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Malnutrition induced by cancer and oncology treatment

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Abstract

Malnutrition as a consequence of the disease occurs most often in cancer patients, not only because of the cancer itself, but also because of the oncological treatment. The most important cause is chemotherapy, followed by radiotherapy and onco-surgery. Therefore, efforts are being made all over the world to find different ways to solve this difficult medical problem. Given that the mechanism of malnutrition caused by cancer is not sufficiently elucidated, the efforts made to design an adequate approach and treatment of this disorder are often unsuccessful. In order to improve the nutritional status of oncology patients, their nutritional disorder should be adequately diagnosed and then specific measurements should be performed (determination of body composition, the proportion of water, fat, muscle, as well as the determination of various biomarkers in the blood, for example markers inflammation). In this way, it is possible to formulate a multimodal approach to the treatment of malnutrition in oncology patients, which would include the intake of adequate foods, increased physical activity and personalized supplementation.

Keywords: *cancer; malnutrition; cachexia; chemotherapy.*

INTRODUCTION

Oncological treatment so as cancer disease causes cancer patients malnutrition, being the most frequent feature compared to any other patients. In the first line malnutrition cause is chemotherapy, but also radiotherapy and onco-surgery. Every fifth oncology patient's death can be ascribed to malnutrition rather than to the cancer itself. Cancer activates systemic inflammation and thus induces inflammatory response. These reactions lead to tissue deterioration and anorexia, which result in weight loss, energy reducing, and metabolic processes reduction. On the other hand, oncology treatment, especially chemotherapy, might have a lot of complications like nausea, vomiting, metal taste in mouth, impairment of food intake, pain which are very disrupting and affecting proper nutrition, decreasing energy, physical activity, protein, fat and carbohydrates needs, anabolic and catabolic processes [1]. Inadequate nutrition has a negative impact on treatment outcomes, including impaired response and tolerance to antineoplastic treatment, higher rates of postoperative complications, extended hospital stay, and possible reduced survival. Furthermore, it worsens muscle function which influences physical function and strength, thus impacting patients' quality of life. It is already proven, that nearly half of the study participants (healthcare professionals-oncologist) would wait for a weight loss of more than 15%, to begin with a treatment of cachexia, and in more than 60% of cancer patients' treatment of cachexia would be started in the IV stage of the disease [2].

Realizing the complexity of nutritional status of oncology patients, different investigators defined malnutrition as serious health disturbance, which is a rather multimodal process. As a result of systemic efforts to combat malnutrition consequences several organizations (American Society for Clinical Nutrition and Metabolism (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN)) are working on development of nutritional guidelines. The practical guideline (which will be presented in following article) provides a set of recommendations for screening, assessment, treatment, and monitoring of malnutrition in cancer patients and it is intended for all professionals working with cancer patients, including physicians, nutritionists, and nurses [3].

MALNUTRITION-RELATED TERMS

There are few malnutrition-related definitions. All of them overlaps each other, regarding definition and/or patients related condition.

Disease-related malnutrition has been defined as a condition that results from the activation of systemic inflammation by an underlying disease such as cancer. The inflammatory response causes anorexia and tissue breakdown that can, in turn, result in significant loss of body weight, alterations in body composition, and declining physical function [4].

Cachexia is a multifactorial wasting syndrome characterized by involuntary weight loss greater than 5% with ongoing loss of skeletal muscle mass with or without loss of fat mass; such wasting cannot be reversed by conventional nutrition care and may lead to functional impairment [5].

Cachexia can be detected in a lot of diseases, such as infections, chronic heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, multiple sclerosis, poisoning, hormonal deficiency, but cancer is the most related to cachexia. Fundament of this statement is systemic inflammation, protein imbalance, and reluctantly loss of body mass, with or without wasting of adipose tissue and skeletal mass [6].

Precachexia is a condition during which early clinical and metabolic signs precede extensive involuntary loss of weight and muscle. The risk for cachexia and its worsening depends on factors such as cancer type and stage, the extent of systemic inflammation, and the degree of response to anticancer therapy [7].

Sarcopenia is characterized by low lean body mass (mostly muscle); fatigue is common symptom, strength may be lessened, and general physical function is also limited. As functionality is lost, patients with cancer may no longer be able to live independently, and they often report lower quality of life [8].

Sarcopenic obesity is low lean body mass in obese individuals. In such patients, clinicians frequently overlook muscle loss due to the presence of excess fat and extracellular water [9].

