Pharmaconutrition in patients with gastrointestinal malignancies

The monograph describes the effects of pharmaconutrition on the results of surgical treatment in patients with stomach or colorectal cancer. The main pathogenetic pathways of the postoperative septic and purulent complications are reviewed in the context of modern presentations on immune regulatory and genomic abnormalities in this population. The monograph is intended for surgeons, oncologists, nutritionists, clinical pathologists, and health professionals.

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978-3-639-66201-6

The important role of pharmaconutrition

Lysenko, Ivanov

**Scholars'
Press**

Vyacheslav Lysenko
Roman Ivanov

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Scholar's Press

Impressum / Imprint

Bibliografische Information der Deutschen Nationalbibliothek: Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über <http://dnb.d-nb.de> abrufbar.

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Bibliographic information published by the Deutsche Nationalbibliothek: The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.d-nb.de>.

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Coverbild / Cover image: www.ingimage.com

Verlag / Publisher:

Scholar's Press

ist ein Imprint der / is a trademark of

OmniScriptum GmbH & Co. KG

Heinrich-Böcking-Str. 6-8, 66121 Saarbrücken, Deutschland / Germany

Email: info@scholars-press.com

Herstellung: siehe letzte Seite /

Printed at: see last page

ISBN: 978-3-639-66201-6

Zugl. / Approved by: Russian Federation, Saratov, Saratov State Medical University, Diss., 2010

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CONTENTS

INTRODUCTION.....	6	
<u>Chapter 1. Stomach cancer</u>		
1.1. Epidemiology of stomach cancer. Classification. Characteristic clinical signs and symptoms. Primary diagnostics methods. Complications.....	9	
1.2. Surgical management of stomach cancer	12	
<u>Chapter 2. Colorectal cancer</u>		18
2.1. Epidemiology of colorectal cancer. Classification. Characteristic clinical signs and symptoms. Primary diagnostics methods. Complicated forms	18	
2.2. Surgical treatment for colorectal cancer	23	
<u>Chapter 3. Malnutrition and its management in surgical patients</u>		32
3.1. Malnutrition and its clinical significance in different groups of surgical patients	32	
3.2. Nutritional support in modulation of homeostatic disturbances in surgical patients: current status.....	37	
<u>Chapter 4. Cytokines – cell-cell interactions molecules in development of systemic inflammatory response syndrome</u>		44
<u>Chapter 5. Clinical and diagnostics significance of lipid peroxidation, oxidative stress, acute phase proteins, markers of lymphocyte apoptosis and genomic abnormalities, as well as oncomarkers specific for gastrointestinal malignancies</u>		50
<u>Chapter 6. Nutritional modulation of immune regulatory abnormalities in surgical treatment of patients with stomach or colorectal cancer</u>		59
6.1. Materials and Methods.....	59	
Patients Characteristics	59	

Clinical characteristics of the stomach cancer patients.....	59
Clinical, X-ray, instrumental, and laboratory methods in the stomach cancer patients.....	64
Clinical characteristics of the colorectal cancer patients.....	66
Clinical, X-ray, instrumental, and laboratory methods in the colorectal cancer patients.....	70
Test methods for oxidative stress markers, immune regulatory parameters, lymphocyte apoptosis triggers, genomic abnormalities, and oncomarkers in studied population.....	71
Statistical methods.....	74
6.2. Stomach cancer.....	75
6.2.1. Nutritional status of the stomach cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used.....	75
6.2.2. Lipid peroxidation and antioxidative protection in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used.....	78
6.2.3. Acute phase proteins in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used.....	83
6.2.4. Serum cytokine profile and systemic inflammatory response syndrome in the stomach cancer patients. Impact of different types of nutritional support on serum cytokine balance and SIRS.....	86
6.2.5. Lymphocyte apoptosis, genomic abnormalities, and changes in CEA and CA 19-9 levels in the stomach cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used	95
6.3. Colorectal cancer.....	102

6.3.1. Nutritional status of the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used.....	102
6.3.2. Lipid peroxidation and antioxidative protection in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used.....	105
6.3.3. Acute phase proteins in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used.....	110
6.3.4. Serum cytokine profile in the colorectal cancer patients. Impact of the different types of nutritional support on serum cytokine balance.....	112
6.3.5. Lymphocyte apoptosis, genomic abnormalities, and changes in CEA and CA 19-9 levels in the colorectal cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used.....	119
6.4. Comparisons of the nutritional status parameters, markers of immune regulatory and genomic abnormalities in the stomach cancer patients and colorectal cancer patients in pre- and postoperative periods.....	126
6.5. Influence of the different types of clinical nutrition on the incidences of postoperative complications in the patients with stomach or colorectal cancer.....	136
CONCLUSION.....	139
SUMMARY.....	149
PRACTICAL GUIDELINES.....	150
REFERENCE	151

LIST OF ABBREVIATIONS

AOP – antioxidative protection
ROS – reactive oxygen species
GSH – reduced glutathione
NSA – nutritional support arm
AEE – actual energy expenditure
PEE – primary energy exchange
GI – gastrointestinal
BMI – body mass index
CN – clinical nutrition
TST – triceps skinfold thickness
MDA – malondialdehyde
ND – nutritional deficiency
NS – nutritional support
APPs – acute phase proteins
GSSG – oxidized glutathione
OMs – oncomarkers
MUAMC – mid-upper arm muscle circumference
MUAC – mid-upper arm circumference
ICU – intensive care unit
PUFAs – polyunsaturated fatty acids
LPO – lipid peroxidation
TPN – total parenteral nutrition
NF – nutritional formula
DIC syndrome – disseminated intravascular coagulation syndrome
SC – stomach cancer
CEA – carcinoembryonic antigen
FR – free radicals
SIRS - systemic inflammatory response syndrome
SOD - superoxide dismutase
CFS - colonofiberscopy
TNF- α - tumor necrosis factor- α .
FEGDS – fiberoptic esophagogastrroduodenoscopy
US – ultrasound
RR - respiratory rate
HR - heart rate
EN – enteral nutrition (tube feeding)
ECG – electrocardiography

CARS - compensatory anti-inflammatory response syndrome

IL-1 β – interleukin-1-beta

IL-4 – interleukin-4

IL-6 – interleukin-6

IL-8 – interleukin-8

IL-10 – interleukin-10

INF- γ - interferon-gamma

LCT – long-chain triglycerides

MCT – medium-chain triglycerides

SIRS – systemic inflammatory response syndrome

TGF- β – transforming growth factor- β

To our Tutor
Professor Stanislav S. Slesarenko

INTRODUCTION

Stomach cancer (SC) ranks second-third place by incidence among all malignancies. Russia takes the 2nd place worldwide by SC incidence (52.8 per 100,000 people) [N.A. Maystrenko, Al.A. Kurygin, 2007]. SC morbidity and mortality are annually increased by 1.0%. According to WHO experts resolution, in 2030, the mortality related to stomach cancer may be increased more than twice. WHO specialists consider that only in 2009 the SC morbidity numbers will be 7,000,000 cases; the mortality numbers will be 500,000 cases. The most marked increase in SC morbidity was observed in China, Russia, and India [<http://www.gastriccancer.ru/news/index/752.html>].

Colorectal cancer is one of the most common types of human malignancies. Based on the statistical data collected over the last decade, the morbidity and mortality in patients with this disease are steadily increased in both Russia and economically developed countries worldwide [Davydov M.I., Aksel E.M., 2005; Barsukov Yu.A., Knysh V.I., 2006; Greenlee R.T. et al., 2000]. According to G. Pott [2006], the number of precancerous conditions, primarily, various types of colitis, functional and degenerative disorders of the colon, is significantly increased in the technically developed countries. If this trend remains stable, colorectal cancer may be the most common pathology in the near future.

As food transit is disrupted leading to protein and energy insufficiency, severe cancer toxicity, and secondary immunodeficiency, the surgical treatment in such patients is related to increased risk for the postoperative purulent and septic complications [A.L. Kostyuchenko, 2001; K.A. Bunatyan, 2007; A.N. Afanaseva, 2008].

It is currently proven that problem to provide the surgical patients with macro- and micronutrients is very actual. Unfortunately, in modern literature, the data on successful nutritional support in different periods of homeostatic disturbances in the patients with stomach or colorectal cancer are occasional and don't review the homeostasis disturbances occurred in the whole body and actions to correct them given the specific surgical treatment.

To date, a variety of modern means for nutritional support (*so called, pharmaconutrients which are used not for nutritional support but for*

immediate realization of its pharmacological effects) and accesses to realize it, were appeared. However, there are a few reports on its successful application in the surgical patients and these reports provide to clinicians no available and reproducible methods to manage the homeostasis disturbances using pharmaconutrients-supplemented clinical nutrition. The primary indication for nutritional support in our country is either critically ill patients staying in the Intensive Care Units [T.S. Popova, A.E. Shestopalov, T.Sh. Tamazashvili, I.N. Leyderman, 2002], or Postoperative Days 1-2 (maximum) after the performed surgery when the patients are staying in the Intensive Care Units (ICUs) [A.L. Kostyuchenko, 2001]. When a patient is transferred to the Surgical Department, the nutritional support is not usually provided or provided partially. The critical period for development of the postoperative purulent and septic complications are Postoperative Days 5-12 (V.V. Zhebrovskiy, 2000; Rivkin V.L. et al., 2004; A.N. Afanaseva, 2008; A.A. Baulin et al., 2008; A.D. Kharagezov, O.S. Serdyukova et al., 2008; Makela J.T. et al., 2003; Kanellos I. et al., 2004; Brennan M.F., 2005].

In practice, it is considered that nutrition interrupted for one or two days is not a problem for even relatively unstable patient as such patient has the internal resources of nutrients. However, these resources are not unlimited, and its depletion is a basis for many pathological disturbances covering the whole body of the patient [A.L. Kostyuchenko, 2001].

In recent years, the investigators (*especially, surgeons*) pay special attention to determination in the patients with stomach or colorectal cancer the most specific and sensitive biomarkers, to date, which directly describe the oncology process, immune regulatory status, and efficacy of various treatment options, with the purpose of early diagnostics, more complete assessment of surgical treatment, decrease in relapse rate and of patient survival [Tenderenda M. et al., 2001; Kooby D.A. et al., 2003; Fondevila C. et al., 2004; Brennan M.F., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005; Kwon J-I., Kim Gi-Y., Park K-Y. et al., 2008; Kaschiato D., 2008].

Therefore, the development and introduction in real clinical practice the algorithm for outcome predicted for the diseases which are investigated by us, are extremely actual using modern highly sensitive and specific genetic markers in early postoperative period in the presence of balanced pharmaconutrients-enriched clinical nutrition to improve results of surgical treatment in the patients with stomach or colorectal cancer.

The combination of the newer methods of clinical nutrition and wide application of modern highly sensitive and specific genetic markers of immune regulatory abnormalities using innovation technologies in development of nutritional support and latest advances in clinical laboratory diagnostics are, to our opinion, perspective scientific issue of both practical and scientific methodological values in the various medical specialties.

Chapter 1. Stomach cancer

1.1. Epidemiology of stomach cancer. Classification. Characteristic clinical signs and symptoms. Primary diagnostics methods. Complications

In Russia, in the structure of oncological morbidity, stomach cancer (SC) steadily occupies the 2nd place accounting for 12.4% in men (second to lung cancer) and 8.5% in women (third to breast cancer and skin cancer) among all malignancies. Patients' mean age is 65.7 years. Most often, this cancer is observed in the subjects older than 50 y.o. In the Russian Federation, the mortality incidences of stomach cancer are 15.3% in men (second to lung cancer) and 13.8% in women (second to breast cancer) of all malignancies [Davydov M.I., Ter-Ovanesov M.D., 2000; Gorbunova V.A. et al., 2006]. According to N.A. Maystrenko and Al.A. Kurygin [2007], Russia takes the 2nd place in SC-related mortality (40.3 per 100,000 men and 16.9 per 100,000 women, second to Costa Rica (42.5 and 17.6, respectively) among 48 countries worldwide submitted the data to the World Health Organization (WHO). M.F. Brennan [2005] reported that in USA, more than 800,000 patients with stomach cancer are newly diagnosed every year, and 25,000 subjects out of them die.

The modern international classification [Blinov N.N., 2003] classifies SC into 4 stages depending on the extent of tumor penetration through the gastric wall, degree of regional lymph node involvement and its numbers, and presence of distant metastasis. N.A. Maystrenko and Al.A. Kurygin [2007] recommend to have clearly anatomical presentation on the stomach when this classification is used:

- cardia (gastroesophageal junction);
- fundus;
- body of the stomach;
- antrum and pylorus.

The majority of authors [Chernousov A.F. et al., 2004; Maystrenko N.A., Kurygin Al.A., 2007; Brennan M.F., 2005; Kaschiato D., 2008] recommends to use the following SC diagnostics algorithm:

1. Clinical assessment;
2. Laboratory tests;
3. Endoscopic evaluation;
4. X-ray diagnostics;

5. Diagnostic laparoscopy;
6. Scheduled exam of the removed stomach;

As for the laboratory diagnostics of the immune status, the most literature data pay insufficient attention to this pathological process, in our opinion.

SC clinical manifestations are well-known, described, and characterized with long-term latent course and lack of the signs specific to this disease at early stages. One or other signs may dominate depending on tumor location. So, if gastroesophageal junction is involved, dysphagia and intensive salivation are observed, if tumor is located at the distal part and there is increased narrowing, the patients suffer from feeling of gastric fullness, foul-smelling eructation, nausea, and vomiting after feedings. Cancer of the stomach fundus is characterized with abdominal pain, decreased appetites, feeling of gastric fullness, fatigue. Back pain is often related to tumor invasion to the pancreas or involvement of retroperitoneal lymph nodes. Peritoneal dissemination causes ascites. Liver or lymph node metastases result in jaundice [Lopukhin Yu.M., Savelev V.S., 1997; Schepotin I.B., Evans S.R., 2000].

The most common complications of this disease are bleedings (10-15%), stenosis of proximal and, especially, distal part of the stomach (up to 60%), tumor perforation (10-15%), intestinal and biliary obstruction (up to 10%) [Rusanov A.A., 1979; Schepotin I.B., Evans S.R., 2000; Chernousov A.F. et al., 2004; Brennan M.F., 2005]. The similar results were obtained by N.E. Chernenkovskaya et al. [2006].

The primary laboratory diagnostics method of SC is peripheral blood test as anemia develops frequently in such patients. Its reasons may be different: tumor cavitation causes blood loss, absorbable degradation products lead to hemolysis, achylia associated with decreased digestive function of the gastric acid, and loss of antipernicious anemia factor result in hypochromic anemia. Leucopenia is diagnosed in the vast majority of patients [Maystrenko N.A., Kurygin A.I., 2007; Kaschiato D., 2008].

Currently, oncomarkers (OMs) assays are obligatory for SC diagnostics. Based on the data obtained by Maystrenko N.A. and Kurygin A.I. [2007], Kaschiato D. [2008], this is primarily carcinoembryonic antigen (CEA). V.A Gorbunova and N.S. Besova et al. [2006] recommend to analyze one more OM – CA19-9. According to these authors' results, these Oms have important prognostic value and are analyzed both prior to and after surgical intervention, in particular, to make a decision on the possibility and reasonability of chemotherapy.

Currently, fiberoptic esophagogastroduodenoscopy (FEGDS) is the most reliable diagnostics option for SC patients [Chernekhovskaya N.E. et al., 2006]. The authors report that over the last years, the accuracy of this method combined with biopsy, and cytology, and genetic assays was increased from 86% up to 100%. The similar results were obtained by Z. Marzhatka, B.K. Poddubniy, E.D. Fedorov [1996], and V.A. Romanov [2007]. The most common endoscopic SC classification was developed by R. Borrmann and R. Schindler; according to it, there are: polypoid tumor (3-18% cases), superficial spreading tumor (10-42% cases), ulcerating tumor (45-60% cases), and diffusely infiltrating tumor (10-30% cases) [Savelev V.S., Buyanov V.M., Lukomskiy G.I., 1985]. N.E. Chernekhovskaya et al. [2006] and V.A. Romanov [2007] recommend to use vital dyes and fluorescent materials (e.g., 0.1% Indigo Carmine) to extent the endoscopic possibilities.

The common radiation diagnostics methods for SC include: X-ray and ultrasound methods.

X-ray method allows to determine both direct signs: filling defect and disrupted mucous ridges, and indirect signs: gastric wall infiltration, gastric outlet stenosis, gastroesophageal junction narrowing. The complete diagnostics should include upright and undertable fluoroscopy and X-ray using different degree of barium and air opacification. The test should be completed under «tight filling» condition to asses the wall patterns and determine the infiltration areas. This diagnostic option is intended for exact determination of tumor location, affected stomach area, involvement of the esophagus and duodenum, its stenosis degree, tumor sizes and shape. The X-ray computed tomography may provide more detailed information on involvement of adjacent organ and lymph nodes [Gorbunova V.A. et al., 2006; Maystrenko N.A., Kurygin Al.A., 2007; Brennan M.F., 2005; Kaschiato D., 2008].

The role of ultrasound diagnostics (US) is of increasing importance to evaluate the stomach cancer patients. US allows to asses the stomach and involvement of adjacent organs, i.e. local expansion of the tumor. Additionally, this diagnostics option allows to reveal metastasis in the abdominal organs and retroperitoneal cavity, to assess the amount of ascetic fluid; it is important for preoperative staging, making decision on treatment strategy, and disease outcome [Maystrenko N.A., Kurygin Al.A., 2007; Brennan M.F., 2005].

In diagnostically difficult cases, some investigators recommend to use additionally computed tomography and magnetic resonance imaging

[Davydov M.I., Ter-Ovanesov M.D., 2000; Chernousov A.F. et al., 2004; Maystrenko N.A., Kurygin A.I.A., 2007; Brennan M.F., 2005].

Laparoscopic diagnostics is performed to clarify the depth of gastric wall invasion (including serosal penetration), tumor spreading to the adjacent organs, presence of peritoneal dissemination and ascites [Savelev V.S., Buyanov V.M., Lukomskiy G.I., 1985; Balalykin A.S., 1996; Chernousov A.F. et al., 2004; Maystrenko N.A., Kurygin A.I.A., 2007; Guy R.J.C., Jonathan D., Paul E. et al., 2003]. The authors recommend to collect materials from the observed lesions for morphological examinations and to perform peritoneal lavage followed by fluid aspiration for cytological examination.

The final diagnostic step is morphological examination if the stomach or its part is removed [Rusanov A.A., 1979; Schepotin I.B., Evans S.R., 2000; Chernousov et al., 2004; Maystrenko N.A., Kurygin A.I.A., 2007; Brennan M.F., 2005].

1.2. Surgical management of stomach cancer

The surgical method is the «gold» standard for the stomach cancer patient [Davydov M.I., Ter-Ovanesov M.D., 2000; Chernousov A.F. et al., 2004; Brennan M.F., 2005]. The extent of surgery may vary from endoscopic mucosal resection of the stomach to extended combined interventions and is depended on tumor spread. Currently, three main types of interventions are performed: **gastrectomy, subtotal proximal and subtotal distal resection of the stomach** [Ruchagov G.P., 1993; Lopukhin Yu.M., Savelev V.S., 1997; Zhebrovskiy V.V., 2000; Davydov M.I., Ter-Ovanesov M.D., 2000; Schepotin I.B., Evans S.R., 2000; Chernousov A.F. et al., 2004; Daly J.M., Thomas P.J.H., John V.R., Sasako M., 2002; Roder J.D., Bonenkamp J.J., Craven J. et al., 2003; Inaba T., Okinaga K., Fukushima R. et al., 2004; Brennan M.F., 2005].

Taking into account the recent advantages in SC diagnostics, introduction of the modern surgical strategies into clinical practice (wide application of laparoscopy, advanced surgical sutures and suturing devices); and appearance of newest pharmacological and technical means of anesthetic management [Koryachkin V.A., Strashnov V.I., 2004], N.A. Maystrenko and A.I.A. Kurygin [2007] consider that the choice of operation type should be determined by the following aspects:

- whether a surgery is curative in a specific patient?

- whether operative injury is comparable to the individual resources of this patient?

- what is a chance for postoperative rehabilitation with satisfactory preservation of the gastrointestinal functions?

Thereafter, the authors determine the specific surgical components to choose a surgery:

1. Surgical approach (endoscopic, laparoscopic or laparotomic), given the adequacy of the extent of the planned intervention.

2. Determination of the extent of resection given tumor spreading over this organ and amount of the removed tissues.

3. Selection of the further reconstructive surgery which determine postoperative recovery of the digestive and absorbable function of the small bowel and possibility to perform repeated intervention in case of local relapse.

The surgical interventions involving lymph system of the stomach (nodal dissections) are currently used relatively widespread, these interventions allow to remove both primary tumor and affected lymph nodes, which sometimes positively influences on the long-term results [Lopukhin Yu.M., Savelev V.S., 1997; Davydov M.I., Ter-Ovanesov M.D., 2000; Schepotin I.B., Evans S.R., 2000; Chernousov A.F., Polikarpov S.A., 2006; Bonenkamp J.J., Hermans J., Sasako M., et al., 1998; Daly J.M., Thomas P.J.H., John V.R., Sasako M., 2002; Roder J.D., Bonenkamp J.J., Craven J. et al., 2003; Brennan M.F., 2005].

In the many authors' opinion [Rusanov A.A., 1979; Lopukhin Yu.M., Savelev V.S., 1997; Davydov M.I., Ter-Ovanesov M.D., 2000; Schepotin I.B., Evans S.R., 2000; Chernousov A.F. et al., 2004; Maystrenko N.A., Kurygin A.I., 2007; Brennan M.F., 2005], the indications for distal resection of the stomach in the patients with outlet tumors complicated with pyloroduodenal stenosis are:

1. Exophytic tumor growth with no evidence of infiltration.
2. Stomach angle which is the lower third of the body of the stomach is not involved.
3. There are no extensive serosal penetration and multicentric tumor lesions.
4. No metastases in the proximal part, retroperitoneal cavity, especially, along with the lienal artery, celiac trunk, and splenic hilum, diagnosed during intervention.

The curative subtotal resection of the stomach is considered to be the resection of the 4/5 of the whole stomach with complete removal of the

lesser curvature up to the gastroesophageal junction combined with D2 lymph node dissection.

Moreover, the results obtained by N.A. Kuznetsov, K.Yu. Danilov, G.A. Bagdasarov, and S.N. Ignatenko [2000] are worthy. The authors analyzed the results from the extended interventions for SC combined with various types of nodal dissection. Group 1 lymph nodes (N1) were removed in 311 patients. This extent of intervention was considered as standard D1. Groups 1 and 2 lymph nodes (N1 + N2) were dissected in 102 subjects, which corresponded to D2. Groups 1-3 lymph nodes (N1 + N2 + N3) were removed in 20 patients (D3 lymph node dissection).

The patients' age varied from 32 to 81 years. 15.2% patients were up to 50 y.o., 53.8% subjects were 51-70 y.o. and 30.9% patients were older than 70 years. Among them, 55.7% were males and 44.3% were females. The suturing material preferable by the authors was absorbable coated Vicryl. Depending on location and spreading of the tumor, the surgical interventions were different (Table 1).

There were combined interventions associated with resection of the pancreas and transverse colon, liver and removal of the spleen (10.2% cases). The investigators consider that the main portion of the performed interventions accounted for **distal subtotal resections of the stomach**, which were not technically difficult at the reconstruction stage in contrast to gastrectomy and proximal resection of the stomach as formation of esophageal anastomosis was the most significant step of these surgeries.

Metastatic sites were observed in all removed lymph nodes in 15.1% cases, not all lymph nodes were involved in 42.9% cases, and regional lymph nodes contained no cancer cells in 42.0% cases. The authors noted that 42.0% patients underwent potentially curative interventions and required no extensive nodal dissection.

There is evidence that the significantly advanced diagnostics does not still allow to determine the true degree of involvement of the regional lymph nodes both prior to and during surgery [Bonenkamp J.J., Hermans J., Sasako M., van de Velde C.J.H., 1998]. Neither small size, nor soft consistency, nor pink colour answer questions concerning their intactness, and the final answer is appeared when careful **histopathology** of the removed tissues was performed [Brennan M.F., 2005].

Therefore, to improve the long-term results, some surgical oncologists vote for principal application of extensive nodal dissection for stomach cancer and in cases where there is no evidence of lymph node

involvement [Daly J.M., Thomas P.J.H., John V.R., Sasako M., 2002; Degiuli M., Sasako M., Calgaro M. et al., 2004].

However, several randomized studies evaluating the immediate results of D2-D3 nodal dissection demonstrated the increased number of complications and increase in operative mortality from 6% to 14% [Bonenkamp J.J., Songun I., Hermans J., 1995; Dent D., Madden M., Prise S., 2002; Edwards P., Blackshaw G.R., Lewis W.G. et al., 2004]. Therefore, M.F. Brennan [2005] stated: “*Extent of nodal dissection continues to be debated*”.

N.A. Kuznetsov, K.Yu. Danilov, G.A. Bagdasarov, and S.N. Ignatenko [2000] concluded that any new treatment option associated with doubling of postoperative mortality compared to standard interventions when improvement of treatment results are not proven, can not be widely used in clinical practice. Based on their results, extension of intervention caused by nodal dissection N2 and N3 prolonged operation time, in average, by 40 minutes. The extensive nodal dissection was associated with intersection of many lymphatic vessels, and large wound area was appeared. This resulted in increased amount of traumatic discharge and required more prolonged drain procedure of the abdominal cavity. Postoperative analysis of 2 study arms allowed to determine higher complication rate after extensive interventions (Table 2).

More frequent development of postoperative pancreatitis and **intraabdominal septic complications** was notable. The fatal necrotizing pancreatitis was developed in 3 cases after extensive nodal dissection.

The main conclusion of this study was the extensive interventions for stomach cancer might be performed if increased survival was not due to significantly worsened immediate results. These interventions can not be performed in all stomach cancer patients and *should take into account patient's global health status*. Reasonable restraint is especially required for D3 nodal dissection.

In conclusion, it should be noted that the extensive and combined surgical interventions can not *completely* resolve the issues related to stomach cancer. The possibilities of extensive nodal dissection for improvement of treatment results in stomach cancer patients concern approximately 30% patient from this population. If tumor is spread over the group 3 lymph nodes, the extensive interventions don't become more curative but help to clarify disease stage more precisely [Sano T., Sasako M., Yamamoto S. et al., 2004]. The removal of intact lymph nodes at stage I stomach tumor does not improve both the long-term and immediate

results [Schepotin I.B., Evans S.R., 2000; Chernousov A.F., Polikarpov S.A., 2006; Bonenkamp J.J., Hermans J., Sasako M., van de Velde C.J.H., 1998; Daly J.M., Thomas P.J.H., John V.R., Sasako M., 2002; Roder J.D., Bonenkamp J.J., Craven J., van de Velde C.J.H., Sasako M., Bottcher K., Stein H.J., 2003].

Table 1

The extent of the surgical interventions

[Kuznetsov N.A., Danilov K.Yu., Bagdasarov G.A., Ignatenko S.N., 2000]

INTERVENTION	Combined surgery	Nodal dissection			
		D1	D2	D3	Total
1. Distal subtotal resection of the stomach	24	229	79	11	319
2. Proximal subtotal resection of the stomach	0	12	0	0	12
3. Gastrectomy	16	59	19	6	84
4. Stomach stump extirpation	4	11	4	3	18
OVERALL	44	311	102	20	433

Table 2

Postoperative complications and mortality

[Kuznetsov N.A., Danilov K.Yu., Bagdasarov G.A., Ignatenko S.N., 2000]

PARAMETER	Rate (%)	
	D1	D2-D3
1. Anastomotic leakage	4.9	6.2
2. Acute pancreatitis	4.5	9.0
3. Abdominal abscess	1.9	4.1
MORTALITY	4.8	5.7

It should be noted that modern abdominal surgery is characterized with application of high technologies including modern suturing devices. Mechanical suture allows to achieve reliable anastomosis and significantly reduce the operation time.

According to S. Hori, T. Ochiai, Y. Gunji et al. [2004], the advantages of mechanical suture include:

1. Reduction of operation time.
2. Decreased tissue injuries due to minimal hand contact, manifested with mild inflammation in the mechanical suture area.
3. High reliability of suture integrity (anastomosis).
4. Reliable hemostasis.

5. Anastomoses may be formed and vessels may be clipped in anatomical areas which are not easily accessible for manual suturing (e.g., gastrectomy, lower rectal resection).

6. Suture simplicity (one-hand and one-step devices); increased operational asepticity.

Nevertheless, anastomosis creation using suturing devices does not guarantee that anastomotic leakage would be absolutely excluded [Egorov V.I., Turusov R.A., Schastlivtsev I.V., Baranov A.O., 2004; Chernousov A.F. et al., 2004; Kasatkin V.F., Kit O.I., Snezhko A.V. et al., 2008; Polikarpov S.A. et al., 2008; Kharagezov A.D., Serdyukova O.S. et al., 2008].

Therefore, the issues of postoperative complications developed in the stomach cancer patients remains very actual regardless from the advantages of modern surgery.

Chapter 2. Colorectal cancer

2.2. Epidemiology of colorectal cancer. Classification. Characteristic clinical signs and symptoms. Primary diagnostics methods. Complicated forms

The term «colon cancer» includes malignant epithelial tumors of the cecum, transverse colon, and rectum varying by shape, location, and histology. Currently, colon cancer (cancer of the transverse colon and rectum) is interpreted collectively, but the term “colorectal cancer” is almost always used, and over the last years this disease morbidity is increased in all economically developed countries worldwide. According to the World Health Organization data, more than 500,000 cases of colorectal cancer are annually diagnosed worldwide. The highest incidences are observed in USA, Canada, West Europe, and Russia. The lower incidences are observed in Asia and Africa [Gorbunova V.A., Besova N.S., Breder V.V., Orel N.F., 2006; Miliaris S.E., Trygonis K., Papadoniou A., 2004; Saliangas K., 2004].

