26, 11.53%), because of massive adhesions during elective surgery (1 case) or because of the risk of bowel injury and perforation during emergency surgery (2 cases). These cases were excluded from the subsequent analyses. The distribution of the various surgical procedure is presented in **Table 2**.

		Laparoscopy (n=23)	Open surgery (n=22)
Two-stage surgery	i. Proctocolectomy, J-pouch, ileostomy	13 (56.5%)	5 (23%)
	ii. Ileostomy closure	11	4
Three-stage surgery	i. Total colectomy, mucous fistula, end ileostomy	8 (34.8%)	13 (59%)
	ii. J-pouch creation, ileostomy	6	12
	iii. Ileostomy closure	5	11
One-stage surgery	Rectum extirpation	2 (8.7%)	0
	Proctocolectomy, end ileostomy	0	2 (9%)
	Colectomy, ileorectostomy	0	1 (4.5%)
	Total colectomy, ileostomy	0	1 (4.5%)

Table 2. Distribution of surgery

From the aspect of the duration of surgery, the open method was found to be significantly shorter than the laparoscopic intervention (**Table 3**).

	Laparoscopy	Open surgery	
Proctocolectomy, J-pouch, ileostomy	245.42	185	*P=0.040
Total colectomy, mucous fistula, end ileostomy	187	151.67	*P=0.012

Table 3. Distribution of duration of surgery (minutes) *$P \leq 0.05$

4.1.3. Postoperative results

There was no death in the perioperative period in either group. There was no significant difference between immediate postoperative results (**Table 4**).

	Laparoscopy (n=23)	Open surgery (n=22)	
Hospital stay (days)	11.50	11.63	*P*=0.914
Time to recovery of bowel function (days)	1.44	1.55	*P*=0.656
Time spent in the ICU (days)	2.50	2.09	*P*=0.437
Need for blood transfusion (units)	2.05	3.13	*P*=0.57

Table 4. Immediate postoperative results in the laparoscopic and open surgery groups

There was no difference (*P*=0.945) between the laparoscopic group and the open surgery group in the rate of early complications requiring or not requiring reoperation, which are listed in **Table 5**.

	Laparoscopy (n=23)	Open surgery (n=22)	
Requiring reoperation	• Ileus (2) • Abdominal wall disruption in the area of the mucous fistula (1) • Stoma repair (1)	• Ileus (3) • Septic condition (1)	
Total	17.4% (4/23)	18% (4/22)	*P*=0.945
Not requiring reoperation	• Subileus (3)	• Subileus (1) • Anal bleeding (1) • Dehydration (1) • Hydrothorax (1) • Urination problems (1)	
Total	13% (3/23)	22% (5/22)	*P*=0.396

Table 5. Early postoperative complications (within 30 days) during the short- and mid-term follow up

4.1.4. Mid-term follow-up results

During the follow-up period, wound infection was detected in 8 patients (34.8% of the cases) in the laparoscopic group, and in 7 patients (31.8% of the cases) in the open surgery group;

from this respect, there was no significant difference between the groups (*P*=0.833). Methicillin-resistant Staphylococcus aureus (MRSA) infection was confirmed in 2 patients and 1 patient, respectively. During the mean follow-up of 36 months, significantly fewer complications, involving intestinal obstruction, septic condition, anastomotic stenosis, anal bleeding and pouch-vaginal fistula formation, occurred in the laparoscopic group (**Table 6**).

	Laparoscopy (n=23)	Open surgery (n=22)	
Septic condition	0	• Severe pouchitis (1) • Perianal abscess (4) • Lesser pelvic abscess (1)	
Total	0% (0/23)	27% (6/22)	***P*=0.007
Intestinal obstruction			
– requiring surgical intervention	• Ileus (1)	• Ileus (4)	
– not requiring surgical intervention	• Subileus (1)	• Subileus (6)	
Total	8.7% (2/23)	45% (10/22)	***P*=0.005
Postoperative hernia	• In the ileostomy scar (2)	• In the midline laparotomy scar (4)	
Total	8.7% (2/23)	18% (4/22)	*P*=0.349
Other	• Anastomotic stenosis (1)	• Anastomotic stenosis (5) • Anal bleeding (2) • Severe sphincter damage (1) • Pouch-vaginal fistula (2) • Dehydration (1)	
Total	4.3% (1/23)	50% (11/22)	****P*=0.001

Table 6. Late postoperative complications (after 30 days) during the short- and mid-term follow up. ***P* ≤ 0.01, ****P* ≤ 0.001

In the laparoscopic group, surgery was performed because of ileus in 1 case, and 1 case of subileus resolved after medical therapy. Abdominal wall reconstruction was carried out electively in 2 cases because of a hernia in the scar of the previous ileostomy. Endoscopic dilatation was performed in 1 case of anastomotic stenosis.

In the conventional surgery group, surgery was performed because of ileus as a late complication in 4 cases. Four perianal abscesses were explored, 3 of which were treated by Seton drainage. Perianal exploration was needed in 1 case because of an abscess in the lesser pelvis. In 1 patient, excision of the pouch was required because of severe pouchitis and a

perianal abscess. Rectum extirpation was necessary in 2 patients because of an impaired sphincter function and anal bleeding. The abdominal wall was reconstructed in 4 cases because of postoperative hernia. Two anastomotic stenoses were dilated surgically, while endoscopic dilatation was performed in 3 patients. Six cases of subileus, 1 case of anal bleeding and 1 case of dehydration were resolved through conservative treatment.

During the course of the follow-up, there were significantly fewer urgent admissions to a medical unit in the laparoscopic group (1 vs. 6, P=0.034).

The clinical symptoms and endoscopic findings confirmed 15 cases of pouchitis, affecting 41% of the patients with a pouch (6 in the laparoscopic group and 9 in the open surgery group). The inflammation of the pouch was accompanied by cuffitis in 10 cases.

Of the 16 patients treated with infliximab, 4 developed an early postoperative complication.

A significant improvement in the general status (scale from 1 to 10) was measured in both groups after the surgery, but there was no significant difference between the two groups. The postoperative mean number of stools daily at the last medical check-up during the follow-up was the same in the two groups. The preoperative and current body weights indicated an increase in both groups, which was significant in the open surgery patient population (**Table 7**).

