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Key Words: *colon cancer, enhanced recovery program, long-term outcomes.*

THE IMPACT OF POSTOPERATIVE COMPLICATIONS AND IMPLICATION OF A MULTIMODAL ENHANCED RECOVERY PROGRAMME ON LONG-TERM OUTCOMES OF SURGICAL TREATMENT OF COLON CANCER PATIENTS

Application of the multimodal enhanced recovery program (ERP) proved its effectiveness in surgical treatment of patients with colon cancer. The impact of an ERP on the long-term outcomes remains a challenge. ***Aim*** *of the study: to assess the impact of an ERP on the long-term outcomes of the surgical treatment of colon cancer patients.* ***Object and methods:*** *a total of 230 patients, who underwent curative surgery for colon cancer from 2008 to 2013, were enrolled and divided into main (130 patients) and control group (100 patients).* ***Results:*** *no significant difference in antropometric data, tumor site, disease stage and surgery type was observed. Grade II–IV according to the Clavien — Dindo classification of surgical complications was determined in 11 (8.5%) patients of main group and in 20 (20.0%) patients of control group ($p < 0.05$) with postoperative mortality 0.8 and 2.0%, respectively ($p < 0.05$). Overall 3-year survival differed significantly: 88.4 ± 9.6% — in main and 72.2 ± 7.6% — in control group ($p < 0.05$) with insignificant shift in disease-free survival — 87.0 ± 7.5% and 90.0 ± 10.2%, respectively ($p = 2.235$). All patients who had grade II–IV complications didn't achieve 3-year survival, with the median of 28.7 and 26.2 months ($p = 1.954$).* ***Conclusion:*** *ERP application leads to the improvement of overall survival by means of reduction of grade II–IV Clavien — Dindo complications.*

INTRODUCTION

In recent decades the application of the multimodal enhanced recovery strategy for surgical treatment of patients with colorectal cancer has convincingly proven its efficiency. According to the results of the survey of 123 major centers of colorectal surgery worldwide in 2012, the enhanced recovery program (ERP) was adjusted as a standard option in 63% of these centers [1]. Results of the meta-analysis of 1353 trials over the past 20 years, provided by J. Zhao et al., suggest undoubtable advantages of the ERP application not only because of the significant reduction of the postoperative morbidity and mortality, but also because of the patient's life quality improvement and treatment costs reduction [2].

Multiple clinical and experimental studies have proven that the main effective component of the ERP is the decrease of the host's stress response to the surgical injury, which is demonstrated by the reduction of the proinflammatory cytokines expression, leading to the minimization of the consequences of the systemic inflammatory response syndrome [3–6]. Prevention of such critical metabolic issues as protein-energy insufficiency syndrome, postoperative insulin resistance and hypermetabolism-hypercatabolism syndrome, together with malignant cell's biochemical atypism, significantly deplete organism's energy resources, causing a negative impact on cellular and humoral immunity, leading to the development of immunosuppression [7]. These factors create a pathological foundation for the development of the main type of postoperative complications, which accompany colorectal surgery in all its way of development [6].

Despite the reduction of the postoperative recovery period, morbidity and mortality, patient's life quality improvement, the impact of the ERP on long-term outcomes of colon cancer patients surgical treatment remains unclear. In theory such impact seems possible due to the reduction of postoperative complications, recovery, maintenance of normal immune system functioning and also due to the reduction of contra-indications to the adjuvant treatment and the term reduction before its beginning. Nowadays, more and more studies deal with the influence of postoperative complications on the long-term outcomes of surgical treatment of colon cancer patients. The results of such studies prove the existence of such consistent pattern, underlining that the ways to prevent the development of such complications can also become an instrument for the long-term outcome improvement [6, 8, 9].

Aim of the study: to evaluate the impact of the multimodal ERP on the long-term outcomes (overall and recurrence-free 3-year survival) of the surgical treatment of colon cancer patients.

MATERIALS AND METHODS

Over the 2008 to 2013 period a randomized trial, aimed to evaluate the impact of the developed ERP on short- and long-term outcomes of surgical treatment of colon cancer patients was held. Inclusion criteria were: presence of histologically verified colon adenocarcinoma stage I–IV (T1–4N0–2M0–1); age above 18 years, intent of rather curative or palliative surgery for resectable disease, patient's common status $\leqslant 2$ by ECOG (Eastern Cooperative Oncology Group) or $\geqslant 50$ by Karnovsky scale; a signed informed concern for treatment. Patients with the complicated disease (ileus, peritonitis, acute bleeding), with previous explorative laparotomies, symptomatic procedures; patients with synchronous and/or metachronous malignancies and with tumors of non-epithelial origin were excluded from the trial.

