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## Effects of Dietary Counseling on Patients with Colorectal Cancer

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### 1. Introduction

Cancers of the colon and rectum together are second most common tumor type worldwide. The prognosis for the survival after disease progression is usually poor (1). Cancer anorexia-cachexia syndrome is highly prevalent among patients with colorectal cancer, and has a large impact on morbidity and mortality, and on patient quality of life. Early intervention with nutritional supplementation has been shown to halt malnutrition, and may improve outcome in some patients (2).

The etiology of cancer-associated malnutrition appears to be related to the pathological loss of inhibitory control of catabolic pathways, whose increased activities are not counterbalanced by the increased central and peripheral anabolic drive (3).

The goals of nutritional support in patients with colorectal cancer are to improve nutritional status to allow initiation and completion of active anticancer therapies (chemotherapy and or radiotherapy) and improve quality of life (3, 4).

Cancer growth and dissemination but also cancer treatments, including surgery, chemotherapy, and radiation therapy, interfere with taste, ingestion, swallowing, and digest food which leads to hypophagia. Also, chemotherapy agents may cause nausea and diarrhea (3, 4). Although many new agents are on the market to combat these symptoms, prevalence of colorectal cancer is still high (1).

We studied the influence of nutritional support (counseling, nutritional supplements, megestrol acetate) on physical status and symptoms in patients with colorectal cancer during chemotherapy. The study was designed to investigate whether dietary counseling or oral nutrition commercial supplements during chemotherapy and/or BSC affected nutritional status and influence survival status prevalence in patients with colorectal cancer.

**Results:** Three hundred and eighty-eight colorectal cancer patients were included in the study. Nottingham Screening Tool Questionnaire, Appetite Loss Scale and Karnofsky Performance Status were taken to evaluate the nutritive status of patients. Group I consisted of 215 patients who were monitored prospectively and were given nutritional support and in this group weight gain of 1,5 kg (0,6-2,8 kg) and appetite improvement was observed in patients with colorectal cancer. In both groups Karnofsky Performance Status didn't change significantly reflecting the impact of the disease itself.

Nutritional counseling, supplemental feeding and pharmacological support do temporarily stop weight loss and improve appetite, QoL and social life, but this improvement has no implications on patients KPS and course of their disease.

**Conclusion:** These results encourage further studies with more specific nutritional supplementation in patients with colorectal cancer and probably in gastrointestinal oncology.

## 2. Colorectal cancer

The incidence and mortality rates for cancers of the colon and rectum are among the highest of all malignancies worldwide (1, 2). Colorectal cancer is second in global cancer incidence and it is the most common cause of cancer death among non-smokers. US and EU incidence figures exceed global averages, which is consistent with an increased risk in industrialized nations (2). Factors associated with increased risk of colorectal cancer are host susceptibility and a sequence of different carcinogenic exposures. Specific etiology for sporadic colorectal cancer is still elusive but predisposing hereditary and environmental factors have been clearly identified (5).

### 2.1 Etiology of colorectal cancer

Important causes of colorectal cancers are uncommon genetic syndromes. A small percentage of "sporadic" colon cancers cluster in families. Relatives of people with colorectal cancer have increased risk for colorectal cancer, and risk varies depending on the number of relatives affected and the age at which cancer occurred (5).

Colorectal cancer is a heterogeneous disease that can develop through only partly known complex series of molecular changes. It is a long-term, gradual process which, besides external factors (carcinogens), also involves ever more recognized hereditary factors that cause genetic changes capable of triggering the uncontrolled mucosal (epithelial) growth (1, 5). The sequence of events that leads to the development of disease are passage from normal mucosa to adenoma - malignantly transformed adenoma and invasive carcinoma is associated with a series of genetic events occurring over long periods (5-7 years), the knowledge of which keeps expanding for the past ten years (1). In other words, the malignant transformation of cells requires various types of genetic damage in the form of gene mutation, deletion, amplification or expression disorder (1). In the 1990-ies, Fearon and Vogelstein first developed an algorithm for genetic events in colorectal cancer. According to their model, sporadic colon cancer arises as a result of a series of genetic changes that affect the process progression from enhanced epithelial proliferation to metastatic disease. The ultimate outcome of the process depends more on the number of accumulated changes than on their chronology.

The syndromes of colorectal cancer are inherited in an autosomal dominant fashion and are categorized by phenotypic, histological and genetic findings. Familial adenomatous

polyposis, hereditary nonpolyposis colorectal cancer, Peutz-Jeghers disease, juvenile polyposis, Cowden disease are rare conditions (6, 7).

Ulcerative colitis, among other diseases in the medical history, is the top risk factor. The longer the disease and the segment of the colon affected, the higher the risk. The risk is also increased in individuals with Crohn's disease. The patient undergoing surgery for colorectal cancer has three times the risk of cancer recurrence (9).

The inheritance determines individual susceptibility to sporadic cancer but the lifestyle and environmental exposures are necessary for cancer expression. Colorectal cancer incidence varies between different geographic regions and incidence and mortality rates have been highest in developed western nations (10, 11). The basic argument that environment plays a huge role in colorectal cancer expression we get from observational studies in migrant populations. Migrants from low-incident regions to the high-incident regions of North America within one generation accept the incidence of the host country. Yet, studies with migrants also suggest that geographic variation in colorectal cancer incidences is due to environmental exposures and not due to the inherent predisposition (racial and ethnic group) (1, 10, 11).

