short review

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Malnutrition and cancer, diagnosis and treatment

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Summary
Background The prevalence of malnutrition in cancer patients ranges from about 20% to more than 70%. However, 10–20% of cancer patients' deaths are related to malnutrition, not the malignancy itself. To reverse the pattern of weight loss, improve the patients' quality of life, reduce the treatment toxicity, the psychological stress and the risk of mortality, the diagnosis of malnutrition should be made as early as possible to facilitate the best possible treatment.
Methods A systematic literature search was conducted following guidelines of ESPEN (European Society for Clinical Nutrition), DGEM (German Society for Nutritional Medicine) and ASPEN (American Society for Parenteral and Enteral Nutrition).
Results and conclusion To assess the risk of malnutrition, all cancer patients should be screened regularly with a valid screening tool (e.g., MUST [Malnutrition Universal Screening Tool], NRS [Nutritional Risk Screening] or PG-SGA [Scored Patient-Generated Subjective Global Assessment]). If risk of malnutrition is present, adequate nutritional therapy is recommended to stop involuntary weight loss. Patients should engage in exercise to maintain and improve muscle mass, strength and function. They should be offered regular dietetic counselling, and their muscle depletion should be monitored by determining fat-free mass. As cachectic patients in particular are at risk, the presence of cachexia should also be recognized at an early stage. Three consensus-based definitions are widely accepted: Fearon et al. and the EPCRC (European Palliative Care Research Collaborative) propose definitions specifically for cancer cachexia, while Evans et al. put forward a definition for cachexia associated with all types of underlying chronic diseases. However, if there is a cancer cachexia diagnosis, additional pharmacological and psychological treatment should be considered.

Keywords Cachexia · Sarcopenia · Obese cancer patients · Involuntary weight loss · Oncology

Introduction

Malnutrition means a significant loss of weight and body resources, which results in an impairment of quality of life and prognosis [1]. Worldwide studies show that the prevalence of malnutrition in cancer patients ranges from about 20% to more than 70%. However, 10–20% of cancer patients' deaths are related to malnutrition, not the malignancy itself. Although certain cancer patient groups are more vulnerable to malnutrition than others, many of these patients are never treated for malnutrition. The risk of malnutrition is particularly evident after gastrointestinal tumor surgery such as gastrectomy, pancreatectomy, small bowel surgery, or high-lying stoma and therapy-induced diarrhea, whereby 80% of patients with these tumor entities, and 30% of all cancer patients have already lost weight prior to diagnosis [1].

Causes of malnutrition

In an interactive network, mutually reinforcing factors are understood to be the causes of malnutrition in cancer patients [1, 2].

Gastrointestinal disorders such as nausea or diarrhea, changes in smell and taste, drug side effects, psychological stress and pain can all lead to a reduced food intake and consequently to weight loss. This in turn leads not only to a weakening of the immune sys-

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tem but also to muscle loss, which is increased both by the inflammation of the tumor stroma and by the reduced mobility. Systemic inflammation processes and the loss of cell and muscle mass associated with weight loss cause fatigue, which in turn leads to reduced physical activity [1].

Immunologic, metabolic and clinical phenomena are related. The upregulated innate immune response causes systemic inflammation which leads to different symptoms such as anorexia, weight loss and reduced physical function, as well as fatigue, pain and depression [2]. Inflammatory factors like TNF-α (Tumor necrosis factor-alpha), IL-6 (Interleukin-6) and IL-1 (Interleukin-1) released by the tumor itself affect muscle, brain, liver and fat functions. This systemic inflammation results in:

- Altered CNS (central nervous system) signals causing anorexia
- Changes in the liver metabolism repressing drug clearance and raising the risk of chemotherapy-related toxicity
- Muscle wasting, a reduction of muscle mass and strength
- Depletion of fat deposits [2].

Diagnosis of malnutrition and cachexia

All patients with unwanted weight loss should be examined to determine the origin. It is important not only to interview the patient, but also to take body weight and size measurements to ensure accurate data, and to identify the presence of edemas, ascites or pleural effusion.

It is advised to use a valid screening tool in order to determine the risk of malnutrition. The use of MUST (Malnutrition Universal Screening Tool), NRS (Nutritional Risk Screening) or PG-SGA (Scored Patient-Generated Subjective Global Assessment) should be considered [3, 4]. Age is assumed to be an additional risk factor for NRS and PG-SGA.

Jensen et al. distinguish between starvation-related malnutrition (which means chronic starvation without inflammation), chronic disease-related malnutrition (with chronic inflammation and of mild to moderate degree), and acute disease- or injury-related malnutrition (which involves acute inflammation and is of severe degree) [5].

As described in the DGEM guideline of clinical nutrition, starvation-related malnutrition is the result of chronic undernourishment in patients showing no signs of inflammation.

General criteria to diagnose disease-related malnutrition are [6]:

- Body mass index (BMI) <18.5 kg/m^2 or
- Involuntary weight loss >10% in the last 3–6 months or
- BMI <20 kg/m^2 and unwanted weight loss >5% in the last 3–6 months.