After the randomization the patients were distributed into the main (enhanced recovery pathway) and control group (standard care). Adaptative design of randomization was used — enrollment started in 1 : 1 proportion, however according to the trial conditions, if a certain group appeared to be non-representative, additional enrollment was declared until both groups reached representative values.

The main statements of the ERP were as follows:

1. Preoperative period: no mechanical bowel preparation; no preoperative starvation — last uptake of carbohydrate enriched solutions 6–8 hours prior to surgery.

2. Intraoperative period: epidural analgesia with 0.125% bupivacaine + phentanyle solution on the level of Th_{VIII-X} 8–9 ml per hour, using of nonsteroid anti-inflammatory drugs (NSAIDs); laparoscopic or laparoscopy-assisted procedures. If impossible — right or left transverse laparotomy, or a surgical approach to the sigmoid colon with the sparing of the left straight muscle and white line of the abdomen; no perioperative hemotransfusions for anemic patients, whose blood loss wasn't associated with hemorrhagic shock or coagulopathy; no routine drains, nasogastric tubes or catheters, extubation by the end of the operation.

3. Postoperative period: early enteral nutrition — mean 8–12 hours after surgery; early activisation on the day of surgery; prolonged epidural analgesia (up to 3 days) with local anesthetics, NSAIDs, diminishing of opioids; preventing postoperative nausea and vomiting — 5-HT3 blockers administration; restriction of perioperative infusions — 1700–2400 ml of rather colloids or crystalloids daily with total osmolarity no more than 75 mmol/l.

Control group patients received similar surgical treatment, but without the application of the above mentioned components of the ERP. Cancer staging was carried out according to American Joint Committee on Cancer (AJCC) Classification of Malignant Tumors TNM (7th ed., 2010). Antibiotical and antithrombotic prophylaxis had been provided in according to ESMO (European Society of Medical Oncology) and NCCN (National Comprehensive Cancer Network) guidelines. Postoperative complications were assessed according to Clavien — Dindo classification (2004). A postoperative complication was defined as any deviation from a normal postoperative period, revealed up to 30 days post surgery. Patients with stages IIB–C, III and IV underwent adjuvant treatment as stated in NCCN (National Comprehensive Cancer Network) guidelines. The differences between the groups were assessed by statistical methods for nonparametric values — χ^2 and Fisher exact T-test. Survival analysis was assessed according to Kaplan — Meier method.

RESULTS AND DISCUSSION

Surgical treatment was provided for 230 patients. The main group included 130 patients, control group — 100. No significant differences in age, gender and body mass index were observed. There were no significant intergroup differences in rates of comorbidity and complications of main disease. Patients' characteristics by primary tumor site is presented in Table 1. Main group patients had a trend towards right colon cancer, control group — the sigmoid colon ($p < 0.05$).

Table 1

Patients' characteristics by primary tumor site

Tumor site	Main group, n (%)	Control group, n (%)
Caecum	33 (25.0)	22 (22.0)
Ascending colon	41 (31.0)	23 (23.0)
Right flexure	18 (14.0)	15 (15.0)
Transverse colon	10 (8.0)	4 (4.0)
Left flexure	8 (6.0)	3 (3.0)
Descending colon	11 (9.0)	7 (7.0)
Sigmoid colon	9 (7.0)	26 (26.0)
Total	130 (100)	100 (100)

Patients distribution by tumor stage is presented in Table 2. The main group had much more patients with moderate and poorly differentiated, and locally advanced tumors — 15.0 and 6.0% ($p < 0.05$), respectively. Taking into account the distribution by primary tumor site, right hemicolectomy was the predominant type of surgery in both groups. The structure of surgical procedures is shown in Table 3.

Postoperative complications. Among the patients from the main group, postoperative complications were observed in 11 (8.5%) cases. The structure of postoperative complications in both groups is shown in Table 4. There were no patients with more than one complication. Grade II complications (postoperative ileus) — 1 (0.8%); grade III — 4 (3.1%) — wound site infection, intraabdominal abscess and anastomotic leakage with an external fistula formation; grade IV — 6 (4.6%): 2 cases — acute mesenteric ischemia, 2 — anastomotic leak, 1 — intraabdominal abscess, 1 — diffuse peritonitis. One case of postoperative mortality was observed (0.8%).