Population based investigations have found many dietary and other environmental factors associated with colorectal cancer incidence (2). Most of these studies have methodologic limitations and therefore the interpretation of such studies has to be made with caution. Many studies have been conducted to investigate external factors that may increase or diminish the incidence of colorectal cancer. Many authors recognize four risk factor categories: epidemiological, intestinal, dietetic and mixed. The most frequently reported factors, among these shown to increase the risk of developing the disease, are diets rich in meat and animal fats (bile salts), physical inactivity, smoking and alcohol consumption (1, 2, 12). Between other diets ingested, consumption of red meat has the strongest correlation with colorectal cancer; over 30 case control studies report increased risk of colorectal cancer with higher red meat intake. Especially fried, barbecued and well-done meat is associated with colorectal cancer risk. Obesity and high caloric intake are the independent risk factors for colorectal cancer, excessive body mass gives a two fold increase in colorectal cancer, and this association is more expressed in men than women (12). Although studies carried out in humans and animal models have shown a positive correlation between the saturated fats/red meat consumption and the development of colorectal cancer, only a few of them are confirmed to be statistically significant. The total amount of fat in terms of daily caloric intake (>40%) and their form appears to have special significance. The conversion of dietary phospholipids to diacylglycerol by intestinal bacteria is assumed to be a potential mechanism of carcinogenesis. Diacylglycerol can enter the epithelial cell directly and by stimulating protein kinase C, it evokes intracellular signal transduction or mucosal proliferation. Another important mechanism is the formation of free radicals during fat metabolism and the mucosal damage induced by the secondary bile acids (lithocholic acid). Nitroso compounds, heat-generated heterocyclic amines and high protein intake (accelerated epithelial proliferation) have potential carcinogenic consequences (12, 13).

Among the factors mentioned to reduce the risk are diet high in plant fibers and calcium, antioxidants (vitamin E, selenium etc.), menopausal hormone replacement therapy and administration of nonsteroidal anti-inflammatory drugs (12). In 1990 more than 13 studies showed significant reductions in colorectal cancer risk comparing the group with higher vs group with lower fibre intake. Some of the potential benefit mechanisms are: increased stool

weight, dilution of potential carcinogens and increased colon transit rate. But other studies did not confirm such results, and today in this field we have inconclusive and controversial results (12, 13).

A complex interaction between inherited predispositions and external factors is responsible for the development of colorectal cancer (Table 1).

RISK FACTORS FOR COLORECTAL CANCER	
Genetic factors	<ul style="list-style-type: none"> <li>- inherited polyposis syndrome</li> <li>- syndromes: Gardner, Turcot</li> <li>- Peutz-Jeghers, juvenile polyposis</li> </ul>
Family factors	<ul style="list-style-type: none"> <li>- inherited colorectal cancer syndrome</li> <li>- hereditary adenocarcinomatosis syndrome</li> <li>- family history of colorectal cancer</li> </ul>
Pre-existing diseases	<ul style="list-style-type: none"> <li>- ulcerative colitis, Crohn's disease</li> <li>- colorectal cancer</li> <li>- radiation therapy to the small pelvis</li> <li>- colorectal polyps</li> </ul>
External factors	<ul style="list-style-type: none"> <li>- diet rich in meat and animal fat</li> <li>- physical activity</li> <li>- smoking</li> </ul>
Other factors	<ul style="list-style-type: none"> <li>- age over 40 years</li> </ul>

Table 1. Risk factors for colorectal cancer development

## 2.2 Pathology

Molecular basis of disease are genetic mutations of somatic cells and the inner innervation of the colon is important in carcinoma pathogenesis and spread. According to their macroscopic appearance, colorectal cancers are divided into exophytic, ulcerative and stenosing tumors. Exophytic tumors are most often located in the right half of the colon, while stenosing tumors are mostly found in its left half. The majority (up to 75%) of colorectal cancer occur within the descending colon, sigmoid colon and rectum, 15% of cases are located in the cecum and ascending colon, and only 10% in the transverse colon (13, 14, 15). Adenocarcinoma accounts for more than 95% of colorectal cancer cases. The prognosis of the disease is associated with the depth of tumor invasion through the colonic wall, peripheral lymph node involvement and absence or presence of distant metastases. The Dukes staging system (Table 2) as used in clinical practice divides this cancer into three stages, depending on the depth of cancer invasion into the colorectal wall (16, 17).

DUKES A	- tumor confined within the colorectal wall
DUKES B	<ul style="list-style-type: none"> <li>- tumor invaded through the colorectal wall</li> <li>B1-tumor limited to muscular mucosa</li> <li>B2-tumor protruding in/through serosa</li> </ul>
DUKES C	- metastases to lymph nodes

Table 2. The Dukes staging system for colorectal cancer

### 2.3 Clinical signs and diagnostic procedures

The symptoms of colorectal carcinoma depend on the anatomical location and size of the tumor. The tumor located in the cecoascendent portion will not necessarily produce obstruction since in this portion the stool has a liquid consistency, and the colonic lumen is wider than in the other parts. Patients complain of weakness, subfebrile temperature and blunt pain in the right lower hemiabdomen, and their laboratory tests show a high sedimentation rate and sideropenic anemia (1, 13).

Tumors of the transverse colon and on the left side of the half usually invade the colonic wall in a ring-shaped pattern mainly producing symptoms of the obstructive nature (cramping pain after meal, meteorism, change in stool form, occasional sudden ileus development and even bowel perforation). Symptoms of tumors confined to the rectosigmoid portion are most often false and/or painful urge to defecate (tenesmus), narrow stool and hematochezia (13).