Starvation lasting for more than seven days is defined as an independent criterion for risk of malnutrition.

The above criteria also apply to obese patients [7]: a 40-year-old person weighing 80 kg, with a height of 160 cm, a BMI of 31 and a weight loss of 10% is also malnourished, although still obese with a BMI of 28. Minor weight loss is often not mentioned in this group of patients and not seriously considered [7].

As a meta-analysis of Winter et al. shows that the all-cause mortality risk increases in older people with a BMI <23 [8], the limit for the BMI to diagnose the risk of malnutrition may need to be set higher for patients older than 65. In the recommendations statement of the European Society of Clinical Nutrition (ESPEN), the use of a higher cut-off point of 22 for elderly patients is also suggested [9]. Ideal reference areas for the BMI for this group from 22–26.99 [10] and 24–29 [11] are already mentioned in the literature.

Cachectic patients have a particularly poor prognosis, and more than 10% of all cancer patients die with or due to this condition [12].

In an international consensus, Fearon et al. defined cancer cachexia as “a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment” [13, 14].

Unwanted weight loss, muscle atrophy, fatigue, weakness, a significant loss of appetite, and the presence of an inflammation are characteristics of cachexia [6].

Evans et al. [15] describes the following criteria to identify cachexia:

Weight loss of ≥5% in ≤12 months due to a pre-existing condition, plus three of the following criteria:

- Reduced muscle strength
- Fatigue
- Anorexia
- Lower fat-free mass index (fat-free mass [kg]/body height^2 [m^2])
- Abnormal blood chemistry
  - CRP >5.0 mg/L, IL-6 >4.0 pg/mL
  - Anemia (Hb <12 g/dL)
  - Albumin (<32 g/L).

As this definition is not specific to cancer, other consensus-based definitions for cancer cachexia have been proposed [13]. There is currently no international standard guideline treatment as there is no single widely accepted definition and assessment of cancer cachexia. Particularly regarding cancer cachexia, two consensus-based definitions by Fearon et al. and the EPCRC (European Palliative Care Research Collaborative) can be used.

Fearon et al. proposed ≥2 out of the following 3 criteria [16]:

- Weight loss (≥10%)
- Low food intake (≤1500 kcal/day)