Table 2

Patients' distribution by tumor stage

AJCC stage	pTNM, 7th ed.	Main group, n (%)	Control group, n (%)
I	T1–2N0M0	1 (0.8)	7 (7.0)
IIA	T3N0M0	18 (14.0)	38 (38.0)
IIB	T4aN0M0	52 (40.0)	12 (12.0)
IIC	T4bN0M0	10 (8.0)	3 (3.0)
IIIA	T1–2N1M0	11 (8.2)	1 (1.0)
IIIB	T3N1–2M0	9 (7.0)	16 (16.0)
IIIC	T4N1–2M0	8 (6.0)	6 (6.0)
Locally advanced	T4bN0M0; T4bN1–2M0	19 (15.0)	6 (6.0)
IV	T1–4N0–2M1	21 (16.0)	17 (17.0)
Grade of differentiation			
G_1		5 (4.0)	41 (41.0)
G_2		75 (58.0)	46 (46.0)
G_3		41 (32.0)	11 (11.0)
G_4		9 (6.0)	2 (2.0)

Table 3

Structure of surgical procedures

Type of surgery	Main group, n (%)	Control group, n (%)
Right hemicolectomy	95 (74.0)	62 (62.0)
Resection of transverse colon	5 (4.0)	0
Left hemicolectomy	22 (17.0)	12 (12.0)
Resection of sigmoid colon	7 (5.0)	26 (26.0)
Laparoscopic procedures	5 (4.0)	0
Multivisceral resections	19 (15.0)	6 (6.0)
Curative surgery	109 (84.0)	82 (82.0)
Palliative surgery	21 (16.0)	18 (18.0)

Table 4

Structure of postoperative complications in both groups (Clavien — Dindo)

Complication grade	Patient groups, n (%)		Significance
	Main group	Control group	
I	–	–	–
II	1 (0.8)	4 (4.0)	$p < 0.05$
III	4 (3.1)	4 (4.0)	$p = 0.574$
IV	6 (4.6)	12 (12.0)	$p < 0.05$
V (postoperative mortality)	1 (0.8)	2 (2.0)	$p < 0.05$
Overall complications	11 (8.5)	20 (20.0)	$p < 0.05$
Patients with complications	11 (8.5)	18 (18.0)	$p < 0.05$
Patients with > 1 complication	0	2 (2.0)	$p < 0.05$

In the control group the postoperative complications were observed in 20 (20.0%) cases. 2 (2.0%) patients had two postoperative complications. Grade II complications included postoperative pneumonia (2.0%), peroneal vein thrombosis (1.0%), transitory cerebral ischemia (1.0%). Grade III complications included anastomotic leak with the external fistula formation (4.0%). Grade IV complications included anastomotic leak with peritonitis (8.0%), postoperative adhesional ileus (4.0%). Postoperative mortality was detected in 2 (2.0%) cases. Significant increase in rates of both postoperative morbidity and mortality was observed in control group ($p < 0.05$).

Long-term outcomes. The average observation period for patients in both groups was 37.4 ± 4.7 months. 4 (3.1%) patients from the main group and 5 (5.0%) from control were lost for contact. Long-term parameters for the main and control groups are shown in Table 5.

Overall 3-year survival among patients with stage I–III colon cancer after the curative surgery had a significant difference in both groups — 88.4 ± 9.6% for the main group and 72.2 ± 7.6% for the control one ($p < 0.05$). There were no statistically significant differences in overall 3-year recurrence-free survival — 87.0 ± 7.5% and 90.0 ± 10.2%, respectively ($p = 0.235$). Survival plots are presented in Figure.

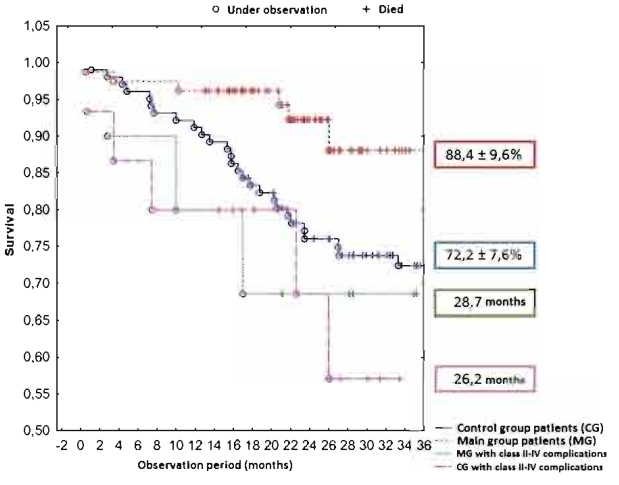

Figure. Survival plots for overall 3-year survival for patients of main and control group

In both groups the patients who had postoperative grade II–IV complications after the curative surgery experienced a significant decrease of overall survival. Three-year survival wasn't achieved in either of the groups. Median survival was 28.7 and 26.2 months, respectively. The difference between groups was insignificant ($p = 0.954$).