The patient with suspicion of colorectal cancer should undergo a complete physical examination which must include digital rectal examination. In a large number of patients, the digital rectal examination already shows a hard lump inside the rectum, bleeding on touch. Colonoscopy is a procedure for visualizing colonic mucosa and obtaining samples for pathohistological analysis. Colonoscopy is the gold standard for detecting colorectal cancer. If for technical difficulties colonoscopy cannot be done, double-contrast irrigography may be considered although only 70-80% of lesions are detected by this method. Virtual colonoscopy and MR colonoscopy are also more and more often used. These radiology techniques use high-speed spiral CT and magnetic resonance imaging, and sophisticated software to process endoluminal images of the air-filled colon. Diagnostic techniques show a sensitivity of about 90% for tumors larger than 10 mm. Disadvantage is an inability to take biopsy samples and perform interventions available during colonoscopy. 'Colon capsule' for minutely detailed inspection of the colonic mucosa is also being gradually introduced, although this technique has the same disadvantage as the above mentioned techniques, and that is its inability to obtain biopsy samples (1, 13). Endoscopic ultrasound of the lower digestive tract is capable of providing assessment of tumor invasion into muscles and adjacent structures, as well as assessment of regional lymph node enlargement. The technique is employed to determine the extent of the spread of rectal tumors. Diagnosis of the spread of the disease involves imaging techniques (US, CT/MSCT/MRI of the abdomen and small pelvis, and CT/MSCT of the thorax). Serum CEA has limitations in sensitivity and specificity but was recommended for detection of recurrence. Molecular detection of tumor cells in circulation may prove to be more sensitive and specific than CEA (13, 18).

### 2.4 Treatment

Treatment for colorectal cancer depends on the extent of cancer spread. Surgery is the method of choice for treatment of localized tumors. Colon resection surgery for colorectal cancer must be as radical as possible. Chemotherapy, immunotherapy and radiotherapy used may be adjuvant, neo-adjuvant, curative or palliative in nature. Adjuvant chemotherapy aims to destroy micrometastases following surgery, and neo-adjuvant chemotherapy is aimed at reducing the tumor mass to allow surgery for either the primary tumor or distant metastases (usually to the liver or lungs) (1, 13). Systemic therapy for disseminated disease has been gaining popularity over the past few years. Treatment options for colorectal cancer include a variety of chemotherapy and immunotherapy

regimens, with 5-fluorouracil/leucovorin, which may be added irinotecan and/or oxaliplatin, and bevacizumab, cetuximab and panitumumab as biological therapy, still remaining the mainstay for the management of patients with disseminated disease (3). The addition of this molecularly targeted therapy to standard chemotherapy improves treatment response, prolongs both the time to disease progression and eventually, median survival for disseminated or metastatic colorectal cancer, which currently is over 30 months (3, 19). In the future, prognostic and predictive factors will allow individual identification of patients who may benefit most from adjuvant chemotherapy, and which therapy should be used for the treatment of disseminated disease (personalized medicine). Therapy of rectal cancer includes adjuvant chemotherapy combined with radiation therapy (19).

Despite huge advances in diagnostic and surgery and despite global and national programs of prevention, about 50% of colorectal carcinomas are diagnosed in advanced stage (11). Advanced disease is largely refractory to conventional therapy and 5 years survival is still poor. Patients with advanced disease suffer from many stress symptoms (pain, vomiting, diarrhea, anorexia-cachexia syndrome, and etc.) and the therapeutic goal for them is maintenance of quality of life (QoL) (13). Many of those symptoms have implications for diagnostic and therapeutic procedures and can heavily disturb the process of chemo-immunotherapy and radiotherapy (3).

### **3. Anorexia-cachexia syndrome**

#### **3.1 Pathophysiology of anorexia-cachexia syndrome**

Anorexia is defined as an unintentional reduction in food intake and anticipated cachexia. Cachexia develops as a result of progressive wasting of skeletal muscle mass and to a lesser extent adipose tissue (20). In cachexia, progressive wasting of skeletal muscle mass is replaced with adipose tissue and this occurs even before weight loss. Anorexia-cachexia syndrome is highly prevalent among patients with malignant diseases. Depending on primary tumor site anorexia-cachexia syndrome is present in 8-88% of cancer patients. Tumors of head and neck, stomach and pancreas have highest percentage of cachexia (21). At the time of diagnosis weight loss is present in about 50% of patients. Weight loss is independent predictive factor of survival (21). Cachexia-anorexia syndrome includes clinical features which are associated with growth of cancer. In addition, it has a large impact on morbidity, mortality and on patients' quality of life. Cancer cachexia develops in a majority of patients with advanced disease (22) (70 %) and directly causes death in 20% of cancer patients. Clinical signs of cancer cachexia are anorexia and weight loss. Abnormalities in carbohydrates, fat, protein and energy metabolism are clinically manifested as weakness, fatigue, malaise, loss of skeletal muscle and adipose tissue. In serum chemistry and haematology tests we can find anaemia, hypertriglyceridaemia, hypoproteinaemia with low albumines, hyperlactacidaemia and glucose intolerance (insulin resistance) (23). Metabolic aberration in cancer cells and cells and microenvironment (inadequate energy intake, increased energy expenditure, mucositis, nausea, vomiting, change in taste or psychological problems as reaction to cancer disease) cause primary cancer cachexia. There are several conditions that can contribute decreased food intake (gastrointestinal obstruction, post-chemotherapy nausea and vomiting, pain and etc) and cause secondary cancer cachexia (24, 25). Anorexia-cachexia syndrome often occurs or worsens after the administration of chemotherapy. Chemotherapeutic agents are toxic to malignant tissue, and also to the quickly proliferating cells. This group of cells also includes cells of the gastrointestinal

mucosa. Consequently, the absorption of nutrients is reduced. Some chemotherapeutics may affect the digestive system causing severe nausea, vomiting, abdominal pain, stomatitis and aversion to food. It should be noted that, in addition to the above mechanism for development of this syndrome, some chemotherapeutic agents also affect the taste buds of the tongue resulting in a changed and reduced sense of taste. It may also lead to reduced saliva production (26).

Sometimes we cannot find a reason for anorexia and weight loss may be unrelated to nutritional intake. In this cases weight loss is reflection of elevated resting energy expenditures and over expression of pro-inflammatory cytokines (27). The most common factors to stimulate the production of proinflammatory cytokines include: TNF-alpha, interleukins, interferon gamma and leukemia inhibitory factor. It should be noted that, due to such complex mechanism, energy supplementation in cachectic patients does not result in an increased body mass index (28).