In the United Kingdom, the rectal cancer accounts for 15% out of all malignancies and is second to lung cancer only. Thus, in England and Wales, approximately 16,000 colorectal cancer patients die annually. In France, 25,000 newly cases of colorectal cancer are diagnosed every year [Hurlstone D.P., Karajeh M.A., Shorthouse A.J., 2004]. In USA, 130,200 colorectal cancer cases were reported in 2003 [Bonnelly L., 2004]. The colorectal cancer takes the 2nd place in oncological female patients, second to breast cancer only, and the 3rd place in oncological male patients, third to prostate cancer and lung cancer [Rivkin V.L., Fayn S.N., Bronshtein A.A., An V.K., 2004; Gorbunova V.A., Besova N.S., Breder V.V., Orel N.F., 2006; Otchy D., Hyman N., Simmang C. et al., 2004; Mahteme H., Pahlman L., 2005; Tjandra J., Kilkenney J., Buie W., Hyman N. et al., 2005].

In Russia, over the last 20 years, colorectal cancer changed from the 6th to 4th place in women and to the 3rd place in men, following lung cancer, stomach cancer, and breast cancer. Although, the incidence of colorectal cancer in men is 8.7%, third to lung cancer (26.5%) and gastric cancer (14.2%). In women, the incidence of colorectal cancer is 11.1%, third to breast cancer (18.3%) and skin cancer (13.7%). Moreover, the incidence of colorectal cancer is increased and is second to lung cancer and breast cancer in men and women, respectively. The incidence of rectal cancer in

man is higher compared to women by 1.5 times. The highest incidences of colon and rectal cancer are observed in subjects older than 60 years (in men – 6.4% and 5.8% and in women – 9.8% and 7.0%). The portions of colon and rectal cancer mortality account for 4.3% and 4.2% men and 7.9% and 6.1% women, respectively [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Gorbunova V.A., Besova N.S., Breder V.V., Orel N.F., 2006; Zheng S., Chen K., Liu X. et al. , 2003; Bonelly L., 2004; Hurlstone D.P., Karajeh M.A., Shorthouse A.J., 2004; Miliaris S.E., Trygonis K., Papadoniou A., 2004; Saliangas K., 2004].

This is alert, that more than 70 subjects out of 100 newly diagnosed colorectal patients die, and approximately 40% patients out of them die over the first year of diagnosis. This circumstance is based on the fact that at initial visit the advanced colon and rectal malignancies (stages III-IV) are diagnosed in 71.4% and 62.4% subjects, respectively [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004].

Therefore, the presented statistical data demonstrate that colorectal cancer is very actual problem both in Russia and worldwide.

The variety of growth and histology patterns promoted a number of colorectal cancer classifications using different parameters to be developed. Currently, the most common tumor classification is by growth patterns: exophytic form spreading primarily into the intestinal lumen; endophytic form expanding mainly in the intestinal wall; saucer-shaped form combining two previous form alike as ulcerative cancer [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004].

To determine histology patterns of colorectal cancer, the international guidelines should be followed [Saliangas K., 2004]:

Colon tumors

1. Adenocarcinoma (well-differentiated, moderately differentiated, and poorly differentiated).
2. Mucinous adenocarcinoma (muroid, mucosal, colloid cancer).
3. Signet-ring cell (mucocellular) carcinoma.
4. Undifferentiated carcinoma.
5. Unclassified carcinoma.

Rectal neoplasms:

In addition to all mentioned above types:

1. Squamous cell carcinoma (squamous, non-squamous).
2. Adenosquamous carcinoma.
3. Basal cell (basaloid) carcinoma – a type of cloacogenic carcinoma.

The most common malignant epithelial tumor is adenocarcinoma accounting for more than 80% of all colon carcinomas. For prognosis, it is very important to determine differentiation (well-, moderately, and poorly differentiated adenocarcinoma), invasion depth, precision of tumor margins, rate of lymph metastasis. The patients with well-differentiated tumors have more favorable outcomes compared to patients with poorly differentiated carcinomas [Otchy D., Hyman N., Simmang C. et al., 2004; Mahteme H., Pahlman L., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005].

According to the national literature data, the colon cancer is classified by extent into 4 stages [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004]:

Stage I — tumor is localized in mucous membrane and submucous intestinal layer.

Stage IIa — tumor spreads over no more than a half of intestinal circumference, not penetrating the intestinal wall, with no regional lymph metastases.

Stage IIb — tumor spreads over no more than a half of intestinal circumference, penetrating the whole intestinal wall not extending outside, with no regional lymph metastases.

Stage IIIa— tumor spreads over more than a half of intestinal circumference, penetrating the whole intestinal wall with no lymph node metastases.

Stage IIIb— tumor of any sizes with multiple regional lymph metastases.

Stage IV— large tumor penetrating the adjacent organs with multiple regional lymph metastases or any tumor with distant metastases.

C. E. Dukes classification (1932) is also widely used in the international literature [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004], according to it, there are 4 stages:

A — tumor confines to the mucosa and submucosa.

B — tumor invades through the muscularis and serosa.

C — any size tumor with regional node metastasis.

D - tumor metastasis to distant sites.

The international TNM system is the most informative classification permitting to assess the staging comprehensively.

TNM classification

[Blinov N.N., 2003]:

Primary Tumor (T):T_x — Primary tumor cannot be assessed.T₀ — No evidence of primary tumor.T_{is} — Carcinoma in situ: intraepithelial or invasion of lamina propria.T₁ — Tumor invades submucosa.T₂ — Tumor invades muscularis propria.

B — Tumor invades through the muscularis propria.

T₄ — Tumor penetrates to the surface of the visceral peritoneum or tumor directly invades or is adherent to other organs or structures.Regional Lymph Nodes (N)N₀ — No regional lymph node metastasis.N₁ — Metastases in 1–3 regional lymph nodes.N₂ — Metastases in at least 4 regional lymph nodes.Distant Metastasis (M)M₀ — No distant metastasis.M₁ — There are distant metastases

The tumor staging should be based on the preoperative results, intraoperative revision, and postoperative examination of removed part of the colon including specific methods of lymph node assessment.

The most specific signs of colon carcinoma are intestinal bleeding, fecal abnormalities, abdominal pain, and tenesmus. Intestinal bleeding, blood in stool, or occult blood are observed in almost all patients with colorectal cancer. Red blood passage is typical to anal and rectal cancer. Dark blood is more typical to the left-sided cancer of the colon. At that, blood mixed with feces and mucous is more significant evidence. The patients with right-sided cancer of the colon usually demonstrate occult bleeding associated with anemia, pallor, and fatigue. Stool abnormalities (most frequently as bowel movement difficulties) are typical to the left-sided advanced carcinomas of the transverse colon and rectum. Sometimes, colon cancer may be firstly manifested as acute bowel obstruction requiring urgent intervention. The rectal cancer patients typically present feeling of incomplete emptying or false rectal urgency. There are often no abdominal signs, generally, the patients present fatigue, loss of appetite, weight loss. Hepatomegaly and ascites appear at the advanced stages [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004].

Currently, there is a possibility to diagnose the colorectal cancer almost in all cases. V.L. Rivkin, S.N. Fayn, A.S. Bronshtein, V.K. An [2004] recommend to adhere 2 conditions:

- 1) follow the diagnostics algorithm;
- 2) use completely the possibilities of all applied diagnostics methods.

The majority of authors [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Romanov V.A., 2007; Wexner S.D., Eisen G.M., Simmang G., 2002; Otchy D., Hyman N., Simmang C. et al., 2004; Tan K.Y., Seow-Choen F., Ng C. et al., 2004; Rockey D., Paulson E., Niedzwiecki D. et al., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005; Pott G., 2006] recommend to use the following diagnostics algorithm for colorectal cancer:

- analysis of complaints and medical history (please, remember, the risk of colorectal cancer in subjects older than 50 years is very high);
- clinical examination;
- digital rectal exam;
- rectoromanoscopy;
- clinical hematology;
- fecal occult blood test;
- colonoscopy;
- irrigoscopy (colonoscopy results are equivocal, if any);
- abdominal and pelvic ultrasound examination;
- rectal ultrasound examination;
- tumor biopsy.

Additionally, in diagnostically difficult cases, some investigators recommend to use virtual colonoscopy and magnetic resonance imaging [Vertyanin S.V., 2007; Cagliardi G., Bayar S., Smith R. et al., 2003; Kanellos I., 2004; Strassburg J., 2004; Rockey D., Paulson E., Niedzwiecki D. et al., 2005].

The most common complication of the colorectal cancer is chronic large bowel obstruction. In different series, its rate varies from 12.0% to 14.0% [Pegaev A.V., Achkasov E.E., 2005; Shevchenko Yu.L., Stoyko Yu.M., Levchuk A.L., Stepanyuk I.V., 2008; Minopoulos G.I., Lyratzopoulos N., Efremidou H.I., 2004; Saliangas K., Economou A., Nikoloudis N. et al., 2004]. Then, there are intestinal bleeding, perifocal intestinal inflammation and perforation located either in tumor area or so called dilated area due to overexpansion of intestinal wall caused by large bowel obstruction. In case of right-sided tumors, the patients usually present anemia resulted from prolonged continuous occult bleedings. All

complications require appropriate treatment, sometimes, urgent or even emergency interventions to save patient's life; e.g., for diffuse bleeding, acute large bowel obstruction, and perforation. In patients with advanced malignancies, the above listed complications may be combined significantly increasing the risks and worsening the outcomes of surgical treatment [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Minopoulos G.I., Lyratzopoulos N., Efremidou H.I., 2004].

2.2. Surgical treatment for colorectal cancer

The main treatment option for colorectal cancer is curative removal of the tumor and its pathways of regional lymph node metastases. The common principles of surgical treatment for colorectal cancer are curative surgery, ablastics, asepticity, and easy passage of intestinal contents, if possible, via natural way [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Tocchi A., Mazzoni G., Lepre L., Liotta G., 2001; Bokey E.L., Chapuis P.H., Dent O.F. et al., 2003; Maurer C.A., 2004; Otchy D., Hyman N., Simmang C. et al., 2004; Mahteme H., Pahlman L., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005].

The experience of colorectal surgery is more than 150 years. In 1833, Keybard reported the first resection of the colon for malignant tumor followed by intestinal anastomosis. In Russia, in 1886 E.V. Pavlov reported the first cecal resection for malignant tumor followed by ileal-ascending colon anastomosis. Among the two-stage operations, special attention should be paid to surgery proposed by Mikulicz in 1900. The author was one of the first persons who assessed the significance of two-stage operation and developed the main principles for such interventions significantly reducing the postoperative mortality rate.

In 1921, at 30th French Surgeons Congress, Mr. Hartman from Paris reported on two surgeries performed himself [Buhre L.M., Plukker J.T., Mehta D.M. et al., 1991]. The main idea of his operation is to resect a part of the colon affected by malignant tumor followed by complete suturing of the distal part and form preternatural anus from the proximal part of the colon. In our country, N.N. Pertov performed Hartman's operation for colon cancer in 1929. The advantages of this surgery include the tumor removal at the first stage, elimination of such tumor complications as large bowel obstruction, tumor perforation, and, especially, preservation of the distal part of the colon required for further reconstructive surgery –

restoration of intestinal integrity. Moreover, Hartman's operation is less traumatic and sufficiently curative.

In contrast to small bowel interventions, colon resection belongs to the most responsible surgical interventions related to such features as pathogenic microflora presented in the contents of the hollow organ, lack of the mesentery in the fixed parts of the transverse colon, thinner muscular layer. The specified features of the colon predetermine increased exactingness to reliability of interintestinal anastomosis given anatomical patterns of different parts of the colon and adequacy of blood supply in anastomosed intestinal parts [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Tocchi A., Mazzoni G., Lepre L., Liotta G., 2001; Bokey E.L., Chapuis P.H., Dent O.F. et al., 2003]. The most preferable anastomoses among the types of formation of interintestinal anastomosis are "end-to-end" ones. Any anastomosis is formed using serous-muscular sutures and internal, double-row suture. Additionally, more recently, single-row continuous suture using synthetic resorbable suturing materials (Vicryl, Polisorb, etc.) has been used widely [Egorov V.I., Turusov R.A., Schastlivtsev I.V., Baranov A.O., 2004; Kim S-H., Choi H-J., Park K-J. et al., 2005]. In addition to manual formation of interintestinal anastomosis, method of anastomosis creation using circumferential staplers should be emphasized [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Picardi N., Pescatori M., 2004]. Concerning the reliability of created interintestinal anastomosis, a special attention should be paid to viability of sutured parts of the colon, adequacy of its blood supply, lack of tension [Egorov V.I., Turusov R.A., Schastlivtsev I.V., Baranov A.O., 2004; Kim S-H., Choi H-J., Park K-J. et al., 2005].

Abnormal trophism of the intestinal wall caused by supragenotic dilation related to large bowel obstruction, inadequate blood supply, diffuse peritonitis resulted from tumor perforation are contraindications for interintestinal anastomosis related to synchronous resections [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004].

The American Society of Colon and Rectal Surgeons guidelines [Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005] state that ablactics and asepticity of surgical treatment in colorectal cancer are achieved by compliance with some measures. The primary measures are gentle handling with the colon and no touch to the tumor, early ligation of the main vessels supplying the tumor, sharply mobilization of the colon. Operative curability is ensured by the adequate extent of resection of the affected colon and removal of

corresponding area of regional lymph metastasis. If distant metastases present, the curability of the operation becomes equivocal, even after removal of the visible lesions. However, palliative (cytoreductive) interventions should be performed to prevent complications developed in the residual tumor (bleeding, severe perifocal inflammation, severe pain). In some advanced cases, the surgical treatment may be symptomatic, i.e. colostomy for large bowel obstruction if tumor can not be removed.

The surgical interventions are divided by extent into typical, combined, extensive, and concurrent ones [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006].

The typical interventions are associated with the extent of resection required for this location and staging. E.g., the typical surgery for stage I or II tumor located at the middle part of the sigmoid colon is the segmented resection of the sigmoid colon, but for stage III tumor of the same location, only left-sided hemicolectomy is adequate. The combined interventions are related to operations when not only the colon but also another body organ is resected due to the tumor spreading. The extensive resections are characterized with increased extent of resection of the colon compared to typical resection due to tumor spreading or presence of synchronous tumor. The concurrent surgeries include the colon resection in combination with removal or resection of the other organs due to concomitant diseases (cholecystectomy, ovariectomy, etc.) [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006].

The surgery of the middle portion of the rectal ampulla has some specific features due to tumor location in the pelvic under the pelvic peritoneum. Under these conditions, when the pelvic peritoneum is incised, the rectum and tumor become mobile at the pelvic depth in the surgical field limited with osseous structures leading to certain difficulties for primary principles of surgical ablastics to be followed [Wibe A., Syse A., Andersen E. et al., 2004; Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006]. So, if the middle portion of the rectal ampulla is affected, although precedential ligation of the superior rectal vessels is not technically difficult, but ligation, especially, separated one, of the middle rectal vessels located at the pelvic depth is impossible without previous mobilization of the whole rectum. Some difficulties arise when the principle «no touch operation» [Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005], i.e. application of «no touch» method to the tumor during the surgery is attempted to be followed.

The tendency to increase in curability of interventions and, simultaneously, preserve the sphincter apparatus in case of cancer of the middle portion of the rectal ampulla encourages the majority of authors [Lopukhin Yu.M., Savelev V.S., 1997; Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Tocchi A., Mazzoni G., Lepre L., Liotta G., 2001; Maurer C.A., 2004; Mahteme H., Pahlman L., 2005] to use the various surgical interventions. The most common interventions for this location of the tumor are abdominoperineal (anterior) resection, abdominoanal pull-through resection, surpaanal resection, etc.

According to A. Wibe, A. Syse, E. Andersen et al. [2004], the affected rectum is mobilized in rectal fascia up to pelvic floor muscles followed by its removal en bloc both in abdominoperineal complete proctectomy and abdominoperineal resection. This extent of mobilization allows to perform total mesorectal excision, which has a key role for prevention from extraintestinal cancer relapses, makes incision at least 2 cm below the tumor preventing submucous spreading of tumor cells. The authors noted that these two surgeries are differed only abdominoperineal resection is characterized with preserving of sphincter and levators, which removal is not oncologically reasonable as these structures are not involved. Another aspect, in these investigators' opinion, when the indications for various sphincter sparing surgeries (transabdominal or abdominoperineal resections) in the cancer of the middle portion of the rectal ampulla are considered, is the possibility to perform complete (adequate) nodal dissection, especially, removal of lymph nodes located along with the middle rectal arteries. The similar data are presented in the American Society of Colon and Rectal Surgeons guidelines [Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005].

Based on the many authors' results [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Kuritsin A.N., Schekochikhin S.A., Yanin V.A., Davydov A.V., 2008; Kharagezov A.D., Serdyukova O.S., Pochkay E.N., Gutshtein Yu.A., 2008; Maurer C.A., 2004; Wibe A., Syse A., Andersen E. et al., 2004; Mahteme H., Pahlman L., 2005], the intestinal anastomosis following transabdominal resection in patients with cancer of the middle portion of the rectal ampulla is very difficult to form without suturing devices.

In case of cancer of the superior portion of the rectal ampulla and rectosigmoid carcinoma, according to the American Society of Colon and Rectal Surgeons guidelines [Otchy D., Hyman N., Simmang C. et al.,

2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005], the surgical method of choice is transperitoneal (intraabdominal, anterior) rectal resection. This surgery is performed in more than 85% subjects. Other surgical interventions (abdominoperineal complete proctectomy, Hartman's operation, and abdominoperineal resection) for this tumor location account for 14-15% operated patients only. However, these interventions are usually performed for complicated carcinomas or severe concomitant conditions, when formation of bowel anastomosis is associated with high risk for anastomotic leakage. In non-complicated cancer of the superior portion of the rectal ampulla and rectosigmoid cancer, the interventions are not technically difficult to be performed, and the possibility of careful intraoperative visualization of local and lymphogenic tumor spreading allows to comply completely with principles of oncological curability (precedential ligation of the arteries and veins, tumor demarcation using sharp technique only, minimal touch to the tumor). In clinical cases of the descending colon tumors when extensive metastases are placed along with the left colic artery, the inferior mesenteric artery should be clipped and at least two thirds of the sigmoid colon should be resected. If the middle and distal portions of the sigmoid colon are affected, the sigmoid colon is resected and all lymph nodes along with the inferior mesenteric artery and sigmoid arteries are removed. Commonly, intervention for non-complicated cancer is followed by bowel anastomosis [Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005].

According to the to American Society of Colon and Rectal Surgeons guidelines [Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005], in case of the left-sided large bowel carcinomas, intervention (left-sided hemicolectomy or segmented resection of the sigmoid colon followed by primary large bowel anastomosis) is indicated for compensated and subcompensated large bowel obstruction as well as cancer complicated with focal and intratumoral inflammation. The extension of indications for primary anastomosis for decompensated large bowel obstruction is possible due to extended surgical intervention up to total or subtotal hemicolectomy followed by ileo- or cecosigmoid anastomosis. These operations are complied with all requirements for oncological curability and slightly prolong the operation time, if certain experience exists.

For the right-sided large bowel carcinomas, the majority of authors recommend to perform right-sided hemicolectomy followed by primary

sutured anastomosis for any type of bowel obstruction [Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Tocchi A., Mazzoni G., Lepre L., Liotta G., 2001; Bokey E.L., Chapuis P.H., Dent O.F. et al., 2003; Maurer C.A., 2004; Otchy D., Hyman N., Simmang C. et al., 2004; Mahteme H., Pahlman L., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005].

In case of carcinomas of the liver (right) angle of the colon and, especially, proximal portion of the transverse colon, the lymph nodes along with the middle colic artery may be involved. The lymph drainage along with the right branch of the middle colic artery and ileocolic artery is secondary. The interventional curability is achieved by increased extent of surgery up to extensive right-sided hemicolectomy. If carcinomas are located at the middle portion of the transverse colon, the most common intervention is segmented resection with ligation of the middle colic artery and vein [Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005].

Over the last decade, new surgical approaches, one of which is endoscopy, are intensively development. The intervention techniques and instruments are annually developed and improved, the novel devices for such interventions to be performed in various anatomical areas appear. These technologies are introduced into all surgical specialties including surgery for colorectal cancer [Vinogradov Yu.A., Aleksandrov V.B., Aleksandrov K.R., Razbirin V.N., Kornev L.V., 2003; Rivkin V.L., Lutsevich O.E., Fayn S.N., Lukin V.V., 2006; Hong D., Tabet J., Anvari M., 2001; Pasupathy S., Eu K.W., Ho Y.H., Seow-Choen F. , 2001; Lumely J., Stitz R., Stevenson A., 2002; Yamomoto S., Watanabe M., Hasegava H., Kitagima M., 2002]. In the first step, this method was seriously criticized, and possibility and appropriateness in colorectal cancer were doubted for oncological reasons. Currently, based on many studies, the adequacy of laparoscopic interventions for colorectal cancer not affecting oncological principles and patients' survival, is recognized [Vinogradov J., Alexandrov V., Alexandrov K., Tumanov A. et al., 2002; Scheidbach H., Rose J., Huegel O. et al., 2004]. Although, based on the results obtained by K.L. Leung, S.P. Kwok, S.C. Lam et al. [2004], there are no significant differences between laparoscopic and open resections (in this case, for rectosigmoid carcinomas). The authors present their own data from the prospective randomized study consisted of 2 arms of patients with rectosigmoid cancer (200 patients underwent open surgeries and 200 patients underwent laparoscopic resection).

Nevertheless, the prevention from the postoperative especially septic and purulent, complications remains actual both in open surgery and laparoscopic or laparoscopically assisted interventions for colorectal cancer. Thus, S.S. Maskin, A.I. Starovidchenko, A.M. Karsanov, Ya.V. Nadelnyuk et al. [2008], B.K. Shurkalin, A.V. Volenko, V.A. Gorskiy et al. [2008], S.A. Schekochikhin, V.A. Yanin, A.H. Kuritsin et al. [2008], I. Kanellos, E. Zacharakis, E. Christophoridis et al. [2002], U. Kressner, W. Graf, H. Mahteme et. al. [2002], M. Kurrum Baig, R. Hua Zhao, O. Batista et al. [2002], M. Knoop, T.Vorwerk [2003], reported that the most common complication related to the above mentioned interventions is anastomotic leak. Based on the data obtained by these authors, the rates of anastomotic leak varied from 5.4% to 7.9%.

C.A. Maurer [2004] reported on 205 colorectal cancer patients. 66 patients out of them underwent right-sided hemicolectomy, 3 – resection of the sigmoid colon, 17 – left-sided hemicolectomy, 98 – resection of the transverse colon, 21 – anterior resection of the rectum. All anastomoses were formed using suturing devices. The anastomotic leak was observed in 5 patients (2.4%), 2 patients out of them developed sepsis. Interestingly, re-laparotomy was performed in these 5 patients on Day 4 (1 patient), Day 5 (2 patients) and Day 7 (2 patients), which is consistent with the most literature data on natural history of postoperative complications in this population [Zhebrovskiy V.V., 2000; Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Baulin A.A., Lesin V.N., Baulina E.A., Kovrigin I.I., 2008; Kharagezov A.D., Serdyukova O.S., Pochkay E.N., Gutstein Yu.A., 2008; Makela J.T., Kiviniemi H., Laitinen S., 2003; Kanellos I., Blouhos K., Demetriades H., 2004]. I. Kanellos, K. Vasiliadis, S. Angelopoulos et al. [2004] reported that the rate of anastomotic leak after anterior resection of the rectum performed using suturing devices was 9.7% cases (in 9 out of 97 rectal cancer patients).

M. Pera, S. Delado, J.C. Garsia-Valdecasas et al., [2002] reported the incidences of anastomotic leak and pelvic abscess in rectal cancer patients were 10.6% and 1%, respectively. Laparoscopically assisted anterior resection of the rectum was performed in 81% cases (76 out of 94 patients).

According to H. Scheidbach, C. Schneider, O. Huegel et al., [2002], the rate of anastomotic leak following laparoscopic colorectal resection for colorectal cancer was 8.6%.

J.T. Makela, H. Kiviniemi, S. Laitinen [2003] reported the main risk factors for transverse sigmoid anastomotic leak after left-sided hemicolectomy, including laparoscopic resections: malnutrition, alcohol

abuse, non-compliance of aseptic rules during interventions, prolonged operation time, frequent transfusions, diabetes mellitus, cerebrovascular accident, smoking, steroid treatment. Based on the investigators' results, the anastomotic leak was observed on Day 8 $\pm$ 5. The mortality rate in all cases of anastomotic leak was 16%. The authors presented very interesting data on the treatment cost in these patients, which is increased in patients with anastomotic leak from 6,776 € to 12,650 €.

G.C. Rovario, F. Varoli, G. Saguatti et al. [2002] reported the data which is very infrequent in the literature (the authors put the question in the title: whether their researches are interesting?) concerning injury of the main vessels related to laparoscopic resection with mortality rates from 8 to 17%.

J. Rose, C. Schneider, C.Yildirim et al. [2004] reported on the complications related to laparoscopic and laparoscopically assisted colorectal resections: results were obtained from the multicenter study involving 4834 patients. The overall rate of the postoperative complications was 14.0%, and anastomotic leak was observed in 3.1% cases. The mortality rate was 1.3%.

W.V. Fazio, P.P. Tekkis, F. Remzi, C. Lavery [2004] reported the data from 5034 colorectal cancer patients, who underwent curative interventions (including laparoscopic ones). The overall mortality rate was 2.3%. The most common complication was large bowel anastomotic leak (3.9%).

The special attention should be paid to the data presented by Lustosa S., Matos D. et al. [2003], in accordance with Cochrane Database of Systematic Reviews standards concerning comparison between manual anastomosis suturing and forming of these anastomoses using suturing devices (the data were obtained from 611 and 622 patients, respectively). The authors *did not observe* statistically significant differences between these arms compared by such parameters as: incidence of the anastomotic leak, postoperative mortality, mean hospital days, postoperative bleedings, re-laparotomy rate.

Therefore, the rates of complications and relapses remain sufficiently high although differentiated approach to choice of indications for colorectal cancer surgeries is adhered to. Many investigators stated that, *it gave reasons to consider that surgical method for colorectal cancer achieved its limits and further development of operational techniques was not able to lead to further improvement in both early and long-term results* [Hong D. et al., 2001; Pasupathy S. et al., 2001; Tocchi A., et al., 2001;

Kanellos I. et al., 2002; Kressner U. et. al., 2002; Kurrum Baig M. et al., 2002; Lumely J. et al., 2002; Pera M. et al., 2002; Scheidbach H. et al., 2002; Yamomoto S. et al., 2002; Bokey E.L. et al., 2003; Knoop M., Vorwerk T., 2003; Lustosa S. et al., 2003; Makela J.T. et al., 2003; Pescatori M., Seow-Choen F., 2003; Fukunaga Y. et al., 2003; Kanellos I., 2004; Kanellos I. et al., 2004; Maurer C.A., 2004; Picardi N., Pescatori M., 2004; Rose J. et al., 2004; Scheidbach H. et al., 2004; Wibe A. et al., 2004; Mahteme H., Pahlman L., 2005]. It should be noted that all authors mentioned in this section carefully investigated the surgical patterns (*first of all, various technical aspects related to both specific techniques of different stages of surgeries, and direct instrumental provision*), but paid no special attention to interaction between nutritional deficiency, immune regulatory abnormalities, evidence of oxidative stress and options to treat it when surgical results of colorectal cancer were analyzed.

Chapter 3. Malnutrition and its management in surgical patients

3.1. Malnutrition and its clinical significance in different groups of surgical patients

At the turn of the 60-70s of XX century it was found that malnutrition was observed in a significant number of hospitalized adult and pediatric patients [Rudman D., 1993; Luft V.M., 1994]. Pathological process affecting the gastrointestinal tract, and especially its upper part, leads to abnormal receipt and uptake of macro - and micronutrients [Luft V.M., 1993; Kostyuchenko A.L., Kurygin A.A., 1996; Khoroshilov I.E., 2000; Cuff P.A., 1990; Buzby G.P., Mullen J., 1980; Bozzetti F., 1996]. There are sufficiently informative results obtained by the foreign and national authors in different years on the basis of which it can be stated that nutritional deficiency is observed in 20-50% of surgical patients (Table 3).

Table 3

Prevalence of malnutrition in surgical patients

Type of surgery	Prevalence, %	Authors, year	Country
<i>General surgery</i>	50	Bistrian B.R., 1974	USA
<i>Abdominal surgery</i>	25-40	Hill G.L., 1992	UK
<i>Oncology</i>	50	Sudjyan A.V. Vretlind A., 1990	Russia - Sweden
<i>General surgery</i>	18-43	Luft V.M., Khoroshilov I.E., 1997	Russia

Thus, according to E.N. Preobrazhenskaya and L.A. Bobrikova [2005], up to 20% of all patients hospitalized in the multifield clinics (including surgical ones) have some degree of nutritional deficiency.

Malnutrition may develop if any essential nutrient is low in the body (proteins, energy sources, vitamins, major and trace elements). However, mostly, protein deficiency or protein-energy malnutrition is observed. The malnutrition may be primary caused by inadequate consumption of the nutrients, and secondary associated with abnormal receipt, assimilation, or metabolism of the nutrients caused by disease or surgery [Khoroshilov I.E., 2000].

Khoroshilov I.E. [2000] considers that the main routine measurements of adequate assessment of malnutrition available in clinical

practice include the somatometric and laboratory methods. The somatometric methods include: body mass index (BMI), mid-upper arm circumference, mid-upper arm muscle circumference, triceps skinfold thickness. BMI or Quetelet index is weight (in kilograms) divided by height (in meters squared [Luft V.M., Khoroshilov I.E.,1997]. Table 4 contains the malnutrition types classified by BMI.

