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REVIEW ARTICLE

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Nutritional therapy during the treatment of head and neck cancer

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ABSTRACT

Multimodality treatments for patients with squamous cell head and neck cancer often produce significant mucositis and dysphagia, resulting in severe weight loss that requires nutritional support. Continuously progressing malnutrition is associated with shorter time to the development of complications, with shorter overall survival (OS), worse response to oncological treatment, deteriorating quality of life, and poorer performance status; moreover, cachexia strongly affects treatment tolerance. This article provides an overview of the methods of nutritional support for patients undergoing treatments for head and neck cancer: surgery, radiochemotherapy, and palliative care. Nowadays, nutritional therapy is a mandatory part of head and neck cancer management.

Key words: head and neck cancer, radiochemotherapy, nutritional support, malnutrition, cachexia

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Introduction

Clinical nutrition is currently an irreplaceable cornerstone of oncological treatment in most malignancies. Just as we cannot imagine effective oncological therapy without proper pain treatment, nutritional support and protection of the nutrition route during treatment is the basis for management of head and neck cancers, but also of upper gastrointestinal tract, patients after major abdominal surgery, and patients during haematopoietic stem cell transplantation or several cancers of the genitourinary system.

Weight loss of > 10% over six months and/or BMI (body mass index) below 20 kg per square metre is diagnosed in up to 75% of patients with newly diagnosed malignant neoplasm of the head and neck region [1]. Cachexia is very often the main disease symptom and the reason to visit a doctor. Aggressive treatment methods for these cancers, both surgical treatment as well as chemoradiation or radiotherapy with cetuximab, are associated with a further deterioration of the nutritional status due to the severity of dysphagia. The positive effect of nutritional treatment on many aspects of oncological treatment is mainly achieved through the prevention and treatment of cancer-related cachexia and dysphagia. The presence of cachexia before treatment is associated with shorter time to development of complications, shorter overall survival (OS), poorer response to oncological treatment, deterioration of quality of life (QoL), and worse general performance status (PS); additionally, cachexia strongly aggravates treatment tolerability [2–8]. Nutritional intervention may have an impact on reducing the incidence of surgical complications and improving the rate of healing of wound and mucosal reactions, it reduces infection frequency and treatment toxicity, improves general PS and QoL, and reduces hospital stay time and treatment costs [9].

In patients undergoing laryngectomy for laryngeal cancer with the loss of body weight above 10% more than six months before surgery the percentage of postoperative complications is up to 65% [10, 11]. Very commonly nutritional preparation allows the patient to start oncological therapy or facilitate its continuation.

Head and neck cancer prophylaxis and diet

The strongest factor increasing the risk of squamous cell carcinoma in this area so far is smoking and drinking alcohol. Based on data from the International Head and Neck Cancer Epidemiology Consortium (INHANCE)

including 22 placebo-controlled clinical trials involving 14,520 patients and 22,737 individuals in a control group, it has been demonstrated that increased risk of this type of cancer is associated with low fruit and vegetable intake and a diet rich in red meat, especially in processed form. Data from pooled analysis were as follows: for fruit consumption OR 0.52, 95% CI 0.43–0.62, $p < 0.01$, vegetables OR 0.66, 95% CI 0.49–0.90, $p = 0.01$, red meat OR 1.40, 95% CI 1.13–1.74, $p = 0.13$, and processed red meat OR 1.37, 95% CI 1.14–1.65, $p < 0.01$, respectively [12].

Malignant neoplasms of the head and neck region account for slightly more than 5% of all malignant tumours registered in Poland, with a predominance among male sex (7% in males, 1% in females). Annually there are about 6000 new cases and about 3800 deaths [13]. As can be seen from the statistical data, the problem is not small and thus the development of standards of nutritional care in this group of patients seems to be very important.