MOLECULAR LEVEL OF MALNUTRITION

Tumor induces production of many proinflammatory cytokines, e.g. tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), interferon-gamma (INF-γ), C-reactive protein (CRP) and fibrinogen which causes systemic inflammatory response and several cachexia and anorexia related symptoms. These cytokines are delivered to the brain structures through blood-brain barrier and interact with endothelial brain cells which leads to appetite loss [10]. The metabolism of proteins, carbohydrates and fats is disrupted by these pro-inflammatory cytokines [11]. It results in many metabolic changes such as increased gluconeogenesis, proteolysis and lipolysis. Tumor-derived cytokines increase lipolysis and regulate loss of adipose tissue accelerating fat depots discharge and serious energy reserves decrease. Tumor-derived cytokines can cause neuroendocrine control of appetite and muscle wasting, resulting in fatigue and impaired physical activity [12].

All kinds of oncology treatments (chemo-, immune-, target-, radiotherapy, surgery) may impair cachexia. Cytokines induce acute-phase protein synthesis in liver, thus suppressing drug clearance pathways and further lead to the increased drug-related toxicity

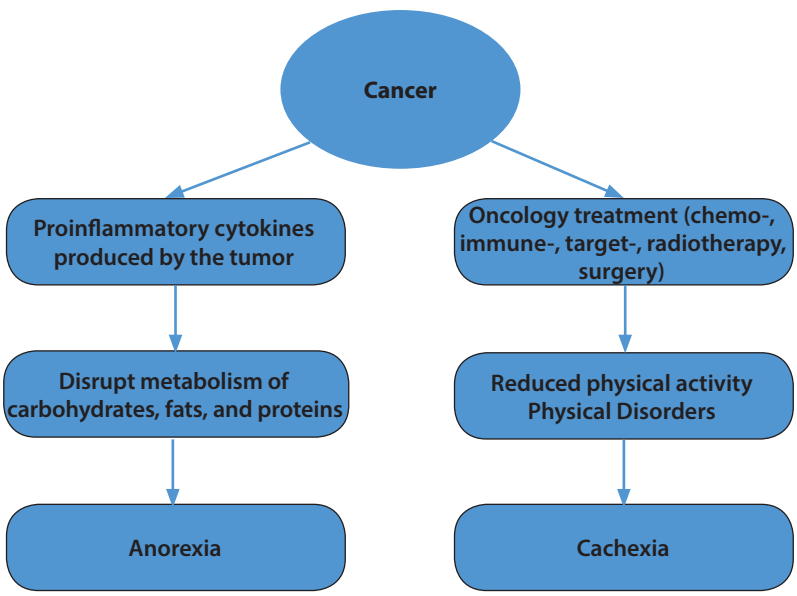

Figure 1. Pathway of cancer-related anorexia and cachexia.

risk. It is already showed that tyrosine kinase inhibitors (TKIs) have strong prooxidative effects, which are a part of their mechanism of action [13]. We could suppose that those oxidative stress connected intense and damaging reactions could additionally force cachexia development. **Figure 1** shows relationship between cancer, anorexia and cachexia.

MALNUTRITION SYMPTOMS

There are a lot of symptoms evolving as a disease consequence, local tumor development like infiltration or obstruction which result in cachexia and food intake aggravation. Many symptoms develop after oncology treatment (especially chemotherapy, but also radiation therapy, surgery, target and immunotherapy). The most frequent malnutrition symptoms include dry mouth or mouth ulcers, chewing difficulties, thick saliva, dysphagia, abdominal pain, nausea, vomiting, constipation or diarrhea, pain and fatigue, tiredness, depression, always feeling, cold sensation, wound healing difficulties [14].

ONCOLOGY PATIENTS' OVERALL HEALTH CONDITION ASSESSMENT

It is important to assess physical, nutritional, metabolic and general systemic patients' conditions in order to find the best method for malnutrition combat. Physical evaluation should include anthropometric parameters (body weight, body mass index (BMI), body surface (BSA), physical examination, performance status (PS), assessment of muscle mass by using bioelectrical impedance computed tomography analysis, X-ray absorptiometry), food barriers estimation (mucositis, anorexia, nausea, dysphagia, gastrointestinal problems, pain), dietary assessment (food diary, dietary recalls, currently intake, food preferences), metabolic status (blood biomarkers measurement: CRP, protein, albumin, cholesterol, triglycerides, glycaemia) [15].