Mid-upper arm circumference which is usually measured using measuring tape at the mid third of the upper arm of the non-operative (left) flexed (nontensional) arm, is a simple and common somatometric parameter [Symreng T.,1983]. G.L. Blackburn and B. R. Bistrian [1976] noted that the normal values are 26-29 cm and 25-28 cm in men and women, respectively. Additionally, according to these authors, reduction of this value by 10-20%, 20-30%, or >30% indicates mild, moderate, and severe malnutrition, respectively.

Triceps skinfold thickness (TST) is measured using a special device – caliper. It is integral parameter of body fat depot [Khoroshilov I.E.,2000]. Mid-upper arm muscle circumference (MUAMC) is calculated as follows: $MUAMC\ (cm) = MUAC\ (cm) - 0.314 \times TST\ (mm)$ [Khoroshilov I.E.,2000]. It characterizes muscle status, especially, somatic pool of the protein [Rudman D.,1993; Saltanov A.I. et al.,1996]. Patients' status assessed by deviation degree of the somatometric values is presented in Table 5.

Table 4
Characteristics of nutritional status by body mass index (kg/m²)
[Khoroshilov I.E., 2000]

Nutritional status	BMI	
	18-25 years	>26 years
Normal (eutrophic)	19.5-22.9	20.0-25.9
Overnutrition	23.0-27.4	26.0-27.9
Undernutrition	18.5-19.4	19.0-19.9
Grade I hypotrophy	17.0-18.4	17.5-18.9
Grade II hypotrophy	15.0-16.9	15.5-17.4
Grade III hypotrophy	<15.0	<15.5

Table 5

Somatometric criteria for malnutrition
[Khoroshilov I.E., 2000]

Somatometric parameters	Sex	Normal	Malnutrition		
			Mild	Moderate	Severe
SCORE		3	2	1	0
MUAC, cm	M	29-26	26-23	23-20	< 20
	F	28-25	25-22.5	22.5-19.5	< 19.5
MUAMC, cm	M	10.5-9.5	9.5-8.4	8.4-7.4	< 7.4
	F	14.5-13	13-11.6	11.6-10.1	< 10.1
TST, cm	M	25.7-23	23-20.4	20.4-18	< 18
	F	23.4-21	21-18.8	18.8-16.4	< 16.4

Laboratory criteria for malnutrition firstly characterize the visceral pool of the protein (protein of the blood and internal organs), which is closely associated with the protein synthesis function of the liver, blood-forming organs and immunity. According to many authors [Kostyuchenko A.L., Kurygin A.I.A., 1996; Khoroshilov I.E., 2000; Karp R.J., 1988; Cuff P.A., 1990; Chandra R.K., 1991; Edington J.et al., 1996], protein deficiency is a leading risk factor for both metabolic disorders and decreased body resistance to infections, immunosuppression, prolonged and atypical course of many internal disorders, occurrence of various complications and worsened outcome after surgeries, more prolonged wound, fractures, and burns healing. The most common and clinically available laboratory assays for nutritional deficiency (ND) are: serum total protein, albumin, transferrin (total iron binding capacity), and absolute lymphocyte count in the peripheral blood [Luft V.M., 1994, 1997, 2000; Khoroshilov I.E., 1997, 1998, 2000; Bistrian B.R., Blackburn G.L., 1976; Chandra R.K., et al., 1985; Matuchansky G., et al., 1985; Andrassy R.J., Durr E.D., 1988; Cederholm T.E., Hellstrom K.N., 1995; Zarcovic M., Milicevic M., 1996]. An insufficient supply of the protein into the body causes marked reduction in the albumin synthesis rate but its degradation time is increased, and the albumin redistributes from the interstitial space into the blood (plasma) [Kostyuchenko A.L., Kurygin A.I.A., 1996]. Therefore, the dynamics of its changes is not sufficiently reliable for quick assessment of the adequacy of the protein nutrition. However, serum albumin should be determined to reveal primary hypoalbuminemia, which, using data obtained by I.E. Khoroshilov [2000], firstly, may indicate on

the previous prolonged protein starvation, and, secondly, allow to recognize the subjects with increased risk for unfavorable outcomes. Some investigators observe direct correlation between hypoalbuminemia and outcome [Schlichtig K., Aures S.M., 1988]. American surgeons G.P. Buzby and J.L. Mullen [1980] established that the rate of the postoperative complications in patients with baseline hypoalbuminemia is increased in 6 times.

Transferrin is a serum beta-globulin with an average half-life of 8 days. It is synthesized by the liver and is of an iron transporter in the blood. Its very small extravascular pool and shorter half-life compared to albumin allow to determine earlier changes in protein nutrition while its serum concentration is decreased [Luft V.M., Khoroshilov I.E., 1997; Schlichtig R., Ayres S.M., 1988]. Therefore, transferrin concentration indicates visceral protein pool status allowing to recognize the degree of protein deprivation, and predict outcomes [Rudman D., 1993]. In addition to the above mentioned method, another simple and informative parameter assessing the protein deficiency is absolute lymphocyte count. V.M. Luft and I.E. Khoroshilov [1997] reported that this parameter **generally** describes the immune status. The primary laboratory criteria for nutritional abnormalities are presented in Table 6. The nitrogen balance is important for evaluation of the protein nutrition, catabolic or anabolic protein metabolism, and it is calculated as follows:

$$\text{NB (g/day)} = \frac{\text{Input protein (g)}}{6.25} - \text{urea nitrogen (g)} - 4.$$

However, this method is complex and tedious, as 24-hour urine should be collected and analyzed, and for more reliability, the urine is recommended to be collected continuously for 3 days. Moreover, it is difficult to calculate the extrarenal nitrogen loss including sweat and feces. This significantly limits the nitrogen balance method to be widely used in clinical practice, especially, when a great number of patients is examined [I.E. Khoroshilov, 2000].

To diagnose the energy deficiency, some authors [Kostyuchenko A.L. et al., 1996; Khoroshilov I.E., 1997, 1998, 2000; Popova T.S., Shestopalov A.E., Tamazashvili T.Sh., Leyderman I.N., 2002; Kleinberger G., Druml W., 1985; Bynoe R.P. et al., 1988; McClave S.A., Shnider H.L. et al., 1992; Meijerink W.J.H.J. et al., 1992; Daly J., Weintraub F., Shou J. et al., 1995; Bozzetti F., 1996; Briggs D., 1996] proposed several formulas and indices:

1. Primary energy exchange (PEE)

$$\text{PEE (men)} = 66 + (13.7 \times \text{BW}) + (5 \times \text{H}) - (6.8 \times \text{A})$$

$$\text{PEE (women)} = 655 + (9.6 \times \text{BW}) + (1.8 \times \text{H}) - (4.7 \times \text{A})$$

Where, BW – body weight (kg); H – height (cm); A – age (years).

2. Actual energy expenditure (kcal/day) (AEE)

$$\text{AEE} = \text{PEE} \times \text{AF} \times \text{IF} \times \text{TF} \times \text{WD}$$

Where, AF – activity factor; IF – injury factor; TF – thermal factor;

WD – weight deficit.

Activity factors:

Bedrest - 1.1

Semilying - 1.2

No restriction - 1.3

Weight deficit:

from 10 to 20% - 1.1

from 20 to 30% - 1.2

> 30% - 1.3

Thermal factor:

Body temperature 38°C - 1.1

Body temperature 39°C - 1.2

Body temperature 40°C - 1.3

Body temperature 41°C - 1.4

Injury factors:

Minor surgery - 1.1

Bone fractures - 1.2

Major surgery - 1.3

Peritonitis - 1.4

Sepsis - 1.5

Multiple trauma - 1.6

Traumatic brain injury - 1.7

Burns (up to 30%) - 1.7

Burns (30-50%) - 1.8

Burns (50-70%) - 2.0

Burns (70-90%) - 2.2

Table 6

Clinical laboratory criteria for nutritional deficiency

[Khoroshilov I.E., 2000]

Parameters	Reference values	Malnutrition		
		Mild	Moderate	Severe
SCORE	3	2	1	0
Albumin, g/L	> 35	35-30	30-25	< 25
Transferrin, g/L	> 2.0	2.0-1.8	1.8-1.6	< 1.6
Lymphocyte count, $\times 10^3$	> 1800	1800-1500	1500-900	< 900

Having reviewed the available literature concerning surgical treatment of the stomach cancer patients, it should be concluded that only some of them mentioned, unfortunately, surface and controversial data on role of malnutrition in course and outcome of this diseases [Snegovoy A.V. et al., 2003; Repin V.N., Tkachenko I.M., Gudkov O.S., Repin M.V.,

2005; Simonov N.N., Makeeva T.K., Galkin A.A., 2005; Snegovoy A.V., Lenkova N.A. et al., 2005; Skoropad V.Yu., Berdov B.A., 2008].

Moreover, the listed above methods evaluating nutritional support are out of date and not specific for assessment of impact **of the modern** types of clinical nutrition on the course and outcome in the stomach cancer patients, especially, in postoperative period. The known data on correlation between malnutrition and postoperative purulent septic complication rate [Luft V.M., 1994, 1997, 2000; Kostyuchenko A.L., Kostin E.D., Kurygin A.A., 1996; Khoroshilov I.E., 1998, 2000; Kostyuchenko A.L., Zhelezniy O.K., Shvedov A.D., 2001; Buzby G.P., Mullen J., 1980; Karp R.J., 1988; Cuff P.A., 1990; Chandra R.K., 1991; Edington J. et al., 1996] are controversial, because the surgical results are depended from many other factors (firstly, **surgical ones**), which are not presented in these researches in detail.

3.2. Nutritional support in modulation of homeostatic disturbances in surgical patients: current status

In 1793, English surgeon J. Hunter proposed to administrate the mixture of the natural products via gastric tube. In 1842, Russian surgeon V.A. Basov developed gastrostomy (artificial fistula of the stomach). In 1849, French surgeon C.E. Sedillot firstly performed gastrostomy in a human. German surgeon W. Busch firstly performed enteral feeding via jejunal fistula [Khoroshilov I.E., 2000], i.e., **namely, the surgeons were the pioneers of the clinical nutrition**. But, unfortunately, currently the **surgeons** in their work do not pay any significant to nutritional deficiency and the options of its correction. In opinion of A.L. Kostyuchenko et al. [2001], the actions taken by physicians in the majority of cases are empirical: if the patient survives, then the nutritional support was not required, but treatment failure is often considered as a defect of medical treatment or, as the baseline insufficiency of the patient's functional resources. Given that during evolution the human body has developed mechanisms allowing to tolerate easily the food deprivations, in practice, it is believed that feeding interruption for a day or two is not a problem even for relatively unstable patient as the internal resources of nutrients are existed. However, these resources are not unlimited, and its depletion is a basis for many pathological changes covering the whole body including the gastrointestinal tract [A.L. Kostyuchenko, 2001]. The authors

concluded that abnormal trophics of the tissues of all organs and systems followed by multiorgan failure is a direct consequence.

The development of types and means of clinical nutrition in the XX century had wave pattern: in 40s-60s of the last century, the enteral feeding was excluded from clinical practice for a long time due to considerable progress in developing of options and means for parenteral nutrition. At the end of 60 of the XX century, the German scientist Weiner R. [Khoroshilov I.E., 2000], said that “renaissance” of the enteral feeding in practical medicine was happened. In 70s–90s of the last century, this option of the feeding was recognized as the most physiological way to introduce the nutrients into the patient’s body and had doubtless advantages over parenteral feeding [Galperin Yu.M., Lazarev P.I., 1986; Luft V.M., 1992, 1993, 1994, 1997; Kostyuchenko A.L. et al., 1996; Khoroshilov I.E., 1997, 1998, 2000; Bistrian B.R., Blackburn G.L., 1976; Cannon I.D., 1981; Fantoni P.A. et al., 1985; Bynoe R.P. et al., 1988; Cunningham J.J., Harris L.G., Briggs S.E., 1988; Havala T. et al., 1989; Meijerink W.J.H.J., Von Meyenfeld M.F. et al., 1993; Daly J., Weintraub F. et al., 1995; Dionigi R., Dominioni L., 1995; Cosnes J., Carbonnel F., 1995; Murchan P.M. et al., 1995; Briggs D., 1996; Bozzetti F., 1996; Chuntrassakul C. et al., 1996; McClave S.A. et al., 1997]:

- firstly, it was caused by the fact that long-term complete parenteral nutrition (longer than 5-7 days) ultimately leads to dystrophy and atrophy of the gastrointestinal mucousal membrane [Galperin Yu.M., Lazarev P.I., 1986; Kostyuchenko A.L., Kurygin A.I., 1996]. The intestinal permeability is significantly increased for microorganisms and its toxins, and a threat that they are getting into the blood with all consequences including sepsis, is developed [Ermolov A.S., Popova T.S., Pakhomova G.V., Uteshev N.C., 2005];

- secondly, early enteral nutrition, in particular, after open gastrointestinal operations promotes fastest recovery of GI motor and evacuation functions, therefore, and is a preventive and treatment factor for postoperative functional large bowel obstruction [Ermolov A.S. et al., 2005];

- thirdly, the cost of total parenteral nutrition, by many authors’ data, is higher than enteral nutrition in 7-15 times [Johansson C., Backman L., Jacobsson J., 1996; Khoroshilov I.E., 1997].

If vial method of total parenteral nutrition (TPN) is used (separate administration of amino acids, lipid emulsions and concentrated glucose), concentration of plasma electrolytes, urine, blood and urine urea,

circulating blood volume, proteinogram, plasma osmolarity, acid-base balance should be daily monitored as metabolic complications may develop (hyperglycemia resulting in coma, hyponatremia, hypokalemia, etc.) [Vretlind A., Sudgyan A., 1990].

However, in recent years, the Investigators' views concerning both enteral and parenteral nutrition were significantly changed because new generation of the admixtures used for nutritional support (including ones for parenteral nutrition), different pharmaconutrients and more advanced options to perform the total parenteral nutrition were developed. It is primarily related to creation and introduction of so called "All-in-one" systems in clinical practice. The basis for creation of "All-in-one" system is a willing to standardize total parenteral nutrition with the purpose to achieve maximum clinical effect and minimize possible complications.

The advantages of this option are as follows: one container, one infusion set, and one infusion pump to be used. Moreover, the volume of parenteral nutrition may be individualized in accordance with the requirements of a specific patient. «All-in-one» system provides stable rate of infusion, reduces risks for errors, incorrect manipulations, additional contamination and significantly decreases load to medical staff. The multicenter studies to evaluate the risk of infection and pharmacological and economical efficacy of parenteral nutrition using 3-compartmental bags compared to vial method, demonstrated decrease in contamination by 50-60% and parenteral nutrition cost by 12–23% [Achach K. et al., 2002].

The compartments in these systems are divided by barriers which are easily destroyed by manual twisting before admixture administration. All three components are mixed, and homogenous solution like milk appears. The elastic EVA bag contains no PVC. Three compartmental structure of the bag prevents interactions between components while storing for a long time and ensures sterility while mixing. The possibility the bag to be sterilized above 120° allows to keep it for 24 months at room-temperature. The presence of two separate infusion ports for mixed solution and administration of additional substances (pharmaconutrients, vitamins, trace elements) reduces contamination risk. Simultaneous regular administration of parenteral nutrients at fixed doses decreases in the risk of possible metabolic complications. The important feature of «All-in-one» systems is physical stability of lipid emulsion which is completely preserved while all three components are mixed [Pichard C., Muhlebach S., 2001].

It should be noted that according to A. Vretlind, A. Sudgyan [1990], N.P.Woodcock, D.Zeigler et al. [2001] and, especially, ESPEN-2006

guidelines [Kreymann K.G., Berger M.M., Hiesmayr M., Jolliet P., Kazandjiev G., Nitenberg G., van den Berghe G., Wernerman J., 2006] *no clinically significant superiority of enteral nutrition over parenteral one affecting the final treatment results were observed.*

Therefore, the modern options of nutritional support should consider specific pattern of a disease in an individual patient (especially, integrity of digestive and absorbable functions of the GI tract), specific features of performed operation, influence of concomitant diseases on selected type of nutritional support (including adequate access), combining enteral and parenteral nutrition supreme rationally.

Over the last decades, approximately 300 adxtures for various types of clinical nutrition and wide spectrum of technical devices for nutritional support are developed and actively used worldwide [Khoroshilov I.E., 2000; Popova T.S., Shestopalov A.E., Tamazashvili T.Sh., Leyderman I.N., 2002; Ermolov A.S. et al., 2005; Sobotka L., Allison S.P., Furst P., 2004].

But practically there are no literature data concerning combined pharmaconutrients supplemented parenteral and enteral nutrition to be used in the patients with stomach or colorectal cancer. So, A.A. Asrarov, A.A. Babakhanov, S.K. Orzimatov [1996], A.A. Kurygin, O.N. Skryabin, A.L. Kostyuchenko [1996], I.V. Maev et al., [2003], A.V. Snegovoy, A.I. Saltanov, V.Yu. Selchuk [2004], N.V. Zarechnova et al., [2005], V.N. Repin et al., [2005], I.P. Artemov et al., [2006] describe positive effect of enteral nutrition on postoperative period after elective gastrointestinal (GI) interventions and gastrectomies including for stomach cancer. However, it is known, that at least for the first 5 postoperative days, enteral nutrition can not completely satisfy the patient's requirements for essential nutrients and energy [Kostyuchenko A.L., Kostin E.D., Kurygin A.A., 1996; Khoroshilov I.E., 2000; Kostyuchenko A.L. et al., 2001; Popova T.S. et al., 2002; Ermolov A.S. et al., 2005; Moss G., 1990; Powell-Tuck J., Goode A.W., 1991; Ryan J.A. et al., 1991; Moore F. et al., 1992; Ripamonti C. et al., 1996; Murchan P.M. et al., 2000; Woodcock N.P. et al., 2001; Sobotka L., Allison S.P., Furst P., 2004]. The interested data were reported by G.B. Doglietto, V. Papa, A.P. Tortorelli et al. [2004] on enteral nutrition for the first 5 postoperative days in the stomach cancer patients who underwent gastrectomy (results of the randomized multicenter study). Having evaluated of 237 patients, the authors did not observe any statistically significant differences in rates of esophago-jejunal anastomotic leak, severe postoperative complications, and postoperative mortality between the patients who received this nutrition and who did not.

Over the last decade, new substances (so called pharmaconutrients) for nutritional support were developed, and the researches concerning its successful application in different surgical patients appeared. These substances include ω -3 polyunsaturated fatty acids, sulphur-containing amino acids, glutamine, nucleotides, and arginine. The pharmaconutrients are used not for nutritional support but to realize its pharmacological effects.

Glutamine is the most investigated substance. Thus, for instance, M.G. O'Riordain, A. De Beaux, K.C.H. Fearon [1996] observed in the randomized clinical study that the total parenteral nutrition (TPN) which included glutamine, resulted in increased autologous T-cell response developed in patients underwent *colorectal resection*. However, this response was not related to abnormal production of pro-inflammatory cytokines– interleukine-6 (IL-6) or tumor necrosis factor-alpha (TNF- α). Thereafter, the authors compared glutamine-supplemented TPN and non-glutamine-supplemented TNP in patients with severe *acute pancreatitis*. The similar moderately increased T-cell response was observed in patients who received glutamine-supplemented food. Although IL-6 and TNF- α production still remained unchanged, significant reduction of IL-8 production was observed in patients who received glutamine-supplemented food. The authors' main conclusion was glutamine might provide immunological effects via direct impact on immune cells. The possible glutamine-mediated effects on immune system are preservation of GI barrier function or protective action of antioxidant - glutathione.

B.J. Morlion et al. [1998] analyzed glutamine dipeptide in patients underwent *elective colorectal resections*. Song Jing-Xiang et al. [2004] investigated glutamine dipeptide in the colorectal cancer patients underwent elective colorectal resections. All listed authors observed the following clinical effects: decreased mortality rate and reduced hospitalization time. However, to date, there are no researches assessing glutamine-supplemented total parenteral nutrition in SC patients.

Although glutamine effects on cell-mediated immunity, apoptosis of immune cells in vivo and especially in vitro were investigated sufficiently detailed. R. Exner, G.Weingartmann, M.M.Eliassen [2002] in vitro observed inhibitory effect of glutamine on specific triggers of monocyte apoptosis compared to the healthy donors (TNF- α , Fas-ligand, heat stress, and UV-irradiation). Notably, this study was published in *SURGERY* in 2002.

The similar data were obtained by R. Curi, C.J. Lagranha, S.Q. Doi, D.F. Sellitti et al. [2005] and B.C. Fuchs, B.P. Bode [2006].

A.E. Shestopalov, V.G. Pasko, A.I. Grigorev, S.G. Polovnikov [2003] performed randomized study of 79 patients with diffuse purulent peritonitis, 41 patients out of them were included in the Control arm (Arm 1) and 38 patients were included in the Test arm (Arm 2). The most common reasons for peritonitis in these patients were acute adhesive small bowel obstruction, GI perforation, and destructive appendicitis. The basic therapy in two arms was identical. In average, parenteral nutrition (amino acids, concentrated glucose, lipid emulsion 30-35 mL/kg/day — 2000-2200 kcal) was included in the infusion solution, in average, 24 hours after surgery. The parenteral nutrition included: 1. amino acids – Aminosteril KE (1000 mL – 16.0 g/L - nitrogen); 2. 20% glucose (800 mL – 160 g - carbohydrates); 3. lipid emulsion (Lipovenous 20% - 500 mL – 100 g - lipids). The parenteral nutrition in Arm 2 compared to Arm 1 additionally included Dipeptiven 20% (Fresenius Kabi, Germany) - 100 mL (20 g N(2)-L-alanyl-L-glutamine).

Analysis of immunomodulating function of glutamine used in nutrition regimen demonstrated that parenteral nutrition had some positive effects, primarily, on humoral response in Arm 1. The authors considered this is as maintenance or preventive therapy which precludes critical immunodeficiency and helps the body to recovery after immunosuppression due to positive treatment effects on primary parameters of homeostasis. Thus, from Day 2 till Day 7 increased numbers of T- and B-cells were observed without significant changes in its subpopulations. The investigators concluded that parenteral nutrition seemed to make no effect on all pathways of affected immunity. Its effect includes stimulation of protein production only and depends on functional status of the liver and severity of immunosuppression.

The similar data were obtained by other investigators [Lozhkin S.N., Tikanadze A.D., Tyuryumina M.I., 2006; Griffiths R.D., Allen K.D. et al., 2002; Daurea A., Lewis J., 2005; Curi R., Lagranha C.J. et al., 2005; Evans M.E., Jones D.P., Ziegler T.R., 2005; Ropeleski M.J., Riehm J. et al., 2005; Fuchs B.C., Bode B.P., 2006; Hise M., Compher C., Brown J., 2008]. Moreover, all above mentioned investigators states that parenteral administration of glutamine is clinically more effective compared to enteral route.

But all specified above reports present no data on *surgical treatment* of investigated patients, especially, in view of modern developments of abdominal surgery.

Unfortunately, there are no available literature data on nutritional modulation of homeostatic disturbances in the colorectal cancer patients. In general, the majority of reports concern general diagnostics principles, particularly, malnutrition and its management in oncological patients [Khoroshilov I.E., 2000; Kostyuchenko A.L. et al., 1996, 2001; Luft V.M., Luft A.V., 2005; Saltanov A.I., 2005; Sobotka L., Allison S.P., Furst P., 2004].

The studies of nutritional support in the colorectal cancer patients in early postoperative period don't present the pattern of diagnosed disease (which portion of the colon is affected; tumor staging) and surgical treatment (type and extent of performed intervention; facilities) [Kostylev E.G. et al., 2007; O'Riordain M.G., De Beaux A., Fearon K.C.H., 1996; Morlion B.J. et al., 1998; Song Jing-Xiang et al., 2004].

Therefore, it is very actual to investigate the effects of glutamine dipeptide supplemented total parenteral/enteral nutrition enriched on the course and outcome in patients with stomach or colorectal cancer using modern, highly sensitive markers of oxidative stress, immune regulatory status, lymphocyte apoptosis and genomic abnormalities to develop and introduce into clinical practice a new preventive and treatment option for the postoperative purulent septic complications in this population.

Chapter 4. Cytokines – cell-cell interactions molecules in development of systemic inflammatory response syndrome

Inflammation is one of the primordial typical defense reactions to local injury specified to mammals; its classic external signs are known since the ancient times.

Evolution of views on the nature of inflammation throughout the history of human society mainly reflects the development of fundamental biological concepts on body response to injury. I.I. Mechnikov (1883) was the first who laid the basis for scientific development of the inflammation, defining it as a protective concentration of phagocytes in the alteration area [Mayansky A.N., 1995]. The technological revolution, rapid development of molecular biology, immunology, biochemistry, genetics have created fundamental background for a significant advancement of knowledge on key medical issues. Summary of the huge amount of the new data has allowed to move to a qualitatively new level of understanding of inflammation as common pathology process being a basis of many critical conditions, including sepsis, severe burns and mechanical trauma, various forms of pancreatic necrosis, etc.

The main contents of modern views on inflammation can include the following items:

1. Classic signs of local inflammation [Chereshnev V.A., 2002; Bone R.C., 1992]: hyperemia, increased local temperature, swelling, pain associated with morphological and functional remodeling of endothelial cells of postcapillary venules, blood coagulation inside them, adhesion and transendothelial migration of white blood cells, complement activation, arteriolar vasodilatation, etc.

2. The cytokine network controlling the immune and inflammatory reactivity takes a special place among the inflammation mediators. Cytokines and growth factors are highly potent proteins (active in the picomolar range) possessing a variety of biological effects. In contrast to hormones maintaining the homeostasis, cytokines and growth factors provide a response to the introduced foreign bodies, immune damage as well as inflammation, reparation and regeneration. They form a network of communication signals between immune cells and cells of other organs and tissues. These proteins provide the development of inflammation and immune response, but they may be produced by other stimuli (microorganisms, waste products). In addition to secretion, cytokines may be expressed on surface of stimulated cells. They are bound to specific

receptors of the target cells. Like hormones, cytokines act on target cells indirectly by changing their activity via secondary messengers. Cytokines may have an effect on the production cells (autocrine activation), adjacent cells to production cells (paracrine activation) or, like hormones, on distant cells (endocrine activation). One cytokine often causes production of the second cytokine via the target cells (cytokine cascade). Own cytokines of the cell often modify the nature of the interaction of other cytokines on the same cell. Such interaction can be synergistic, additive, inhibitory or even can lead to development of a new effect unknown to any specific cytokine. White blood cells are the main target for cytokines. On one hand, white blood cells are sources of cytokine production, on another hand, their target. Therefore, they are called «interleukins». The main producers of cytokines are T-cells and activated macrophages, and, to a greater or lesser degree, other types of white blood cells, endothelial cells of postcapillary venules, platelets and different types of stromal cells. Cytokines mainly act in the inflammation area and in the territory of reactive lymphoid organs, performing a number of protective functions [Chereshnev V.A., Gusev E.Yu., 2002; Kozlov I.G., Rytikova N.S., Smirnova M.A., Ugolkova N.V., Silina I.A., Romanov S.V. et al., 2007; D. Male, J. Brostoff, D. Roth, I. Roitt, 2007].

3. Small amounts of cytokines may activate macrophages and platelets, induce the release of adhesion molecules from the endothelial cells and secretion of growth hormone. Developing acute phase response is controlled by pro-inflammatory mediators - interleukins: IL-1 β , IL-6, IL-8, tumor necrosis factor-TNF, as well as their endogenous antagonists such as IL-4, IL-10, IL-13, soluble TNF receptor, etc. called pro-inflammatory cytokines. Due to balance between pro - and anti-inflammatory cytokines under normal conditions, there is background for wound healing, pathogen destruction, and homeostasis maintenance. The systemic adaptive changes in acute inflammation may include neuroendocrine stress reactivity; fever; neutrophils migration in the circulation from the vascular and bone marrow depots; enhancement of leukocytopoiesis in the bone marrow; hyper-production of acute phase proteins in the liver; development of generalized immune response [Bone R.C., 1992; Rodriguez M. et al., 2001; Mail D. et al., 2007].

4. In case of marked local inflammation or failed mechanisms restricted its course, some cytokines: TNF- α , IL-1 β , IL-6, IL-10, TGF- β (transforming growth factor- β), INF- γ (interferon-gamma) may pass in the systemic circulation demonstrating systemic effects. If regulatory systems

are not able to maintain homeostasis, the destructive effects of cytokines and other mediators become dominant, which leads to abnormal permeability and affected function of the capillary cells, initiation of disseminated intravascular coagulation syndrome (DIC-syndrome), formation of distant foci of systemic inflammation, development of organ dysfunction [Kostyuchenko A.L., Belskikh A.N., Tulupov A.N., 2000].

5. The accumulation of pro-inflammatory cytokines in the blood and realization of their systemic effects (outside the primary lesion) is considered as the *systemic inflammatory response syndrome (SIRS)* [Bone R.C., 1992]. So, the normal concentrations of some pro-inflammatory cytokines in the blood don't exceed 5-20 pg/mL, but in case of SIRS, their levels may increase in ≥ 5 -10 times [Mainous M., Ertel W., Chaudary I., 1995; Bone R.C., 1996; Rodriguez M., Santolaria F., Jarque A. et al., 2001].

SIRS is diagnosed if at least 2 out of 4 clinical laboratory criteria are met: **1)** body temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; **2)** heart rate (HR) > 90 bpm; **3)** RR > 20 breaths/min or $\text{PaCO}_2 < 32$ mmHg; **4)** peripheral white blood cell count $> 12 \times 10^9/\text{L}$ or $< 4 \times 10^9/\text{L}$ or band cell count > 10 [Bone R.C., 1992].

It is obvious that the nature of injury may, in some cases, be systemic, and this fact is fundamentally changes the nature of the inflammatory process in general. V.A. Chereshev [2000] believes that fundamental differences between systemic and classic inflammation are expressed in response on system alteration, and in this case, pro-inflammatory mechanisms lose their protective basis on localization of injury factors, and become the main driving force of pathological process.