Surgical treatment and nutritional support

Surgical methods are the cornerstone of the treatment of head and neck malignant neoplasms in the lower clinical stages (CS I–II). It should be remembered that even small surgical procedures in the area of the mouth, throat, and larynx are associated with temporary dysphagia or even the inability to intake food by oral route. European standards [14] recommend the use of immunonutrition for a minimum of 7–14 days before surgery, regardless of current body weight. In case of cachectic patients, the postponement of surgery by 10–14 days to improve nutritional status is recommended by ESPEN (the European Society for Clinical Nutrition and Metabolism) because it translates into a lower number of surgical complications and infections after operation [15]. The concept of immunonutrition means the supply in supraphysiological doses of nutrients (arginine, glutamine, essential unsaturated fatty acids from the omega-3 family, zinc, selenium, nucleotides, fibre, and many others), which are to improve the immune system and thus have a positive effect on the healing rate of wounds or post-radiation reactions, as well as reducing the frequency of infections. Ingredients of special importance for patients with head and neck cancer are arginine and essential unsaturated fatty acids from the omega-3 family (omega-3 fatty acids). Arginine is a relatively essential amino acid, which means that in conditions of metabolic stress it is needed in larger quantities than the human body is able to produce. Arginine is a precursor molecule for the production of other amino acids and proteins, it is necessary for the transfer of nitrogen groups in the urea cycle, it also modulates the function of lymphocytes and increases the secretion of anabolic hormones such as growth hormone, insulin, or glucagon. In turn, essential omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), interfere in the mechanism of action of proinflammatory cyclooxygenase cycle. They reduce the production of proinflammatory and prothrombotic cytokines such as the series 2 prostanoids, series 2 thromboxane, and series 4 leukotrienes, and increase the production of cytokines with lower proinflammatory potential such as series 3 prostanoids, series 3 thromboxane, series 5 leukotrienes, and resolvins. The anti-inflammatory effect of essential omega-3 fatty acids is crucial for overcoming hypoxia in the tumour microenvironment, which is well known as one of the main drivers of neoangiogenesis and apoptosis inhibitors, which gives a chance of tumour vascularisation, lack of programmed cell death, and opens the possibility of metastasis. At the molecular level, anti-inflammatory action of EPA and DHA means, among others, HIF-1 (hypoxia induced factor-1) and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) blockade [16].

Positive effects of arginine and essential omega-3 fatty acids have been described so far in many studies [17–21] and this is related to: lower incidence of fistulas after laryngectomy, less frequent infection, and shorter hospital stay. Also, a higher number of CD4 lymphocytes was observed at four and eight days after surgery, as well as higher albumin levels. There were no effects on CRP (C reactive protein), IL-6 (interleukin 6), or TNF-alpha (tumour necrosis factor-alpha). However, the most interesting conclusions come from the study by Buijs N et al. on the use of perioperative nutrition with arginine supplementation in patients suffering from head and neck cancer [22]. OS was significantly better and the locoregional relapse rate was significantly lower in the study group than in the control group. Interestingly, nutrition with arginine had no effect on the frequency of recurrence after surgery.

In clinical practice, immunonutrition can be accomplished by oral, enteral, or parenteral routes. Most often, at the level of outpatient care, the surgeon who qualifies for surgery may recommend ONS (oral nutrition supplement) to patients with arginine and essential omega-3 fatty acids for oral intake (drinking solutions), twice a day for a minimum of 14 days before surgery. If for some reason the patient cannot take a meal orally, one should consider inserting a nasogastric tube or gastrostomy with endoscopic or surgical method and administer commercially-available enteral diets containing arginine and omega-3 fatty acids in the amount of 25–30 kcal per kg body weight, in some cases even 35 kcal per kg body weight. Parenteral nutrition in this group of patients is used very rarely, only if there is no possibility