NUTRITIONAL ASSESSMENT AND DIAGNOSIS OF MALNUTRITION

It is very important to screen and make extensive assessment of nutritional status of all oncology patients. Screening of nutritional status should be as important as evaluating oncology treatment. The diagnosis of malnutrition could be based on certain phenotypic criteria (decreased BMI, unintentional weight loss, and decreased muscle mass) and etiological criteria (reduced food intake or assimilation, and disease burden or inflammation) where at least one criteria from both categories must be present. Several validated nutritional screening tools are available with high predictive value, sensitivity, and specificity in the oncology setting [16].

First malnutrition parameter, suggested by clinical guidelines is assessing body weight changes in period 3–6 months, then BMI, nutritional and eating habits analysis [17]. There are several scoring systems which could help in cancer-related cachexia screening. Cachexia Score (CASCO) includes five parameters: body weight loss and composition, inflammation/metabolic disturbances/immunosuppression, physical performance, anorexia, and Quality of Life (QOL) [18]. The other scoring system, cachexia staging score (CSS) is consisted of five parameters divided in three-level staging systems [17] and is presented in **Table 1**.

Table 1. Cachexia Staging Score (CSS).

Cachexia Staging Score (CSS)			
	Parameters	Score range	Level
I	Weight loss in the last 6 months	0–3	Non-cachexia (score 0–2) Pre-cachexia (score 3–4) Cachexia (score 5–8) Refractory cachexia (score 9–12)
II	A simple SARC-F questionnaire assessing muscle function and sarcopenia	0–3	
III	ECOG performance status	0–3	
IV	Appetite loss	0–2	
V	Abnormal biochemistry	0–2	

The CSS is important because it can distinguish different stages of cachexia according to patient-related outcomes, including body composition, symptom burden, QoL and overall status [17].

The European Society of Clinical Nutrition and Metabolism, in 2017 has published evidence-based guidelines for nutritional care and recommended three terms: 1. All oncology patients should be screened for early nutritional risk early regardless of BMI and previous weight records, 2. Extend nutritional assessment so they reconcile measures of anorexia, body composition, inflammatory biomarkers, resting energy expenditure (REE) and physical function, 3. Using nutritional individualized plans, focusing on increasing nutritional intake, physical activity, lowering inflammation and catabolic distress [17, 19].

There are few QOL scales specific for cancer patients with cachexia. The functional assessment of anorexia-cachexia therapy (FAACT) scale consists of the functional assessment of cancer therapy general (FACT-G) scale and the anorexia-cachexia subscale

(ACS) [16]. FAACT scale includes five subscales: 7 items for physical well-being, 6 items for emotional well-being, 7 items for social well-being, 7 items for functional well-being, and 12 items for ACS with each item rated as a five-level scoring system (0 – 4 points) with a higher sum of all 39-item score equating with a better QOL [20].

There are designed heterogeneous questionnaires and tests in order to reveal malnutrition risk. All those questionnaires should be controlled by validated tests such as the Malnutrition Universal Screening Tool (MUST) (https://www.bapen.org.uk/screening-and-must/mustcalculator), Malnutrition Screening Tool for Cancer Patients, Malnutrition Screening Tool for Cancer Patients (MSTC) and Global Leadership Initiative on Malnutrition (GLIM) [15].

The MUST is frequently used malnutrition screening tool, recognized as very useful for intensive care unit, cancer and chronic diseases patients. MUST malnutrition estimation relies on BMI, weight loss (expressed in %) in the previous 3 – 6 months of acute illnesses burden. The score ranges from 0 to 6, with 0 = low risk, 1 = medium risk and ≥ 2 high risk. Higher MUST score is associated with worse clinical outcomes for oncology patients [21]. Almasaudi et al. concluded that MUST score is important for colorectal cancer patients undergoing surgery because it was independently related to the patients' length of stay and decreased survival. According to previous experience with this scoring system, it is suggested that MUST should be evaluated by healthcare professionals [22].

The PG-SGA scoring system includes four patient-generated historical components (weight history, food intake, symptoms and activities and function), clinical part data (diagnosis, age, metabolic stress, and physical exam), the global assessment of nourishment status (A = well nourished, B = moderately malnourished or suspected malnutrition, C = severely malnourished), the total numerical score, and nutritional triage recommendations. This score allows triaging of specific nutrition interventions, as well as facilitating quantitative outcomes data collection [23].