IL-1 β is a multifunctional cytokine that plays a key role in the development and regulation of nonspecific protection and specific immunity, and one of the first is included in protective body response to pathogens. The main IL-1 β production cells are macrophages and monocytes. The target cells include immunocompetent, endothelial and epithelial cells, fibroblasts. IL-1 β initiates and regulates inflammatory immune processes, activates neutrophils, T - and B-lymphocytes, stimulates the production of acute phase proteins, interleukins - 2, -3, -6, TNF- α , and adhesion molecules, procoagulants, and prostaglandins. This IL increases chemotaxis, phagocytosis, hemopoiesis, vascular permeability, cytotoxic and bactericidal activity, has pyrogenic effect.

IL-4 is a glycoprotein with a molecular weight of 18-20 kDa, a natural inhibitor of inflammation. It is a key cytokine produced by T-cells. The primary biological effects are: increase in eosinophilia, accumulation of

mast cells, IgG-4 production, T-cell mediated humoral immune response; local anti-tumor activity due to stimulating of cytotoxic T-lymphocytes and tumor infiltration with eosinophils; suppression of the inflammation cytokines (TNF- α , IL-1 β , IL-8) and prostaglandins released from activated monocytes.

IL-6 is a glycoprotein with a molecular weight of 21-28 kDa. It is a pleiotropic cytokine with a wide range of biological activity, produced by both lymphoid and non-lymphoid cells. IL-6 regulates maturation of antibody producing cells from B-lymphocytes and production of immunoglobulins. This interleukin participates in T-lymphocyte activation, initiates production of many acute phase proteins: fibrinogen, haptoglobin, serum amyloid A, C-reactive protein (CRP), etc. It also inhibits production of pro-inflammatory cytokines, such as IL-1 β and TNF- α , may have hormone-like effects on the liver maintaining glucose homeostasis. IL-6 play a key role in inflammatory and immune response to infections or tissue damage. Increased IL-6 production is often associated with tissue damage and stress: trauma or major surgeries, ischemia, and burns.

IL-8 belongs to the chemokines and is a protein with a molecular weight of 8 kDa. It is produced by mononuclear phagocytes, polymorphonuclear leukocytes, endothelial cells and other cells in response to various stimuli, including bacteria and viruses as well as its metabolism products, including pro-inflammatory cytokines such as IL-1 β and TNF- α . The primary role of IL-8 is to enhance leukocyte chemotaxis. It plays an important role both in acute and chronic inflammation. Its plasma concentration is increased in the septic patients, and its high level is correlated with increased mortality. The results of IL-8 measurements may be used to control over treatment and to predict outcome.

TNF- α is a pleiotropic pro-inflammatory cytokine, consisting of two elongated β -chains with a molecular weight of 17 kDa and possessing regulatory and effector functions in immune response and inflammation. The primary **TNF- α** production cells are monocytes and macrophages as well as lymphocytes and granulocytes, natural killer cells, and T-cell subsets. The general biological effects are: selective cytotoxicity against some tumor cells, activation of granulocytes, macrophages, endothelial cells, and synthesis of other pro-inflammatory cytokines; stimulation of proliferation and differentiation of neutrophils, fibroblasts, endothelial cells (angiogenesis), T- and B-lymphocytes; antitumor and antiviral activity in vivo and in vitro; is one of the mediators of the tissue destruction related to prolonged chronic inflammation.

IL-1 β and IL-6 are also called «cachectins», as its increased expression may lead to cachexia in the patients [Popova T.S., Shestopalov A.E., Tamazashvili T.Sh., Leyderman I.N., 2002].

It is well known that as a result of tissues **injury** and/or infection in the human body, complex and multicomponent cascade is developed which aim is to prevent further tissue destruction, isolate and destruct pathogen, activate repair and restore initial homeostasis. Initiation and main steps of inflammatory response is controlled mainly by pro-inflammatory cytokines, which are produced by macrophages, neutrophils and T-cells in response to stimulation by bacterial antigens. To avoid excessive manifestations of systemic inflammation in the body, the mechanisms of negative control which are mediated by production of anti-inflammatory cytokines and soluble inhibitors of pro-inflammatory cytokines, are triggered. To definite this condition, R.C. Bone [1996] proposed to use acronym *CARS*, or *compensatory anti-inflammatory response syndrome*. In case of balanced process, CARS suppresses systemic inflammatory response. However, in case of excessively severe or prolonged process, CARS can induce severe immunosuppression, which is clinically manifested by chronic or disseminated infection, abnormal reparation, increase in endotoxemia and development of late multiple organ failure, which together predetermine fatal outcome at the late stages of purulent septic process.

Thus, the pathogenesis basis of the postoperative purulent septic complications is the cytokine cascade triggering, which includes, on one hand, pro-inflammatory cytokines, and on another hand, anti-inflammatory mediators. The balance between two opposite groups largely determines the status and outcome of the above mentioned complications. *Accordingly, management of cytokine balance is currently considered as a new target of immunotherapy effects of surgical treatment in the patients with purulent septic complications* [Ostanin A.A., Leplina O.Yu. et al., 2002].

The basis of this developed concept of two-phase pattern of septic purulent process mostly consists of the experimental data and theoretical understanding on the systemic inflammatory response [Bone R.C., 1992, 1996].

At the same time, there are no clinical studies and direct evidence for relationship between the nature/severity of immune disorders and changes in cytokine balance, on one hand, and the frequency and severity of postoperative purulent septic complications, on another hand, in the

patients with stomach or colorectal cancer in postoperative period while balanced pharmaconutrients supplemented nutritional support is given.

Chapter 5. Clinical and diagnostics significance of lipid peroxidation, oxidative stress, acute phase proteins, markers of lymphocyte apoptosis and genomic abnormalities, as well as oncomarkers specific for gastrointestinal malignancies

In recent years, interest in clinical aspects of free radical-induced lipid peroxidation grew rapidly. This is primarily related to the fact that the defect in this metabolic pathway can significantly reduce the body's resistance to adverse factors, as well as create conditions for onset, accelerated development and increased severity of various diseases of vital organs and systems: cardiovascular, respiratory, urinary, and gastrointestinal. The main pattern of this free radical pathology is a damaged cell membrane (membrane abnormality) [Kamyshnikov V.S., 2004].

Normally, free radical oxidation is a metabolic process needed to realize and regulate various physiological parameters: proliferation, cell differentiation, phagocytosis, synthesis and degradation of numerous bioregulators, reception control of membrane microviscosity, etc. Under normal conditions, free radical oxidation is well balanced and depended on systems generating free radicals (FRs) and systems disposing them at various steps of chain reactions. The main difference between free radicals and typical molecules is that the electronic layer of one of their atoms on the outer orbital path has not two electrons mutually holding each other, but only one providing specific effect on the chemical activity of the substance. However, outer orbital path is unfilled. FRs affect various cellular components, primarily plasma membrane lipids which contain unsaturated fatty acids (so called *lipid peroxidation* - LPO). An important property of FRs is its number constancy while radical reacts to molecule. This explains their action as inhibitors of free radical processes. Mainly, polyunsaturated fatty acids are oxidated in biomembranes, and detection of diene conjugation (conjugated double-bond molecules - diene conjugates) is a sensitive test for free radicals and acyl hydroperoxides (LPO primary products). Its formation leads to cell membrane defects through which both cellular and organelle contents pass into the extracellular space. Therefore, cytolysis syndrome develops, and in some cases (acute pancreatitis, pancreatic necrosis) cellular self-destruction is initiated [Kostyuchenko A.L., Filin V.I., 2000], as well as peroxide and osmotic hemolysis of red blood cells are increased. Easily oxidized phospholipids determining fluidity and low cellular microviscosity are eliminated from

cell membrane as a result cell membrane is enriched with saturated, slow-moving phospholipids and “aging”. The lipid environment of the receptors perceiving hormonal signals is also changed. Primary LPO products (lipid hydroperoxides) are unstable substances which are very soon destroyed to yield secondary LPO products: aldehydes, ketones, alcohols, and epoxides.

Superoxide desmutase (SOD) is the most important component of the body's antioxidant protection. This enzyme contains copper and zinc atom each. It accelerates oxygen destruction by 4 orders. SOD concentration is lower in the patients with affected immune system.

Glutathione (oxidized (GSSG) and reduced (GSH)) contains unusual peptide bond between amino group of cysteine and carboxyl group of glutamate side chain. The significance of cellular glutathione is determined by its antioxidative functions. Actually, glutathione not only protects the cell from such toxic agents as free radicals, but, in general, determines the intracellular redox status. Intracellular thiol groups are reduced (SH) and its concentration is high. This intracellular glutathione concentration leads to it reduces any disulfide bond (S-S) between cysteines of cytosolic proteins. Therefore, reduced glutathione (GSH) is converted to oxidized glutathione (GSSG). The oxidized glutathione is reduced by glutathione reductase, which is permanently active in the cell and induced by oxidative stress.

Intracellular reduced/oxidized glutathione ratio is one of the most important parameters indicating severity of intracellular toxicity (level of the oxidative stress). Glutathione takes part in synthesis of leukotrienes and is a co-factor of glutathione peroxidase. Additionally, it is an important hydrophilic molecule, which binds to hydrophobic toxic substances by the liver enzymes in the course of biotransformation with the purpose of removal from the body (as a bile component). Normal concentration in the blood is 2.5-6.0 μM .

Malondialdehyde (MDA) is a final product of lipid peroxidation. Lipid peroxidation in the tissues is monitored by the level of malondialdehyde (MDA). Intoxication associated with many diseases is explained by its accumulation in the blood. Reacting to SH- and CH_3 -groups of the proteins, MDA suppresses activity of some enzymes: cytochrome oxidase leading to inhibition of cellular respiration; hydroxylase converting cholesterol into the bile acids. MDA typically changes in the structure of elastic fibers of lung tissue affecting arohematic barrier. MDA activity is maintained at a defined level using enzymes of antioxidant protection or antioxidant activity which

allows to claim on peroxidation homeostasis. Its normal concentration in the blood is 2.5-6.0 μM . Increased concentration indicates enhanced LPO and failed antioxidant protection.

Moreover, LPO play a significant role in the development of disorders under prolonged stress, which is, in particular, hypermetabolism/hypercatabolism syndrome diagnosed in undernourished surgical patients after major surgery and in critically ill patients [Popova T.S., Shestopalov A.E., Tamazashvili T.Sh., Leyderman I.N., 2002]. According to V.S. Kamysnikov [2004], there is a correlation between accumulation of LPO products contained in vital organs, plasma (including apolipoproteins) and red blood cells which allows the use the blood samples to determine the intensity of free radical-induced lipid oxidation in other tissues.

Pathological role of LPO is also proven in development of tumors [Petrov V.I., Khvastunov R.A., Chukhnin A.G., Zaytsev V.G., 1999].

Oxidative stress is a variety of conditions under which the pathological processes are developed in the body when reactive oxygen species (ROS), peroxides and secondary products are accumulated. Its pathological role is related to damage of DNA, lipids, proteins, disturbed cellular homeostasis and accumulation of molecules with changed structure [Zakharova N.B. et al., 2005; Burtis C., Ashwood E., Bruns D., 2006]. ROS play leading role in induction and progression of abnormal reactions induced by cytokines. Acting intracellularly as signaling molecules ROS enhance production of pro-inflammatory cytokines. These cytokines, in turn, are able to activate ROS synthesis by cell membranes of immune cells. Inhibitory effect related to antioxidants on IL-1 β , TNF- α , and IL-6 expression is reported [Burtis C., Ashwood E., Bruns D., 2006]. The cytokine production factors are regulated by reduced glutathione, which helps to maintain a specific redox balance in the cells. The oxidative stress plays a significant role in apoptosis.

Apoptosis (in Greek Απόπτωσης – falling leaves) is a phenomenon of programmed cell death, followed by a set of specific cytological evidence (markers of apoptosis) and molecular processes that have differences between unicellular and multicellular organisms, i.e., this is a process of cell self-destruction in response to critical, unrecoverable damage of the genome or in response to signals received by the cell via specific receptors ("receptors of death") [McWilliams R., Erlichman C., 2005].

Apoptosis is a type of cell death manifested as its size reduction, chromatin condensation and fragmentation, consolidation of the outer and

cytoplasmic membranes with no cellular contents to be released in the environment. Apoptosis is proven to regulate the genetic integrity of the body. Apoptosis helps to destroy cells which are able to cause malignant growth, cells infected with viruses, etc. Apoptosis regulates the immune response, selects immunocompetent cells, mediates killer activity of lymphocytes. Some tumors induce lymphocyte apoptosis suppressing the antitumor activity of the body [McWilliams R., Erlichman C., 2005].

Oxidative stress can activate triggers of apoptosis and modulate cell death [Exner R., Weingartmann G., Eliassen M.M. et al., 2002].

Apoptosis is activated by [Mail D. Et al., 2007]:

TNF- α , FAS-ligand, TGF- β , IL-1 β , IL-10, glucocorticoids, interferons, dopamine, and FRs;

- elimination of growth factors, disruption of signaling pathway between the cell and matrix, X-ray and UV radiation;

- viruses, cytotoxic lymphocytes;

- intracellular inductors of apoptosis (cellular senescence);

- lack of external anti-apoptotic signals;

- irreversible damage of cellular structures while integrity of cell membrane is preserved.

Apoptosis is inhibited by:

- growth factors;

- copper and zinc-containing substances;

- androgens and estrogens;

- IL-3 and IL-4;

- protease inhibitors;

- tumor growth activators.

Apoptosis which develops similarly in the cells of different types and various life expectancy, can be divided into two phases [D. Male, J. Brostoff, D.B. Roth, I. Roitt, 2007]:

1. Reversible changes when cell structures may be repaired.

2. Irreversible changes when cell structures are significantly destroyed and can not be repaired and this cell forms apoptotic bodies.

Cytokine-induced apoptosis is triggered by signaling from so called death domains on FAS-ligand binding to specific cell surface receptors. These receptors include: DR3, DCR1, DCR2, DR4, DR5, FAS, TNFR1, and TNFR2, as well as receptors stimulating cell activation, e.g.: RANK, ATAR, and TACI. Genes participating in apoptosis regulation can mutate affecting apoptosis. *If the p53 gene is damaged, the cell cycle would be changed, and, therefore, the cell will continue to be divided uncontrollably,*

that, in turn, may lead to development of malignancies including stomach and colorectal carcinomas [Delektorskaya V.V., 2007; Galizia G., Ferraraccio P., Lieto E. et al., 2004; Liang J-T., Huang K-C., Jeng Y-M. et al., 2004; D. Male, J. Brostoff, D.B. Roth, I. Roitt, 2007; Kaschiato D., 2008].

Soluble APO/FAS (sFAS), also called CD 95 or ARO-1, belongs to the TNF/NGF receptors and is a cell surface protein with a molecular weight of 36 kDa, which contains a single membrane-spanning domain and induces cell death by binding of APO/FAS to FAS-ligand. sFAS is formed by cleavage of 21-amino acid residues from the membrane-spanning domain. FAS-ligand (FASL) known as «death factor» binds to FAS-receptor (APO/FAS) and induces cell death. When FAS-ligand is expressed on tumor cells, its soluble form can pass in the circulation provoking apoptosis in FAS-positive cells and thus resulting in multiorgan failure frequently observed in cancer patients [D. Male, J. Brostoff, D.B. Roth, I. Roitt, 2007]. *Therefore, apoptosis can not be induced if there is no increased expression of the FAS-ligand.*

p53 is the most mutating gene related to tumor growth in humans [Kaschiato D., 2008]. p53 is a stress-dependent protein: in response to DNA damage, it inhibits cell cycle alternation or induces apoptosis. p53 effect on apoptosis is demonstrated to be related to APO-1/FAS on cell surface [Kaschiato D., 2008]. p53 activity is regulated by phosphorylation of specific protein kinases. As a result, autoproteolysis is activated.

To date, more than 500 mutations of p53 gene are known. These mutations were observed in different types of transformed cells of the blood and solid tumors. Mutation range is varied in SC, colorectal cancer, lung cancer, esophageal cancer, breast cancer, brain cancer, and liver cancer [Delektorskaya V.V., 2007; Galizia G., Ferraraccio P., Lieto E. et al., 2004; Liang J-T., Huang K-C., Jeng Y-M. et al., 2004; D. Male, J. Brostoff, D.B. Roth, I. Roitt, 2007].

Therefore, there is a definite close relationship between free radical oxidation (including LPO), on one hand, and cytokine regulation of homeostasis, apoptosis and genomic abnormalities on another hand.

So called acute phase proteins (APPs) include:

1. coagulation proteins (fibrinogen, prothrombin).
2. transport proteins (**ceruloplasmin**, ferritin, haptoglobin, **C-reactive protein (CRP)**).

APPs can act alike immune mediators, participate directly in removal of damaging factor, localization of lesion and recovery of damaged structure and function. Additionally, all listed above APPs (except for fibrinogen) participate in immune processes due to its multi-functionality. APPs are produced by the liver. Their concentrations are widely varied and depend from tumor staging, severity, and nature of the disease. This underlie the clinical laboratory tests for determination of APPs levels, disease monitoring and control over efficacy of different treatment options (including surgical methods) [Radchenko V.G., Shabrov A.V., Zinoveva E.N., 2005; Burtis C., Ashwood E., Bruns D., 2006].

Moreover, it is very important that **IL-1 β , IL-6, and TNF- α** regulate APPs production in the liver. This acute phase response lasts in average 7-10 days, and APPs concentrations (after appropriate induction) are increased for 24-48 hours [Kozlov I.G., Rytikova N.S., Smirnova M.A., Ugolkova N.V., Silina I.A., Romanov S.V. et al., 2007]. CRP is one of the most sensitive and specific markers of inflammation caused by bacterial infections and immune diseases. Measurement of CRP level is used both for diagnosis and monitoring of different inflammatory processes, differential diagnosis between bacterial and viral infections, detection of postoperative (including septic purulent) complications, monitoring the efficacy of treatment measures [Kamyshnikov V.S., 2004]. In particular, C. Burtis, E. Ashwood, D. Bruns [2006] indicate the fact that *consistently high CRP concentrations within 4-5 days after surgery correspond to a high risk for postoperative infectious complications*. Increased CRP levels is an important risk factor for cancer recurrence and has prognostic significance [Kozlov I.G., Rytikova N.S., Smirnova M.A., Ugolkova N.V., Silina I.A., Romanov S.V. et al., 2007].

Ceruloplasmin is a copper-containing plasma protein, which plays an important role in the metabolism of copper and iron and pro-oxidant/antioxidant reactions. This is α_2 -globulin, which contains about 95% of total copper in the blood: one molecule of ceruloplasmin contains 6 - 8 copper atoms. Ceruloplasmin is mainly produced by parenchymal cells of the liver and, to a lesser extent, by macrophages and lymphocytes. Ceruloplasmin belongs to the acute phase reactants. Increase in its concentration in the blood is caused by inflammation, infection, trauma and malignancies as a result of activation of ceruloplasmin gene transcription by α -interferon and **cytokines**. Ceruloplasmin level is increased relatively slow; its peak is achieved on Days 4-20. The main physiological value of ceruloplasmin is determined by its participation in

redox reactions. Acting as ferroxidase, ceruloplasmin plays the most important role in regulation of iron ionic status, i.e. oxidation of Fe^{2+} to Fe^{3+} . It makes possible the iron to be included in transferrin without formation of toxic products of iron. Ceruloplasmin can act as a pro-oxidant or as an antioxidant depending on other factors. In the presence of superoxide (for example, in the inflamed vascular endothelium), it acts as a **catalyst for oxidation of low density lipoproteins (LPO)** [Radchenko V.G., Shabrov A.V., Zinoveva E.N., 2005; Burtis C., Ashwood E., Bruns D., 2006].

Tumor markers (oncomarkers, OMs) play an important diagnostic role in oncology. The malignant growth is accompanied by production of abnormal types/levels of biological substances. Biochemical OMs are substances produced by tumor cells and secreted in the biological fluids, in which they can be quantified by non-invasive methods [D. Male, J. Brostoff, D. Roth, I. Roitt, 2007]. To date, the measurement of OM levels is widely used in diagnostics, treatment, monitoring of the cancer patients and preclinical detection of relapses. OMs include many factors which serum concentrations are depended from oncological process. They are macromolecules, which are primarily proteins containing carbohydrate or lipid components. They differ from substances produced by normal cells qualitatively (tumor specific) or quantitatively (tumor-associated but also present in the normal cells). They are formed inside or on surface of malignant cells or in normal cells as a result of induction. Some OMs are produced in the circulation and their levels can be determined by ELISA [Kozlov I.G., Rytikova N.S., Smirnova M.A., Ugolkova N.V., Silina I.A., Romanov S.V. et al., 2007; Kaschiato D., 2008].

There is the term "ideal marker", which includes the following characteristics:

1. 100% clinical specificity: presence in case of malignancies only, none in healthy subjects and benign tumors.
2. 100% clinical sensitivity, i.e. «ideal OM» should be determined at the early stages of malignancies.
3. its concentration should correlate to tumor size, staging, and outcome.
4. it should reflect tumor heterogeneity.
5. The half-life of this OM should be short to reflect treatment efficacy.
6. It should provide adequate advance time for early diagnostics and treatment.

Many different classes of substances, which may be considered as tumor markers for different types of tumor are known. For example: tumor

associated antigens and/or antibodies, hormones, enzymes, intermediates - creatine, hydroxyproline, polyamines, plasma proteins - ferritin, ceruloplasmin, α 2-microglobulin, cytokines, adhesion molecules, metalloproteinases, cell cycle markers, apoptotic markers, extracellular matrix degradation substances, etc. But, currently, none OM, which would meet the above criteria for “ideal OM” is known.

Approximately 20 markers of sufficient diagnostic values are used in clinical practice. Determination of OM level may be efficient and cost-effective addition to other assays. The combined testing of several OMs can be used for tumor diagnostics to identify primary lesion in metastatic settings. OMs can be used for differential diagnostics of benign and malignant diseases. For many OMs, the degree of increased concentration can be used to assess the tumor staging. However, partial overlap of OM concentrations at different stages should be considered. Moreover, there are markers which levels depend on the degree of tumor differentiation (for example, placental alkaline phosphatase) or don't depend on spreading of malignancy (e.g., gastrin-releasing peptide, proform - ProGRP). Oncomarkers have prognostic values: marker level prior to treatment or concentration and rate/magnitude of its change after primary therapy corresponds to outcome. Thus, in many tumors, the absolute value of OM level reflects the tumor weight. So, aggressive rapidly growing tumor with multiple metastases produces a very high OM levels indicating a poor outcome. In contrast, well-differentiated tumor is less aggressive and produces a smaller amount of markers [D. Male, J. Brostoff, D. Roth, I. Roitt, 2007; Kaschiato D., 2008].

The most important application of OM determination is to evaluate the efficacy of the treatment and disease monitoring. Thus, OM concentration most quickly and accurately reflects the **efficacy of the performed surgery**, various types and regimens of treatment, indicates complete or partial remission, and allows to detect relapses long before their clinical manifestations. It should also be noted that the changes of several OMs over the time have much greater importance compared to measurement of single OM [Gataullin I.G., Petrov S.V., Valiev A.A., 2008; Engaras B., 2003; Morita S., Nomura T., Pukushima Y. et al., 2004; Kaschiato D., 2008].

B. Engaras [2003], R. Palmqvist, B. Engaras, G. Lindmark et al. [2003], S. Morita, T. Nomura, Y. Pukushima et al. [2004], A. Ntinis, N. Zambas, S. Al Mogrambi et al. [2004] recommend to collect pretreatment samples. The authors demonstrate that it will be much appropriate to

assess the level of several markers at the time of diagnosis and in the future to use the same OM, which have been the most informative in the observed disease, and consider the influence of concomitant diseases that may be specific to each OM. This, in turn, should be taken into account when test results are interpreted.

The primary OM for stomach and colorectal cancer are CA 72-4, CA 19-9, CA 242, and CEA. These OM levels correlate to response. The outcomes in patients of the same staging vary significantly depending on the concentration of these OM [Engaras B., 2003; Palmqvist R., Engaras B., Lindmark G. et al., 2003; Morita S., Nomura T., Pukushima Y. et al., 2004; Ntinis A., Zambas N., Al Mogrambi S. et al., 2004; D. Male, J. Brostoff, D.B. Roth, I. Roitt, 2007; Kaschiato D., 2008, 2008]. According to B. Engaras [2003] and S. Morita, T. Nomura, Y. Pukushima et al. [2004], Kaschiato D. [2008] carcinoembryonic antigen (CEA) is a glycoprotein with a high content of carbohydrates. It is produced in the digestive tissues of the embryo and fetus. After birth, its production is inhibited and this antigen is practically not detected in the blood or other biological fluids of the healthy subjects. In stomach or colorectal cancer, CEA level is increased and reflects malignancy pretty exactly. CEA is an acute phase protein, so its level can be increased in the patients with a variety of autoimmune, acute and chronic inflammatory diseases, cirrhosis, chronic hepatitis and pancreatitis, ulcer disease, pneumonia, etc. However, rate of growth and peak of the marker are significantly lower than in malignancies.

CA19-9 is a carbohydrate antigen of Lewis blood group system and normally presents on the leukocyte membrane. This OM is responsible for adhesion of white blood cells to the vascular endothelium and cell migration to inflammation areas. CA19-9 overexpression leads to increased malignant potential due to greater ability for metastasis [Palmqvist R., Engaras B., Lindmark G. et al., 2003; Morita S., Nomura T., Pukushima Y. et al., 2004; Kaschiato D., 2008].

Chapter 6. Nutritional modulation of immune regulatory abnormalities in surgical treatment of patients with stomach or colorectal cancer

6.1. Materials and Methods

Patients Characteristics

The study included the results obtained from the patients with stomach or colorectal cancer before and after surgery while different types of nutritional support were used in postoperative period. The investigations of the nutritional status, biochemical parameters of homeostasis, oxidative stress markers, genetic markers of immune and genomic abnormalities as well as specific oncomarkers were performed involving 141 patients. All these patients underwent surgical treatment in the Clinic of Faculty Surgery and Oncology of the Saratov State Medical University.

The Control arm consisted of 30 practically healthy subjects selected from the donors aged from 40 to 62 y.o. Totally, 171 subjects were enrolled.

Clinical characteristics of the stomach cancer patients

This was open-label, prospective study conducted from 2007 to 2009. There were inclusion, exclusion, and withdrawal criteria (Table 6), which were used for selection of 45 patients with stomach cancer.

The patients were distributed by sex and age (Table 7). The men were predominant (30 patients); women were 15 persons. Mean age of intervened patients was 61.09 ± 7.83 years. The age of the majority of patients varied from 51 to 70 years (39 patients, 86.66 %). The obtained data are consistent with the literature data indicating that stomach cancer prevails in men and observed more frequently in subjects aged from 50 to 70 years [Brennan M.F., 2005; Kaschiato D., 2008].

The prevailed comorbidities were as follows (Diagram 1.1): cardiovascular diseases (atherosclerosis, coronary heart disease - 20 patients), pancreatobiliary disorders (chronic acalculous cholecystitis – 11 patients), respiratory diseases (chronic bronchitis – 7 patients), and leg veins disorders (varicose vein disease – 2 patients). 5 patients had no comorbidities.

Table 6

Inclusion, exclusion, and withdrawal criteria

Inclusion criteria	Exclusion criteria	Withdrawal criteria
1. Distal stomach cancer. 2. Staging: $T_{1-3}N_{0-1}M_0$. 3. Nutritional status – grade II hypotrophy. 4. Type of surgery: distal stomach resection (Roux) followed by D1 lymph node dissection; total gastrectomy with splenectomy followed by D2 lymph node dissection. 5. SIRS.	1. Two or more affected portions of the stomach. 2. Staging: $T_4N_{0-3}M_{0-1}$. 3. Nutritional status – cachexia. 4. Diabetes mellitus. 5. Palliative or cytoreductive intervention 6. Comorbidities requiring for surgical treatment.	1. Intolerance of parenteral nutrition and nutritional formulas (allergic reactions). 2. Patient's refusal from nutritional support. 3. Severe comorbidities occurred in postoperative period (acute myocardial infarction, cerebrovascular accident, pulmonary edema, pulmonary embolism, etc.)

Table 7

Distribution of the stomach cancer patients (%)

AGE	Men	Women	TOTAL
21-30 y.o.	- (0)	- (0)	- (0)
31-40 y.o.	- (0)	- (0)	- (0)
41-50 y.o.	4 (8.88)	1 (2.22)	5 (11.11)
51-60 y.o.	11 (24.4)	6 (13.33)	17 (37.77)
61-70 y.o.	14 (31.1)	7 (15.55)	21 (46.66)
71-80 y.o.	1 (2.22)	1 (2.22)	2 (4.44)
> 80 y.o.	- (0)	- (0)	0 (0)
OVERALL	30 (66.66)	15 (33.33)	45 (100)

Severity of comorbidities and exacerbations were considered when interventions were performed or anesthetic or postoperative period were managed.

The interventions were performed by surgeons who worked in the Clinic for at least 15 years. All operations were elective. To minimize blood loss and coagulate bleeding vessels, electrosurgical generator OLYMPUS UES-10 (*as a part of endosurgical videosystem*) and harmonic scalpel LigaSure were used.

*Diagram 1.1***Comorbidities in the stomach cancer patients**

Therefore, the amount of blood loss in all enrolled patients did not exceed 250.0-300.0 mL, what, in turn, is explained by reduction of operation time. The latter was achieved using staplers for linear mechanical suture when lesser curvature of the gastric stump was formed and duodenal stump was sutured. Moreover, synthetic surgical sutures were widely used (absorbable sutures): Dexon, Vicryl, Occelon, Polysorb, etc.

In interventions, the suturing principles generally accepted in the surgery were carefully followed:

- assessment of tissue status (inflammation, scars);
- blood supply;
- tissue tension of formed anastomosis;
- careful hemostasis;
- maximum asepticity.

The distal subtotal resection of the stomach with D1 nodal dissection and total gastrectomy were followed by abdominal drain procedure in subhepatic and subdiaphragmatic spaces. Anesthetic management and intensive therapy in recovery period were commonly recognized. Antibacterial preventive therapy of postoperative purulent septic complications was performed in accordance with the recommendations

given by V.S. Savelev and B.R. Gelfand [2006]. The patients were not differed by these criteria.