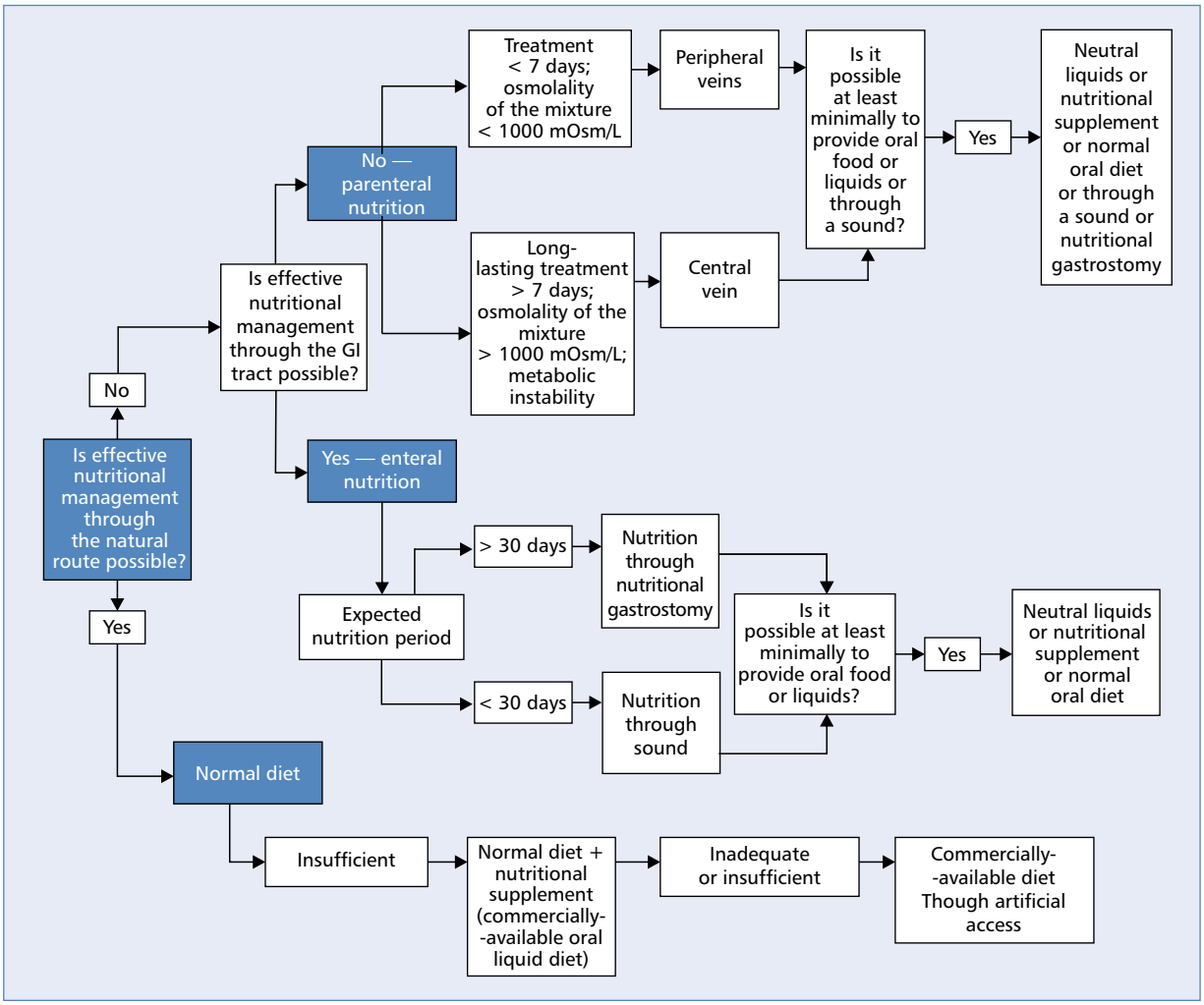

Figure 1. Algorithm of nutritional management in cancer patients

of using GI tract as a route of nutrition. Nutrition via GI is always a priority over parenteral nutrition.

In the case of patients undergoing tumour resection, the need for a nasogastric tube insertion or gastrostomy depends on the amount of food being taken orally, as well as the anticipated feeding time. If the patient consumes less than 60% of the amount of protein and calories needed per day by oral route for more than seven days, the possibility of feeding with artificial access should be protected. If the anticipated feeding time exceeds 30 days, the patient should be offered a nutritional gastrostomy. If the feeding time does not exceed one month, the nasogastric tube can stay. The reverse principle applies when removing access to nutrition. The tube or gastrostomy could be safely removed if the patient is able to take over 60% of the daily protein and energy needs by oral route. The algorithm of nutritional management in accordance with the position of Polish standards of oncological patients' nutrition [23] is presented in Figure 1.