The pathophysiologic mechanism is correlated with the production of catabolic factors either by the tumor or via factors produced by the host. Cancer cachexia differ from starvation. It is an unquestionable fact today that cancer cachexia is pro-inflammatory condition. The pathophysiology of cachexia involves very complex pathways; cachexia is caused with numerous metabolic changes mediated with pro-inflammatory cytokines. The most known mediators are tumor necrosis factor  $\alpha$ , interleukin-1 (IL-1), interleukin 6 (IL-6), interferon- $\gamma$  (from patients mononuclears) and molecules from tumor cells as lipid mobilisation factor (LMF) and proteolysis inducing factor (PIF). PIF is stimulating adenosine-triphosphate ubiquitin proteolytic pathway that is important in degradation of muscle mass and its stimulating synthesis of C-reactive protein (28, 29).

The result of these changes is impairment of immune functions, quality of life, and performance status. The worst consequence is inability of patient to endure chemo, immunotherapy and radiotherapy. Cachexia decreases response to therapy due to frequent toxicity and severe complications, what leads to shortened survival time (3, 20).

### 3.2 Nutritional support

Although increasing nutritional intake is insufficient to prevent the development of cachexia, nutritional support (taking into account the specific needs of the patient group), is required to reduce the consequences of nutritional decline and to improve quality of life and possibility to support the anticancer therapy (30). However, data from published studies are divided; some studies suggest that aggressive nutritional support can improve response to the antitumor treatment and decrease complications, but some deny any impact of nutritional support on tumor response, chemotherapy toxicity and survival (3, 30). Aggressive nutritional therapy does not significantly influence the outcome of patients with advanced cancer; „super“nutrition alone cannot reverse cachexia. But its use is still warranted because the patients QoL is significantly improved (3). The pharmacological treatments of cachexia antagonize the main symptoms (anorexia and chronic nausea) and improve the muscle metabolism. A significant number of studies (many uncontrolled) have suggested that anorexia and asthenia can be alleviated in cancer patient under corticosteroid treatment; also, the feeling of well-being is observed (31).

We must not underestimate advantage of nutritional treatment in improvement of asthenia and patients body image. Oral nutrition (after nutritional counseling) is ideal for cancer patients with a functional bowel. Enteral nutrition is useful in patients with advanced head and neck cancers or esophageal and gastric cancer and the use of parenteral nutrition (due



to high costs and morbidity of 15%) with exception of high selected cases has no major role in care of cancer patients, especially in terminal disease (30, 31). In patients with colorectal cancer, enteral nutrition is usually provided by administration of food and/or commercial nutrient solutions and formulas (32). They either supplement daily diet or provide basic nutritional needs to patients who are unable to ingest sufficient amounts of food. The baseline requirements to administer such feeding include preserved swallowing function and the ability of the esophagus and stomach. There is a wide range of enteral nutrition formulas available for everyday use (33). Enteral nutrition formulas are classified into the following categories: monomeric (elementary) formulas, oligomeric formulas, polymeric formulas (32, 34, 35). The essential difference between them is in their size and/or the amount and type of molecules present. Accordingly, formulas containing a larger number of molecules that are also shorter at the same time, have a higher osmolality and can therefore cause side effects, such as diarrhea. The osmolality of an enteral formula depends on the type and amount of carbohydrates. Polysaccharides account for the vast majority of carbohydrate types present in the enteral feeding formulas. According to their solubility, fibers in the digestive system are divided into two categories: soluble and insoluble. Soluble fiber absorbs water in the intestinal lumen and increase the volume of the stool. They thus help regulate bowel motility. Soluble fibers are fermented by bowel bacteria using the aerobic pathway. Pectin slows down the emptying of the stomach and prolongs the passage of contents through the colon resulting in formation of the stool of satisfactory consistency even in tube fed patients (37). Normal metabolism requires daily protein intake of 0.8-1.0 g/kg body weight, and in the hypercatabolic state daily protein needs range from 1.2 to 1.6 g/kg body weight. According to the presence of nitrogen-containing compounds the diet may be divided into three groups: polymeric diet (includes natural proteins), oligomeric diet (includes small peptides), elementary diet (containing amino acids). Patients with the preserved gastrointestinal function require a diet in which complete proteins prevail (38). In case of compromised digestion, peptides should be the most represented. Among the amino acids, glutamine should be singled out. Glutamine helps maintain normal intestinal integrity by stimulating RNA, DNA and protein synthesis, resulting in an increase in the number and size of intestinal villi. Glutamine also prevents damage to intestinal permeability, preserves mucosal structure and prevents translocation of bacteria and toxins in the intestine. Glutamine is an important nutritional substrate for the intestinal cell line. In catabolic conditions including colorectal cancer, the intestinal system's requirements for glutamine are increased. The deficiency can be compensated for by addition of glutamine to the enteral nutrition formula (39). Arginine is another amino acid that plays a significant role in the immune events. It stimulates nitrogen oxide (NO) synthesis and the CD4/CD8 ratio, as well as the release of insulin, glucagon, prolactin and somatostatin (40, 41). The use of arginine requires caution as increased NO synthesis may accelerate the synthesis of proinflammatory cytokines and thereby cause a number of side effects. The main role of lipids in enteral formulas is to ensure large amounts of energy stored in relatively small volumes and sufficient amount of essential fatty acids which are a vital component of cell membranes and organelles. Corn oil and soybean oil used in enteral formulas provide long-chain triglycerides (LCT), while coconut and palm oil provide medium-chain triglycerides (MCT). These products have a favorable effect on: 1) growth, differentiation and function of lymphocytes, macrophages and granulocytes; 2) release of trophic hormones or growth factors; 3) function of NK cells; 4) IL-2 synthesis; 5) improvement of mesenteric blood flow;

6) reduction of skeletal and visceral muscle proteolysis; 7) prevention of bacterial translocation; 8) reduction in the frequency and severity of infectious complications and 9) shortening hospital stay (42). Fatty acids are thus formed providing a basic substrate for the colonic mucosa. Formulas containing omega-3 fatty acids from fish oil have been recently introduced. Omega-3 fatty acids reduce the synthesis of immunosuppressive and proinflammatory mediators. Meta-analyses of several studies have shown that immunomodulatory formulas do not significantly reduce mortality compared with standard enteral formulas. Their administration, however, achieves a lower rate of infection and septic complications, reduces dependency on assisted ventilation and shortens length of hospital treatment (43).