		Preoperative	Current	
General status	Laparoscopy (n=23)	8.88±1.5	2.38±2.03	***P<0.0001
	Open surgery (n=22)	8.8±1.74	2.6±2.03	***P=0.001
Number of stools daily	Laparoscopy (n=23)	10.78±5.80	7.83±3.28	P=0.061
	Open surgery (n=22)	9.64±5.38	7.81±3.31	P=0.238
Body weight	Laparoscopy (n=23)	67.61±16.19	70.83±18.31	P=0.554
	Open surgery (n=22)	63.24±16.15	73.68±12.73	*P=0.030

Table 7. Pre- and postoperative general status, number of stools daily and body weight in the laparoscopic and open surgery groups. *$P \leq 0.05$, ***$P \leq 0.001$

The mean length of the midline laparotomy incision in the open surgery group was 13.9±7 cm, and the mean length of the Pfannenstiel incision in the laparoscopic group was 10.5±3.5 cm. From the aspect of the cosmetic result, the patients graded their satisfaction on a five-item scale, which demonstrated that those who had undergone open surgery were on average “rather satisfied”, while the laparoscopic patients were on average “very satisfied”.

4.2. Comparison of the conventional and the minimally invasive surgical method in treatment for UC, long-term results (Study II.)

4.2.1. Preoperative results

No difference was found between the two groups in the preoperative data. The preoperative laboratory test results (WBC count, CRP, Hgb, Htc and albumin) revealed a significant difference between the two groups in WBC count and CRP (**Table 8**).

	Laparoscopy (n=33)	Open surgery (n=23)	
Age (years)	45.09	38.26	*P*=0.074
ASA	2.27	2.05	*P*=0.125
BMI	22.76	22.59	*P*=0.906
Time (years) from the onset of UC to surgery	9.05	8.26	
WBC (G/L)	8.5	10.42	**P*=0.032
CRP (mg/L)	23.29	51.51	**P*=0.031
Albumin (g/L)	37.8	33.46	*P*=0.096
Hgb (g/L)	109.72	109.52	*P*=0.969
Htc (L/L)	34.27	33.95	*P*=0.828

Table 8. Mean age, American Society of Anesthesiologists physical status (ASA) class, Body Mass Index (BMI) and preoperative laboratory data in the laparoscopic and open surgery groups. $*P \leq 0.05$

WBC: White Blood Cell; CRP: C-Reactive Protein; Hgb: Hemoglobin; Htc: Hematocrit

The preoperative laboratory data for the patients who participated in emergency surgery indicated an increased inflammatory response. In the preoperative period, 23 patients (41.07%) received biological therapy with infliximab.

As concerns the extraintestinal manifestations of the disease, eye abnormalities were found in 5 cases (10.7%), skin disorders in 7 patients (12.5%), and bone and joint complaints in 18 patients (32.14%). The possibility of primary sclerosing cholangitis arose in 3 patients (5.3%), there were 7 cases (12.5%) of prior deep vein thrombosis, a history of tumour disease (in the kidney or the oral cavity) and tuberculosis were present in 2-2 cases (3.57-3.57%). There are no current smokers among these patients; prior smoking was confirmed in 8 cases, and there was a history of appendectomy in 2 case.

4.2.2. Surgical Procedures

The laparoscopic technique was used in 33 (58.9%) and the conventional method in 23 (41.1%) cases. Twenty (35.7%) of the surgical interventions were emergency procedures, while 36 (64.3%) were elective interventions. The indication for emergency surgery was the presence of a severe, toxic condition, which was accompanied by bleeding in 4 cases, perforation and ileus in 1-1 cases, and severe malnutrition in 2 patients, whereas elective interventions were performed because of a condition that could not be controlled with conservative treatment.

The distribution and characteristics of the various surgical procedures are presented in **Table 9**.

		Laparoscopy (n=33)	Open surgery (n=23)	
Two-stage surgery	***i.* Proctocolectomy, J-pouch, ileostomy**	**21 (63.6%)**	**5 (21.7%)**	
	Duration of surgery (minutes)	221	185	*P*=0.187
	***ii.* Ileostomy closure**	**17**	**5**	
	Time from first surgery (months)	3.8	4.4	
Three-stage surgery	***i.* Total colectomy, mucous fistula, end ileostomy**	**9 (27.2%)**	**14 (60.8%)**	
	Duration of surgery (minutes)	186.88	151.54	**P*=0,006
	***ii.* J-pouch creation, ileostomy**	**6**	**13**	
	Time from first surgery (months)	5	5.15	
	***iii.* Ileostomy closure**	**6**	**12**	
	Time from first surgery (months)	7.83	9.25	
One-stage surgery	**Rectum extirpation**	**3 (9%)**	0	
	Proctocolectomy, end ileostomy	0	**2 (8.6%)**	
	Colectomy, ileorectal anastomosis	0	**1 (4.3%)**	
	Total colectomy, ileostomy	0	**1 (4.3%)**	

Table 9. Distribution and characteristics of surgical procedures *$P \leq 0.05$

Following a histological diagnosis of Crohn's disease, the mucous fistula was converted to ileorectostomy in 2 case in the laparoscopic group.

4.2.3. Postoperative results

There was no significant difference between the groups in the length of hospital stay, the time to the recovery of the bowel function, the number of days spent in the ICU, or the need for transfusion. There was no death in the perioperative period in either group.

4.2.4. Long-term follow-up results

During the long-term follow up there were no significant differences between the two groups regarding early postoperative complications. Of the 23 patients treated with infliximab, 6 developed an early postoperative complication. During the mean follow-up of 47 months, significantly fewer late complications occurred in the laparoscopic group (**Table 10**).