It should be also remembered that cancer-free patients after surgical procedures in head and neck region still face significant problems that make proper nutrition difficult or even impossible. In some cases there is a dramatic cachexia and a significant deterioration of PS and quality of life. These include the following clinical situations: loss of taste and smell, difficulty in chewing food, outflow of saliva and food particles from the mouth (especially after tongue resections), poor peristalsis in the upper gastrointestinal tract, long meal time, regurgitations to the mouth and/or nose, delayed wound healing (separation of the anastomosis, fistula, infection, necrosis of the flap), cranial nerve damage, aspiration/asphyxiation with food particles due to malfunctioning swallowing reflex, lymphatic fistula, postoperative stenosis (lower throat, upper oesophagus) requiring secondary endoscopic expansion [24]. A patient with permanent damage to oral nutrition, which will lead to continuous deterioration of nutritional status, should be fed enterally with a commercially-available

diet (high-protein, high-energy) through permanent artificial access to the gastrointestinal tract (endoscopic or surgical gastrostomy, exceptionally jejunostomy if access to the stomach is impossible) under the supervision of the Nutritional Clinic.

Radiochemotherapy and nutritional management

The standard management in patients with head and neck cancers in higher clinical stages (CS III–IV) is radiotherapy combined with cisplatin-based chemotherapy, or radiotherapy with simultaneous use of cetuximab. In addition, the combination treatment is often preceded by induction chemotherapy. Combination treatment lasts for 6–7 weeks and is associated with gradual deterioration of nutritional status and intensification of dysphagia as a result of development of radiation-induced reactions on the mucous membranes and skin. Weight loss during combination therapy is inevitable, and in addition this kind of treatment is associated with many side effects. The first symptom is xerostomia already seen in the second week of treatment. As a result of radiotherapy, the salivary glands are irreversibly damaged at a dose of 25 Gy. The consistency of saliva changes, making it uncomfortably thick and difficult to expectorate, and its production decreases. Lack of saliva results in intensification of caries, susceptibility of mucous membranes even to minimal injuries, the inability to form a bite of food, and difficulty in swallowing. Loss of taste is reported by all patients at the end of treatment and it begins in the third week of therapy. The patient does not taste meals, which further discourages him/her from eating. Increased radiation-induced mucosal reactions that cause pain and dysphagia usually begin in the fourth week of treatment and persist for weeks after treatment (minimum six weeks to several months); during treatment with cetuximab they may appear a week earlier. At the end of treatment, the reaction grade II–III according to EORTC is usually observed, which is clinically characterised by single or confluent erosions coated with fibrin in the oral cavity, on the surface of swollen and reddened mucous membrane. Intake of ordinary solid foods during this period is practically impossible, some patients tolerate oral liquid or pulpy diet, but it should be stressed that the mixed dietary food does not cover nutrient needs at that time [25]. Some patients are not able to swallow even liquid foods. Other side effects of combination therapy include: lockjaw, nausea caused by constant irritation of vomiting receptors on the back of the throat through mucous inflammation and thick salivary accumulation, chronic fatigue, and side effects typical for cisplatin treatment (anorexia, haematological complications, nephrotoxicity, and ototoxicity). Having knowledge about the, typical for this treatment method, development of side effects that cannot be avoided, it seems obvious to protect the nutrition route before treatment in order to minimise the number and severity of complications. In the Head and Neck Cancer Clinic in Maria Sklodowska-Curie Institute — Oncology Center in Warsaw all patients undergoing chemoradiotherapy or radiotherapy with use of cetuximab have access to nutritional care (Fig. 2).