Omega-3 polyunsaturated fatty acid, eicosapentaenoic acid (EPA) can down-regulate the production of pro-inflammatory cytokines such as IL-6, IL-1 and TNF in patients with cancer and in healthy individuals. EPA can also inhibit the effects of proteolysis inducing factor (PIF). EPA normalizes metabolic pathways changed due to malignant disease and stabilize weight gain through the competitive metabolism with arachidonic acid. EPA metabolites have lower inflammatory and immunosuppressive effect versus arachidonic acid metabolites. Especially interestingly is inhibitory effect of EPA on pancreatic and colorectal cancer cell line growth observed „in vitro“ (44, 45). Wigmor and Bruera, like many other investigators, showed that EPA can stabilize body weight in cancer patients (46). We investigated if dietary counseling and oral nutrition supplement during chemotherapy affected nutritional status and symptom prevalence in our first study on 388 patients with colorectal cancer receiving chemotherapy for advanced disease (FOLFIRI/XELIRI/FOLFOX) (47, 48).

Megestrol acetate is a type of medicine that comes in suspension form recommended in treatment guidelines for appetite and body weight loss in patients with malignant diseases. The drug belongs to a group of steroid hormones - progesterone. Its empirical formula is  $C_{24}H_{32}O_4$ . Progestational derivate megestrol acetate has been evaluated in many studies; conclusion is that megestrol acetate significantly increases appetite, caloric intake and nutritional status with mild side effects as edema and hypercalcaemia. It is not completely clear through which mechanisms megestrol is acting. It is assumed that megestrol acetate changes the cytokines which are inhibiting TNF effects. Stimulation of appetite is due to stimulation neuropeptide Y in lateral hypothalamus. Megestrol acetate enhances appetite and increases food intake, enables the administration of specific treatments, and improves both patient treatment tolerance and their quality of life. Implementation of megestrol acetate in nutritional support plan is necessary; according to the highlights of the 2004 Cachexia Cancer Conference anorexia preceding to weight loss and orexigenics are necessary even when weight loss is absent. Furthermore, patients with cancer cachexia do not react on isolated over caloric food intake. Mild side effects (edema) are not enough pronounced over the social benefits caused by appetite stimulation; patients do not withdraw megestrol acetate therapy (49). Therefore, the International Association for Hospice and Palliative Care, NCCN Guidellines and European Palliative Care Research Collaborative Group recommend megestrol acetate as a mandatory drug for treatment cancer cachexia (50). The recommended starting dose is 400 mg (10 ml) once a day. The dose may be increased up to 800 mg (20 ml) / day. The most common side effects of megestrol acetate include edemas, insomnia, impaired libido, and very rarely thromboembolic complications (48, 50).

The choice of enteral route depends on the underlying pathology, anticipated duration of enteral feeding and patient's preferences (30). In addition to the oral route of nutrition administration the transnasal route can also be considered. Indications for transnasal tube feeding include conditions or illnesses where normal feeding cannot be provided, and where the gastrointestinal tract maintains its function. For this purpose, nasogastric, nasoduodenal and nasojejunal types of tubes may be used. The tubes are usually placed 'blindly', however they may be placed by radiological and endoscopic means. The tubes are used when it is anticipated that tube feeding will be needed for up to 4 weeks. If enteral feeding is likely to be needed for more than 4 weeks, percutaneous endoscopic gastrostomy tubes or percutaneous endoscopic jejunostomies may be placed via an endoscopic access. The surgical placement of the gastrostomy or jejunostomy tube may also be taken into consideration. Two types of feeding can be used for patients requiring tube feeding: bolus (6 to 10 doses a day, each ranging from 50 to 200 ml, given over 5 to 30 minutes) or continuous feeding (20 to 150 ml per hour during 16-18 hours). The method of 'bolus feeding' is more frequently reported to cause side effects than continuous feedings (30, 35).

In some clinical situations, enteral feeding may be unsafe or contraindicated. Reasons for postponing enteral nutrition administration are as follows: persistent nausea/vomiting, intensive postprandial pain, diarrhea, mechanical obstruction, diminished bowel motility, malabsorption, gastrointestinal bleeding. In mentioned situations, parenteral feeding is used. Parenteral feeding may be administered by peripheral or central vein access. Risk-benefit assessment of parenteral nutrition is necessary for each patient (30, 31, 35).