	Laparoscopy (n=33)		Open surgery (n=23)		
	Complication	Therapy	Complication	Therapy	
Septic condition	Lesser pelvic abscess (1)	Radiological intervention	Lesser pelvic abscess (1)	Perianal exploration	
	Perianal abscess (1)	Seton drainage	Perianal abscess (9)	Seton drainage	
	Abdominal wall abscess (1)	Conservative treatment	Severe pouchitis (1)	Pouch excision	
Total	9% (3/33)		47.8% (11/23)		***P=0.001
Intestinal obstruction	Ileus (1)	Reoperation	Ileus (5)	Reoperation	
	Subileus (7)	Conservative treatment	Subileus (9)	Conservative treatment	
Total	24.2% (8/33)		60% (14/23)		**P=0.006
Postoperative hernia	In the ileostomy scar (3)	Abdominal wall reconstruction	In midline laparotomy scar (4)	Abdominal wall reconstruction	
Total	9% (3/33)		17.3% (4/23)		P=0.355
Other	Anastomotic stenosis (1)	Endoscopic dilatation	Anastomotic stenosis (6)	Surgical and endoscopic dilatation	
	Vascular failure of terminal ileum (1)	Resection of ileum	Anal bleeding (3)	Rectum extirpation (1)	
			Severe sphincter damage (1)	Rectum extirpation	
			Pouch-vaginal fistula (2)	-	
			Dehydration (2)	Conservative treatment	
Total	6% (2/33)		60% (14/23)		*P=0.01

Table 10. Late postoperative complications and treatment (after 30 days) during the long-term follow up. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$

During the follow-up, 2 patients died, as a result of an oral cavity tumour or a cardiorespiratory insufficiency; the causes of death were not related to the UC. During the course of the follow-up, there were 9 and 12 urgent admissions to a medical unit because of need for transfusion and abdominal pain.

The clinical symptoms and endoscopic findings confirmed 17 cases of pouchitis (7 in the laparoscopic group and 10 in the open surgery group), affecting 40% of the patients with a pouch. The inflammation of the pouch was accompanied by cuffitis in 10 cases. During the follow-up period, wound infection was detected in 8 patients in the laparoscopic group (5 in the wound line, 1 on the perineum, 1 at the site of the drain, and 1 at the site of re-suture on the abdominal wall), and in 7 patients in the open surgery group (4 in the wound line, 1 at the site of the closed ileostomy, 1 at the site of the drain, and 1 at the site of the mucous fistula. MRSA infection was confirmed in 2 patients in the laparoscopic group and 1 patient in the open surgery group. Changes in the general condition, the body weight, the number of stools daily, and the cosmetic results after the surgical interventions were also assessed.

A significant improvement in the general status (scale from 1 to 10) (P=0.000 and P=0.000) was measured in both groups after the surgery. The preoperative and current body weights indicated an increase in both groups, which was significant (P=0.033) in the open surgery patient population. There was a decreasing tendency of the postoperative mean number of stools daily in the two patient groups. From the aspect of the cosmetic result, those patients who had undergone open surgery were on average “rather satisfied”, while the laparoscopic patients were on average “very satisfied” on a five-item scale.

4.3. Evaluate quality of life after surgery for UC by investigating the connection between gastroenterological and psychological conditions, daily activities (Study III.)

4.3.1. Patients

41 patients had undergone laparoscopic surgery, and 17 patients had had open surgeries. Thirty-nine cases were elective interventions, while 19 were emergency surgery. No significant difference was found in the case of the BMI (24.85 vs. 26.82) or the ASA score (2.25 vs. 2.13). There was an average 8.2 years from diagnosing the disease to surgery. In the laparoscopic group, 25 proctocolectomies with IPAA and ileostomy were performed, 13 patients had a total colectomy with end ileostomy and mucous fistula, and 3 rectum

extirpations were carried out. In the open group, a pouch was created in 4 cases, 9 patients had a total colectomy with mucous fistula, and 4 other colon resections were performed. 17 patients had a stoma during the study. In order to homogenize the groups, 6 patients, who were operated dissimilarly from the standard surgical technique (n=3 rectum extirpation, n=3 other colon resection) were excluded during the comparison of laparoscopic and open surgery groups, and during the analysis of complications.

4.3.2. Representation of illnesses

92.3% of the patients enrolled in the study considered a psychological factor (psychological causes, family or work stress) to be in the background of their disease. 42.3% of the patients pointed to genetic factors, 46.2% of them mentioned environmental hazards (such as inappropriate diet), and 1 patient noted the Chernobyl nuclear disaster as the cause of the disease. Patients viewing genetic factors as being in the background of the disease reached significantly higher scores on the BIPQ (44.14 vs. 35.73; P=0.022), so they are more threatened by their disease and know less about the nature of it (coherence subscale: 2.14 vs. 1.10; P=0.013).

4.3.3. Psychological consequences of having a stoma

There were differences in personal control between patients with a stoma (n=17) and patients without a stoma (n=41) (6.12 vs. 4.12; P=0.045). Patients with a stoma felt they had less control over their disease. No difference was found between the two groups during gastroenterological follow-up examinations.

4.3.4. Results for emotional state and mood

There was a significant connection between depression and the functional scoring system (P=0.002; r=0.419), the GIQLI (P<0.001; r=-0.867), the SIBDQ (P<0.001; r=-0.795) and the BIPQ (P<0.001; r=0.751), as well as the consequences, personal and treatment control, identity, concern and emotional representation subscales (P<0.05 in all cases). State anxiety significantly correlated with the total score for the GIQLI (P<0.001, r=-0.624), the SIBDQ (P<0.001, r=-0.579) and the BIPQ (P<0.001, r=0.615), as well as with the consequences, personal and treatment control, identity, concern and emotional representation subscales (P<0.05 in all cases). There was a significant connection between trait anxiety and the functional scoring system (P=0.012; r=0.344), the GIQLI (P<0.001; r=-0.682), the SIBDQ (P<0.001; r=-0.684) and the BIPQ (P<0.001; r=0.608), as well as the consequences, personal

and treatment control, identity, concern and emotional representation subscales (P<0.001) (**Table 11**).