Before the start of combination therapy, the patient is referred for insertion of percutaneous endoscopic gastrostomy, often by "push" method — percutaneous endoscopic gastrostomy (PEG). Preventing the nutrition route will allow not only provision of the right amount and quality of nutrients, even in the case of severely intensified dysphagia, but also allows patients to be hydrated and supplied with certain medicines. Statistical data from European centres dealing with head and neck cancer treatment show that PEG is used in 30–50% of centres [26]. The most important thing seems to be not only the ability to perform this procedure, but also meticulous care of the access after its establishment. It should be strongly emphasised that the presence of PEG requires the cooperation of a well-educated patient as well as constant nursing supervision (dressing changes, gastrostomy tube turning and rinsing) to prevent potentially serious complications — ranging from redness and maceration of abdominal skin through gastrointestinal leakage, local infections, buried bumper syndrome (a severe complication, in which the internal fixation device migrates alongside the tract of the stoma outside the stomach), and even peritonitis requiring urgent surgical intervention. In the literature, there is a lot of evidence for clinical benefit from PEG. Establishing a PEG is a safe procedure and requires only minimal sedation. The average weight loss in the case of feeding through PEG in relation to baseline is 2.8%, the frequency of infection is lower, and in 82% of patients after the treatment completion PEG could be removed [27]. A study by Burney RE et al. [28], involving a group of 565 patients after establishing PEG, assessed the effects of PEG during 33–38 months: 44% of patients increased their body weight, 4% had dermatitis, 2% had a gastrointestinal leakage, 2.5% complained of pain, and one patient experienced bleeding, while no cases of cancerous grafts were observed as a result of implantation of tumour cells into the stomach or abdominal wall. Interesting data are provided by a study by Moleiro et al. [29] in which nutritional status was assessed 30 days and six months after establishing PEG. It seemed that despite the presence of PEG, 76% of patients lost body weight; however, in the PEG group only 22% showed a weight loss > 10% of initial body weight. A year after treatment, 20% of patients were still dependent on PEG. Generally, the conclusions from the studies available in