We can evaluate nutritional status of the cancer patient with quick screening methods (NRS-2002, NSTQ, ect) or more detailed examination (laboratory findings, anthropometric measurement, body composition measurement, BMI). Nottingham Screening Tool Questionnaire is simple, quick, and proper for re-evaluating. Another simple model (Fearon) is suggested for quick evaluation: if patient unintentionally decrease in weight gain more than 5% in 3 to 6 months, if caloric intake is less than 1500 kcal/day and C-reactive protein value is 10 and higher. Based on these data we can assume that cancer cachexia is developing (34, 35, 36, 43, 46, 50)

### 3.3 Study results

Our study was conducted at the Gastrointestinal Oncology Department, Clinic for Internal Medicine, University Hospital Center Rijeka, from January 2001 to December 2007. The aim of the study was to evaluate the effect of nutritional support in patients with colorectal cancer. The follow-up included 338 patients divided into two groups. Group I: patients receiving nutritional support (215 patients), and group II patients who did not receive nutritional support (173 patients); retrospectively collected data. Visit 0 took place one week before initiation of chemotherapy. The nutritional status was evaluated according to body weight change. The body mass index (BMI) was calculated for all patients and all patients were also evaluated through three questionnaires: Nottingham Screening Tool (Table 3), Appetite Loss Scale and Karnofsky Performance Status. The reassessments were done at control visits, each visit taking place before the next chemotherapy course. There were, in total, 12 visits performed. The aim of the study was to assess the effects of nutritional support in colorectal cancer patients on chemotherapy. For all patients, the following parameters were monitored and statistically evaluated: selection of nutritional support regimen in group I, BMI in groups I and II, at

visit 0 and visit 12, Nottingham Screening Tool Questionnaire in groups I and II, at visit 0 and visit 12, Appetite Loss Scale in groups I and II, at visit 0 and visit 1, Weight loss in groups I and II, at visit 0 and visit 12, Karnofsky Performance Status in groups I and II, at visit 0 and visit 12, side effects of megestrol acetate. Evaluating the initial risk measurement according to BMI, decrease in weight gain and NST, we did not find any significant difference between the two groups. We performed 12 visits in follow-up according to chemotherapy schedule. Before initiation of chemotherapy, we re-evaluated nutritional status of our patients using evaluation tools. After chemotherapy was completed, in group I (consisted of 215 patients who were monitored prospectively and were given nutritional support) we observed weight gain of 1.5 kg (0.6-2.8 kg) and appetite improvement, the most commonly seen result after 4 weeks of therapy with megestrol acetate. The appetite also improved on Appetite Loss Scale from 3.1 (pre-chemotherapy) to 4.7 (post-chemotherapy). But KPS did not change significantly (74.2% before chemo versus 80.4% after chemo respectively) reflecting the impact of the disease itself. The most common side effects in patients receiving enteral nutrition were diarrhea (12% of patients), abdominal pain (9%) and altered taste sensation (5%). The most frequently reported side effect in patients receiving megestrol acetate was the occurrence of edema (20% of patients).

This clinical study is ongoing and preliminary results from more than 600 patients are similar to this one.

BMI	Score
>20	0
18-20	1
<18	2

Has the patient unintentionally lost weight during last 3 months?	Score
No	0
A little, up to 3 kg	1
A lot, more than 3 kg	2

Table 3. Nottingham Screening Tool Questionnaire

Score: 0-2 Patient is not in nutritive risk and does not need nutritional support

3-4 Patient need re-evaluation weekly

≥ 5 Patient is in nutritive risk and needs nutritive support

#### 4. Discussion

Anorexia-cachexia syndrome often occurs in patients with gastrointestinal cancers. Malnutrition has huge impact on outcome in patients who underwent major surgical resections, and also in patients who have chemo/radiotherapy treatment (3, 22).

Although manifestations of chemotherapy injury on nutritional status is well-known, the potential role of nutritional supplementing is still not explored in detail. When treating cancer patients with chemotherapy we observed two problems and one of them is general failure in recognition of the weight loss early enough to perform nutritional support (30).

But if we know that patients will undergo to stress-full procedure which can have impact on his nutritional status (diagnostic procedures, colonoscopy for example, major gastrointestinal surgery) we have to give adequate nutritional support according to different clinical algorithms (3).

Adequate substitution with metabolites, increased caloric intake, inhibition of catabolic and inflammatory mediators leads to decrease of surgery, chemo and radiotherapy complications, but still has no significant impact on survival. Nutritional counseling, supplemental feeding and pharmacological support do temporarily stop weight loss and improve appetite, QoL and social life but this improvement has no implications on patient's KPS and course of their disease. An improved knowledge of the pathophysiology of cancer induced cachexia will lead to development of more effective treatments (26).

In clinical practice, the role of nutrition therapy is often assumed to be less important than role of chemo, immunotherapy and radiotherapy as outcomes are less clear in literature (22, 26, 30). Our study showed that early nutritional intervention can decrease course of weight deterioration in the early course or locally advanced or metastatic colorectal cancer. Karnofsky Performance Status did not change significantly, what we expected.

Taking food is not only a physiologic necessity, but also cultural and a social event reflecting life and religious philosophy. Nutritive support can facilitate life of oncology patients, their family support and caregivers understand (1). Therefore we have to recognize nutrition-related issues and to implement strategies that will lead to a better outcome for patient and his caregivers. In the end of the life the wish of dying patient is most important factor regarding enteral/parenteral nutrition. The interaction between major syndromes in terminal disease (pain, cachexia, cognitive failure) should be better established because it seems that severity of them has impact on the others. If we improve pain and depression we can expect impact on cachexia syndrome (3, 21).

## 5. Conclusion

The role of nutritional therapy in oncology patients has been neglected. This mainly results from failure to recognize malnutrition and untimely introduction of nutritional support.

Our study shows that early introduction of nutritional support can decrease weight loss and in some cases even enable weight gain in patients with locally advanced and metastatic colorectal cancer.

To achieve better treatment results for patients with colorectal cancer, nutritional therapy should be considered as a highly important part of their treatment and more attention should be paid to timely recognition of malnutrition and introduction of nutritional support. Patients with anorexia-cachexia syndrome should undergo to individualized nutritional intervention where nutrition counseling is base for improvement of nutritional status, quality of life and social life. Anorectic patients have changes in taste and smell and do not support high-fat food and therefore frequent but small meals are highly recommended (20).