Mean time of patient's staying in ICUs after surgery was 2.11 ± 0.56 days.

When the study design was developed (Figure 1), we followed the ESPEN guidelines 2006, according to it «*Studies investigating the maximum time ICU patients can survive without nutritional support would be considered unethical*» (Clinical Nutrition 2006, Vol.25.– P.210-223). The abovementioned 45 patients who met inclusion criteria were assigned into 2 arms by means of a random figure table. Even numbers were assigned to the Test arm; uneven numbers were assigned to the Control arm. The Control arm included 22 patients. The Test arm consisted of 23 subjects. These arms were similar by sex, age, comorbidities, types of interventions, postoperative management.

Since Postoperative Day 2, the patients from the Control arm had a partial parenteral nutrition for, in average, 5-7 days: amino acids (Infesol-100, 500.0 mL/day corresponding to 50 g/day of amino acids; or 8% Highmix, 800.0 mL/day corresponding to 64 g/day of amino acids, or 10% Aminosteril KE, 500.0 mL/day corresponding to 50 g/day of amino acids) and concentrated glucose (20% solution, 800.0 mL/day corresponding to 160 g/day of glucose). The solutions were infused via a central line. The rate of amino acids and glucose infusions did not exceed 100.0 mL/h and 80.0 mL/h, respectively. Thus, blood glucose was monitored every 4 hours, and, if glucose level did not exceed 8.0 mM, insulin was not administrated. The facts that as a result of metabolic response to aggression (operative injury) hyperglycemia caused by increased endogenous glucose production is developed and insulin tolerance is increased were considered.

Additionally, insulin effect and its nitrogen-preservation effect are reduced under stress, **although insulin level in the blood is increased** [Popova T.S., Shestopalov A.E., Tamazashvili T.Sh., Leyderman I.N., 2002]. Since Postoperative Day 2, the patients from the Test arm had combined parenteral-enteral nutrition “*All-in-one*” for, in average, 5-7 days (Kabiven central, 2053.0 mL/day (1900.0 kcal/day) or Oliclinomel №7-1000, 1500.0 mL/day (1800.0 kcal/day) with 20% N(2)L-alanyl-L-glutamine dipeptide – Dipeptiven, 200.0 mL/day) and 10% semi-elemental formula PEPTAMEN from 600.0 mL/day to 1500.0 mL/day via nasojejunal tubes (5.0 and 6.85 mm in diameter) placed during the operation.

Figure 1. Study design

These solutions were parenterally administrated via a central line. The rate of infusion did not exceed 100.0 mL/h. Blood glucose was monitored every 4 hours and, if glucose level did not exceed 8.0 mM, insulin was not administrated.

Clinical tolerance test was performed prior to administration of nutritional formula via nasojejunal tubes [Khoroshilov I.E., 2000]. Nutritional formula, 100 mL was administrated via the placed tube using Janet's syringe and then, 10 minutes later, the remained intestinal contents was aspirated. The test was positive if less than 50%, i.e. 50 mL from the initial amount of the administrated formula was aspirated indicating the lack of maldigestion and malabsorption.

Nutritional formulas were administrated using infusion pump KANGAROO-324. The special bag containers for nutritional formulas 1500.0 mL were used.

Clinical, X-ray, instrumental, and laboratory methods in the stomach cancer patients

After admission at the Clinic, collection of complaints, medical history, record of life chart, physical exams, and preliminary diagnosis, all patients underwent commonly accepted clinical methods.

The primary biochemistry parameters of homeostasis in the evaluated patients included: blood glucose, red blood cell count, hemoglobin, total protein, serum albumin and globulin, albumin/globulin index, blood electrolytes (potassium, sodium, and chlorides). The somatometric and laboratory methods available in routine clinical practice were used to assess adequately the patients' nutrition. The somatometric methods included: body mass index (BMI), mid-arm circumference, mid-arm muscle circumference, triceps skinfold thickness. BMI or Quetelet index is weight (in kilograms) divided by height (in meters squared). The laboratory methods to assess the nutrition status were as follows: total protein, albumin, transferrin (total iron binding capacity) in the blood serum, and absolute lymphocyte count in the peripheral blood [Khoroshilov I.E., 1997]. The water loss was also considered (L): 24-hour urinary output, sweat loss (about 0.8 L [Khoroshilov I.E., 2000]), fluid losses via gavages and drain tubes.

All listed biochemistry methods to assess homeostasis and nutritional status in the stomach cancer patients were performed before surgery, on Postoperative Day 1 and Day 7. All used laboratory methods and procedures are presented in Table 8.

The fiberoptic esophagogastroduodenoscopy (FEGDS) has a huge importance in diagnostics of stomach cancer. Endoscopic interventions were performed using OLYMPUS endoscopes. All procedures were performed under fasted condition, and in case of stomach contents, after preliminary gastric lavage via nasogastric tube. The remained contents were aspirated during endoscopy using endoscopic suction unit OLYMPUS SSU-2 which allows to clearly define the amount of the obtained contents. During endoscopies, the following parameters were evaluated in the stomach cancer patients: nature and amount of the contents, sizes of mucous ridges, severity of mucosal inflammation, motility, affected area of the distal part of the stomach and transit degree though at this anatomical level. The targeted sample collection were obtained from the following 4 points of the affected area during endoscopies to verify morphological diagnosis: lesser curvature, greater

curvature, anterior, and posterior walls. The standard histological and cytological assays were used.

Table 8

Laboratory methods

PARAMETERS	METHOD	REFERENCE VALUES
Hematology Red blood cells White blood cells Platelets ESR Hemoglobin	Automatic blood cell counter	$(4.0-5.0) \times 10^{12}/L$ $(4.0-8.0) \times 10^9/L$ $(180-320) \times 10^9/L$ 2-10 mm/h 115-165 g/L
Hemostasis Blood glucose Total protein Protein fractions albumin globulines α_1 α_2 β γ Lymphocytes (1 μ L) Transferrin	Exan-G Biuret electrophoresis Absolute counts with white blood cell differential Electrophoresis	3.8-6.0 mM 60-80 g/L 50-61% 3-6% 5-8% 11-13% 15-22% ≥ 1800 ≥ 2.0 g/L

X-ray method (fluoroscopy and radiography) included upright and undertable barium suspension exams of the esophagus, stomach, duodenum in the known and strictly determined planes for each portion of the stomach and gastric wall using different degree of barium and air opacification. A special attention was paid to position, shape and size of the stomach, its motor-evacuation function, the length of affected output and stenosis degree of the output; anatomical relationship with the adjacent organs. Moreover, plain chest X-ray was performed to diagnose distant metastases. All exams were performed using APELEM X-Ray Unit DX 90.

Ultrasound examinations (Aloka-1700) were performed to detect distant metastasis in the liver and pancreas and diagnose comorbidities (hepato-pancreato-biliary diseases).

In diagnostically difficult cases, computed tomography and magnetic resonance tomography were performed to detect the distant metastases.

Electrocardiography (ECG) was performed in all patients to evaluate cardiovascular system before and after surgery.

Clinical characteristics of the colorectal cancer patients

Using inclusion, exclusion, and withdrawal criteria (Table 9) 96 patients were enrolled in the open-label prospective study conducted from 2007 to 2009. The patients were distributed by sex and age (Table 10). The women and men were 52 and 44 subjects, respectively. Mean age of the operated patients was 52.84 ± 8.25 years. The age of the majority of patients varied from 51 to 70 years (64 patients, 66.66 %).

The obtained results are consistent with the literature data indicating the similar incidences of colorectal cancer between men and women and this disease is most frequently observed in subjects aged from 50 to 70 years [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Zheng S., Chen K., Liu X. et al., 2003; Bonelly L., 2004; Hurlstone D.P., Karajeh M.A., Shorthouse A.J., 2004; Miliaris S.E., Trygonis K., Papadoniou A., 2004; Saliangas K., 2004; Otchy D., Hyman N., Simmang C. et al., 2004; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005; Kaschiato D., 2008].

The following comorbidities were predominant (Diagram 1.2): respiratory diseases (chronic bronchitis - 34 patients (35.41%)), pancreatobiliary disorders (chronic acalculous cholecystitis – 13 patients (13.54%)); chronic pancreatitis – 15 patients (15.62%), cardiovascular diseases (atherosclerosis, coronary heart disease – 11 patients (11.45%)), and leg veins disorders (varicose vein disease – 10 patients (10.41%)). 13 patients (13.54%) had no co-morbidities. Severity of comorbidities and exacerbations were considered when interventions were performed or anesthetic or postoperative period were managed.

To minimize blood loss and coagulate bleeding vessels, electrosurgical generator OLYMPUS UES-10 and harmonic scalpel LigaSure were used during surgeries. Therefore, the amount of blood loss in all enrolled patients did not exceed 200.0-250.0mL, what, in turn, is explained by reduction of operational time. Moreover. it was achieved using:

1. wide application of video laparoscopy (laparoscopy assisted right-sided and left-sided hemicolectomy (totally, 34 patients) improves the final diagnostics of the tumor and allows to plan intervention more rational and significantly reduce its severity.

2. application of staplers for mechanical circular suture to form interintestinal anastomoses.

Table 9

Inclusion, exclusion, and withdrawal criteria

Inclusion criteria	Exclusion criteria	Withdrawal criteria
1. Tumor affects one portion of the rectum or colon. 2. Staging: T ₂₋₃ N ₀₋₁ M ₀ . 3. Nutritional status – grade I-II hypotrophy. 4. Type of surgery: right-sided and left-sided hemicolectomy, sigmoid resection, resection of the transverse colon, anterior resection of the rectum.	1. Tumor affects two or more portions of the colon. 2. Staging: T ₄ N ₀₋₁ M ₀₋₁ . 3. Nutritional status – cachexia. 4. Diabetes mellitus. Palliative or cytoreductive intervention 6. Comorbidities requiring for surgical treatment.	1. Intolerance of parenteral nutrition and nutritional formulas (allergic reactions). 2. Patient's refusal from nutritional support. 3. Severe comorbidities occurred in postoperative period (acute myocardial infarction, cerebrovascular accident, gastrointestinal bleedings, pulmonary edema, etc.)

Table 10

Distribution of operated patients with colorectal cancer by age and sex (%)

AGE	Men	Women	TOTAL
21-30 y.o.	- (0)	- (0)	- (0)
31-40 y.o.	- (0)	2 (2.08)	2 (2.08)
41-50 y.o.	8 (8.33)	10 (10.41)	18 (18.75)
51-60 y.o.	18 (18.75)	17 (17.70)	35 (36.45)
61-70 y.o.	13 (13.54)	16 (16.66)	29 (30.02)
71-80 y.o.	5 (5.20)	7 (7.29)	12 (12.5)
> 80 y.o.	- (0)	- (0)	0 (0)
OVERALL	44 (45.34)	52 (54.65)	96 (100)

Comorbidities in the colorectal cancer patients

Anesthetic management and intensive therapy in recovery period were commonly recognized. Antibacterial preventive therapy of postoperative purulent septic complications was performed in accordance with the recommendations given by V.S. Savelev and B.R. Gelfand [2006]. The patients were not differed by these criteria.

Mean time of patient's staying in ICUs was 1.89 ± 0.48 days.

The abovementioned 96 patients who met inclusion criteria, were assigned into 2 arms by means of a random figure table. Even numbers were assigned to the Test arm, uneven numbers were assigned to the Control arm. The Control arm included 46 patients. The Test arm consisted of 50 subjects. These arms were similar by sex, age, comorbidities, and types of interventions.

Since Postoperative Day 2, the patients from the Control arm had a partial parenteral nutrition for, in average, 5-7 days: amino acids (Infesol-100, 500.0mL/day corresponding to 50g/day of amino acids; or 8% Highmix, 800.0mL/day solution corresponding to 64g/day of amino acids,

or 10% Aminosteril KE, 500.0mL/day corresponding to 50 g/day of amino acids) and concentrated glucose (20% solution, 800.0mL/day corresponding to 160g/day of glucose).

Figure 2. Study design

The rates of amino acids and glucose infusions did not exceed 100.0mL/h and 80mL/h, respectively. Thus, blood glucose was monitored every 4 hours, and, if glucose level did not exceed 8.0 mM, insulin was not administrated. Since Postoperative Day 2, the patients from the Test arm had the total parenteral nutrition “All-in-one” for, in average, 5-7 days (Kabiven central, 2053.0mL/day (1900.0kcal/day) or Oliclinomel №7-1000, 1500.0mL/day (1800.0kcal/day) with 20% N(2)L-alanyl-L-glutamine dipeptide - Dipeptiven, 200.0mL/day). These solutions were

administrated via a central line. The rate of infusion did not exceed 100.0mL/h. Blood glucose was monitored every 4 hours and, if glucose level did not exceed 8.0 mM, insulin was not administrated. Since Postoperative Day 3, oral enteral nutrition was started: sip feeding regimen with Modulen 10% in amount of 400.0-800.0mL/day. The rate of administration was 100.0mL/h.

In addition to completely balanced contents, this nutritional formula contains anti-inflammatory cytokine TGF- β_2 exerted significant anti-inflammatory effect in the mucosal membrane of the colon. We used Modulen to prevent postoperative inflammatory complications, firstly, related to the new sutured interintestinal anastomoses.

Clinical, X-ray, instrumental, and laboratory methods in the colorectal cancer patients

After admission in the Clinic, collection of complaints, medical history, record of life chart, physical exams, and preliminary diagnosis, all patients underwent commonly accepted clinical methods. The primary biochemistry parameters of homeostasis in the evaluated patients, assessments of nutritional status and its time periods were not differed from the stomach cancer patients.

Colonofiberscopy (CFS) has very important role in diagnostics of colorectal cancer. Endoscopic procedures were performed using flexible colonoscopes OLYMPUS (CF-30I and CF-P20L). All examinations were performed under fasting condition after the appropriate preparation on the preceding day. Dicetel and Duspatalin were used for, in average, 3 days prior to the procedure (to treat spastic dyskinesia of the colon and to clean more adequately the lumen of the colon and to minimize painful discomfort during the procedure). To clean the lumen of the colon immediately before CFS and prior to surgery Duphalac was administrated according to the regimen developed by us. The application of this drug compared to others (alike Fortrans) allows to reduce significantly the water load and discomfort during preparation of CFS and surgery.

When CFS was performed, the following parameters were assessed in the colorectal cancer patients: level of the affected colon, anatomical features of the colon (e.g., dolichosigmoid or dolichocolon), motility, narrowing of the intestinal lumen in the affected area. At least, 4 tumor target samples were collected from the affected area during CFS to verify

morphological diagnosis. The standard histological and cytological assays were used.

The X-ray method significantly complements the diagnostics of colorectal cancer. It included double contrast barium irrigoscopy. The preparation to this exam was similar to CFS preparation. The region and length of intestinal lesion, patency of the affected colon, motility, anatomical patterns of the colon (dolichocolon, colonoptosis, etc.), and anatomical relationship to the adjacent organs were assessed.

Distribution of patients with colorectal cancer based on CFS and irrigoscopy data by the lesion levels is presented in Table 11. Moreover, plain chest X-ray was performed to diagnose the distant metastases. All exams were performed using APELEM X-Ray Unit DX 90.

Table 11
Distribution of the colorectal cancer patients by tumor location

Tumor location	Test arm, n=50	Control arm, n=46
1. Cecal carcinoma	4 (8.0%)	4 (8.69%)
2. Cancer of the ascendant colon	5 (10.0%)	4 (8.69%)
3. Colon cancer at the hepatic flexure	2 (4.0%)	2 (4.34%)
4. Cancer of the transverse colon	1 (2.0%)	1 (2.17%)
5. Colon cancer in the splenic flexure	1 (2.0%)	1 (2.17%)
6. Sigmoid cancer	18 (36.0%)	16 (34.78%)
7. Rectal cancer (<i>mid-ampullary portion and above</i>)	19 (38.0%)	18 (39.13%)
OVERALL	(50) 100.0%	(46) 100.0%

Ultrasound examinations (Aloka-1700) were performed to detect distant metastasis in the liver and pancreas and diagnose comorbidities (hepato-pancreato-biliary disorders).

Electrocardiography (ECG) was performed in all patients to evaluate cardiovascular system before and after surgery.

Test methods for oxidative stress markers, immune regulatory parameters, lymphocyte apoptosis triggers, genomic abnormalities, and oncomarkers in the studied population

The assays were performed in the Central Scientific Research Laboratory of the Saratov State Medical University.

The test results of the above listed parameters obtained in the healthy donors are presented in Table 12.

The blood was drawn in the patients with stomach or colorectal cancer from the Test and Control arms in the mornings under fasting condition. With the purpose of standardization, Vacuette tubes containing various chemical substances were used:

- for serum – tubes containing clot activator (silica) and separation gel isolating serum from clotted blood after centrifugation.
- for whole blood – K2EDTA tubes (1.8 mg/mL).
- for glucose – lithium-heparin tubes or sodium-heparin tubes.
- for mononuclear cells and separation – tubes containing 0.1 M sodium citrate, separation gel, and ficoll to create density gradient (BD Vacutainer CPT).

To separate mononuclear cells from the drawn blood, tubes were centrifugated for 20 minutes at 1500-1800g. Then, a ring located above the separation gel containing mononuclear cells (lymphocytes and monocytes) with plasma was detected. Plasma mononuclear cells suspension was prepared, and numbers of cells were counted and identified using hematology cell counter. Levels of apoptotic factors (soluble FAS-receptor and FAS-ligand) and inactivated tumor suppressor genes (p53) were determined in the prepared suspension using enzyme-linked immunosorbent assay and Bender Med Systems reactants. FAS-receptor and FAS-ligand are measured in ng/mL. Unit of p53 measurements is U/mL.

Serum cytokines levels (IL-1 β , IL-4, IL-6, IL-8, and TNF- α) were also determined using enzyme-linked immunosorbent assay and BIOSOURCE reactants. Units are pg/mL.

Malondialdehyde (MDA) levels were determined using a method based on formation of stained complex after reaction with thiobarbituric acid [Kamyshnikov V.S., 2004]. Units are μ M.

Superoxide dismutase (SOD) activity was measured by Mistra and Fridovich method [1972] modified by Brusov O.S. et al. [1983]. This method is based on SOD ability to inhibit adrenaline self-oxidation at pH 10. Units are IU/mL [Kamyshnikov V.S., 2004].

Oxidized and reduced glutathione was determined by V.G. Chernysheva method [1983]. Units are – mM [Kamyshnikov V.S., 2004].

C-reactive protein (CRP) and serum ceruloplasmin were determined using photometric assay. To determine CRP, antigen-antibody reaction was used between human anti-CRP antibodies and reference CRP

manufactured by Diagnostic Systems GmbH kits. Units are g/L. To determine ceruloplasmin, Sentinel Diagnostics reactant kits were used. The results were expressed in g/L.

Table 12

Test results of the primary evaluated parameters in the healthy donors (n=30)

Studied parameters	Manufacturer	Reference values (according to manufacturer data)	Reference values (results obtained from the healthy donors)
IL-1 β	BIOSOURCE (USA)	0-11 pg/mL (mean 1.6)	5.27 $\pm$ 2.1 pg/mL
IL-4	BIOSOURCE (USA)	0-10 pg/mL (mean 1.66)	80.67 $\pm$ 48.96 pg/mL
IL-6	BIOSOURCE (USA)	0-15 pg/mL (mean 1.59)	11.38 $\pm$ 5.98 pg/mL
IL-8	BIOSOURCE (USA)	0-30 pg/mL (mean)	4.29 $\pm$ 1.99 pg/mL
TNF- α	BIOSOURCE (USA)	0-5.9 pg/mL (mean 0.5)	0 $\pm$ 0 pg/ml
CEA	Vektor-Brest (Russia)	0-5 ng/mL (mean 1.77)	3.64 $\pm$ 5.06 ng/mL
Ca 19-9	Vektor-Brest (Russia)	0-45 U/mL (mean 6.7)	5.37 $\pm$ 4.47 ng/mL
MDA	--	2.5-6.0 μ M	2.80 $\pm$ 0.1 μ M
SOD	--	--	7.39 $\pm$ 2.76 IU/mL
Oxidized glutathione	--	--	0.1 $\pm$ 0.17 mM
Reduced glutathione	--	2.5-6.0 μ M	1.02 $\pm$ 0.18 mM
ApoFAS	Bender Med Systems (Austria)	160.9 pg/mL	67.45 $\pm$ 57.14 pg/mL
FASL	Bender Med Systems (Austria)	0 pg/mL	0.01 $\pm$ 0.03 ng/mL
P53	Bender Med Systems (Austria)	0.6-1.2 U/ml	1.12 $\pm$ 1.01 U/ml
CRP	Diagnostic Systems (Germany)	1.47-2.55 g/L	1.27 $\pm$ 1.31 g/L
Ceruloplasmin	Sentinel Diagnostics (Italy)	0.2-0.6 g/L	0.35 $\pm$ 0.18 g/L

Oncomarkers (carcinoembryonic antigen (CEA) and Ca19-9) were detected using enzyme-linked immunosorbent assay and Vektor-Brest reactants. Units are ng/mL.

Statistical methods

Statistical tests were performed on the PC using the software package Microsoft Statistica 6.0 and special software for nonparametric statistics determining the differences reliability in minor size samples.

The following statistic methods were used:

1. Mean, error, confidence interval, asymmetry, excess, minimum and maximum. The confidence interval was 95%; when it was calculated, normal distribution was assumed.
2. Student's t-test was used to obtain a test to compare the means. If there was doubt to use t-test, non-parametric Mann-Whitney test was used for two independent populations.
3. Mann-Whitney test for two independent populations is intended to check hypotheses on inequality of means. This is a non-parametric test which was used when criteria of t-test did not meet.
4. Analysis of normal distribution of the random variable. It was used to check hypothesis on normal distribution. The critical area was above 5% upper χ^2 distribution point with 3 degrees of freedom.
5. Spearman's rank correlation coefficient describing powers between the analyzed variables were used to assess the clinical efficacy of the evaluated ordinal and categorical variables.

6.2. Stomach cancer

6.2.1. Nutritional status of the stomach cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used

All enrolled SC patients had grade II malnutrition according to our results.

On Postoperative Day 1, the nutritional status was changed as follows: somatometric parameters in the Test and Control arms did not differ and were similar to the pre-operative data (Table 13). Prior to surgery, the laboratory parameters in the Test and Control arms were significantly differed ($p < 0.05$). There were no statistically significant differences in laboratory parameters between these arms after surgery ($p > 0.05$). Therefore, the negative effects of surgical intervention on laboratory parameters of nutritional status indicating depletion of visceral protein pool were observed. When combined glutamine-supplemented parenteral and enteral nutrition was given to the patients from the Test arm and partial parenteral nutrition was administrated to the patients from the Control arm, the following changes of nutritional status were observed. The somatometric parameters were not significantly differed between the Test and Control arms ($p > 0.05$ for all variables; grade II hypotrophy).

On the contrary, when the laboratory parameters were analyzed, the Test and Control arms were significantly differed ($p < 0.01$): laboratory parameters were normal and corresponded to grade I-II hypotrophy in the Test and Control arms, respectively. On Postoperative Day 7, grade I and II hypotrophy were observed in the Test and Control arms, respectively.

Moreover, it should be noted that all evaluated SC patients had anemia: RBC count – $3.47 \pm 1.04 \times 10^{12}/L$, hemoglobin level – 111.85 ± 5.89 g/L (Diagrams 2.1. and 2.2). This coincided with the literature data [Kuznetsov N.A., Danilov K.Yu. et al., 2000; Schepotin I.B., Evans S.R., 2000; Chernousov A.F., Polikarpov S.A., 2006; Bonenkamp J.J. et al., 1998; Daly J.M. et al., 2002; Roder J.D. et al., 2003; Brennan M.F., 2005].

Table 13

Nutritional status of the stomach cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used

PARAMETER	Preoperatively			POSTOPERATIVE PERIOD					
	Test arm (n=23), M ₁ ±m ₁	Control arm (n=22), M ₂ ±m ₂	P	Day 1			Day 7		
				Test arm (n=23), M ₁ ±m ₁	Control arm (n=22), M ₂ ±m ₂	P	Test arm (n=23), M ₁ ±m ₁	Control arm (n=22), M ₂ ±m ₂	P
<u><i>L.</i></u>									
<u><i>Somatometric:</i></u>									
1. BMI, kg/cm ²	16.94±2.1	17.01±1.9	>0.05	16.4±0.4	16.8±0.3	>0.05 >0.05*	17.5±0.4	16.5±0.35	>0.05
2. TST, mm (males)	8.21±1.1	8.29±1.45	>0.05	8.2±0.15	8.0±0.1	>0.05 >0.05*	8.47±0.2	8.2±0.4	>0.05
(females)	11.35±1.7	11.3±0.94	>0.05	10.9±0.1	10.9±0.1	>0.05 >0.05*	11.1±0.3	10.98±0.2	>0.05
3. MUAMC, cm (males)	19.2±0.95	19.3±1.1	>0.05	18.9±0.4	19.1±0.1	>0.05 >0.05*	19.8±0.4	19.02±0.1	>0.05
(females)	17.6±1.41	17.5±0.9	>0.05	17.1±0.4	16.9±0.3	>0.05 >0.05*	17.8±0.9	17.2±0.7	>0.05
4. MUAC, cm (males)	22.74±0.9	22.15±0.6	>0.05	21.8±0.2	21.7±0.1	>0.05 >0.05*	22.1±0.2	21.86±0.1	>0.05
(females)	20.85±1.3	21.1±1.4	>0.05	20.1±0.2	20.9±0.1	>0.05 >0.05*	20.6±0.2	20.7±0.15	>0.05
<u><i>Laboratory:</i></u>									
1. Albumins, g/L	31.64±1.9	31.88±2.75	>0.05	25.5±1.2	26.0±0.9	>0.05 <0.05*	40.5±1.35	32.8±0.65	<0.01
2. Transferrin, g/L	1.51±0.09	1.49±0.09	>0.05	1.3±0.08	1.3±0.03	>0.05 <0.05*	2.01±0.17	1.33±0.05	<0.01
3. Lymphocytes, 10 ³	1141±341	1194±316	>0.05	909±79	932±67	>0.05 <0.05*	1843±278	1103±32	<0.01

* - compared to the preoperative data

These parameters were decreased after surgery both in the Test arm (RBC count – $3.23 \pm 1.03 \times 10^{12}/L$, hemoglobin level – 101.07 ± 4.41 g/L), and Control arm (RBC count - $3.34 \pm 1.23 \times 10^{12}/L$, hemoglobin level – 102.01 ± 5.37 g/L).

Although, the differences between the arms and corresponding parameters before and after surgery were not significant ($p > 0.05$)

indicating that surgical intervention had no negative effects on RBC parameters.

Diagram 2.1

RBC count in the stomach cancer patients before and after surgery while the different types of nutritional support were used

Diagram 2.2

Hemoglobin levels in the stomach cancer patients before and after surgery while the different types of CN were used

On Postoperative Day 7, RBC count and hemoglobin level were changed as follows: Test arm – $4.82 \pm 1.56 \times 10^{12}/L$ and $118.64 \pm 5.74 g/L$, respectively; Control arm – $3.49 \pm 1.42 \times 10^{12}/L$ and $105.71 \pm 6.25 g/L$, respectively. The differences were significant ($p < 0.05$ and $p < 0.04$, respectively). No blood transfusion was needed in both arms.

Therefore, the negative effects of operative injury on laboratory parameters of nutritional status and marked positive effects of combined glutamine-supplemented parenteral enteral nutrition on nutritional status, as well as on changes in RBC count and hemoglobin levels were observed in the Test arm by Day 7.

6.2.2. Lipid peroxidation and antioxidative protection in stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

When PLO and antioxidative protection (AOP) parameters were analyzed, it was detected that preoperative **MDA** levels in stomach cancer patients were significantly lower compared to healthy donors (7.10 ± 0.92 vs $2.8 \pm 0.1 \mu M$ ($p < 0.01$)) (Figure 3). On Postoperative Day 7, we noted no changes in MDA levels in both arms:

- Control arm: after surgery (Day 1) – $6.7 \pm 2.46 \mu M$; Day 7 – $6.66 \pm 0.19 \mu M$ ($p > 0.05$).

- Test arm: after surgery (Day 1) – $7.01 \pm 1.20 \mu M$; Day 7 – $6.79 \pm 1.269 \mu M$ ($p > 0.05$).

On Postoperative Day 7, there were no statistically significant differences in MDA levels between the Test and Control arms: $6.79 \pm 1.26 \mu M$ vs $6.66 \pm 0.19 \mu M$ ($p > 0.05$).

We observed no significant differences in **oxidized and reduced glutathione levels** (see Figures 4 and 5):

- between the patients with stomach cancer and healthy donors (GSSG: 0.1 ± 0.04 vs $0.1 \pm 0.17 \mu M$ ($p > 0.05$); GSH: 0.77 ± 0.32 vs $1.02 \pm 0.18 \mu M$ ($p > 0.05$));

- in patients from the Test and Control arms compared to preoperative values (including Day 1 values) (GSSG: Control arm – $0.14 \pm 0.24 \mu M$; Test arm – $0.15 \pm 0.04 \mu M$ ($p > 0.05$). GSH: Control arm – $0.81 \pm 0.31 \mu M$; Test arm – $0.75 \pm 0.35 \mu M$ ($p > 0.05$).

- Test and Control arms did not differed on Day 7 and compared to Day 1 values (GSSG: Control arm – $0.1 \pm 0.05 \mu M$; Test arm – $0.12 \pm 0.04 \mu M$

($p>0.05$). GSH: Control arm – 0.79 ± 0.31 μM ; Test arm – 0.76 ± 0.30 μM ($p>0.05$).