Mini Nutritional Assessment (MNA) is a 5-10 minute screening nutritional tool for elderly patients. The MNA is recording BMI, mid-arm circumference, nutritional risk factors, diet history, and any acute and chronic illness, psychological disorder and cognitive capability with drugs associated with malnutrition risk. The MNA score categorizes elderly patients with risk for malnutrition and presence of protein-calorie malnutrition [24].

LABORATORY BIOMARKERS

Measuring specific biomarkers like CRP, albumin and prealbumin are useful for checking severity of acute inflammations, infections, acute, chronic diseases and malignancies. Higher values of neutrophil/lymphocyte ratio, CRP (> 10 mg/L), lower values of albumin (< 30 g/L) and prealbumin (< 110 mg/L) are related to malnutrition and cachexia. Two scores have been incorporated in laboratory scoring assessments, Prognostic Inflammation Nutrition Index (PINI) [25] and the Nutritional Risk Index (NRI) [26]. The formulas for two scores are given below:

- PINI = [CRP (mg/L) × α1-acid glycoprotein]/[albumin (g/L) × transthyretin (g/L)];
- NRI = $1.519 \times \text{albumin}\,(\text{g/L}) + 0.417 \times$ (current weight/usual weight × 100)

Modified Glasgow Prognostic Score also could be used, as already reported this score shows significant correlation with malnutrition, weight loss, oncology treatment failure and level of treatment-caused toxicity [27].

Baracos et al. concluded that cytokines produced in an acute phase response (IL-6, IL-1b, tumor necrosis factor-a, IL-8, interferon-γ) are not as valuable biomarkers for weight loss in cancer patients as CRP [28]. Takahach et al. revealed that leptin may have impact in cachectic cancer patients, while ghrelin has negative so as positive trials, regarding its relationship with weight loss [29].

NUTRIENTS INTAKE

Macronutrients and micronutrients should be represented in adequate amounts regarding total daily energy intake in each patient. It is preferable to advise less processed and more fresh foods if possible, taking into account the health status of each patient. Every patient has specific macronutrients needs, which is especially true for oncology patients. Planning healthy, nutrients reach diet should be conducted with respect of patient's gender, age, BMI and the level of physical activity [30].

BMI is frequently used as a reliable indicator of nutrition. Estimates for daily caloric intake range from 1600 to 2400 calories per day for adult women and 2000 up to 3000 calories a day for adult men. Daily caloric needs are lower for people with sedentary lifestyles, and higher for the subjects who are more physically active. Healthy model of eating must include fruits, vegetables, cereals, oils, low-fat or no fat dairy products, proteins [31].

NUTRITION SUPPORT

A general nutritional advice is to achieve energy and nutrient balance based on the patient's lifestyle, disease state, current food intake, and food preferences. In achieving nutritional goals, it is important to involve also physicians who estimate severity of nausea, diarrhea, dysphagia, abdominal bloating or cramping and

constipation [30]. Physicians and nutritionists are able to motivate and convey patient to accept and follow nutritional recommendations. The main nutritional strategy is to decrease adverse inflammatory and catabolic effects related to cancer. Patients should be encouraged to take the food spontaneously. If energy requirements are not fulfilled by regular food intake, it should be advised the use of oral nutritional supplements, enteral nutrition (for those patients with higher nutritional risk), and parenteral nutrition (for patients with partially or totally impaired gastrointestinal function) [32]. In order to maintain a stable nutritional status, dietary patterns must be adjusted to daily energy needs of individuals, total energy expenditure (TEE), which makes a sum of energy required for basal metabolism, resting energy expenditure (REE), physical activity and a small percentage of the energy released in the body from food in the form of heat. There is no evidence that a proper and balanced diet encourages the growth of tumor cells, so it should be no reason for refusal or cessation of any nutritionally rich and healthy type of food [33]. Daily energy needs need to be individualized taking into account TEE values (25-30 kcal/kg/day) and also initial body weight of the patient. It should be considered that TEE is not an ideal energy need estimation, because it overestimates energy needs of obese people while underestimating the needs of severely malnourished people [34].