### Future perspectives:

Cancer patients have increased level of growth hormone (GH), low serum concentrations of insulin growth factor-1 (IGF-1) and insulin resistance. Loss of lean mass and inflammatory processes are closely connected to the action of three signaling molecules: insulin, growth hormone and insulin growth factor-1 is essential (51). Basic stimuli of insulin, IGF-1 and GH does not provide response in muscle cells in cachexia, its reasonable to target post-receptor

pathways or using alternative pathways in muscle cells. A number of molecules exhibiting anti cytokines activity have been tested without significant clinical data (20). Ghrelin is a hormone that stimulates the release of GH and increases appetite. In a phase II clinical study, ghrelin agonist anamorelin produced an improvement in total body mass (52).

Despite cachexia is very common condition in cancers, there are still very few trials of drug therapies to reduce weight loss in cancer cachexia. Cachexia remains poorly studied and often undertreated condition that causes severe impairment of quality of life and increases mortality.

## 6. References

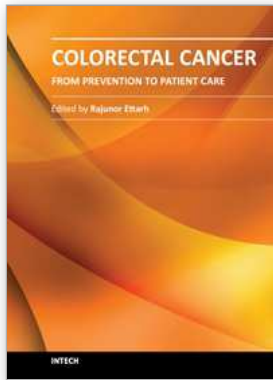
- [1] Brkić M, Grgić T. Kolorektalni karcinom. *Medicus* 15 (1): 89-97, 2006.
- [2] Heavey PM, McKenna D, Rowland IR. Colorectal cancer and the relationship between genes and the environment. *Nutr Cancer*, 48 (124), 2004.
- [3] Dobrila-Dintinjana R, Guina T, Krznarić Ž, Radić M, Dobrila M. Effects of Nutritional Support in Patients with Colorectal Cancer during Chemotherapy. *Collegium Antropologicum* 32: 737-740, 2008.
- [4] Markman B, Rodríguez-Freixinos V, Tabernero J. Biomarkers in colorectal cancer. *Clin Transl Oncol*. 2010;12:261-70.
- [5] Sobczak A, Wawrzyn-Sobczak K, Sobaniec-Lotowska M. [The colorectal carcinoma risk factors]. *Pol Merkuriusz Lek*, 19:808, 2005.
- [6] Gala M, Chung DC. Hereditary colon cancer syndromes. *Semin Oncol*. 2011;38:490-9.
- [7] Migliore L, Migheli F, Spisni R, Coppedè F. Genetics, cytogenetics, and epigenetics of colorectal cancer. *J Biomed Biotechnol*. 2011;2011:792362.
- [8] Hans F.A. Vasen, Patrice Watson, Jukka-Pekka Mecklin, Henry T. Lynch and the ICG-HNPCC. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology* 1999;116:1453-1456.
- [9] Billioud V, Allen PB, Peyrin-Biroulet L. Update on Crohn's disease and ulcerative colitis. *Expert Rev Gastroenterol Hepatol*. 2011;5:311-4.
- [10] Watson AJ, Collins PD. Colon cancer: a civilization disorder. *Dig Dis*. 2011;29:222-8.
- [11] Kujundžić M, Banić M, Bokun T. Epidemiologija kolorektalnog karcinoma. *Medix* 75/76: 70-76, 2008
- [12] Sung MK, Bae YJ. Linking obesity to colorectal cancer: application of nutrigenomics. *Biotechnol J*. 2010;5:930-41.
- [13] Wactawski-Wende J, Kotchen JM, Anderson GL. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N. Engl. J. Med*. 2006; **354** (7): 684-96.
- [14] Astin, M; Griffin, T, Neal, RD, Rose, P, Hamilton, W . The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2011;**61** (586): 231-43.
- [15] Cervera P, Fléjou JF. Changing pathology with changing drugs: tumors of the gastrointestinal tract. *Pathobiology*. 2011;78:76-89.

- [16] Kyriakos M: The President cancer, the Dukes classification, and confusion, *Arch Pathol Lab Med* 109:1063, 1985.
- [17] Dukes CE. The classification of cancer of the rectum. *Journal of Pathological Bacteriology* 1932;35:323.
- [18] Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. *Br J Gen Pract*. 2011;61:e231-43.
- [19] Orbell J, West NJ. Improving detection of colorectal cancer. *Practitioner*. 2010;254:17-21, 2-3.
- [20] Laviano A, Meguid MM, Inui A, Muscaritoli M, Rossi-Fanelli F. Therapy insight: Cancer anorexia-cachexia syndrome--when all you can eat is yourself. *Nat Clin Pract Oncol*. 2:158, 2005.
- [21] Penet MF, Winnard PT Jr, Jacobs MA, Bhujwala Understanding cancer-induced cachexia: imaging the flame and its fuel. *Curr Opin Support Palliat Care*. 2011.
- [22] Van Cutsem E, Arends The causes and consequences of cancer-associated malnutrition. *J. Eur J Oncol Nurs*, 9:51, 2005.
- [23] Bing C. Lipid Mobilization in cachexia: mechanisms and mediators. *Curr Opin Support Palliat Care*. 2011; 5(4):356-360.
- [24] Inui A. Nippon Ronen Igakkai Zasshi, [Pathogenesis and treatment of cancer anorexia-cachexia, with special emphasis on aged patients]. *Nihon Ronen Igakkai Zasshi*. 20;4:460-7.
- [25] Esper DH, Harb WA. The cancer cachexia syndrome: a review of metabolic and clinical manifestations. *Nutr Clin Pract*, 20:369.2005.
- [26] Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. *Eur J Oncol Nurs*. 2005;9 Suppl 2:S51-63.
- [27] Scheede-Bergdahl C, Watt HL, Trutschnigg B, Kilgour RD, Haggarty A, Lucar E, Vigano A Is IL-6 the best pro-inflammatory biomarker of clinical outcomes of cancer cachexia? *Clin Nutr*. 2011.
- [28] Ravasco P, Monteiro-Grillo I, Camilo M How relevant are cytokines in colorectal cancer wasting? *Cancer J*. 2007;13:392-8.
- [29] Shibata M, Nezu T, Kanou H, Abe H, Takekawa M, Fukuzawa M. Decreased production of interleukin-12 and type 2 immune responses are marked in cachectic patients with colorectal and gastric cancer. *J Clin Gastroenterol*. 2002;34:416-20.
- [30] Krznarić Ž: Klinička prehrana u gastroenterologiji. *Medicus* 15: 169-181, 2006.
- [31] Bozzetti F. Guidelines on Artificial Nutrition versus Hydration in terminal cancer patients. *Nutrition* 12:163-167, 1996.
- [32] Mirhosseini N, Fainsinger RL, Baracos V. Parenteral nutrition in advanced cancer: indications and clinical practice guidelines. *J Palliat Med*, 8:914. 2005.
- [33] Ries A, Trottenberg P, Elsner F, Stiel S, Haugen D, Kaasa S, Radbruch L. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: An EPCRC cachexia guidelines project. *Palliat Med*. 2011.
- [34] Ockenga J, Valentini L. Anorexia and cachexia in gastrointestinal cancer. *Aliment Pharmacol Ther*. 2005, 22(7):583-594.