Figure 3. MDA levels in the stomach cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

When changes in preoperative **SOD** levels in the stomach cancer patients were compared to values obtained in the healthy donors, the following significant differences were observed: 3.08 ± 1.05 vs 7.39 ± 2.76 IU/mL ($p<0.01$) (see Figure 6). After surgery and on Day 7 we noted no changes in SOD levels in both arms:

- Control arm: after surgery (Day 1) – 3.44 ± 1.52 IU/mL; Day 7 – 2.79 ± 0.67 IU/mL ($p > 0.05$).

- Test arm: after surgery (Day 1) – 3.73 ± 1.05 IU/mL; Day 7 – 3.76 ± 1.01 IU/mL ($p > 0.05$).

There were no significant differences between the Test and Control arms on Day 7: 3.76 ± 1.01 vs 2.79 ± 0.67 IU/mL ($p > 0.05$).

Figure 4. Oxidized glutathione levels in the stomach cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

For oxidative stress in the evaluated patients to be described more details, it is necessary to pay attention to the changes in serum albumin (see Section 6.2.1.), which is considered to be the main component of the antioxidant system in plasma. Products of proteolytic degradation of albumin are able to bind to the free radicals or modify its functional groups.

Anti-free radical and anti-peroxidative properties of albumin are largely due to thiol groups in its composition. The neutralization of oxygen free radicals is an important factor of albumin pathways in the inflammatory reactions. Moreover, albumin is able to protect vessels [Afanaseva A.N., 2008]. Increased albumin levels by Postoperative Day 7 in stomach cancer patients indicated that the oxidative processes were resolved.

Figure 5. Reduced glutathione levels in the stomach cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Figure 6. SOD levels in the stomach cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Therefore:

Firstly, increased MDA levels and decreased SOD levels in stomach cancer patients before surgery compared with healthy donors indicated activation of lipid peroxidation;

Secondly, the operative injury had no negative effect on PLO;

Thirdly, by Postoperative Day 7, both partial parenteral nutrition and pharmaconutrition had no effect on PLO in stomach cancer patients.

6.2.3. Acute phase proteins in stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

When preoperative changes in CRP levels in the evaluated patients were analyzed, there were significant differences compared to healthy donors: 98.53 ± 39.56 vs 1.27 ± 1.31 g/L ($p < 0.001$) (Diagram 2.3. and Table 14).

A slight increase (insignificant) in CRP levels was observed after surgery in both arms compared to the preoperative data: 99.41 ± 41.17 g/L (Test arm) and 112.93 ± 14.22 g/L (Control arm) ($p > 0.05$).

On Postoperative Day 7, CRP levels were significantly lower in the Test arm compared to the Control arm: 54.10 ± 14.77 g/L vs 89.60 ± 23.16 g/L ($p < 0.05$) and compared to the Day 1 values ($p < 0.05$).

Table 14

Acute phase protein levels in stomach cancer patients before and after surgery while the different types of nutritional support were used

ARMS		Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation
Healthy donors		CRP	1.27	0.90	0.00	3.10	0.00	3.00	1.31
		Ceruloplasmin	0.35	0.37	0.12	0.64	0.17	0.51	0.18
STOMACH CANCER	Pre-operatively								
			CRP	98.53	108.40	11.30	140.10	71.50	39.56
			Ceruloplasmin	0.80	0.81	0.18	1.05	0.74	0.23
	Control arm	Day 1							
			CRP	112.93	115.80	97.5	125.50	97.50	14.22
			Ceruloplasmin	0.82	0.90	0.66	0.91	0.66	0.14
		Day 7							
			CRP	89.60	39.80	7.90	114.60	7.90	23.16
			Ceruloplasmin	0.64	0.54	0.24	0.84	0.24	0.26
	Test arm	Day 1							
			CRP	99.41	114.90	8.30	131.50	92.40	41.17
			Ceruloplasmin	0.79	0.76	0.17	1.02	0.68	0.27
		Day 7							
			CRP	54.10	96.20	0.90	130.40	35.75	53.16
			Ceruloplasmin	0.32	0.74	0.19	0.84	0.44	0.26

When ceruloplasmin levels were compared between the evaluated patients and healthy donors, the significant differences were observed:

0.80 ± 0.23 g/L vs 0.35 ± 0.18 g/L ($p < 0.01$). This coincided with the literature data [Kamyshnikov V.S., 2004].

After surgery, there were no significant differences compared to the preoperative data both in the Test and Control arms: 0.79 ± 0.27 g/L (Test arm) and 0.82 ± 0.14 g/L (Control arm) ($p > 0.05$).

On Postoperative Day 7, ceruloplasmin levels were significantly lower in the Test arm compared to the Control arm: 0.32 ± 0.26 g/L vs 0.64 ± 0.26 g/L ($p < 0.01$) and even lower compared to the healthy donors (0.35 ± 0.18 g/L) (Diagram 2.4. and Table 14).

Diagram 2.3

CRP levels in the stomach cancer patients before and after surgery while the different types of nutritional support were used

Ceruloplasmin levels in the stomach cancer patients before and after surgery while the different types of nutritional support were used

Therefore:

1. Increased CRP and ceruloplasmin levels in stomach cancer patients compared to the healthy donors indicated marked inflammation in the evaluated patients prior to surgery.
2. On Postoperative Day 1, the operative injury had no negative effects on changes in acute phase parameters in the stomach cancer patients.
3. Positive effects of combined glutamine-supplemented parenteral enteral nutrition (pharmaconutrition) on changes in CRP, ceruloplasmin, and albumin levels were observed in the stomach cancer patients by postoperative Day 7.

6.2.4. Serum cytokine profile and systemic inflammatory response syndrome in the stomach cancer patients. Impact of different types of nutritional support on serum cytokine balance and SIRS

The following results were obtained when the serum cytokine profile was investigated (Table 15).

IL-1 β (Figure 7)

1. Preoperatively: 5.27 ± 2.1 pg/mL (healthy donors) vs 5.56 ± 2.05 pg/mL (stomach cancer patients). There were no significant differences ($p > 0.05$), although IL-1 β levels did not exceed normal values in both arms.
2. After surgery (Day 1), significant decrease ($p < 0.01$) of this parameter was noted in both arms compared to the preoperative values: 1.13 ± 1.15 pg/mL (Control arm) vs 1.07 ± 1.57 pg/mL (Test arm). The arms were not differed ($p > 0.05$).
3. On day 7, there were significant differences between the Test arm (0.61 ± 0.50 pg/mL) and Control arm (28.10 ± 9.22 pg/mL) ($p < 0.01$). Although after surgery, when protein and energy deficiency existed (IL-1 β is one of the cachectins [Popova T.S. et al., 2002]), this cytokine level in both arms was decreased more than in 4 times, and by Postoperative Day 7, while partial parenteral nutrition was given, IL-1 β levels were increased by 27 times and were significantly higher compared to normal values!

IL-4 (Figure 8)

1. Preoperatively, there were significant differences (11.85 ± 5.94 pg/mL (stomach cancer patients) vs 80.67 ± 48.96 pg/mL (healthy donors) ($p < 0.01$).
2. After surgery (Day 1), insignificant decrease was observed in the Test and Control arms compared to the preoperative values: 7.10 ± 5.66 pg/mL and 7.49 ± 6.82 pg/mL, respectively ($p > 0.05$). There were no differences between the arms ($p > 0.05$).
3. On Day 7, the Test and Control arms were significantly differed (37.87 ± 15.66 pg/mL and 7.22 ± 3.17 pg/mL, respectively ($p > 0.01$)).

IL-6 (Figure 9)

1. Preoperatively, there were significant differences between the stomach cancer patients and healthy donors (250.01 ± 155.98 pg/mL and 11.38 ± 5.98 pg/mL, respectively ($p < 0.001$)).

2. Post-operatively (Day 1): 115.99 ± 135.07 pg/mL in the Control arm and 275.64 ± 177.17 pg/mL in the Test arm. However, IL-6 levels in the Control arm was significantly decreased compared to the preoperative data ($p < 0.04$) and were significantly lower compared to the Test arm ($p > 0.05$).
3. On day 7, there were significant differences between the Test arm (25.78 ± 34.40 pg/mL) and Control arm (111.45 ± 159.31 pg/mL) ($p < 0.01$). Therefore, IL-6 levels were insignificantly changed compared to the Day 1 values in the Control arm, and were significantly lower in the Test arm no less than in 10 times: 275.64 ± 177.17 pg/mL vs 25.78 ± 34.40 pg/mL ($p < 0.001$).

Figure 7. IL-1 β levels (pg/mL) in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used
Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Table 15

Cytokine expression in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

ARMS			Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation
HEALTHY DONORS			IL-1 β	5.27	4.58	3.86	9.42	3.89	5.30	2.11
			IL-4	80.67	74.40	25.8	149.23	40.02	139.42	48.96
			IL-6	11.38	10.91	5.08	19.22	5.53	16.93	5.98
			IL-8	4.29	3.70	2.11	7.83	2.73	5.75	1.99
			TNF α	2.38	2.13	1.11	5.25	1.28	2.15	1.67
STOMACH CANCER	Preoperatively									
			IL-1 β	5.56	6.00	2.58	8.11	3.69	7.23	2.05
			IL-4	11.85	11.75	4.17	21.87	6.66	14.84	5.94
			IL-6	250.01	269.74	72.0	411.56	88.75	388.28	158.98
			IL-8	50.61	31.73	1.53	235.54	7.90	57.50	65.00
			TNF α	2.07	0.83	0.00	12.00	0.00	1.85	3.43
	Control arm	Day 1								
			IL-1 β	1.13	1.13	0.31	1.94	0.31	1.94	1.15
			IL-4	7.49	6.67	0.00	16.41	0.00	15.62	6.82
			IL-6	115.99	52.53	10.5	375.77	10.68	179.66	135.07
			IL-8	10.54	6.44	2.29	24.64	3.32	22.86	9.24
			TNF α	0.73	0.30	0.00	1.96	0.00	1.74	0.82
		Day 7								
			IL-1 β	28.10	30.66	15.0	42.08	18.79	33.40	9.22
			IL-4	7.22	8.53	2.50	10.00	4.09	10.00	3.17
			IL-6	111.45	24.24	10.6	344.80	10.99	344.14	159.31
			IL-8	111.71	10.07	1.51	544.50	3.54	201.14	204.10
			TNF α	5.73	1.52	0.00	29.30	0.54	5.24	10.53
	Test arm	Day 1								
			IL-1 β	1.07	0.44	0.00	3.40	0.14	2.01	1.57
			IL-4	7.10	5.55	1.70	14.06	1.70	14.06	5.66
			IL-6	275.64	274.58	63.2	496.50	95.00	450.00	177.17
			IL-8	70.54	20.29	4.83	264.80	7.59	131.60	93.43
			TNF α	5.45	0.00	0.00	29.30	0.00	6.71	10.04
		Day 7								
			IL-1 β	0.61	0.61	0.00	1.21	0.26	0.96	0.50
			IL-4	33.87	35.67	13.9	50.24	21.98	45.76	15.66
			IL-6	25.78	12.33	4.09	86.70	8.47	17.30	34.40
			IL-8	15.13	14.68	3.23	33.00	4.73	22.98	11.49
			TNF α	0.32	0.00	0.00	1.80	0.00	0.38	0.62

IL-8 (Figure 10)

- Preoperatively, the stomach cancer patients and healthy donors were significantly differed (50.61 ± 65.0 pg/mL vs 4.29 ± 1.99 pg/mL ($p < 0.01$)) and the values obtained in the stomach cancer patients were significantly higher compared to the normal values (Table 15).
- After surgery (Day 1), this parameter was significantly increased in the Test arm (compared to the preoperative data, $p < 0.05$) –

70.54±93.43 pg/mL; and significantly decreased in the Control arm up to 10.54±9.24 pg/mL (compared to the preoperative data and Test arm) ($p<0.01$).

3. On Day 7, there were significant differences between the Test and Control arms (15.13±11.49 pg/mL and 111.71±204.10 pg/mL, respectively ($p>0.01$)). Although, while pharmaconutrition was given, the patients from the Test arm demonstrated significantly decreased IL-8 levels ($p<0.04$), but in the patient from the Control arm (to whom partial parenteral nutrition was given) this parameter was significantly increased more than in 10 times ($p<0.001$) compared to the Day 1 values.

TNF- α (Figure 11)

1. Preoperatively, there were no significant differences between the stomach cancer patients and healthy donors: 2.07±3.43 pg/mL vs 2.38±1.67 pg/mL ($p<0.05$).
2. After surgery (Day 1), this parameter was significantly increased in the Test arm (5.45±10.04 pg/mL) compared to the preoperative data ($p<0.04$), and significantly decreased in the Control arm (0.73±0.82 pg/mL) ($p<0.01$). The differences between the arms were significant ($p<0.001$).
3. On Day 7, the significant differences were observed between the Test and Control arms: 0.32±0.62 pg/mL vs 5.73±10.04 pg/mL ($p<0.001$). However, pharmaconutrition in the Test arm led to decreased TNF- α levels more than in 10 times ($p<0.001$). In the contrary, partial parenteral nutrition given in the Control arm resulted in significantly increased TNF- α levels compared to the Day 1 values (from 0.73±0.82 pg/mL up to 5.73±10.53 pg/mL ($p<0.001$)).

Systemic inflammatory response syndrome (SIRS) was diagnosed on Day 1 in all enrolled stomach cancer patients.

Therefore, in the Test arm, mean body temperature was 38.5±0.78°C; mean heart rate (HR) was 93.64±4.35 bpm; mean respiratory rate (RR) was 19.67±2.53 breaths/min; mean peripheral WBC count was 2.98±1.34⁹/L. In the Control arm mean body temperature was 38.3±1.01°C; mean HR 94.79±5.17 bpm; mean RR was 20.07±1.33 breaths/min; mean peripheral WBC count was 3.11±1.57⁹/L. These parameters were not significantly differed between the arms ($p>0.05$).

Figure 8. IL-4 levels (pg/mL) in the stomach cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

On Day 7, the following results were observed in the Control arm: mean body temperature was $36.3 \pm 0.78^{\circ}\text{C}$; mean HR was 82.45 ± 2.64 bpm; mean RR was 20.27 ± 1.24 breaths/min; mean peripheral WBC count was $2.87 \pm 1.57^9/\text{L}$. In the Test arm mean body temperature was $36.7 \pm 0.43^{\circ}\text{C}$; mean HR was 78.65 ± 4.96 bpm; mean RR was 18.44 ± 1.51 breaths/min; mean peripheral WBC count was $4.94 \pm 0.89^9/\text{L}$.

Figure 9. IL-6 levels (pg/mL) in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Although according to R.C. Bone [1996], SIRS is diagnosed if at least two out of four abovementioned clinical and laboratory parameters are observed, the stomach cancer patients who had pharmaconutrition (unlike the patients from the Control arm) had no systemic inflammatory response syndrome by Day 7. In our opinion, it is very interesting to review the data obtained by A.N. Afanaseva [2008], who investigated SIRS effects on development of the postoperative purulent-septic complications in the stomach cancer patients.

Figure 10. IL-8 levels (pg/mL) in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

As our data presented, immediate effect of operative injury (Day 1) on cytokine balance is controversial: where an increase of these parameters was expected, e.g., such pro-inflammatory cytokines as IL-8 and TNF- α , it was not observed. Moreover, TNF- α levels in the Control arm was even decreased (like IL-6 levels). By Day 7, all pro-inflammatory cytokine levels were significantly decreased in the Test arm compared to the Control arm. The results obtained by A.N. Afanaseva indicated that SIRS in the stomach cancer patients had 2 wave-shaped peaks after surgery: Postoperative Days 2-3 and Days 5-8. Moreover, the latter coincides with the time period when the purulent-septic complications are developed [Zhebrovskiy V.V., 2000; Afanaseva A.N., 2008; Baulin A.A. et al., 2008; Kharagezov A.D., Serdyukova O.S. et al., 2008; Makela J.T. et al., 2003;

Kanellos I. et al., 2004; Brennan M.F., 2005]. Not surprisingly, we have obtained such contradictory results immediately after intervention. The results obtained on Day 7, from the point of view of SIRS coincided completely with the data obtained by A.N. Afanaseva [2008].

Figure 11. TNF- α levels (pg/mL) in the stomach cancer patients with in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Therefore:

1. Significantly decreased IL-4 levels and increased IL-6 and IL-8 levels were observed in the stomach cancer patients prior to surgery compared to the healthy donors indicating severe cytokine imbalance.
2. The pharmaconutrition demonstrated marked positive influence on SIRS resolving and cytokine imbalance improving.

6.2.5. Lymphocyte apoptosis, genomic abnormalities, and changes in CEA and CA 19-9 levels in the stomach cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used

In recent years, the investigators paid attention to identify in the stomach cancer patients the most specific and sensitive biomarkers, to date, that characterize both cancer process and immune regulatory systems, and efficacy of surgical and other treatment options with the purpose of early diagnosis, more complete evaluation of surgical and other treatment options, reduction of SC relapses rate and prediction of survival. Thus, according to M. Tenderenda et al. [2001], D.A. Kooby et al. [2003], C. Fondevila et al. [2004], M.F. Brennan [2005], the most informative biomarkers are: mutant p53 expression and serum oncomarkers (OMs) – carcinoembryonic antigen (CEA) and CA19-9.

J-I. Kwon, Gi-Y. Kim, K-Y. Park et al. [2008] recommend to determine p53 expression and expression of such apoptotic markers as sFAS (APO/FAS) and FAS-ligand (FASL), as there is a direct correlation between these biomarkers expression in SC patients. However, sFAS and FASL describe the intensity of immune cell apoptosis, and p53 expression characterizes severity and outcome of the stomach cancer.

Preoperatively, when the Test and Control arms were compared, the following results were obtained (Diagrams 2.5. and 2.6.; Figures 12, 13, 14 and Table 16).

- CEA: 3.64 ± 5.06 ng/mL in the healthy donors and 29.01 ± 2.89 ng/mL in the stomach cancer patients. The differences were significant ($p < 0.05$);

- CA19-9: 5.37 ± 4.47 ng/mL in the healthy donors and 21.37 ± 3.62 ng/mL in SC patients. The differences were significant ($p < 0.05$);

- p53: 1.12 ± 1.01 U/mL in the healthy donors and 3.27 ± 2.78 U/mL in SC patients. The differences were significant ($p < 0.05$);

- sFAS-positive lymphocytes: healthy donors - 89.58 ± 90.60 ng/mL and 150.51 ± 89.86 ng/mL. The differences were significant ($p < 0.05$);

- FASL-positive lymphocytes: healthy donors – 0.01 ± 0.03 ng/mL; stomach cancer patients – 0.10 ± 0.14 ng/mL. The differences were significant ($p < 0.001$);

Table 16

Lymphocyte apoptosis markers and genomic abnormalities in the stomach cancer patients before and after surgery while the different types of nutritional support were used

ARMS		Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation	
Healthy donors		sFAS	89.58	88.33	0.00	308.00	0.00	124.2	90.60	
		FasL	0.01	0.00	0.00	0.13	0.00	0.00	0.03	
		p53	1.12	2.79	0.84	5.55	2.62	3.38	1.01	
STOMACH CANCER	Preoperatively									
			sFAS	150.51	136.40	42.91	310.80	71.50	227.4	89.86
			FasL	0.10	0.00	0.00	0.28	0.00	0.24	0.14
			p53	3.27	3.53	0.00	9.76	0.74	5.16	2.78
	Control arm	Day 1								
			sFAS	138.60	146.50	0.00	281.57	73.94	193.7	93.60
			FasL	0.00	0.00	0.00	0.00	0.00	0.00	0.00
		p53	6.04	5.55	1.60	15.90	2.40	8.53	4.32	
		Day 7								
			sFAS	350.23	296.65	91.0	711.00	129.0	578.0	244.8
	FasL		0.32	0.00	0.00	0.95	0.00	0.80	0.43	
	p53	10.79	2.24	0.00	52.80	0.74	13.62	19.09		
	Test arm	Day 1								
			sFAS	124.56	99.61	87.4	187.38	91.80	156.6	44.86
			FasL	0.21	0.00	0.00	0.50	0.00	0.47	0.24
		p53	6.23	4.35	2.23	16.60	3.04	6.83	5.31	
Day 7										
		sFAS	160.50	155.20	108.1	241.74	113.6	189.0	51.34	
	FasL	0.11	0.00	0.00	0.67	0.00	0.09	0.24		
p53	2.21	2.33	0.00	4.80	0.59	3.51	1.78			

On Postoperative Day 1, the analyzed biomarkers were changed in the Test and Control arms as follows:

- CEA: 15.22±2.65 ng/mL and 14.75±2.23 ng/mL, respectively ($p>0.05$);
- CA19-9: 15.84±3.11 and 16.01±3.38 ng/mL, respectively ($p>0.05$);
- p53: 6.23±5.31 U/mL and 6.04±4.32 U/mL, respectively ($p>0.05$);
- sFAS-positive lymphocytes: 124.56±44.86 ng/mL and 138.60±93.60 ng/mL, respectively ($p>0.05$);
- FASL-positive lymphocytes: 0.21±0.24 ng/mL and 0.00±0.00 ng/mL, respectively ($p>0.05$).

The evaluated parameters did not significantly differed (except for FASL) between the Test and Control arms on Day 1 ($p>0.05$). FASL levels were significantly higher in the Test arm compared to the Control arm. When preoperative biomarkers levels were compared to the postoperative data, the following results were obtained: On Day 1, mutant p53 expression was significantly higher in both arms ($p<0.01$); and FASL levels were significantly higher in the Test arm only ($p<0.05$).

Alternatively, FASL levels were significantly lower in the Control arm – up to 0.00 ± 0.00 ng/mL ($p < 0.001$). Similarly, CEA and CA19-9 levels were significantly decreased ($p < 0.01$).

Diagram 2.5

CEA expression in the stomach cancer patients before and after surgery while the different types of nutritional support were used

Thus, tumor suppressor genes in the stomach cancer patients were activated after surgery, although the pre- and postoperative changes in OM levels indicated on curative nature of the performed surgical interventions.

On Postoperative Day 7, when pharmaconutrition and partial parenteral nutrition were given to the patients from the Test and Control arms, respectively, the following biomarkers data were obtained:

- CEA: 8.11 ± 1.346 ng/mL and 14.38 ± 2.66 ng/mL, respectively ($p < 0.01$).

- CA19-9: 7.03 ± 2.17 and 16.14 ± 2.94 ng/mL, respectively ($p < 0.01$);

- p53: 2.21 ± 1.78 U/mL and 10.79 ± 19.09 U/mL, respectively ($p < 0.01$);

- sFAS-positive lymphocytes: 160.50 ± 51.34 ng/mL and 350.23 ± 244.89 ng/mL, respectively ($p < 0.001$).

- FASL-positive lymphocytes: 0.11 ± 0.24 ng/mL and 0.32 ± 0.43 ng/mL, respectively ($p < 0.01$).

Diagram 2.6

CA19-9 expression in the stomach cancer patients before and after surgery while the different types of nutritional support were used

Although, postoperatively, lymphocyte apoptosis in the Test arm was more pronounced than in the Control arm, by Postoperative Day 7, the pathological activities were critically decreased after pharmaconutrition.

Therefore:

1. Lymphocyte apoptosis and tumor suppressor genes were activated and oncomarkers (CEA and CA19-9) were over-expressed in the stomach cancer patients (compared to the healthy donors).
2. Operative injury enhanced activated tumor suppressor genes, although oncomarkers expressions were decreased.
3. In the stomach cancer patients, pharmaconutrition (in contrast to partial parenteral nutrition) had significant positive influence on OMs levels as well as inhibitory effect on lymphocyte apoptosis and activation of tumor suppressor genes in early postoperative period (Table 17).

Figure 12. p-53 expression (U/mL) in the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

- 0 – healthy donors
- 6 – SC patients before surgery
- 7 – evaluated levels in the Control arm versus Day 1 levels
- 8 – evaluated levels in the Control arm versus Day 7 levels
- 9 – evaluated levels in the Test arm versus Day 1 levels
- 10 – evaluated levels in the Test arm versus Day 7 levels

Figure 13. Apo/FAS expression (ng/mL) in the serum lymphocytes isolated from the stomach cancer patients before and after surgery while the different types of nutritional support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Figure 14. FASL expression (ng/mL) in the serum lymphocytes isolated from the stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

6 – SC patients before surgery

7 – evaluated levels in the Control arm versus Day 1 levels

8 – evaluated levels in the Control arm versus Day 7 levels

9 – evaluated levels in the Test arm versus Day 1 levels

10 – evaluated levels in the Test arm versus Day 7 levels

Table 17

WBC count in the stomach cancer patients

Arms	WBC											
	Preoperatively						After surgery (Day 1)				Day 7	
	Absolute count, x10 ⁹ /L	% Lymphocytes	% monocytes	% Neutrophils	Absolute count, x10 ⁹ /L	% Lymphocytes	% Monocytes	% Neutrophils	Absolute count, x10 ⁹ /L	% Lymphocytes	% monocytes	% Neutrophils
Test arm, n=23 M1±m1	1.59 ± 0.77	86.08 ± 3.17	9.23 ± 1.51	4.15 ± 1.35	1.49 ± 0.86	76.02 ± 4.51	14.1 ± 0.94	9.2 ± 1.11	2.98 ± 1.01	85.71 ± 3.59	7.3 ± 2.34	7.58 ± 2.11
Control arm, n=22 M2±m2	1.70 ± 0.53	93.0 ± 3.05	4.23 ± 1.13	2.76 ± 0.82	2.02 ± 0.67	73.43 ± 2.78	16.3 ± 2.01	10.26 ± 1.89	1.04 ± 0.74	88.46 ± 5.65	4.53 ± 1.04	7.9 ± 0.41
<i>p</i>	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.01 <0.02 *	>0.05 >0.05 *	<0.05 <0.05	>0.05

* - compared to the preoperative data

6.3. Colorectal cancer

6.3.1. Nutritional status of the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Our results show that all enrolled patients with colorectal cancer had grade I-II malnutrition (Table 18). On Postoperative Day 1, the nutritional status was changed as follows: somatometric parameters in the Test and Control arms did not differ and were similar to the preoperative data. The differences in laboratory parameters were statistically significant in the Test and Control arms compared to the preoperative data ($p < 0.05$). The arms were not significantly differed in the postoperative laboratory values ($p > 0.05$). (Table 18).

Therefore, surgery had negative effects on laboratory parameters of the nutritional status indicating the visceral protein pool was depleted.

When pharmaconutrition and partial parenteral nutrition were given to the patients from the Test and Control arms, respectively, the nutritional status was changed as follows: the somatometric values in the Test arm Control arms were not significantly differed ($p > 0.05$ for all variables, grade I hypotrophy). When laboratory values were analyzed, the Test and Control arms were significantly differed ($p < 0.01$): laboratory values were normal and corresponded to grade I-II hypotrophy in the Test and Control arms, respectively. On Postoperative Day 7, grade I and II hypotrophy was observed in the Test and Control arms, respectively.

Anemia was diagnosed in all enrolled patients with colorectal cancer: red blood cell count – $3.29 \pm 1.17 \times 10^{12}/L$, hemoglobin level – 110.41 ± 4.87 g/L (Diagrams 3.1. and 3.2). This coincided with the literature data [Rivkin V.L. et al., 2004; Wexner S.D., Eisen G.M., Simmang G., 2002; Otchy D., Hyman N., Simmang C. et al., 2004; Tan K.Y., Seow-Choen F., Ng C. et al., 2004; Rockey D., Paulson E., Niedzwiecki D. et al., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005; Pott G., 2006; Kaschiato D., 2008].

Postoperatively, these parameters were decreased both in the Test arm (RBC count – $3.07 \pm 1.05 \times 10^{12}/L$, hemoglobin level – 101.56 ± 4.88 g/L), and Control arm (RBC count - $3.1 \pm 1.23 \times 10^{12}/L$, hemoglobin level – 101.88 ± 4.18 g/L). Although, the differences between the arms and pre-postoperative values were not significant ($p > 0.05$) indicating that operative injury had no negative impact on RBC parameters.

Table 18

Nutritional status of the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

PARAMETER	Preoperatively			POSTOPERATIVE PERIOD					
	Test arm (n=50), M ₁ ±m ₁	Control arm (n=46), M ₂ ±m ₂	P	Day 1			Day 7		
				Test arm (n=50), M ₁ ±m ₁	Control arm (n=46), M ₂ ±m ₂	P	Test arm (n=50), M ₁ ±m ₁	Control arm (n=46), M ₂ ±m ₂	P
<u>Somatometric:</u>									
1.BMI, kg/cm ²	18.78±2.24	18.0±1.8	>0.05	18.53±0.45	18.73±0.35	>0.05 >0.05*	18.5±0.4	17.9±0.5	>0.05
2.TST, mm (males)	9.21±1.1	9.29±1.4	>0.05	9.25±0.15	9.0±0.1	>0.05 >0.05*	9.47±0.2	9.2±0.4	>0.05
(females)	12.35±1.78	12.3±0.9	>0.05	11.95±0.15	11.93±0.1	>0.05 >0.05*	12.09±0.3	11.9±0.2	>0.05
3.MUAMC, cm (males)	20.2±0.95	20.3±1.1	>0.05	19.99±0.4	20.01±0.15	>0.05 >0.05*	20.85±0.4	20.0±0.1	>0.05
(females)	18.6±1.41	18.5±0.9	>0.05	18.05±0.45	17.92±0.3	>0.05 >0.05*	18.88±0.9	18.2±0.7	>0.05
4.MUAC, cm (males)	23.74±0.92	23.1±0.6	>0.05	22.88±0.25	22.74±0.1	>0.05 >0.05*	23.1±0.2	22.8±0.1	>0.05
(females)	21.85±1.35	21.4±1.4	>0.05	21.1±0.2	21.89±0.15	>0.05 >0.05*	21.6±0.2	21.7±0.1	>0.05
<u>Laboratory:</u>									
1.Albumine, g/L	32.43±1.9	32.4±2.3	>0.05	26.47±1.25	27.01±0.94	>0.05 <0.05*	41.5±1.35	32.8±0.6	<0.05
2.Transferrin, g/L	1.61±0.09	1.6±0.09	>0.05	1.3±0.08	1.28±0.03	>0.05 <0.05*	2.01±0.17	1.3±0.05	<0.01
3.Lymphocyte s, 10 ³	1157±341	1174±316	>0.05	919±79	932±67	>0.05 <0.05*	1945±278	1107±32	<0.01

* compared to the preoperative data

On Postoperative Day 7, RBC count and hemoglobin level were changed as follows: Test arm – $4.83 \pm 1.73 \times 10^{12}/L$ and 119.11 ± 6.55 g/L, respectively; Control arm – $3.31 \pm 1.7 \times 10^{12}/L$ and 106.34 ± 5.63 g/L, respectively. The differences were significant ($p < 0.05$ and $p < 0.04$, respectively). No blood transfusions were needed in both arms.