RECOMMENDATIONS

Protein intake should be higher than 1 g/kg/day and, if possible up to 1.5 g/kg/day. Fats should cover 30-50% of TEE. Current recommendations regarding carbohydrates strictly suggest additional sugar avoidance. Vitamins and minerals should be supplied in amounts approximately equal to the recommended daily allowance, and the use of high-dose micronutrients should be discouraged in the absence of specific deficiencies [17]. Energy and protein-rich food and fluids intake is the preferred way to maintain or improvement of nutritional status. Oral nutritional supplementation should be considered when an enriched diet (fortified foods, additional snacks) does not reach nutritional target. All patients with chronic insufficient dietary intake and/or uncontrolled malabsorption who are unable to eat, digest or absorb food should take enteral and parenteral nutrition. If oral food intake has been decreased severely for a prolonged period, food intake (oral, enteral, or parenteral) should be increased slowly over several days (precautions are needed to prevent feeding syndrome) [17, 35]. Electrolytes (sodium, potassium, phosphate and magnesium) should be monitored, and, if necessary, substituted. Before and during nutritional repletion supply of vitamin B1 in daily doses of 200 – 300 mg as well as a balanced micronutrient mixture should be considered. Use of food supplements with long-chain n-3 fatty acids or fish oil in dosages up to 2 g/day seems safe to maintain and ameliorate appetite and weight gain [36]. Physical activity especially aerobic and yoga exercises increase muscle mass, physical motility and metabolic performance. Exercise if possible should be supervised or home-based on moderate-intensity endurance and aerobic training (3 sessions per week, for 10 – 60 min per session). Another option is to motivate patients to take a daily walk [17].

ROLE OF FOOD SUPPLEMENTS AND PHARMACOLOGY TREATMENT IN MANAGEMENT OF CANCER-RELATED MALNUTRITION

Eicosapentaenoic acid (EPA) is one of several omega-3 polyunsaturated fatty acids found abundantly in fish oil. Omega-3 fatty acids are reducing cachexia-associated tissue wasting [37] and tumor growth [38]. EPA regulates the production of pro-inflammatory cytokines and proteolysis cancer-inducing factor. Colomer et al [39] have concluded that 8 weeks of EPA treatment upgrade biochemical, clinical and quality of life parameters related to cancer cachexia syndrome.

Corticosteroids are among the most widely used appetite stimulants [40]. Megestrol acetate (MEGACE) and corticosteroids seem equally effective, although for long-term use, corticosteroids result in more serious adverse effects such as protein breakdown, insulin resistance, water retention, and adrenal suppression. Therefore, corticosteroids are not suitable for long-term use and should be used in a limited fashion, such as during the preterminal phase of cachexia [41].

MEGACE

MEGACE and medroxyprogesterone (MPA) are synthetic, orally active progesterone derivatives. MEGACE has been found to improve appetite, caloric intake and nutritional status of patients in several clinical trials. MPA has similarly been shown to increase appetite and food intake with a stabilization of body weight in patients with cancer anorexia and cachexia. MPA reduces the *in vitro* production of serotonin and cytokines (IL-1, IL-6 and TNF-α) by peripheral blood mononuclear cells of cancer patients. These findings have also been replicated in the clinical setting, with IL-1, IL-6, and TNF-α levels in serum reported to be decreased in cancer patients after MEGACE or MPA treatment [42].

MICRONUTRIENTS

There are several micronutrients, like vitamins A, B, C, D, E, zinc, selenium – important nutritional sources of antioxidants, also there are omega-3 fat acids: eicosa-

pentaenoic (EPA) and docosahexaenoic (DHA). EPA and DHA with their anti-inflammatory and antioxidant properties are confirmed as effective nutraceuticals in many acute and chronic diseases with elevated inflammation. Also, EPA and DHA are potent immune cells modulators (macrophages, neutrophils, natural killer cells) and could activate antigen-specific responses generating antibodies and long-term protection specific to repeated infection or tumor [43, 44].

European Food Safety Authority (EFSA) defines food supplements as "concentrated sources of nutrients (i.e. minerals and vitamins) or other substances with a nutritional or physiological effect that is marketed in "dose" form (e.g. pills, tablets, capsules and liquids in measured doses)" [45]. There are also various combined preparations that can contain both vitamins and minerals (vitamins A, C, E, minerals selenium and zinc) with established antioxidant effects [43]. Considering the biological mechanism of antioxidants, they seem like an adequate choice effect through the production of reactive oxygen species (ROS) and stimulating apoptosis, antioxidants may reduce the effectiveness of such therapy. Food supplements are a category of food intended to supplement for the fight against chemo/radiotherapy side effects, capable to reduce oxidative stress, proliferation, angiogenesis and to induce apoptosis. On the other side, radiotherapy and many chemotherapeutics achieve it's a regular diet to improve nutritional deficit or sustain an adequate intake of necessary nutrients, but should not be used as a food replacement.