- [35] Coss CC, Bohl CE, Dalton JT. *Curr Opin Clin Nutr Metab Care*. Cancer cachexia therapy: a key weapon in the fight against cancer. 2011 May;14:268-73 *Aliment Pharmacol Ther*. 22: 583. 2005.
- [36] Mattox TW, Treatment of unintentional weight loss in patients with cancer. *Nutr Clin Pract*, 20:400, 2005.
- [37] Klosterbuer A, Roughead ZF, Slavin J. Benefits of dietary fiber in clinical nutrition. *Nutr Clin Pract*. 201.26:625-35.
- [38] Blum D, Strasser F. Cachexia assessment tools. *Curr Opin Support Palliat Care*. 2011, 5(4):350-355.
- [39] Evans MA, Shronts EP. Intestinal fuels: glutamine, short-chain fatty acids, and dietary fiber. *J Am Diet Assoc*. 1992;92:1239-46,1249.
- [40] Jobgen WS, Fried SK, Fu WJ, Meininger CJ, Wu G. *J Nutr Biochem*. Regulatory role for the arginine-nitric oxide pathway in metabolism of energy substrates. 2006;17:571-88.
- [41] Parry RV, Ward SG. Protein arginine methylation: a new handle on T lymphocytes? *Trends Immunol*. 2010;31:164-9.
- [42] Swails WS, Kenler AS, Driscoll DF, DeMichele SJ, Babineau TJ, Utsunamiya T, Chavali S, Forse RA, Bistrrian BR. Effect of a fish oil structured lipid-based diet on prostaglandin release from mononuclear cells in cancer patients after surgery. *JPEN J Parenter Enteral Nutr*. 1997;21:266-74.
- [43] Mantovani G, Maccio A, Madeddu C, Gramignano G, Serpe R, Massa E, Dessi M, Tanca FM, Sanna E, Deiana L, Panzone F, Contu P, Floris C. Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. *Nutrition*, 24:305, 2008.
- [44] Calder PC. Immunomodulation by omega-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids*. 2007;77:327-35.
- [45] La Guardia M, Giammanco S, Di Majò D, Tabacchi G, Tripoli E, Giammanco M. Omega 3 fatty acids: biological activity and effects on human health. *Panminerva Med*. 2005;47:245-57.
- [46] Wigmore SJ, Ross JA, Falconer JS, Plester CE, Tisdale MJ, Carter DC, Fearon KC. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. *Nutrition*. 1996;12(1 Suppl):S27-30
- [47] Dintinjana RD, Guina T, Krznarić Z, Radić M, Dintinjana M. Effects of nutritional support in patients with colorectal cancer during chemotherapy. *Coll Antropol*. 2008 ; 32:737-40.
- [48] Krznarić Ž, Juretić A, Šamija M, Dintinjana-Dobrića R, Vrdoljak E, Samaržija M, Kolaček S, Vrbanec D, Prgomet D, Ivkić M, Zelić M. [Croatian guidelines for use of eicosapentaenoic acid and megestrol acetate in cancer cachexia syndrome]. *Lijec Vjesn*, 129:381, 2007.
- [49] Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, Rowland KM, Camoriano JK, Novotny PJ, Christensen BJ. Randomised Comparison of Megestrol Acetate Versus Dexamethasone Versus Fluoxymestron for the Treatment of Cancer Anorexia/Cachexia . *JCO* 1999(17);10:3299-3306.



- [50] Evans JW. Megestrol Acetate Use for Weight Gain should be Carefully Considered. *The Journal of Endocrinology and Metabolism* 2007(92);2:420-421.
- [51] Trobec K, Haehling S, Anker SD, Lainscak M. Growth hormone, insulin-like growth factor 1, and insulin signaling-a pharmacological target in body wasting and cachexia. *J Cachexia Sarcopenia Muscle* (2011) 2:191-200.
- [52] Coats AJS, Surendran J, Vangipuram SRKG, Jain M, Shah S, Irhfan ABH, Fuang HG, Hassan MZM, Beadle J, Tilson J, Kirwan AB, Anker SD. The ACT-ONE trial, a multicentre, randomized, double blind, placebo-controlled, dose-finding study of the anabolic/catabolic transforming agent, MT-102 in subjects with cachexia related to stage III and IV non-small cell lung cancer and colorectal cancer: study design. *J Cachexia Sarcopenia Muscle* (2011) 2:201-207.



## **Colorectal Cancer - From Prevention to Patient Care**

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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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