Variables	GIQLI
Psychological variables	
Beck Depression Inventory	-0.87**
Spielberger's State Anxiety Scale	-0.62**
Spielberger's Trait Anxiety Scale	-0.69**
Brief Illness Perception Questionnaire	-0.84**
Consequences	-0.89**
Timeline	-0.07$^{(NS)}$
Personal control	-0.37**
Treatment control	-0.39**
Identity	-0.73**
Concern	-0.71**
Coherence	-0.01$^{(NS)}$
Emotional representation	-0.78**
Clinical variables	
Functional scoring system	-0.55**
Short Inflammatory Bowel Disease Questionnaire	0.89**

Table 11. Pearson's or Spearman's correlation between clinical and psychological variables and Gastrointestinal Quality of Life Index (GIQLI)

**$P \leq 0.01$; NS: non significant

4.3.5. Comparing laparoscopy and open surgery

Trait anxiety was significantly lower in patients having undergone laparoscopic surgery (n=38) compared with patients who had had open surgery (n=14) (P=0.018) (average value of trait anxiety in patients with open surgery was 48.71, SD=10.91; this value was 40.22, SD=9.82 in the laparoscopic group). Both patient groups had >5 stools in the daytime and >1 at night per week, with no significant difference observed between the groups. No difference was noted between the two surgical methods based on the total score on the gastroenterological questionnaires, although the following statistical differences were found

when evaluating each questionnaire item individually. Incontinence was registered during the day and at night in both patient groups (**Table 12**).

	Laparoscopy (n=28) n(%)	Open surgery (n=11) n(%)
Urgency (Inability to defer evacuation ≥ 30 minutes)	14 (50)	6 (54.5)
Evacuation difficulties	5 (17.85)	3 (27.3)
Soiling or seepage in daytime	7 (25)	3 (27.3)
Soiling or seepage at night	11 (39.28)	6 (54.5)
Perianal soreness	15 (53.57)	9 (81.8)
Protective pad in daytime	7 (25)	3 (27.3)
Protective pad at night	12 (42.85)	3 (27.3)
Dietary restrictions	21 (75)	5 (45.5)
Medication (continuous or occasional)	14 (50)	10 (90.9)
Social handicap	13 (46.6)	4 (36.4)

Table 12. Total values from the functional scoring system (Based on Ref. [14])

The incidence of abdominal pain was significantly less common (1.895 vs. 2.769; *P*=0.024) in the laparoscopic group based on the GIQLI.

4.3.6. Complications

No difference was found between the minimally invasive and conventional methods in cases requiring early reoperation (ileus, stoma correction, bleeding and sepsis) and in cases not requiring reoperation (subileus, bleeding, septic condition, pancreatitis and dehydration). There were significantly more late complications (septic condition, intestinal obstruction, postoperative hernia and "other" complications, such as bleeding, anastomotic stenosis, pouch-vaginal fistula, perforation and disruption of the abdominal wall) in patients who had undergone open surgery (*P*=0.001), of whom the incidence of intestinal obstruction and "other" complications were significantly higher (*P*≤0.001) (**Figure 1**).

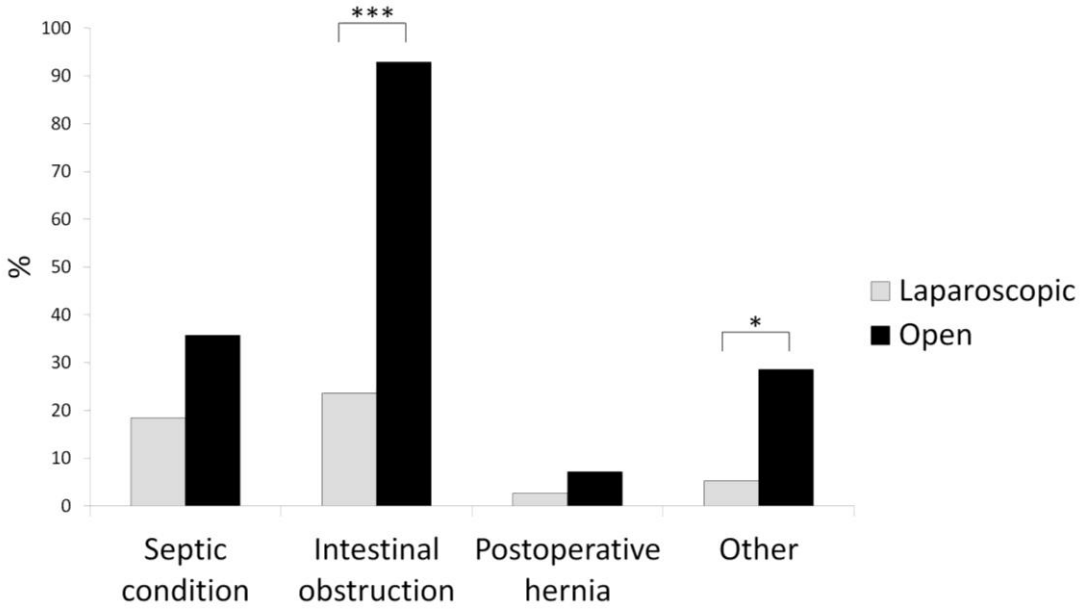

Figure 1. Late postoperative complications

Among late complications the incidence of intestinal obstruction and "other" complications were significantly higher in patients who had had open surgery than in patients who had undergone laparoscopic surgery. *$P \leq 0.05$, ***$P \leq 0.001$

Pouchitis was detected in 17 cases (35.41% of patients with a pouch). Cuffitis occurred in 13 (27.08%) cases. The personal control (3.43 ± 2.35 vs. 5.57 ± 3.31; $P = 0.024$) was higher in patients with no late complication.

4.3.7. Headache

As a result, 43 (74.1%) patients had headaches, of whom 27 (62.8%) had primary headache and 16 (37.2%) had the secondary (symptomatic) type. Among the primary headaches (n=27), tension-type headache was the most common, occurring in 19 (70.4%) cases, of which 17 (89.5%) patients experienced episodic tension-type headache and 2 (10.5%) suffered from chronic tension-type headache; in addition, 8 (29.6%) patients had migraine. Headache influenced quality of life and daily activities slightly to moderately in 79.1% (n=34) of the patients. No difference was found regarding headaches in the laparoscopic and open surgery groups and between patients with a stoma and those without a stoma. In the case of patients with headache, the BIPQ score was significantly higher (P=0.036).