Vitamin D is endogenously synthesized in the skin under the influence of ultraviolet radiation. The most important source of vitamin D is endogenous synthesis and then food sources. Vitamin D deficiency is relatively frequent in cancer patients, most probably because of reduced sun exposure. Some chemotherapeutics can generate skin changes due to nonspecific inhibitions of keratinocyte proliferative activity (e.g. irritation, dryness, pruritus), therefore, direct sun exposure is not recommended during chemo-/radiotherapy [34,42,46]. Sun protection measures (protective cream, protective clothes) are also needed in the shade. Although vitamin D deficiency is common in oncology patients, it is not completely clear whether vitamin D supplementation will improve the cancer patients' prognosis. Some studies have shown that vitamin D has poor antitumor activity, but also potential toxicity when taking high doses of calcitriol and its derivatives, therefore the use of such supplements should be strictly controlled. Accepted dosage of 10 μg (400 IU) of vitamin D3 should be taken daily in autumn and winter, when synthesis in the skin is additionally reduced. Doses of 25 and 50 μg/day (1000 and 2000 IU/day) are indicated if there is laboratory confirmed deficiency, and it can be accomplished with supplements. The safe upper level (SUL) of intake for vitamin D was revised to 100 μg (4000 IU) by EFSA in 2012 [47].

CONCLUSIONS

Chemotherapy, radiotherapy, or a combination of these two the most common anti-cancer therapy, significantly affects the risk of malnutrition primarily due to possible side effects caused by non-selectivity of the therapy. Side effects caused by this kind of therapy vary significantly from person to person. Malnutrition increases the risk of infection and hospitalization and has a negative impact on treatment response, quality of life, and mortality in cancer patients. Therefore, nutritional screening and assessment should be performed early in the course of the disease, and nutritional intervention, if it is indicated, should be performed in parallel with cancer therapies. The energy and nutrient requirements should be met by an optimal balanced diet and patients with inadequate food intake should receive dietary counseling as well as advice for use of fortified food and oral nutritional supplements. If oral nutrition remains inadequate because of impaired oral intake or food digestion, medical nutrition (enteral and parenteral nutrition) is indicated. Supplementation of vitamins and minerals in doses close to recommended daily amount is considered safe and beneficial during chemo and radiotherapy, but the intake of micronutrients in high doses should be avoided, unless a deficit is proven. Adverse effects have been reported for the use of antioxidant supplements, but not for high antioxidant intake through food, therefore the intake of antioxidants through the food should be always recommended. The use of supplements containing omega 3 fatty acids in doses per day up to 2 grams is considered to be safe and can be recommended for malnourished patients to improve appetite and gain body weight. Although vitamin D deficiency is commonly observed in cancer patients, there are no sufficient clinical data to support vitamin D supplementation in cancer patients. In the end, to improve muscle mass and function in cancer patients, controlled physical activity including endurance training and aerobic exercise should be recommended, taking into account general patients' performance.

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Malnutricija uzrokovana karcinomom i onkološkom terapijom

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Kratak sadržaj

Pothranjenost kao posledica bolesti se najčešće javlja kod onkoloških pacijenata i to ne samo zbog samog kancera, već i zbog onkološkog lečenja. Najznačajniji uzročnik je hemioterapija, potom radioterapija i onko-hirurgija. Zbog toga se širom sveta ulažu napori i pronalaze različiti načini za rešavanje ovog teškog medicinskog problema. S obzirom na to da mehanizam nastanka pothranjenosti uzrokovane karcinomom nije dovoljno rasvetljen, napori koji se ulažu da se osmisli adekvatan pristup i tretman ovog poremećaja se često neuspešno završe. Da bi se nutritivni status onkoloških pacijenata popravio njima pre svega treba da bude dijagnostikovan nutritivni poremećaj, a zatim da se sprovedu specifična merenja (određivanje sastava tela, udeo vode, masti, mišića, kao i da se u krvi odrede različiti biomarkeri, na primer markeri zapaljenja). Na taj način je moguće formulisati multimodalni pristup u lečenju pothranjenosti onkoloških bolesnika koji bi obuhvatio unos adekvatnih namirnica, povećanje fizičke aktivnosti i personalizovanu suplementaciju.

Ključne reči: *karcinom; malnutricija; kaheksija; hemioterapija.*