Therefore, operative injury had no negative effects on laboratory parameters of nutritional status and pharmaconutrition had marked positive effects on nutritional status, as well as RBC count and hemoglobin levels in the patients from the Test arm by Day 7.

Diagram 3.1

RBC count in the colorectal cancer patients before and after surgery while the different types of nutritional support were used

Diagram 3.2

Hemoglobin levels in the colorectal cancer patients before and after surgery while the different types of nutritional support were used

6.3.2. Lipid peroxidation and antioxidative protection in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Preoperative **MDA** levels were significantly higher in the colorectal cancer patients compared to the healthy donors: 7.08 ± 0.94 vs 2.8 ± 0.1 μM ($p < 0.01$) (Figure 15).

After surgery and on Postoperative Day 7 we noted no changes in MDA levels in both arms:

- Control arm: after surgery (Day 1) – 6.46 ± 0.42 μM ; Day 7 – 6.53 ± 0.38 μM ($p > 0.05$).

- Test Arm: after surgery (Day 1) – 6.47 ± 0.73 μM ; Day 7 – 6.27 ± 0.60 μM ($p > 0.05$).

On Day 7, there were no statistically significant differences in MDA levels between the Test and Control arms: 6.27 ± 0.60 μM vs 6.53 ± 0.38 μM ($p > 0.05$).

When **oxidized** and **reduced glutathione** levels were analyzed, the following data were obtained:

GSSG:

0.1 ± 0.17 μM (healthy donors) vs 0.05 ± 0.03 μM (colorectal cancer patients); the differences were significant ($p < 0.01$);

Day 1: 0.07 ± 0.03 μM (Control arm) vs 0.07 ± 0.03 μM (Test arm); the differences were not significant ($p > 0.05$);

Postoperative Day 7: 0.08 ± 0.03 μM (Control arm) vs 0.08 ± 0.03 μM (Test arm); the differences were not significant ($p > 0.05$) (Figure 16).

GSH:

1.02 ± 0.18 μM (healthy donors) vs 0.58 ± 0.27 μM (colorectal cancer patients); the differences were significant ($p < 0.01$);

Day 1: 0.56 ± 0.44 μM (Control arm) vs 0.62 ± 0.26 μM (Test arm); the differences were insignificant ($p > 0.05$);

Postoperative Day 7: 0.8 ± 0.3 μM (Test arm) vs 0.62 ± 0.44 μM (Control arm); the differences were insignificant ($p > 0.05$) (Figure 27).

Figure 15. MDA levels in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 - evaluated levels in the Test arm versus Day 7 levels

Figure 16. Oxidized glutathione levels in the colorectal cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

Preoperative SOD levels were significantly lower in the colorectal cancer patients compared to the healthy donors (3.58 ± 2.43 IU/mL vs 7.39 ± 2.76 IU/mL, respectively) ($p < 0.01$).

After surgery and on Day 7 we noted no changes in SOD values in both arms:

- Control arm: after surgery (Day 1) – 2.78 ± 1.02 IU/mL; Day 7 – 2.63 ± 1.02 IU/mL ($p > 0.05$).

- Test Arm: after surgery (Day 1) – 3.51 ± 0.72 IU/mL; Day 7 – 3.66 ± 0.76 IU/mL ($p > 0.05$).

There were no significant differences between the Test and Control arms on Day 7 (3.66 ± 0.76 vs 2.63 ± 1.02 IU/mL) ($p > 0.05$) (Figure 18).

Figure 17. Reduced glutathione levels in the colorectal cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

figure 18. SOD levels in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

- 0 – healthy donors
- 1 – colorectal cancer patients before surgery
- 2 – evaluated levels in the Control arm versus Day 1 levels
- 3 – evaluated levels in the Control arm versus Day 7 levels
- 4 – evaluated levels in the Test arm versus Day 1 levels
- 5 – evaluated levels in the Test arm versus Day 7 levels

Therefore:

1. Decreased SOD and GSH levels as well as increased MDA level (compared both to the normal values and data obtained from the healthy donors) indicated enhanced PLO and reduction of antioxidative protection (AOP) in the colorectal cancer patients.
2. Operative injury had no negative effect on PLO parameters;
3. Both partial parenteral nutrition and phramaconutrition did not affect PLO and AOP in the intervened patients.

6.3.3. Acute phase proteins in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

When acute phase proteins (CRP and ceruloplasmin) were analyzed in the colorectal cancer patients, we obtained the following data (Diagrams 3.3. and 3.4, Table 19).

Table 19

Acute phase proteins in the colorectal cancer patient in pre- and postoperative periods while the different types of nutrition support were used

ARMS			Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation
Healthy donors			CRP	1.27	0.90	0.00	3.10	0.00	3.00	1.31
			Ceruloplasmin	0.35	0.37	0.12	0.64	0.17	0.51	0.18
C O L O R E C T A L C A N C E R	Preoperatively		CRP	73.94	89.90	0.00	138.40	17.05	114.95	46.50
			Ceruloplasmin	0.71	0.77	0.14	0.99	0.62	0.84	0.23
	Control arm	Day 1	CRP	87.60	88.60	17.80	125.80	61.35	104.65	34.80
			Ceruloplasmin	0.78	0.74	0.69	0.97	0.71	0.84	0.10
			CRP	89.53	95.65	11.40	171.50	53.50	117.50	50.66
			Ceruloplasmin	0.72	0.73	0.57	0.83	0.65	0.80	0.09
	Test arm	Day 1	CRP	91.02	81.40	0.00	136.90	19.65	113.80	49.95
			Ceruloplasmin	0.69	0.74	0.17	0.98	0.63	0.83	0.23
		Day 7	CRP	57.00	72.25	0.90	136.60	8.00	113.50	50.84
			Ceruloplasmin	0.36	0.63	0.13	1.03	0.47	0.87	0.24

When preoperative CRP levels were compared between the evaluated patients and healthy donors, the differences were statistically significant: 73.94 ± 46.50 vs 1.27 ± 1.31 mg/L ($p < 0.001$).

After surgery, slight increase (statistically insignificant) of this marker was observed in both arms compared to the preoperative data: 91.02 ± 49.95 mg/L (Test arm) and 87.60 ± 34.80 mg/L (Control arm) ($p > 0.05$). On Postoperative Day 7, CRP levels were significantly lower in the Test arm compared to the Control arm: 57.00 ± 50.84 mg/L vs 89.53 ± 50.66 mg/L ($p < 0.05$). When ceruloplasmin levels were compared between the evaluated patients and healthy donors, significant differences were observed: 0.71 ± 0.23 g/L vs 0.35 ± 0.18 g/L ($p < 0.01$). This was consistent with the literature data [Kamyschnikov V.S., 2004].

Diagram 3.3

CRP levels in the colorectal cancer patients before and after surgery while the different types of nutritional support were used

Diagram 3.4

Ceruloplasmin levels in the colorectal cancer patients before and after surgery while the different types of nutritional support are used

After surgery, there were no significant differences compared to the preoperative data both in the Test and Control arms: 0.78 ± 0.10 g/L (Test arm) and 0.69 ± 0.23 g/L (Control arm) ($p > 0.05$). On Postoperative Day 7, ceruloplasmin levels were significantly lower in the Test arm compared to the Control arm: 0.36 ± 0.24 g/L vs 0.72 ± 0.09 g/L ($p < 0.01$).

Therefore:

1. Increased CRP and ceruloplasmin levels in the colorectal cancer patients compared to the healthy donors indicated on marked inflammation prior to surgery.
2. The operative injury had no negative effects on acute phase parameters in the colorectal cancer patients.
3. Pharmaconutrition provided positive effect on CRP, ceruloplasmin and albumin levels by Postoperative Day 7 in the colorectal cancer patients (see Section 6.3.1.).

6.3.4. Serum cytokine profile in the colorectal cancer patients. Impact of the different types of nutritional support on serum cytokine balance

When serum cytokine profile was analyzed in the colorectal cancer patients, the following results were obtained (Table 20).

IL-1 β (Figure 18)

1. There were no differences compared to the healthy donors: 5.27 ± 2.11 pg/mL vs 5.30 ± 8.36 pg/mL (the colorectal cancer patients) ($p < 0.05$).
2. On Day 1, there were insignificant increased values in both arms: 6.79 ± 2.73 pg/mL (Control arm) vs 6.65 ± 8.73 pg/mL (Test arm). ($p > 0.05$). There were differences between the arms ($p > 0.05$).
3. On Day 7, the Test and Control arms were significantly differed: 2.88 ± 5.35 pg/mL vs 4.30 ± 3.28 pg/mL ($p < 0.05$).

IL-4 (Figure 19)

1. There were significant differences compared to the healthy donors: 1.44 ± 3.55 pg/mL (the colorectal cancer patients) vs 80.67 ± 48.96 pg/mL (the healthy donors) ($p < 0.001$).
2. On Day 1, there were no significant differences in the Test and Control arms compared to the preoperative data (1.03 ± 0.27 pg/mL and 1.27 ± 1.26 pg/mL, respectively ($p < 0.05$). Moreover, preoperatively, there were no significant differences between both arms ($p < 0.05$).

3. On Day 7, there were significant differences between the Test and Control arms: 8.70 ± 4.38 pg/mL vs 1.34 ± 0.33 pg/mL, respectively ($p < 0.001$).

Table 20

Serum cytokine expression in the colorectal cancer patients before and after surgery while the different types of nutritional support were used

ARMS			Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation
Healthy donors			IL-1 β	5.27	4.58	3.86	9.42	3.89	5.30	2.11
			IL-4	80.67	74.40	25.8	149.23	40.02	139.42	48.96
			IL-6	11.38	10.91	5.08	19.22	5.53	16.93	5.98
			IL-8	4.29	3.70	2.11	7.83	2.73	5.75	1.99
			TNF α	2.38	2.13	1.11	5.25	1.28	2.15	1.67
C O L O R E C T A L C A N C E R	Preoperatively		IL-1 β	5.30	2.36	0.00	36.60	0.09	7.08	8.36
			IL-4	1.44	0.38	0.00	19.43	0.04	1.03	3.55
			IL-6	152.5	148.7	98.0	210.58	119.85	189.34	44.47
			IL-8	75.80	21.18	0.86	475.80	9.62	54.48	127.79
			TNF α	1.18	0.00	0.00	12.25	0.00	0.31	2.65
	Control arm	Day 1	IL-1 β	6.79	6.57	2.48	10.21	5.83	9.08	2.73
			IL-4	1.03	0.95	0.81	1.42	0.86	1.21	0.27
			IL-6	334.3	339.3	271.1	408.00	290.56	381.00	48.55
			IL-8	88.28	58.43	3.27	227.92	8.66	170.44	92.16
			TNF α	6.88	4.68	0.00	22.80	0.00	11.43	8.23
		Day 7	IL-1 β	4.30	4.73	0.90	7.90	0.97	7.00	3.28
			IL-4	1.34	1.48	0.97	1.71	1.02	1.53	0.33
			IL-6	43.20	31.65	6.58	105.95	7.81	64.00	42.12
			IL-8	61.28	24.02	1.87	196.20	11.70	110.38	70.00
			TNF α	2.25	0.00	0.00	16.85	0.00	0.59	5.90
	Test arm	Day 1	IL-1 β	6.65	4.08	0.00	29.10	0.77	5.57	8.73
			IL-4	1.27	0.58	0.00	4.50	0.43	2.13	1.26
			IL-6	333.8	254.9	28.90	694.30	87.20	682.50	304.65
			IL-8	71.71	32.05	0.00	535.20	8.73	97.44	112.75
			TNF α	1.98	0.00	0.00	23.00	0.00	0.38	5.51
		Day 7	IL-1 β	2.88	1.18	0.00	19.00	0.29	1.80	5.35
			IL-4	8.70	9.21	2.73	15.04	4.69	12.01	4.38
			IL-6	20.13	18.56	15.48	28.40	15.67	25.90	5.10
			IL-8	35.96	11.87	1.18	195.08	5.21	57.16	51.04
			TNF α	1.88	0.00	0.00	30.94	0.00	0.00	6.75

IL-6 (Figure 20)

1. The following significant differences were observed compared to the healthy donors: 11.38 ± 5.98 pg/mL (the healthy donors) vs 152.55 ± 44.47 pg/mL (the colorectal cancer patients) ($p < 0.001$).

2. On Day 1, there were significant increase in both arms compared to the preoperative data: 334.36 ± 48.55 pg/mL (Control arm) vs 333.81 ± 34.65 pg/mL (Test arm) ($p < 0.05$). There were no differences between the arms ($p > 0.05$).
3. On Postoperative Day 7, this parameter was significantly decreased ($p < 0,001$) compared to Day 1 values in both arms: 43.20 ± 42.12 pg/mL in the Control arm and 20.13 ± 5.10 pg/mL in the Test arm. When the arms were compared, serum IL-6 levels in the Test arm were significantly lower compared to the Control arm ($p < 0.05$).

Figure 18. IL-1 β levels (pg/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

- 0 – healthy donors
- 1 – colorectal cancer patients before surgery
- 2 – evaluated levels in the Control arm versus Day 1 levels
- 3 – evaluated levels in the Control arm versus Day 7 levels
- 4 – evaluated levels in the Test arm versus Day 1 levels
- 5 – evaluated levels in the Test arm versus Day 7 levels

IL-8 (Figure 21)

1. The following significant differences were observed compared to the healthy donors: 4.29 ± 1.99 pg/mL (the healthy donors) vs 75.80 ± 127.79 pg/mL ($p < 0.001$).
2. On Day 1, there were no statistically significant differences between the Test and Control arms (71.71 ± 112.75 pg/mL and 88.38 ± 92.16 pg/mL, respectively ($p > 0.05$), and compared to the preoperative data obtained from the colorectal cancer patients ($p > 0.05$).
3. On Day 7, there were significant differences between the Test and Control arms (35.96 ± 51.04 pg/mL and 61.28 ± 70.00 pg/mL, respectively ($p > 0.01$)).

Figure 19. IL-4 levels (pg/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used
Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

Figure 20. IL-6 levels (pg/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

- 0 – healthy donors
- 1 – colorectal cancer patients before surgery
- 2 – evaluated levels in the Control arm versus Day 1 levels
- 3 – evaluated levels in the Control arm versus Day 7 levels
- 4 – evaluated levels in the Test arm versus Day 1 levels
- 5 – evaluated levels in the Test arm versus Day 7 levels

TNF- α (Figure 22)

1. There were significant differences compared to the healthy donors (2.38 ± 1.67 pg/mL – the donors; 1.18 ± 2.65 – the patients) ($p < 0.05$). TNF- α levels did not exceed normal values in both arms.
2. On Day 1, there were no significant changes between the preoperative and postoperative data in the Test arm (1.98 ± 5.51 pg/mL ($p > 0.05$)). In the Control arm this cytokine level was significantly higher compared to the preoperative data (6.88 ± 8.23 pg/mL ($p < 0.01$)). However, there were statistically significant differences between the arms ($p < 0.01$).
3. On Day 7, TNF- α levels were 2.25 ± 5.90 pg/mL and 1.88 ± 6.75 pg/mL in the Control and Test arm, respectively. Although there

were no significant differences between the arms ($p>0.05$), this parameter was significantly lower in the Control arm compared to the results obtained on Day 1: 6.88 ± 8.23 pg/mL vs 2.25 ± 5.90 pg/mL ($p<0.02$).

Figure 21. IL-8 levels (pg/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used
Where,

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

Figure 22. TNF- α levels (pg/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutritional support were used
Where,

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

Systemic inflammatory response syndrome (SIRS) was not diagnosed on Day 1 in all enrolled patients with colorectal cancer.

Therefore, in the Test arm, mean body temperature was $37.3 \pm 0.84^{\circ}\text{C}$; mean heart rate (HR) 88.22 ± 2.78 bpm; mean respiratory rate (RR) 19.71 ± 2.66 breaths/min; mean peripheral WBC count $1.78 \pm 1.34^9/\text{L}$.

In the Control arm mean body temperature was $37.5 \pm 0.81^{\circ}\text{C}$; mean HR 85.14 ± 5.44 bpm; mean RR was 19.07 ± 1.78 breaths/min; mean peripheral WBC count was $1.70 \pm 1.57^9/\text{L}$. These parameters were not significantly differed in the arms ($p > 0.05$).

On Postoperative Day 7, the following results were observed in the Control arm: mean body temperature was $36.3 \pm 0.78^{\circ}\text{C}$; mean HR was 82.45 ± 2.64 bpm; mean RR was 20.32 ± 1.34 breaths/min; mean peripheral WBC count was $2.07 \pm 1.57^9/\text{L}$. In the Test arm mean body temperature

was $36.6 \pm 0.40^{\circ}\text{C}$; mean HR was 78.05 ± 3.55 bpm; mean RR was 18.17 ± 1.48 breaths/min; mean peripheral WBC count was $2.94 \pm 1.89^9/\text{L}$.

Therefore:

1. Preoperatively, the colorectal cancer patients had pronounced imbalance of serum cytokines accompanied by IL-6 and IL-8 overexpression and IL-4 underexpression.
2. After surgery, significant changes in cytokine profile were not observed and no SIRS was developed.
3. Pharmaconutrition was noted to have marked positive effect on IL-1 β , IL-4, IL-6, and IL-8 levels by Postoperative Day 7 compared to partial parenteral nutrition.

6.3.5. Lymphocyte apoptosis, genomic abnormalities, and changes in CEA and CA 19-9 levels in the colorectal cancer patients in pre- and postoperative periods while the different types of clinical nutrition were used

When CEA, CA19-9, p53, sFAS, and FASL were analyzed in the Test and Control arms, the following results were obtained (Table 21).

Preoperatively:

- CEA: 3.64 ± 5.06 ng/mL in the healthy donors and 19.09 ± 2.89 ng/mL in the colorectal cancer patients ($p < 0.05$) (Diagram 3.5).
- CA19-9: 5.37 ± 4.47 ng/mL in the healthy donors and 18.22 ± 3.63 ng/mL in the colorectal cancer patients ($p < 0.05$) (Diagram 3.6);
- p53: the healthy donors – 1.12 ± 1.01 U/mL; the colorectal cancer patients – 3.94 ± 3.24 U/mL ($p < 0.02$);
- sFAS-positive lymphocytes: the healthy donors 89.58 ± 90.60 ng/mL and 143.69 ± 186.94 ng/mL, respectively ($p < 0.05$);
- FASL-positive lymphocytes: the healthy donors – 0.01 ± 0.03 ng/mL; the colorectal cancer patients – 0.08 ± 0.10 ng/mL ($p < 0.001$).

Therefore, the differences in these parameters between the colorectal cancer patients and healthy donors were statistically significant.

On Day 1, the evaluated biomarkers were changed in the Test and Control arms as follows:

- CEA: 15.24 ± 2.65 ng/mL and 14.96 ± 2.23 ng/mL, respectively ($p > 0.05$);
- CA19-9: 16.84 ± 3.11 and 16.01 ± 3.38 ng/mL, respectively ($p > 0.05$);

- p53: 7.71 ± 6.02 U/mL and 8.40 ± 8.86 U/mL, respectively ($p > 0.05$) (Figure 23);

- sFAS-positive lymphocytes: 138.67 ± 62.47 ng/mL and 191.40 ± 54.46 ng/mL, respectively ($p > 0.05$) (Figure 24);

- FASL-positive lymphocytes: 0.20 ± 0.26 ng/mL and 0.23 ± 0.35 ng/mL, respectively ($p > 0.05$) (Figure 25).

There were no significant differences in the evaluated parameters between the Test and Control arms on Postoperative Day 1 ($p > 0.05$). When preoperative biomarkers levels were compared to the postoperative data, the following results were obtained: On Postoperative Day 1, mutant p53 expression and FASL levels were significantly increased ($p < 0.01$; $p < 0.05$); moreover, CEA and CA19-9 levels were significantly decreased ($p < 0.01$).

Table 21

Apoptotic markers expression in serum lymphocytes and genomic abnormalities in the colorectal cancer patients before and after surgery while different types of nutritional support were used

ARMS			Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation
Healthy donors			sFAS	89.58	88.33	0.00	308.00	0.00	124.29	90.60
			FasL	0.01	0.00	0.00	0.13	0.00	0.00	0.03
			p53	1.12	2.79	0.84	5.55	2.62	3.38	1.01
C O L O R E C T A L C A N C E R	Preoperatively		sFAS	143.69	55.47	0.00	524.86	0.00	256.04	186.94
			FasL	0.08	0.00	0.00	0.24	0.00	0.17	0.10
			p53	3.94	2.91	0.06	10.96	1.50	6.26	3.24
	Control arm	Day 1	sFAS	191.40	166.00	113.0	281.57	166.00	229.00	54.46
			FasL	0.23	0.08	0.00	0.96	0.00	0.25	0.35
			p53	8.40	6.79	0.00	25.00	2.59	9.27	8.86
		Day 7	sFAS	334.02	292.63	60.33	690.50	131.17	536.88	271.93
			FasL	0.27	0.14	0.00	0.91	0.00	0.43	0.32
			p53	11.89	12.66	6.00	17.50	9.40	13.10	3.87
	Test arm	Day 1	sFAS	138.67	107.75	77.52	255.71	85.73	191.85	62.47
			FasL	0.20	0.07	0.00	0.80	0.00	0.31	0.26
			p53	7.71	6.65	0.39	17.90	1.57	12.49	6.02
		Day 7	sFAS	96.05	63.54	32.86	188.60	63.54	141.50	55.24
			FasL	0.07	0.07	0.00	0.17	0.03	0.09	0.05
			p53	3.17	2.80	0.00	9.97	0.00	4.81	3.66

Diagram 3.5

CEA expression in the colorectal cancer patients before and after surgery while the different types of nutritional support were used

Diagram 3.6

CA19-9 expression in the colorectal cancer patients before and after surgery while the different types of nutritional support were used

On Postoperative Day 7, when pharmaconutrition and partial parenteral nutrition were given to the patients from the Test and Control arms, respectively, the following data were obtained:

- CEA: 7.1 ± 1.36 ng/mL and 14.38 ± 2.66 ng/mL, respectively ($p < 0.01$).

- CA19-9: 7.03 ± 2.17 and 14.41 ± 2.94 ng/mL, respectively ($p < 0.01$);

- p53: 3.71 ± 3.66 U/mL and 11.89 ± 3.87 U/mL, respectively ($p > 0.01$) (Figure 23);

- sFAS-positive lymphocytes: 96.05 ± 55.24 ng/mL and 334.02 ± 271.93 ng/mL, respectively ($p < 0.01$) (Figure 24);

- FASL-positive lymphocytes: 0.07 ± 0.05 ng/mL and 0.20 ± 0.26 ng/mL, respectively ($p < 0.01$) (Figure 25).

Figure 23. p53 levels (U/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used
Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

Figure 24. ApoFAS levels (ng/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutrition support were used

Where:

- 0 – healthy donors
- 1 – colorectal cancer patients before surgery
- 2 – evaluated levels in the Control arm versus Day 1 levels
- 3 – evaluated levels in the Control arm versus Day 7 levels
- 4 – evaluated levels in the Test arm versus Day 1 levels
- 5 – evaluated levels in the Test arm versus Day 7 levels

Figure 25. FASL levels (ng/mL) in the colorectal cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the Control arm versus Day 1 levels

3 – evaluated levels in the Control arm versus Day 7 levels

4 – evaluated levels in the Test arm versus Day 1 levels

5 – evaluated levels in the Test arm versus Day 7 levels

Therefore:

1. In the colorectal cancer patients lymphocyte apoptosis and tumor suppressor genes are activated when oncomarkers are overexpressed (CEA and CA19-9).
2. Lymphocyte apoptosis and tumor suppressor genes are activated after surgery in the colorectal cancer patients, although the pre- and postoperative changes in OM levels indicate on curative surgical intervention was performed.
3. In the colorectal cancer patients, pharmaconutrition (unlike partial parenteral nutrition) had marked positive influence on OM levels as well as inhibitory effect on lymphocyte apoptosis and tumor suppressor genes in early postoperative period (Table 22).

Table 22

WBC count in the colorectal cancer patients

Arms	WBC											
	Preoperatively				After surgery (Postoperative Day 1)				Postoperative Day 7			
	Absolute count, x10 ⁹ /L	% Lympho- cytes	% Mono- cytes	% Neutro- phils	Absolute count, x10 ⁹ /L	% Lympho- cytes	% Mono- cytes	% Neutro- phils	Absolute count, x10 ⁹ /L	% Lympho- cytes	% Mono- cytes	% Neutro- phils
Test arm, n=50 M1+M1	2.64 ± 1.77	84.55 ± 4.18	10.48 ± 1.47	5.72 ± 1.21	2.50 ± 1.80	80.31 ± 4.01	11.21 ± 2.94	9.2 ± 1.18	3.90 ± 2.01	85.71 ± 3.59	7.85 ± 2.34	7.58 ± 2.11
Control arm, n=46 M1+M2	2.80 ± 0.96	90.31 ± 4.25	6.48 ± 1.83	3.33 ± 1.55	2.74 ± 1.38	84.17 ± 2.23	7.31 ± 1.59	8.98 ± 1.89	1.96 ± 0.84	86.46 ± 5.65	6.53 ± 1.04	7.9 ± 1.41
<i>p</i>	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.01 <0.05*	>0.05 >0.05*	<0.05 <0.05	>0.05

* - compared to the preoperative data

6.4. Comparisons of the nutritional status parameters, markers of immune regulatory and genomic abnormalities in the stomach cancer patients and colorectal cancer patients in pre- and postoperative periods

Our researches demonstrate that the pathological processes observed in the stomach cancer patients were more severe, especially after surgery:

1. More severe malnutrition which was treated more difficult (Tables 13 and 18).
2. More severe imbalance between pro- and anti-inflammatory cytokines (Figures 26, 27, 28, and 29 and Table 23).
3. In contrast to the colorectal cancer patients, the stomach cancer patients develop systemic inflammatory response syndrome.

The intensity of lymphocyte apoptosis and p53 expression on Postoperative Day 1 (the Control arms and Test arms consisted of the patients with stomach or colorectal cancer), and after pharmaconutrition (Day 7) (Test arms consisted of the patients with stomach or colorectal cancer) were not differed between the patients with stomach or colorectal cancer (Figures 30, 31, and 32, Table 23).

The literature data [Shestopalov A.E. et al., 2003] and the obtained results allowed to consider the optimal daily dose of glutamine when pharmaconutrition is given in early postoperative period to be **40.0 g/day** of N(2)L-alanyl-L-glutamine and **20g/day** of N(2)L-alanyl-L-glutamine in the stomach cancer patients and colorectal cancer patients, respectively.