5. DISCUSSION

The epidemiological data reveal that the incidence of UC is constantly rising [1]. The treatment of UC is primarily based on medical/biological therapy. A surgical intervention is considered in the event of the failure of the conservative therapy and the emergence of severe complications of the disease. An estimated 25-45% of patients with UC needs surgery at some time [1, 5, 6]. The use of minimally invasive surgical technique gathers ground widely also in Hungary, which can be applied safely during the therapy of IBD [21-23]. First proctocolectomy with pouch was performed by *Parks et al.* in 1978, which became the gold-standard technique during the surgical treatment of UC, while its laparoscopic implementation was first mentioned in the early '90s [8, 10, 24]. Proctocolectomy and IPAA creation are adequate alternatives in the surgical treatment of UC, and are currently the most frequently chosen types of surgery [8, 25-27]. Rather limited experience is available, however, as regards the short and long-term results of the laparoscopic surgical management of UC. Limited data are available on quality of life in patients with UC undergoing surgery.

In our study, the perioperative results on patients with UC were analyzed retrospectively in order to compare the laparoscopic and open surgical techniques, with a short- and long-term follow-up. The preoperative laboratory test results revealed a significant difference between the two groups in WBC count and CRP. The preoperative laboratory data for the patients who participated in emergency surgery indicated an increased inflammatory response. Extraintestinal manifestations were found in 42 cases. A number of studies have demonstrated that smoking has a protective effect against the development and the relapse of UC [1, 28], and the finding was similar with appendectomy as a protective factor [1, 29]. There were no current smokers in our patient population, but a history of smoking was present in 8 cases, and 2 patients had undergone appendectomy previously. There was no difference between the open surgery and laparoscopic groups as concerns the length of the hospital stay, the number of days spent in the ICU, the blood loss, or the time required for the recovery of the bowel function.

The minimally invasive technique has also gained popularity in the treatment of UC and, similarly to the open technique, can be used safely [23]. Its advantages include a shorter hospital stay, less postoperative pain, a shorter time for recovery of the bowel function and a better cosmetic result, but it has the disadvantage of a longer duration of surgery [11]. A considerable number of the studies published to date have reported on the various advantages of the laparoscopic technique. An Australian study found that laparoscopy is associated with a

shorter hospital stay, a faster recovery of the bowel function, and a better cosmetic result; however, the two surgical techniques have the same morbidity rate due to the proctocolectomy [30]. Laparoscopic completion proctectomy and IPAA creation following laparoscopic colectomy were studied by *Gu et al.*, who reported a low blood loss, rapid recovery of the bowel function, and a short hospital stay [31]. A Dutch study on colectomies performed because of non-toxic colitis concluded that the minimally invasive technique is more advantageous in cases involving wound infection and abdominal abscess [32]. *Koh et al.* demonstrated that the laparoscopic technique was safe in emergency surgery for UC, and yielded better results in cases of ileus and wound infection as compared with open surgery [33]. Similarly advantageous results concerning the hospital stay, the need for blood transfusion, the cosmetic result and wound infection were reported from two US studies on emergency laparoscopic subtotal colectomies [34, 35]. Current data available in a large international database confirm better rates of both morbidity and mortality in the minimally invasive patient group [21]. Our own results indicate that, other than the cosmetic results, laparoscopic surgery has no clear advantage in the perioperative period. However, the duration of surgery differed significantly in the two patient groups: the laparoscopic interventions took longer to complete.

Fajardo et al. did not also observe a difference in the rate of morbidity during the short-term follow-up of two-stage laparoscopic and open IPAA surgery [36]. A meta-analysis published in 2010 did not find a difference between the conventional open and the minimally invasive procedure from the aspect of complications such as a lesser pelvic abscess, anastomotic leakage and ileus [37]. Similarly, a recent randomized study likewise confirmed only the cosmetic advantage of the laparoscopic method [38].

Complications were classified as early (within 30 days) or late (after 30 days) with regard to their onset after primary surgery. Our study led to the finding that the minimally invasive method does not have an advantage as concerns the early complications, but it is demonstrably more advantageous in terms of the incidence of late complications. Our study indicated that only 26% of patients who had received infliximab treatment had early postoperative complications and therefore suggests that prior biological therapy is not associated with a higher rate of complications. In several studies, prior biological therapy was considered to have a negative effect on the results of the surgical treatment in UC [39, 40], although this is not supported by other observations [5, 41, 42] or a most recent case-matched study [43]. During the mean follow-up of 47 months, significantly fewer complications,

involving an intestinal obstruction, a septic condition and “other complications” occurred in the laparoscopic group. The obvious explanation for the higher, but not significant rate of hernias in the open surgery group is the more extensive entry opening. The higher rate of ileus and subileus in the open surgery group is probably caused by the higher level of surgical trauma and the adhesions due to the wound surface. *Hull et al.* observed significantly more cases of adhesion after open IPAA surgery, and a similar result was reported by *Indar et al.* [44, 45]. The research by *Bartels et al.* revealed that the incidence of adhesions and postoperative hernias was significantly higher following emergency open colectomies performed because of UC [46].

One of the most common complication in the long term after IPAA surgery performed because of UC is pouchitis [47, 48]. A total of 17 cases of pouchitis were recorded in our study, corresponding to 40% of the patients with a pouch. The exact aetiology of pouchitis is still unknown; no independent risk factor has been recognized. The study by *Kalkan et al.* pointed to the fulminant colitis leading to the surgery and the steroid dependence as the possible causes of pouchitis, whereas *Uchino et al.* were of the opinion that a toxic megacolon and the onset of UC before the age of 26 years may predispose to chronic pouchitis [49, 50]. There was a decreasing tendency of the postoperative mean number of stools daily and an increase in the postoperative body weights in the two patient groups. *Polle et al.* did not detect a difference in the quality of life, the morbidity rate or the functional results following open and laparoscopic proctocolectomies, but confirmed a better cosmetic result among laparoscopic female patients [51]. An Italian study emphasized the importance of the accurate assessment, selection and follow-up of surgical patients with regard to complications, pouchitis, pouch excision, the risk of cancer and the quality of life following IPA surgery [52]. Success of the surgical intervention is determined by quality of life in case of a benign, non-neoplastic disease. In case of UC, abdominal complaints, high number of bowel movements a day, surgical interventions and their consequences are very demanding somatically and psychologically. Social integration of patients, their quality of life and daily routine activities may often be difficult. Regarding disease representation, 92.3% of our patients considered their disease to be caused by psychological factors, 42.3% thought that genetic factors were behind the disease, and 46.2% though that their disease was caused by environmental hazards. In conclusion, patients with UC are well informed, and are aware of the nature and characteristics of their disease. Consequences of wearing a stoma were examined as well, which was significant regarding the “Personal control” subscale of the BIPQ, patients with a