Enhanced recovery concept is not new. Since early 90s it intrenched itself in many clinics and gained wide acceptance in cardiac surgery, orthopedics and traumatology, urology, gynecology, and others [3]. More and more data demonstrate multiple benefits of this strategy not only for patients, but for healthcare administrators as well. The most important among these convincing factors traditionally are the reduction of postoperative recovery, the terms of hospital stay, the postoperative complications rates decrease, the quality of life improvement and the cost-effectiveness of treatment, that's why it is widely accepted in multiple protocols of standard surgical care [1, 3, 10]. But in parallel with the growing progress in understanding of the fundamental mechanisms

Table 5

Long-term parameters for main and control group

Study parameter	Number of patients, n (%)		Overall 3-year survival, n (%)		Overall disease-free 3-year survival, n (%)		Median survival (months)		p
	Main group	Control group	Main group	Control group	Main group	Control group	Main group	Control group	
Patients underwent curative surgery	105 (81.0)	77 (77.0)	88.4 ± 9.6	72.2 ± 7.6	87.0 ± 7.5	90.0 ± 10.2	–	–	$p = 0.578$
Patients who had grade III–IV complications	11 (8.5)	20 (20.0)	–	–	–	–	28.7	26.2	$p = 1.954$

of an organism stress response to traumatic, metabolic, neuroendocrine and immunologic shifts in colorectal cancer patients, some questions arise inevitably: is such pathologically based program, aimed at strictly determined pathologic events blockage, capable of granting with something more than reduction of the of hospital stay length and postoperative morbidity?

G. Snyder et al. in their review suggest, that a condition of perioperative immunosuppression persistently exists in all colorectal cancer patients who undergo a surgery. The main trigger factors of this condition are both surgical injury, accompanied by the increase of proinflammatory mediators expression and cytokines, and anesthesiological components (inadequate anesthesia, infusion overload, opiates use) [11]. J. Coffey et al. point out stable lesions of cellular immunity in patients, who underwent colonic resections for cancer: reduced concentration of proinflammatory cytokines — IL-2, IL-6, IFN-γ and increased level of anti-inflammatory ones (IL-10), reduced level of circulating dendritic cells, NK-lymphocytes, T-killers and cytotoxic T-lymphocytes, which gains peak on postoperative day 3 [12]. The impact of acquired immunosuppression on the colorectal cancer progression was proven in both clinical and experimental studies on animal models [13, 14]. Despite the existence of a link between severe postoperative complications (in particular, anastomotic leak) and worse survival in patients with colorectal, gastric and esophageal cancer isn't something new for more than 10 years, pathologic pathways, explaining this trend, still remain unclear [8]. In a study of X. Xia et al. it is stated that systemic inflammatory response syndrome development is a key element in this sequence of adverse events development, affecting long-term results of colorectal cancer surgical treatment [6]. According to the results of multivariate analysis, conducted by those authors, two independent prognostic factors for the poor survival after the surgical treatment of colorectal cancer are the regional lymph nodes involvement and the presence of grade II complications and higher. Overall 5-year survival for patients with stage I–III disease was 78.5% for patients without grade II–IV complications and 41.4% if they were present. Overall 5-year disease-free survival was 82.1 and 40.9%, respectively. Similar correlation was also observed in our study. Patients who developed grade II–IV complications after the curative surgery showed poor long-term outcomes — 3-year survival was not achieved in either of the groups with median survival of 28.7 and 26.2 months, respectively. On the other hand, patients who didn't have complications demonstrated similarly satisfying results for both overall and disease-free survival — 90.0 ± 9.7 and 92.0 ± 9.2%.