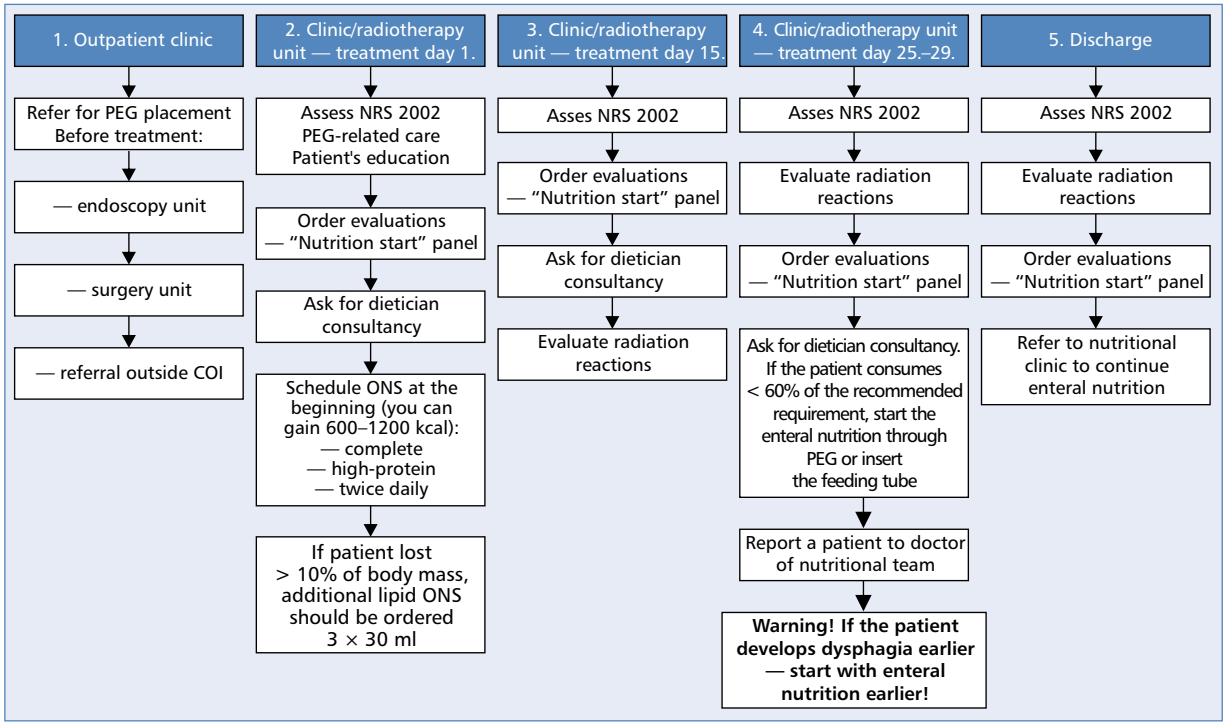

Figure 2. Model of nutritional care for patients diagnosed with head and neck cancers in the Head and Neck Cancer Clinic in Maria Sklodowska-Curie Institute — Oncology Center in Warsaw. Author: A. Kapała

Table 1. Anthropometric and biochemical parameters of the nutritional status routinely assessed during combined treatment

Anthropometric parameters of the nutritional status	Biochemical parameters of the nutritional status — panel "nutrition start"
Weight, height, BMI, weight loss before starting treatment	Complete blood count (CBC), urea, creatinine, uric acid, glucose, sodium, potassium, chlorides, magnesium, phosphorus, total and ionised calcium, total white, albumin, AST, ALT, GGTP, ALP, total bilirubin, CRP, INR, APTT, D-dimers, TSH, lipidogram

GGTP — gamma-glutamyl trasferase; ALP — alkaline phosphatase; CRP — C-reactive protein; INR — international normalized ratio; APTT — activated partial thromboplastin time; TSH — thyroid-stimulating hormone

the literature say that PEG is a safe procedure provided that proper care is taken over access and education of the patient. PEG improves nutritional status; in the group of patients with very high nutritional risk it allows cessation of weight loss, or minimisation of its severity in comparison to patients without secured access to the gastrointestinal tract [30]. After admission to the ward, on the day of commencement of combination therapy, the patient is consulted by a dietitian, anthropometric and biochemical parameters of the nutritional status are evaluated (see Table 1), and patients receive written recommendations for an oral diet and ONS (oral nutritional supplements).

The most important elements of the oral diet are prohibition of consumption of: raw fruits and juices, silage, olives, highly salted and smoked products, hard and crispy products (wafers, nuts, some hard vegetables such as radish), as well as sweet and carbonated beverages, and a strict ban on taking stimulants (cigarettes, alcohol). Starting from the first day of hospital stay, regardless of body weight, patients receive ONS in the form of complete high-protein nutrients (twice per day), additionally enriched with 3 × 30 ml fat nutrients if the body weight loss before treatment is > 10%. Nutritional status of the patient and the ability to take oral foods, and anthropometric and biochemical parameters are assessed by the dietician every two weeks for the whole treatment period. At the same time, the patient is educated about access care (PEG). Access to nutrition is covered by routine, daily nursing care. Typically, between 4–5 weeks of treatment, the possibility of taking oral foods falls below 60% of the demand and

at this time point the enteral nutrition is introduced with commercially-available diets through previously established PEG. If, for some reason, PEG has not been established, for example due to lack of patient's consent, a thin silicone nasogastric tube with a diameter of 10–12F is inserted, and its location is confirmed by RTG before feeding (exclusion of the catheter repositioning or presence in the bronchial tree). It should be strongly emphasised that old type "thick" probes made of PVC, with a diameter of 14F and more, are only suitable for gastric decompression but not for feeding. Old type probe can be used for 7–10 days, after this time it should be removed or replaced — which in a patient with severe radiation-induced reaction can be very difficult to achieve. On the other hand, maintaining a PCV probe may be associated with a bedsore in the nasal cavity or oesophagus, which may cause pain, infection, and later stenosis. Thin silicon probes can be used for 6–8 weeks (see manufacturer's recommendations). Regardless of whether the patient is fed through PEG or sound, the enteral nutrition lasts until the end of treatment with minimal oral feeding. Patients are encouraged to take orally at least a small amount of fluids to prevent fibrosis in the muscles involved in the swallowing reflex. In the period of intensified dysphagia or even aphagia it is very valuable to work with a speech therapist who, by means of special exercises and head-positioning techniques, allows the patient to swallow even small amounts of fluids. After completion of combination treatment, the last dietary consultation and assessment of the patient takes place on the day of hospital discharge. The patient receives a referral to a regional nutritional clinic to continue the enteral nutrition with a commercially-available diet at home. Removal of access will be possible if oral supply of food exceeds 60% of the patient's daily needs for protein and energy.