stoma felt less control over their condition. Therefore the presence of an anus prae either temporary or permanent, was psychologically demanding for the patients, it made healing and daily activities more difficult. Besides these results, no difference was found in quality of life of patients living with an ileostoma or a pouch in a prospective cross-sectional observational study [53]. Quality of life was examined regarding laparoscopic surgery and open surgery as well. Examination of psychological differences between the two groups showed that trait anxiety and the average value of "Treatment control" subscale of BIPQ were significantly different, that is patients having open surgery were more anxious and had less faith in the success of the surgical treatment. Based on the total score of gastroenterological questionnaires, there was no difference between the two surgical methods, although perianal and abdominal pain, stress, social and recreational activities were more favorable in the laparoscopic group based on the Functional score system, the SIBDQ and the GIQLI. A German and an Irish study with 10-year follow-up found favorable quality of life after IPAA surgery [54, 55]. Nutritional difficulties, bowel movement problems, as well as daily and night-time incontinence were found in both groups. Incontinence, increased number of bowel movements at night and bowel urgency were found to be negative prognostic factors of quality of life in the literature [56]. Our patients reported >5 stools a day and >1 stool at night weekly in the postoperative period. *Fischera et al.* found high rates of continence and an average of 6 bowel movements a day after laparoscopic IPAA [9]. No difference was found between the two groups regarding early complications; these complications were more common in shorter and thinner patients. Late complications occurred significantly more often in case of emergency and open surgeries. The values of "Personal control" and "Understanding" subscales of BIPQ regarding psychological factors were higher in patients having no late complications, so who felt more control over their disease. Early and late complications correlated with the "Understanding" subscale of BIPQ, so patients having no complication understand their disease more. Logistic regression was used to confirm that the laparoscopic intervention and the "Understanding" subscale of BIPQ were predictive regarding the development of complications, that is the incidence of complications is lower in case of laparoscopic surgeries and in patients understanding their disease better. Significant correlation was found between the results of psychological and gastrointestinal questionnaires, negative emotional condition and mood resulted in lower quality of life, patients were more anxious and depressive, these patients had a negative image of their disease, and had less faith in the success of the surgical interventions (**Figure 2**).

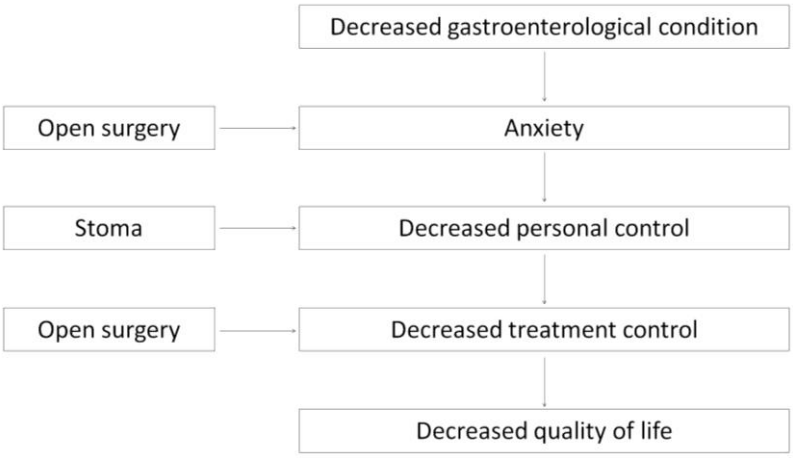

Figure 2. Effect of gastroenterological and psychological conditions and surgical technique on quality of life

74.1% of our patients had headaches, 79.1% of these patients had slight to moderate problems with everyday life. Based on the results of BIPQ, headache further worsened the emotional condition of our patients. It should be emphasized that patients having headaches had mainly tension type headaches, stress and psychological tension have primary role in the development of tension headaches [57, 58]. Tension type headache negatively influences quality of life [59].

6. CONCLUSION

i. Our working group was the first to publish short- and long-term results on laparoscopic treatment of UC in Hungary, which proved the success of the method.

ii. Laparoscopic surgical treatment can be used safely for both emergency and elective cases in UC patients. During the long-term follow-up period, significantly fewer late complications occurred in the laparoscopically operated group of patients.

iii. Our study is the first to examine quality of life among patients operated with laparoscopy on UC with regard to psychological and gastroenterological conditions. The long-term positive effect of laparoscopic surgery was confirmed regarding quality of life.

iv. Favourable gastroenterological condition leads to better psychological state and favourable quality of life, which can be negatively influenced by having a stoma, headache or complications.

v. Successful treatment of UC should be performed in centers with close gastroenterological and surgical co-operation.

vi. Psychological guiding is essential. Psychologists, neurologists and social workers may have to be involved in the treatment of these patients.

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REFERENCES

1. Kovács Á, Lakatos L. Gyulladásos bélbetegségek. Medicina; 2011.

2. Vegh Z, Burisch J, Pedersen N, Kaimakliotis I, Duricova D, Bortlik M, Avnstrom S, Vinding KK, Olsen J, Nielsen KR, Katsanos KH, Tsianos EV, Lakatos L, Schwartz D, Odes S, Lupinacci G, De Padova A, Jonaitis L, Kupcinskas L, Turcan S, Tighineanu O, Mihu I, Barros LF, Magro F, Lazar D, Goldis A, Fernandez A, Hernandez V, Niewiadomski O, Bell S, Langholz E, Munkholm P, Lakatos PL, EpiCom g. Incidence and initial disease course of inflammatory bowel diseases in 2011 in Europe and Australia: results of the 2011 ECCO-EpiCom inception cohort. *J Crohns Colitis* 2014;8:1506-1515.