Hypothesis of the key role of systemic inflammatory response syndrome in tumor progression development was confirmed by the study of A. Mantovani et al. [15]. Since the main inflammatory mediators and their receptors are responsible for the cell motility, invasive pattern and apoptosis blockage, increase of their concentration, induced by the systemic inflammatory response, is capable of increasing the metastatic potential of the free circulating cancer cells. The same statement found confirmation for patients undergoing surgery for breast cancer as well [16]. Another point of view is shared by K. Walker et al., according to which the dissemination of tumor cells takes place in cases of anastomotic leak, affecting patient's survival [17]. However, the studies of H. Ptok et al. disproved this statement by comparing the frequency of local recurrence rate in patients who had anastomotic leak and in *in vivo* models [18]. Despite the fact that the molecular pathologic pathways of tumor progression development in patients with grade II and higher complications still remain unclear, the key role of systemic inflammatory response syndrome, state of chronic inflammation, causing immunosuppression and affecting long-term outcomes doesn't raise any doubts. In the study of T. Paholyuk et al., it is demonstrated, that the main factors of systemic inflammation, such as leukocytes level, C-reactive protein and core body temperature remained more elevated particularly in the subgroup of patients, who had poor long-term outcomes after the surgical treatment of colorectal cancer [19]. It is notable that similar correlations between the laboratory parameters of the systemic inflammation and survival were obtained by T. Kubota et al. for surgical treatment of gastric cancer [20].

CONCLUSIONS

1. Developed ERP of surgical treatment of patients with colon cancer gives an opportunity to not only improve the short-term outcomes, but to influence long-term outcomes by means of postoperative grade II–IV complications reduction.

2. Multimodal ERP implementation resulted in reduction of postoperative morbidity by 11.6% and mortality — by 1.2% among patients, who underwent curative surgery for colon cancer.

3. Postoperative grade II–IV complications were associated with the dramatic decrease in survival — 3-year survival was not achieved, median survival resulted in 28.2 and 26.7 months in main and control group, respectively.

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ВЛИЯНИЕ ПОСЛЕОПЕРАЦИОННЫХ ОСЛОЖНЕНИЙ И ПРИМЕНЕНИЯ МУЛЬТИМОДАЛЬНОЙ ПРОГРАММЫ БЫСТРОГО ВОССТАНОВЛЕНИЯ НА ОТДАЛЕННЫЕ РЕЗУЛЬТАТЫ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ БОЛЬНЫХ РАКОМ ОБОДОЧНОЙ КИШКИ

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Резюме. *Применение мультимодальной программы быстрого восстановления (ПБВ) продемонстрировало свою эффективность в отношении непосредственных результатов хирургического лечения больных раком ободочной кишки. На сегодня влияние ПБВ на отдаленные результаты терапии остается недостаточно изученным.* ***Цель:*** *оценить влияние ПБВ на отдаленные результаты хирургического лечения больных раком ободочной кишки.* ***Объект и методы:*** *включены 230 пациентов, которым в период с 2008 по 2013 г. проводили хирургическое лечение по поводу рака ободочной кишки. В основную группу (хирургическое лечение по ПБВ) включено 130, в группу сравнения (стандартная тактика) — 100 больных.* ***Результаты:*** *значимых межгрупповых различий по антропометрическим данным, локализации опухоли, стадии заболевания и объему оперативного вмешательства не отмечено. Среди пациентов основной группы послеоперационные осложнения II–IV класса по классификации Clavien — Dindo зарегистрированы в 11 (8,5%), а контрольной группы — в 20 (20,0%) случаях ($p < 0,05$). Послеоперационная летальность составила 0,8 и 2,0% соответственно ($p < 0,05$). Период наблюдения — 37,4 ± 4,7 мес. Общая 3-летняя выживаемость имела достоверное различие: 88,4 ± 9,6% — в основной и 72,2 ± 7,6% — в контрольной группе ($p < 0,05$). Общая 3-летняя безрецидивная выживаемость составила 87,0 ± 7,5 и 90,0 ± 10,2% для основной и контрольной группы соответственно ($p = 2,235$). У пациентов обеих групп, у которых возникли послеоперационные осложнения II–IV класса, 3-летняя выживаемость не достигнута. Медиана — 28,7 и 26,2 мес для основной и контрольной группы соответственно ($p = 1,954$).* ***Выводы:*** *применяемая ПБВ влияет на отдаленные результаты лечения за счет уменьшения количества послеоперационных осложнений II–IV класса.*

Ключевые слова: рак ободочной кишки, программа быстрого восстановления, отдаленные результаты хирургического лечения.

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Submitted: 08.06.2015