Palliative treatment setting and nutritional management

Palliative treatment of advanced head and neck cancers can be led with use of radiotherapy (usually in two steps, up to 2000 cGy/t) or chemotherapy: the first line of treatment is based on cisplatin and 5-fluorouracil, and the second line of treatment is usually chronic methotrexate therapy. The disease in incurable phase is characterised by gradual deterioration of nutritional status on the one hand due to increasing dysphagia, and on the other hand due to the development of cachexia driven by metabolic mechanisms: systemic inflammation, changing of hepatic protein production into acute phase proteins, protein loss through fistulas and extensive ulcerations as well as chronic bleeding, damage to metabolism of major macronutrients like proteins and carbohydrates, and predominance of catabolic processes over anabolism. Additionally, frequently there is difficult-to-treat pain, often of neuropathic origin, and depression. Currently, it seems that supportive treatment in this phase of disease is of fundamental importance for maintaining the patient in palliative therapy, to improve the quality of life and the patient's performance status. The basis of the intervention is diet consultation based on an easily digestible, high-fat diet (fats may account for 50% of calories in the daily portion) supported by ONS preparations (currently we have at least a few dozen complete and incomplete preparations on the market that may be recommended for patients in the palliative phase of treatment). It is very important to adjust the consistency and texture of the diet to the patient's ability to chew and swallow; diet types (type B–E) for a patient with dysphagia are described in detail in the document of the British Society of Parenteral and Enteral Nutrition [31]. Letters B–E refer to the consistency of the diet — from a liquid diet, through a liquid diet reinforced, pulpy, to a soft solid diet, easy to divide with a fork. In order to control anorexia in accordance with ESPEN recommendations, megestrol acetate or glucocorticoids may be included, taking into account typical contraindications to the use of these drugs. The ESPEN position regarding the use of omega-3 fatty acids in the treatment of cachexia is negative due to the lack of unambiguous evidence of the highest statistical value as to their effectiveness. On the other hand, the literature contains a lot of data describing the positive effect of omega-3 fatty acids on cachexia: weight gain, also fat-free, reduction of inflammatory parameters, improvement of appetite and physical activity, improvement of quality of life, as well as mitigation of chemotherapy side effects [32–38]. Some data indicate even the extension of OS [39]. Ultimately, if it is decided to use omega-3 fatty acids with intention of cachexia treatment, the total dose of EPA and DHA should be 1.5–2.0 g/day. In palliative patients, it is also worth sticking to the principle that if a patient is permanently unable to orally receive more than 60% of his/her daily nutritional needs, it is a reasonable solution to establish an endoscopic gastrostomy (PEG), in some cases a surgical gastrostomy or an ordinary nasogastric tube. Progressive cachexia is inevitable in this group of patients, so if the possibility of feeding the patient begins to be limited, the patient's PS is good (WHO 0–2), and life expectancy is more than two months, establishing PEG should be of choice. If predicted life expectancy is only a few weeks, it is enough to insert a nasogastric tube. If the patient is in terminal condition, minimal amounts of fluids administered by the oral, subcutaneous, or intravenous route are sufficient. Implementation of enteral or parenteral nutrition in the terminal phase of disease is contraindicated because it does not bring the patient any clinical benefit and may provoke additional ailments and/or complications.

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