3. Miheller P, Nagy F, Palatka K, Altorjay I, Horvath G, Lorinczy K, Ujszaszy L, Viranyi Z, Szepes A, Molnar T, Farkas K, Szepes Z, Nyari T, Wittmann T, Tulassay Z. [Hungarian data on inflammatory bowel diseases: analytical data on ulcerative colistis]. *Orv Hetil* 2012;153:702-712.

4. Shouval DS, Rufo PA. The Role of Environmental Factors in the Pathogenesis of Inflammatory Bowel Diseases: A Review. *JAMA Pediatr* 2017.

5. Ferrante M, Declerck S, De Hertogh G, Van Assche G, Geboes K, Rutgeerts P, Penninckx F, Vermeire S, D'Hoore A. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. *Inflamm Bowel Dis* 2008;14:20-28.

6. Roses RE, Rombeau JL. Recent trends in the surgical management of inflammatory bowel disease. *World J Gastroenterol* 2008;14:408-412.

7. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991;1:144-150.

8. Bennis M, Tiret E. Surgical management of ulcerative colitis. *Langenbecks Arch Surg* 2012;397:11-17.

9. Fichera A, Silvestri MT, Hurst RD, Rubin MA, Michelassi F. Laparoscopic restorative proctocolectomy with ileal pouch anal anastomosis: a comparative observational study on long-term functional results. *J Gastrointest Surg* 2009;13:526-532.

10. Peters WR. Laparoscopic total proctocolectomy with creation of ileostomy for ulcerative colitis: report of two cases. *J Laparoendosc Surg* 1992;2:175-178.

11. Zoccali M, Fichera A. Minimally invasive approaches for the treatment of inflammatory bowel disease. *World J Gastroenterol* 2012;18:6756-6763.

12. Pellino G, Sciaudone G, Miele E, Candilio G, De Fatico GS, Riegler G, Staiano A, Canonico S, Selvaggi F. Functional outcomes and quality of life after restorative proctocolectomy in paediatric patients: a case-control study. *Gastroenterol Res Pract* 2014;2014:340341.

13. Pica R, Cassieri C, Pronio AM, Zippi M, Avallone EV, Montesani C, Occhigrossi G, Paoluzi P. Quality of life in ulcerative colitis patients treated medically versus patients undergoing surgery. *Eur Rev Med Pharmacol Sci* 2014;18:693-698.

14. Oresland T, Fasth S, Nordgren S, Hulten L. The clinical and functional outcome after restorative proctocolectomy. A prospective study in 100 patients. *Int J Colorectal Dis* 1989;4:50-56.

15. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E, Troidl H. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;82:216-222.

16. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;96:804-810.

17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-571.

18. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. Palo Alto: Consulting Psychologists Press; 1970.

19. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006;60:631-637.

20. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808.

21. Causey MW, Stoddard D, Johnson EK, Maykel JA, Martin MJ, Rivadeneira D, Steele SR. Laparoscopy impacts outcomes favorably following colectomy for ulcerative colitis: a critical analysis of the ACS-NSQIP database. *Surg Endosc* 2013;27:603-609.

22. Hata K, Kazama S, Nozawa H, Kawai K, Kiyomatsu T, Tanaka J, Tanaka T, Nishikawa T, Yamaguchi H, Ishihara S, Sunami E, Kitayama J, Watanabe T. Laparoscopic surgery for ulcerative colitis: a review of the literature. *Surg Today* 2015;45:933-938.

23. Sica GS, Biancone L. Surgery for inflammatory bowel disease in the era of laparoscopy. *World J Gastroenterol* 2013;19:2445-2448.

24. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. *Br Med J* 1978;2:85-88.

25. Biondi A, Zoccali M, Costa S, Troci A, Contessini-Avesani E, Fichera A. Surgical treatment of ulcerative colitis in the biologic therapy era. *World J Gastroenterol* 2012;18:1861-1870.

26. Ikeuchi H, Uchino M, Matsuoka H, Bando T, Matsumoto T, Tomita N, Syoji Y, Kusunoki M, Yamamura T, Utsunomiya J. Surgery for ulcerative colitis in 1,000 patients. *Int J Colorectal Dis* 2010;25:959-965.

27. Lefevre JH, Bretagnol F, Ouaissi M, Taleb P, Alves A, Panis Y. Total laparoscopic ileal pouch-anal anastomosis: prospective series of 82 patients. *Surg Endosc* 2009;23:166-173.

28. Tobin MV, Logan RF, Langman MJ, McConnell RB, Gilmore IT. Cigarette smoking and inflammatory bowel disease. *Gastroenterology* 1987;93:316-321.

29. Gilat T, Dotan I. Ulcerative colitis and appendectomy. What is the nature of the (negative) association? *Ital J Gastroenterol Hepatol* 1997;29:212-213.

30. Tan JJ, Tjandra JJ. Laparoscopic surgery for ulcerative colitis - a meta-analysis. *Colorectal Dis* 2006;8:626-636.

31. Gu J, Stocchi L, Geisler DP, Kiran RP. Staged restorative proctocolectomy: laparoscopic or open completion proctectomy after laparoscopic subtotal colectomy? *Surg Endosc* 2011;25:3294-3299.

32. Bartels SA, Gardenbroek TJ, Ubbink DT, Buskens CJ, Tanis PJ, Bemelman WA. Systematic review and meta-analysis of laparoscopic versus open colectomy with end ileostomy for non-toxic colitis. *Br J Surg* 2013;100:726-733.

33. Koh FH, Tan KK, Tsang CB, Koh DC. Laparoscopic versus an open colectomy in an emergency setting: a case-controlled study. *Ann Coloproctol* 2013;29:12-16.

34. Bell RL, Seymour NE. Laparoscopic treatment of fulminant ulcerative colitis. *Surg Endosc* 2002;16:1778-1782.

35. Telem DA, Vine AJ, Swain G, Divino CM, Salky B, Greenstein AJ, Harris M, Katz LB. Laparoscopic subtotal colectomy for medically refractory ulcerative colitis: the time has come. *Surg Endosc* 2010;24:1616-1620.