Figure 26. Comparison of IL-1 β levels (pg/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Fi

Figure 27. Comparison of IL-4 levels (pg/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Fi

Figure 28. Comparison of IL-6 levels (pg/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Fi

gure 29. Comparison of IL-8 levels (pg/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Fi

Figure 30. Comparison of Apo/FAS levels (ng/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Figure 31. Comparison of FASL levels (ng/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Fi

Figure 32. Comparison of p53 expressions (U/mL) in the colorectal cancer patients and stomach cancer patients in pre- and postoperative periods while the different types of nutritional support were used

Where:

0 – healthy donors

1 – colorectal cancer patients before surgery

2 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 1 levels

3 – evaluated levels in the colorectal cancer patients from the Control arm versus Day 7 levels

4 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 1 levels

5 – evaluated levels in the colorectal cancer patients from the Test arm versus Day 7 levels

6 – stomach cancer patients before surgery

7 – evaluated levels in the stomach cancer patients from the Control arm versus Day 1 levels

8 – evaluated levels in the stomach cancer patients from the Control arm versus Day 7 levels

9 – evaluated levels in the stomach cancer patients from the Test arm versus Day 1 levels

10 – evaluated levels in the stomach cancer patients from the Test arm versus Day 7 levels

Table 23

Comparative statistical data of the genetic markers in the healthy donors, patients with stomach or colorectal cancer before surgery and in postoperative period

ARMS		Parameters	Mean	Median	Min	Max	Lower quartile (25%)	Upper quartile (75%)	Standard deviation		
Healthy donors		IL-1 β	5.27	4.58	3.86	9.42	3.89	5.30	2.11		
		IL-4	80.67	74.40	25.8	149.23	40.02	139.42	48.96		
		IL-6	11.38	10.91	5.08	19.22	5.53	16.93	5.98		
		IL-8	4.29	3.70	2.11	7.83	2.73	5.75	1.99		
		TNF- α	2.38	2.13	1.11	5.25	1.28	2.15	1.67		
		sFAS	89.58	88.33	0.00	308.00	0.00	124.29	90.60		
		FasL	0.01	0.00	0.00	0.13	0.00	0.00	0.03		
		p53	1.12	2.79	0.84	5.55	2.62	3.38	1.01		
		CRP	1.27	0.90	0.00	3.10	0.00	3.00	1.31		
C O L O R E C T A L	Preoperatively		IL-1 β	5.30	2.36	0.00	36.60	0.09	7.08	8.36	
			IL-4	1.44	0.38	0.00	19.43	0.04	1.03	3.55	
			IL-6	152.55	148.75	98.0	210.58	119.85	189.34	44.47	
			IL-8	75.80	21.18	0.86	475.80	9.62	54.48	127.79	
			TNF- α	1.18	0.00	0.00	12.25	0.00	0.31	2.65	
			sFAS	143.69	55.47	0.00	524.86	0.00	256.04	186.94	
			FasL	0.08	0.00	0.00	0.24	0.00	0.17	0.10	
			p53	3.94	2.91	0.06	10.96	1.50	6.26	3.24	
			CRP	73.94	89.90	0.00	138.40	17.05	114.95	46.50	
	Cerulo plasmin	0.71	0.77	0.14	0.99	0.62	0.84	0.23			
	Control arm		Day 1	IL-1 β	6.79	6.57	2.48	10.21	5.83	9.08	2.73
				IL-4	1.03	0.95	0.81	1.42	0.86	1.21	0.27
				IL-6	334.36	339.33	271.1	408.00	290.56	381.00	48.55
				IL-8	88.28	58.43	3.27	227.92	8.66	170.44	92.16
				TNF- α	6.88	4.68	0.00	22.80	0.00	11.43	8.23
				sFAS	191.40	166.00	113.0	281.57	166.00	229.00	54.46
				FasL	0.23	0.08	0.00	0.96	0.00	0.25	0.35
				p53	8.40	6.79	0.00	25.00	2.59	9.27	8.86
			CRP	87.60	88.60	17.80	125.80	61.35	104.65	34.80	
Cerulo plasmin			0.78	0.74	0.69	0.97	0.71	0.84	0.10		
Day 7	IL-1 β	4.30	4.73	0.90	7.90	0.97	7.00	3.28			
	IL-4	1.34	1.48	0.97	1.71	1.02	1.53	0.33			
	IL-6	43.20	31.65	6.58	105.95	7.81	64.00	42.12			
	IL-8	61.28	24.02	1.87	196.20	11.70	110.38	70.00			
	TNF- α	2.25	0.00	0.00	16.85	0.00	0.59	5.90			
	sFAS	334.02	292.63	60.33	690.50	131.17	536.88	271.93			
	FasL	0.27	0.14	0.00	0.91	0.00	0.43	0.32			
	p53	11.89	12.66	6.00	17.50	9.40	13.10	3.87			
	CRP	89.53	95.65	11.40	171.50	53.50	117.50	50.66			
	Cerulo plasmin	0.72	0.73	0.57	0.83	0.65	0.80	0.09			
Test arm	Day 1	IL-1 β	6.65	4.08	0.00	29.10	0.77	5.57	8.73		
		IL-4	1.27	0.58	0.00	4.50	0.43	2.13	1.26		
		IL-6	333.81	254.99	28.90	694.30	87.20	682.50	304.65		
		IL-8	71.71	32.05	0.00	535.20	8.73	97.44	112.75		
		TNF- α	1.98	0.00	0.00	23.00	0.00	0.38	5.51		
		CRP	89.53	95.65	11.40	171.50	53.50	117.50	50.66		
		Cerulo plasmin	0.72	0.73	0.57	0.83	0.65	0.80	0.09		

C A N C E R			sFAS	138.67	107.75	77.52	255.71	85.73	191.85	62.47			
			FasL	0.20	0.07	0.00	0.80	0.00	0.31	0.26			
			p53	7.71	6.65	0.39	17.90	1.57	12.49	6.02			
			CRP	91.02	81.40	0.00	136.90	19.65	113.80	49.95			
			Cerulo plasmin	0.69	0.74	0.17	0.98	0.63	0.83	0.23			
			Day 7	IL-1β	2.88	1.18	0.00	19.00	0.29	1.80	5.35		
				IL-4	8.70	9.21	2.73	15.04	4.69	12.01	4.38		
				IL-6	20.13	18.56	15.48	28.40	15.67	25.90	5.10		
				IL-8	35.96	11.87	1.18	195.08	5.21	57.16	51.04		
				TNF-α	1.88	0.00	0.00	30.94	0.00	0.00	6.75		
				sFAS	96.05	63.54	32.86	188.60	63.54	141.50	55.24		
				FasL	0.07	0.07	0.00	0.17	0.03	0.09	0.05		
				p53	3.17	2.80	0.00	9.97	0.00	4.81	3.66		
				CRP	57.00	72.25	0.90	136.60	8.00	113.50	50.84		
				Cerulo plasmin	0.36	0.63	0.13	1.03	0.47	0.87	0.24		
G A S T R I C C A N C E R		Preoperatively	IL-1β	5.56	6.00	2.58	8.11	3.69	7.23	2.05			
			IL-4	11.85	11.75	4.17	21.87	6.66	14.84	5.94			
			IL-6	250.01	269.74	72.00	411.56	88.75	388.28	158.98			
			IL-8	50.61	31.73	1.53	235.54	7.90	57.50	65.00			
			TNF-α	2.07	0.83	0.00	12.00	0.00	1.85	3.43			
			sFAS	150.51	136.40	42.91	310.80	71.50	227.40	89.86			
			FasL	0.10	0.00	0.00	0.28	0.00	0.24	0.14			
			p53	3.27	3.53	0.00	9.76	0.74	5.16	2.78			
			CRP	98.53	108.40	11.30	140.10	71.50	132.10	39.56			
			Cerulo plasmin	0.80	0.81	0.18	1.05	0.74	0.94	0.23			
			Control arm	Day 1	IL-1β	1.13	1.13	0.31	1.94	0.31	1.94	1.15	
					IL-4	7.49	6.67	0.00	16.41	0.00	15.62	6.82	
					IL-6	115.99	52.53	10.57	375.77	10.68	179.66	135.07	
					IL-8	10.54	6.44	2.29	24.64	3.32	22.86	9.24	
					TNF-α	0.73	0.30	0.00	1.96	0.00	1.74	0.82	
		sFAS			138.60	146.50	0.00	281.57	73.94	193.70	93.60		
		FasL			0.00	0.00	0.00	0.00	0.00	0.00	0.00		
		p53			6.04	5.55	1.60	15.90	2.40	8.53	4.32		
		CRP			112.93	115.80	97.5	125.50	97.50	125.50	14.22		
		Cerulo plasmin			0.82	0.90	0.66	0.91	0.66	0.91	0.14		
		Day 7		IL-1β	28.10	30.66	15.0	42.08	18.79	33.40	9.22		
				IL-4	7.22	8.53	2.50	10.00	4.09	10.00	3.17		
				IL-6	111.45	24.24	10.68	344.80	10.99	344.14	159.31		
				IL-8	111.71	10.07	1.51	544.50	3.54	201.14	204.10		
				TNF-α	5.73	1.52	0.00	29.30	0.54	5.24	10.53		
		G A S T R I C		Test arm	Day 1	sFAS	350.23	296.65	91.0	711.00	129.00	578.00	244.89
						FasL	0.32	0.00	0.00	0.95	0.00	0.80	0.43
						p53	10.79	2.24	0.00	52.80	0.74	13.62	19.09
						CRP	89.60	39.80	7.90	114.60	7.90	114.60	23.16
						Cerulo plasmin	0.64	0.54	0.24	0.84	0.24	0.74	0.26
Day 1	IL-1β				1.07	0.44	0.00	3.40	0.14	2.01	1.57		
	IL-4				7.10	5.55	1.70	14.06	1.70	14.06	5.66		
	IL-6				275.64	274.58	63.2	496.50	95.00	450.00	177.17		
	IL-8				70.54	20.29	4.83	264.80	7.59	131.60	93.43		
	TNF-α				5.45	0.00	0.00	29.30	0.00	6.71	10.04		
	sFAS				124.56	99.61	87.4	187.38	91.80	156.60	44.86		
	FasL				0.21	0.00	0.00	0.50	0.00	0.47	0.24		
	p53				6.23	4.35	2.23	16.60	3.04	6.83	5.31		
	CRP				99.41	114.90	8.30	131.50	92.40	125.50	41.17		

C A N C E R		Day 7	Cerulo plasmin	0.79	0.76	0.17	1.02	0.68	0.81	0.27
			IL-1 β	0.61	0.61	0.00	1.21	0.26	0.96	0.50
			IL-4	33.87	35.67	13.9	50.24	21.98	45.76	15.66
			IL-6	25.78	12.33	4.09	86.70	8.47	17.30	34.40
			IL-8	15.13	14.68	3.23	33.00	4.73	22.98	11.49
			TNF- α	0.32	0.00	0.00	1.80	0.00	0.38	0.62
			sFAS	160.50	155.20	108.1	241.74	113.69	189.00	51.34
			FasL	0.11	0.00	0.00	0.67	0.00	0.09	0.24
			p53	2.21	2.33	0.00	4.80	0.59	3.51	1.78
			CRP	54.10	96.20	0.90	130.40	35.75	120.80	53.16
			Cerulo plasmin	0.32	0.74	0.19	0.84	0.44	0.78	0.26

6.5. Influence of the different types of clinical nutrition on the incidences of postoperative complications in the patients with stomach or colorectal cancer

The assessment of the nature, severity and incidence of postoperative purulent-septic complications showed that on Postoperative Days 5-7, the stomach cancer patients from the Control and Test arms developed the following complications (Table 24).

The incidences of postoperative complications in the Control and Test arms were 13.63% and 4.34%, respectively ($p < 0.01$). Re-laparotomy and abdominal drain procedure were required in all cases.

Mean hospital days were 12.24 ± 2.75 and 20.47 ± 3.58 days in the Test and Control arms, respectively ($p < 0.02$). There was no mortality on both arms.

On Postoperative Day 7, the significant differences between the assessed biomarkers correlated with the significant differences of the postoperative complications rates, i.e. there was noted direct correlation between increased mutant p53 expression, lymphocyte apoptosis (sFAS/FASL) as well as CRP and ceruloplasmin levels ($r_s = 0.847$, $r_s = 0.681$, $r_s = 0.811$, $r_s = 0.734$, $r_s = 0.692$ respectively) and increased incidence of the purulent-septic complications.

The following complications were diagnosed in the colorectal cancer patients from the Control and Test arms on Days 5-7 (Table 25).

In the Control arm, the postoperative complications occurred in 10.85% patients (thus, the patients developed anastomotic leakage and they underwent re-laparotomy followed by debridement, abdominal drain procedure and protective ileostomy; the patients with abdominal abscesses underwent also re-laparotomy followed by debridement and abdominal

drain procedure; the female patient with pelvic abscess underwent opening and draining of pelvic abscess). There were no complications in the Test arm ($p<0.001$).

Mean hospital days were 14.56 ± 2.79 and 22.54 ± 4.18 days in the Test and Control arms, respectively ($p<0.02$). There was no mortality on both arms.

On Postoperative Day 7, the significant differences between the assessed biomarkers correlated with the significant differences of the postoperative complications rates, i.e. there was noted direct correlation between increased mutant p53 expression, lymphocyte apoptosis (sFAS/FASL) as well a CRP and ceruloplasmin ($r_s=0.876$, $r_s=0.829$, $r_s=0.817$, $r_s=0.679$, $r_s=0.712$ respectively) and increased incidence of the purulent-septic complications.

Table 24

Postoperative complications and mortality in the stomach cancer patients

COMPLICATION	Rate, % (n=number of patients)	
	Test arm, n=23	Control arm, n=22
1. Anastomotic leakage	4.34 (1)	9.09 (2)
2. Abdominal abscess	-	4.54 (1)
MORTALITY	0	0

Table 25

Postoperative complications and mortality in the colorectal cancer patients

COMPLICATION	Rate, % (n=number of patients)	
	Test arm, n=50	Control arm, n=46
1. Anastomotic leakage	0	4.34 (2)
2. Abdominal abscess	0	4.34 (2)
3. Pelvic abscess	0	2.17 (1)
MORTALITY	0	0

It should also be noted that pharmaconutrition was continued (SC patients) or prescribed to all patients with stomach or colorectal cancer who developed the postoperative purulent-septic complications. In the stomach cancer patients after re-laparotomy, debridement and abdominal drain procedure, the capillary nasojejunal probe NJFT-8 was placed endoscopically beyond gastroduodenostomy or gastrojejunostomy at a

distance of 30-40 cm distal to the ligament of Treitz (intestinal pacemaker area). Enteral nutrition was started with semi-elemental formulas (Peptamen) so-called starting regimen [Popova T.S. et al., 2002], progressively increasing of its concentration and volume (from 400.0 mL/day of 5% SEF up to 1200.0 mL/day of 10% SEF; infusion rate did not exceed 120.0 mL/h).

Kabiven central 2053.0 mL/day or Oliclinomel No.7-1000, 1500.0 mL/day containing Dipeptiven 200.0 mL/day was parenterally administrated both in the stomach cancer patients and colorectal cancer patients (via central line). The infusion rate did not exceed 100.0-120.0 mL/h. There were complications related to this type of nutritional support neither in the stomach cancer patients nor colorectal cancer patients.

Mean times of pharmaconutrition for postoperative complications developed in the stomach cancer patients and colorectal cancer patients were 9.86 ± 2.15 days and 7.35 ± 3.18 days, respectively.

There were no mortality both in the stomach cancer patients and colorectal cancer patients.

Therefore, pharmaconutrition had statistically significant impact on reduction of the incidence and severity of the postoperative purulent-septic complications in the patients with stomach or colorectal cancer.

CONCLUSION

Currently, surgical treatment in the patients with stomach and colorectal malignancies, which primarily aims to remove the tumor and restore maximum patency of the gastrointestinal tract for further adequate replacement with macro - and micronutrients and energy, almost reaches its perfection (see Sections 1 and 2, Sub-sections 1.2 and 2.2). As our data shows these patients are intervened while nutritional deficiency and severe immune regulatory abnormalities accompanying the underlying disease, exist.

As K.A. Bunyatyan rightly stated [2007]: *«Surgical intervention is not only a surgery, this is a multifactorial complex effect on the patient's body provided by anesthesia, mechanical ventilation, blood loss and blood transfusion, hypothermia, and extracorporeal circulation. The difficult numerous changes of homeostasis observed after surgery are the basis of post-operative pyoinflammatory and septic complications. Abnormal immune functions in surgical patients with pyoinflammatory processes developed in the postoperative period, have complex pathogenesis. Along with severe endotoxemia, microcirculatory disorders and anabolic disturbances, the changes in the main immune regulatory pathways have critical value. Therefore, the efficacy of surgical treatment depends on identifying of immune failure in the patients in pre - and postoperative periods and its adequate pharmacological management».*

However, the possibilities of etiopathogenetic therapy to improve the surgical results in these patients are not used comprehensively. Over the last years, a large number of different medicinal products for chemotherapy and immunotherapy indented for colorectal and stomach malignancies is appeared; different regimens of preoperative and postoperative therapy using various options of medical therapy and radiotherapy are developed in details [Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Beloborodov V.B., 2006; Gorbunova V.A. et al., 2006; Bunyatyan K. A., 2007; Sakaeva D.D., Lazareva D.N., 2007; Skoropad V.Yu., Berdov B.A., 2008; Otchy D., Hyman N., Simmang C. et al., 2004; Brennan M.F., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005; Kaschiato D., 2008]. However, unfortunately, it is not always possible to treat effectively purulent-septic complications developing in early postoperative period which incidences according to various authors, are 14.0% in the colorectal cancer patients and achieve 16.7%-22.3% in the stomach cancer patients, the mortality rates are 2.3% and 3.7%,

respectively [Zhebrovsky V.V., 2000; Kuznetsov N.A., Danilov K.Yu. et al., 2000; Chernousov A.F., Polikarpov S.A., 2006; Bunyatyan K. A., 2007; Afanaseva A.N., 2008; Maskin S.S. et al., 2008; Shurkalin B.K. et al., 2008; Schekochikhin S.A. et al., 2008; Kanellos I. et al., 2002; Kressner U. et. al., 2002; Kurum Baig M. et al., 2002; Knoop M., Vorwerk T., 2003; Makela J.T. et al., 2003; Kanellos I., Vasiliadis K. et al., 2004; Maurer C.A., 2004; Rose J. et al., 2004; Brennan M.F., 2005].

The cornerstone of any nutritional support is its timeliness, as to prevent malnutrition is much easier than to treat it [Vretlind A., Sudgyan A., 1990]. Unfortunately, in our country most studies investigated clinical artificial nutrition in the patients critically ill staying in ICUs. *This is very important!* But what to do with those patients who underwent major traumatic elective operations. The vast majority of these patients (after stabilization of vital functions) stays in ICUs for no more than 1-2 days. Then, they are transferred to the appropriate surgical department where according to the clinical practice; these patients don't receive timely and adequate nutrition in early postoperative period. However, as mentioned above, Days 5-12 are critical period in development of postoperative purulent-septic complications [Zhebrovsky V.V., 2000; Rivkin V.L., Fayn S.N., Bronshtein A.S., An V.K., 2004; Baulin A.A., Lesin V.N., Baulina E.A., Kovrigin I.I., 2008; Kharagezov A.D., Serdyukova O.S., Pochkay E.N., Gutstein Yu.A., 2008; Makela J.T., Kiviniemi H., Laitinen S., 2003; Kanellos I., Blouhos K., Demetriades H., 2004]. Just before this time period, the surgical patients transferred from ICUs remain actually fasting. To date, somatometric and laboratory parameters of nutritional status were the main indications and efficacy criteria for nutritional support. The foreign authors proposed various questionnaires for earlier detection of malnutrition and, more importantly, the risk of its occurrence [Detsky A., 1987; Sobotka L., Allison S.P., Furst P., 2004].

However, in recent years, latest tools for clinical artificial nutrition was developed (pharmakonutrients, "All-in-One" systems, wide range of various nutritional admixtures for enteral nutrition) and the preliminary results were obtained from the studies investigating influence of these products on both the parameters of nutritional status and some of the leading pathogenetic mechanisms, in particular, immune abnormalities in the surgical patients and critically ill patients [Shestopalov A.E. et al., 2003; O'Riordain M.G. et al., 1996; Exner R., Weingartmann G., Eliassen M.M. et al., 2002]. Moreover, the investigators (*especially, surgeons*) pay

special attention to determination in the patients with stomach and colorectal cancer the most specific and sensitive biomarkers, to date, which directly describe oncology process, immune regulatory status, and efficacy of various treatments, with the purpose of early diagnostics, more complete quality assessment of surgical treatment and other options, decrease in relapse rate and prognosis of patients survival [Tenderenda M. et al., 2001; Kooby D.A. et al., 2003; Fondevila C. et al., 2004; Brennan M.F., 2005; Tjandra J., Kilkenny J., Buie W., Hyman N. et al., 2005; Kaschiato D., 2008; Kwon J-I., Kim Gi-Y., Park K-Y. et al., 2008]. All above mentioned determined the actuality and necessity of our study to be performed.

In other words, whether the latest types of CN affect both nutritional status and leading pathogenetic mechanisms of the postoperative purulent-septic complications in the surgical patients (in our study patients with stomach and colorectal cancer)? If yes, how do they affect? Which biomarker should be used to prove it? However, it is desirable that these markers were highly sensitive and specific being integral parameters characterizing not only the efficacy of pharmaconutrition, but others, and, first of all, surgical treatment, and were used as prognostic parameters for future course of these nosologies after surgical treatment. And the main question is as follows: is it necessary to prescribe early balanced pharmaconutrition to all above mentioned surgical patients to prevent development of the postoperative purulent-septic complications?

The main components to resolve these tasks were, firstly, formation of the patients arms highly uniform for the trial; secondly, application of the most modern methods of surgical treatment, anesthetic management, intensive care in ICUs, antibiotic therapy; thirdly, for the analysis of molecular genetics markers to apply the most diagnostically accurate kits and reagents of the leading world manufacturers and, finally, when pharmaconutrition is given, modern techniques of clinical artificial nutrition should be also used.

First of all, based on the results of our study with a high degree of probability it can be stated that SIRS, oxidative stress and immune cell apoptosis in the patients with stomach cancer are closely related, but not all of them are enhanced immediately on Day 1. Within the first 1-2 days of ICUs staying, vital functions of these patients are stabilized and they are transferred to specialized medical departments, where, in particular, according to A.N. Afanasieva [2008] pathogenetic pathways leading to SIRS are triggered, and according to our data (in ICUs) *nutritional*

deficiency is exacerbated and lymphocyte apoptosis is increased while tumor suppressor genes are activated. All listed above pathological conditions may result in purulent-septic complications within Days 1-3 despite of semblable well-being. The same conditions, based on our data, are developed in the colorectal cancer patients (except for SIRS) (Figures 33 and 34). In early postoperative period, the oncomarkers are decreased, but the acute phase proteins (CRP and ceruloplasmin), some interleukins (IL-1 β , IL-4, IL-6, IL-8), lymphocyte apoptosis markers (sFAS, FASL) and p53 expression are growing and correlate with the incidences of postoperative purulent-septic complications.

Therefore, if the efficacy of surgical treatment will be assessed by measuring of OM levels only, it would be not enough, and its reduced levels can not be effective measures of favorable course of early postoperative period in the patients with stomach and colorectal cancer.

All evaluated pathological processes related to stomach cancer (including incidence and severity of postoperative complications) were more aggressive compared to colorectal cancer, which we primarily associate with more marked disorders of gastrointestinal digestion and absorption (due to affected upper GI tract), presence of more severe protein-energy malnutrition before surgery and features of performed operations. Moreover, in early postoperative period, nutritional deficiency, lymphocyte apoptosis and imbalance of serum cytokines were more severe in the stomach cancer patients compared to the colorectal cancer patients. First of all, daily dose of glutamine was based on this fact when pharmaconutrition was given in the SC patients (Dipeptiven 200.0 mL/day) and colorectal cancer patients (Dipeptiven 100.0 mL/day).

When pharmaconutrition was given in the patients with stomach or colorectal cancer, laboratory parameters of nutritional status normalized and positive changes in IL-1 β and IL-6 (cachectin) expression were observed that was an important evidence of pharmaconutrition to be effective [Popova T.S. et al., 2002] . However, normalization of nutritional status in the stomach cancer patients was slower than in the colorectal cancer patients. Moreover, all evaluated patients with stomach or colorectal cancer had no specific medicinal methods (than proposed ones by us) to correct cytokine imbalance and lymphocyte apoptosis, and activity of the tumor-suppressor genes.

Figure 33. Influence of operative injury on primary pathological pathways of purulent-septic complications in the stomach cancer patients

Additionally, we would like to present more detail the results of our research associated with the postoperative changes in the lipid peroxydation marker levels in the patients with stomach or colorectal cancer while the different nutritional supports were used. As described above, *there is a definite close relationship between free radical oxidation (including LPO) on one hand and cytokine modulation of homeostasis, apoptosis and genomic abnormalities on other hand (Chapter 1, Section 5).*

Figure 34. Influence of operative injury on primary pathological pathways of purulent-septic complications in the colorectal cancer patients

We did not obtain any results that both pharmaconutrition and partial parenteral nutrition affected PLO. And if it is easily explained in case of partial parenteral nutrition, as no positive effects of this CN type on normalization of cytokine balance, lymphocyte apoptosis, mutant p53 expression, reduction of acute phase protein levels by Day 7 were observed in the patients with stomach or colorectal cancer from the Control arms, but the cancer patients from the Test arms who had pharmaconutrition demonstrated positive changes in the listed above molecular and genetic markers. Why did PLO parameters demonstrate no positive changes? Therefore, we consider that the lipid emulsions applied in our study is to be discussed more details. It is believed that the ideal lipid emulsion as a source of energy should be easily metabolized, and

should not cause any inflammatory or oxidative stress or disrupt immune function [Geert J.A., Calder P.C., 2007]. However, to date, there is no «ideal» lipid emulsion.

Kabiven includes fat emulsion Intralipid (long-chain triglycerides – LCT) based on soybean oil with n-6/n-3 ratio of polyunsaturated fatty acids (PUFAs) being 7:1. According to K.C. Switzer et al. [2003], V. Bansal et al. [2005], this is its disadvantage which can lead to excessive production of pro-inflammatory mediators (including cytokines) and increase oxidative burden in the surgical patients, especially after surgical interventions. Oliclinomel includes fat emulsion ClinOleic based on soybean oil with n-6/n-3 ratio being 9:1 (although 20% phospholipids contained in ClinOleic are fatty acids based on soybean oil). J.A. Geert and P.C. Calder [2007] consider this type of fat emulsions to be immune neutral and has no significant positive or negative influence on oxidative stress.

There are fat emulsions based on medium-chain triglycerides (MCT), e.g. Lipofundin MCT/LCT, which according to J.M. Stouthard et al. [1994] are resistant to peroxydation, but:

- firstly, they cannot be used in its native form, as they are not sources of essential fatty acids (as compared to LCT);
- secondly, this type of fat emulsions increases the risks for ketogenesis and acidosis [Geert J.A., Calder P.C., 2007];
- thirdly, the data on positive effects of MCT fat emulsions were obtained from the small (less than 10-15 patients) and short-term (not longer than 5 days) studies [Grau T. et al., 2003].

The fish oil-based fat emulsions containing of n-3 PUFAs, which have no above mentioned disadvantages [Versleijen M. et. al., 2005] are applied only as pharmaconutrients due to its high cost and cannot be simultaneously used as an energy source. Moreover, this type of fat emulsions has recently appeared in the Russian market.

When Oliclinomel (ClinOleic) or, especially, Kabiven (Intralipid) was administrated, we did not observe increased oxidative stress or immune suppression. In our opinion, this is, primarily related to glutamine application which numerous positive effects are well investigated, including our research.

Therefore, we consider it is necessary to administrate glutamine obligatory when total parenteral nutrition is given to the surgical patients in postoperative period to treat and prevent possible negative effects of fat emulsion on oxidative stress and immune function.

Generally, summarizing the glutamine, SIRS, oxidative stress and immunosuppression topics we should cite A.S. Yermolov, I.E. Popova et al. [2005]: «The general SIRS trigger is intestinal penetration by bacteria and endotoxin which primary pathogenetic component is lipopolysaccharide (LPS) contained in the cell membranes of gram-negative microorganisms. After releasing LPS binds to serum protein and forms LPS-binding protein. The latter activates macrophages and polymorphonuclear leukocytes and stimulates these cells to produce cytokines (highlighted by the authors) and other mediators of septic reaction improving the intestinal mucosal integrity through glutamine infused intravenously (highlighted by the authors)... inhibits intestinal absorption of endotoxin».

Therefore, the algorithm for prescription and management of early pharmaconutrition in the patients with stomach or colorectal cancer can be presented as follows (Figure 35).

Figure 35. Algorithm of pharmaconutrition in the patients with stomach or colorectal cancer

Pathological changes investigated by us in the patients with stomach or colorectal cancer and effects of operative injury and early postoperative pharmaconutrition are shown in Figures 36 and 37.

Figure 36. Pharmaconutrition for modulation of the primary pathogenetic pathways of postoperative complications in the stomach cancer patients

Figure 37. Pharmaconutrition for modulation of the primary pathogenetic pathways of postoperative complications in the colorectal cancer patients

SUMMARY

1. Operative injury in the patients with stomach or colorectal cancer leads to deterioration of protein-energy insufficiency, increased lymphocyte apoptosis and imbalance of serum cytokines, increased activity of the tumor suppressor genes, and, in the stomach cancer patients only, to the systemic inflammatory response syndrome to be developed. These pathological processes are ones of the main reasons for postoperative purulent-septic complications.
2. Timely pharmaconutrition (glutamine-supplemented) in the patients with stomach or colorectal cancer in early postoperative period resolves systemic inflammatory response syndrome and immune regulatory abnormalities, thus reducing the incidences and severity of postoperative purulent-septic complications.
3. Measurements of inflammation and lymphocyte apoptosis markers as well as evaluation of serum cytokine balance and activity of the tumor suppressor genes along with determination of oncomarkers specific to stomach or colorectal cancer is an effective method to assess the quality of performed surgical treatment and prognosis of early postoperative period.
4. Measurements of inflammation and lymphocyte apoptosis markers as well as evaluation of serum cytokine balance and activity of the tumor suppressor genes along with determination of somatometric and laboratory parameters of nutritional status are effective criteria for assessment of nutritional support in the patients with stomach or colorectal cancer.
5. The proposed method of management of the clinical artificial nutrition in the surgical patients in a multidisciplinary hospital is available and easily reproducible option of management of the clinical nutrition in the healthcare institutions of the Russian Federation for wider implementation of nutrition support in clinical practice.

PRACTICAL GUIDELINES:

1. To predict the patterns of early postoperative period in the patients with stomach or colorectal cancer, prior to surgery, on Days 1-2 and Day 7, it is reasonable to determine mutant p53 expression, lymphocyte apoptotic markers (APO/FAS and FASL), serum pro-inflammatory cytokine expression: IL-1 β and IL-6 (kacheptins), as well as IL-8 and anti-inflammatory cytokine - IL-4.
2. To assess the efficacy of nutritional support along with determination of commonly accepted somatometric and laboratory parameters of nutritional status in the patients with stomach or colorectal cancer in early postoperative period (Days 1-2 and Day 7), it is reasonable to determine mutant p53 expression, lymphocyte apoptotic markers (APO/FAS and FASL), and serum pro-inflammatory cytokines: IL-1 β , IL-6, IL-8 and anti-inflammatory cytokine - IL-4.
3. The patients with stomach or colorectal cancer after curative operations should be timely prescribed with glutamine-supplemented pharmaconutrition starting from Day 2 to prevent development of purulent-septic complications.
4. Glutamine should be administrated obligatory when total parenteral nutrition is given in postoperative period in the surgical patients to prevent possible negative effects of fat emulsions on oxidative stress and immune function. The daily doses of N(2)L-alanyl-L-glutamine in the patients with stomach and colorectal cancer should be 40.0 g/day and 20.0 g/day, respectively.
5. After curative operation, the total parenteral nutrition in the patients with stomach or colorectal cancer it is reasonable to combine either with enteral feeding, or (in colorectal cancer patients) with oral enteral nutrition in sip feeding regimen (depending on performed interventions).
6. If the postoperative purulent-septic complications are developed in the stomach cancer patients, combined parenteral enteral nutrition ("All-in-One" systems) should be prescribed and contain N(2)L-alanyl-L-glutamine (at least 40.0 g/day), and semi-elemental formulas should be given via endoscopically placed nasojejunal feeding tube.

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