36. Fajardo AD, Dharmarajan S, George V, Hunt SR, Birnbaum EH, Fleshman JW, Mutch MG. Laparoscopic versus open 2-stage ileal pouch: laparoscopic approach allows for faster restoration of intestinal continuity. *J Am Coll Surg* 2010;211:377-383.

37. Wu XJ, He XS, Zhou XY, Ke J, Lan P. The role of laparoscopic surgery for ulcerative colitis: systematic review with meta-analysis. *Int J Colorectal Dis* 2010;25:949-957.

38. Schiessling S, Leowardi C, Kienle P, Antolovic D, Knebel P, Bruckner T, Kadmon M, Seiler CM, Buchler MW, Diener MK, Ulrich A. Laparoscopic versus conventional ileoanal pouch procedure in patients undergoing elective restorative proctocolectomy (LapConPouch Trial)-a randomized controlled trial. *Langenbecks Arch Surg* 2013;398:807-816.

39. Mor IJ, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008;51:1202-1207; discussion 1207-1210.

40. Selvasekar CR, Cima RR, Larson DW, Dozois EJ, Harrington JR, Harmsen WS, Loftus EV, Jr., Sandborn WJ, Wolff BG, Pemberton JH. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007;204:956-962; discussion 962-953.

41. Kunitake H, Hodin R, Shellito PC, Sands BE, Korzenik J, Bordeianou L. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. *J Gastrointest Surg* 2008;12:1730-1736; discussion 1736-1737.

42. Schluender SJ, Ippoliti A, Dubinsky M, Vasiliauskas EA, Papadakis KA, Mei L, Targan SR, Fleshner PR. Does infliximab influence surgical morbidity of ileal pouch-anal anastomosis in patients with ulcerative colitis? *Dis Colon Rectum* 2007;50:1747-1753.

43. Coquet-Reinier B, Berdah SV, Grimaud JC, Birnbaum D, Cougard PA, Barthet M, Desjeux A, Moutardier V, Brunet C. Preoperative infliximab treatment and postoperative complications after laparoscopic restorative proctocolectomy with ileal pouch-anal anastomosis: a case-matched study. *Surg Endosc* 2010;24:1866-1871.

44. Hull TL, Joyce MR, Geisler DP, Coffey JC. Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis. *Br J Surg* 2012;99:270-275.

45. Indar AA, Efron JE, Young-Fadok TM. Laparoscopic ileal pouch-anal anastomosis reduces abdominal and pelvic adhesions. *Surg Endosc* 2009;23:174-177.

46. Bartels SA, Vlug MS, Henneman D, Ponsioen CY, Tanis PJ, Bemelman WA. Less adhesiolysis and hernia repair during completion proctocolectomy after laparoscopic emergency colectomy for ulcerative colitis. *Surg Endosc* 2012;26:368-373.

47. Helavirta I, Huhtala H, Hyoty M, Collin P, Aitola P. Restorative proctocolectomy for ulcerative colitis IN 1985-2009. *Scand J Surg* 2015.

48. Sagar PM, Pemberton JH. Intraoperative, postoperative and reoperative problems with ileoanal pouches. *Br J Surg* 2012;99:454-468.

49. Kalkan IH, Dagli U, Onder FO, Tunc B, Oztas E, Ulker A, Sasmaz N. Evaluation of preoperative predictors of development of pouchitis after ileal-pouch-anastomosis in ulcerative colitis. *Clin Res Hepatol Gastroenterol* 2012;36:622-627.

50. Uchino M, Ikeuchi H, Matsuoka H, Bando T, Takesue Y, Tomita N. Clinical features and management of pouchitis in Japanese ulcerative colitis patients. *Surg Today* 2013;43:1049-1057.

51. Polle SW, Dunker MS, Slors JF, Sprangers MA, Cuesta MA, Gouma DJ, Bemelman WA. Body image, cosmesis, quality of life, and functional outcome of hand-assisted laparoscopic versus open restorative proctocolectomy: long-term results of a randomized trial. *Surg Endosc* 2007;21:1301-1307.

52. Delaini GG, Scaglia M, Colucci G, Hulten L. The ileoanal pouch procedure in the long-term perspective: a critical review. *Tech Coloproctol* 2005;9:187-192.

53. Kuruvilla K, Osler T, Hyman NH. A comparison of the quality of life of ulcerative colitis patients after IPAA vs ileostomy. *Dis Colon Rectum* 2012;55:1131-1137.

54. Browne C, Shaikh F, Iqbal N, McGovern B, Rowe S, Neary P. Quality of life, continence and frequency of pouchitis following laparoscopic versus open colectomy and ileal pouch-anal anastomosis: an Irish perspective. *Ir J Med Sci* 2015;184:655-658.

55. Leowardi C, Hinz U, Tariverdian M, Kienle P, Herfarth C, Ulrich A, Kadmon M. Long-term outcome 10 years or more after restorative proctocolectomy and ileal pouch-anal anastomosis in patients with ulcerative colitis. *Langenbecks Arch Surg* 2010;395:49-56.

56. Andersson T, Lunde OC, Johnson E, Moum T, Nesbakken A. Long-term functional outcome and quality of life after restorative proctocolectomy with ileo-anal anastomosis for colitis. *Colorectal Dis* 2011;13:431-437.

57. Clark GT, Sakai S, Merrill R, Flack VF, McCreary C. Cross-correlation between stress, pain, physical activity, and temporalis muscle EMG in tension-type headache. *Cephalalgia* 1995;15:511-518, discussion 451.

58. Torelli P, Abrignani G, Castellini P, Lambru G, Manzoni GC. Human psyche and headache: tension-type headache. *Neurol Sci* 2008;29 Suppl 1:S93-95.

59. Risal A, Manandhar K, Holen A, Steiner TJ, Linde M. Comorbidities of psychiatric and headache disorders in Nepal: implications from a nationwide population-based study. *J Headache Pain* 2016;17:45.