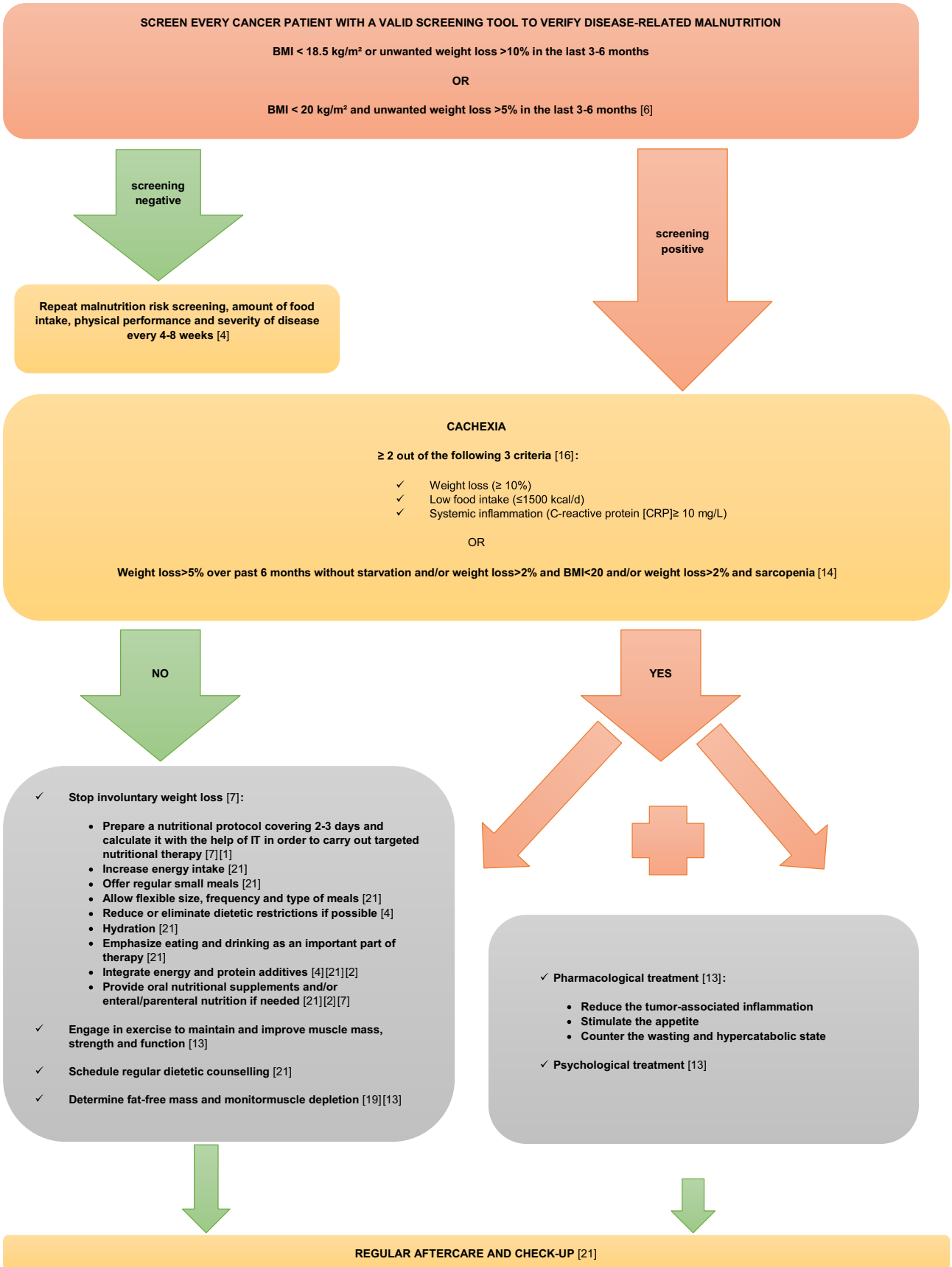

Fig. 1 Diagnosis and treatment. Regular aftercare and check-up [20]. *BMI* body mass index

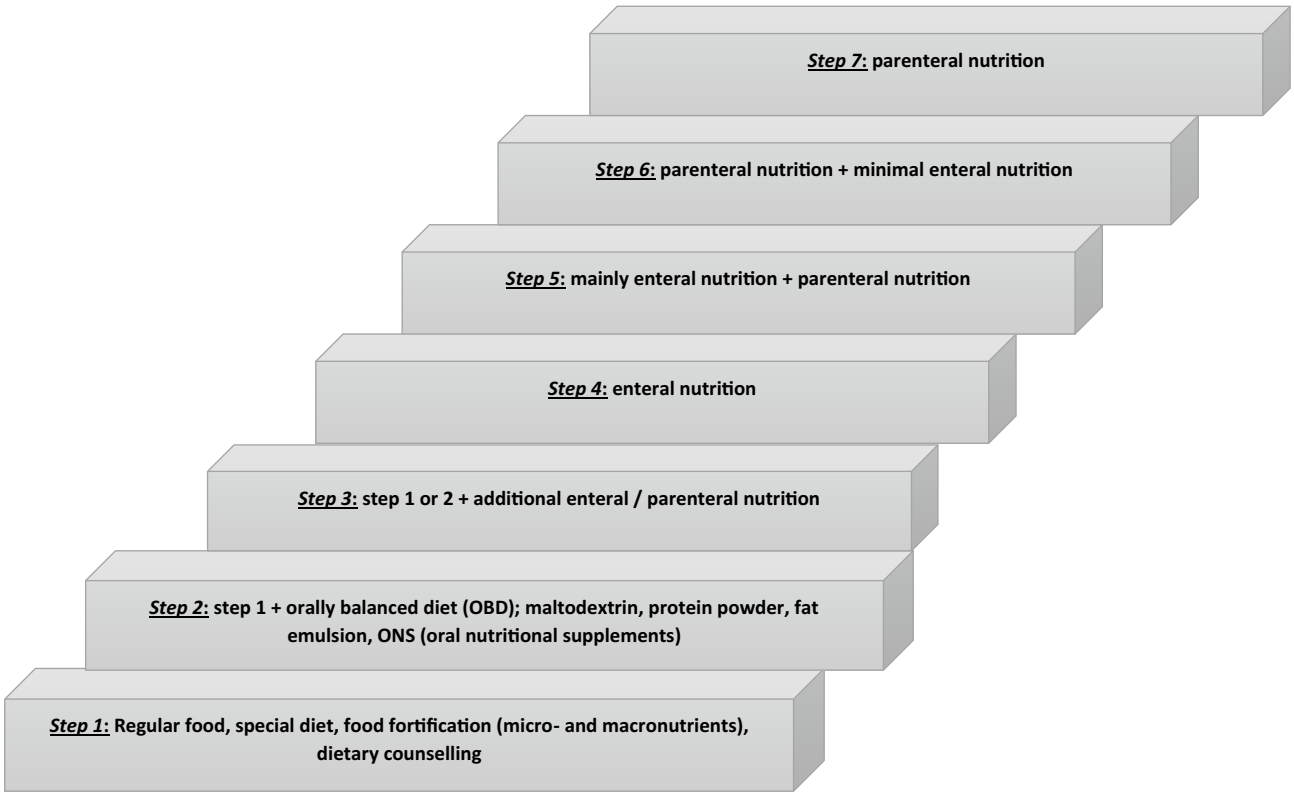

Fig. 2 Always pay attention to refeeding in regard to enteral/parenteral nutrition

- Systemic inflammation (C-reactive protein [CRP] ≥10 mg/L).

EPCRC (European Palliative Care Research Collaborative) proposed [14]:

- Weight loss >5% over past 6 months without starvation and/or
- Weight loss >2% and BMI < 20 and/or
- Weight loss >2% and sarcopenia.

Cruz-Jentoft et al. defined sarcopenia as a "syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death [17]". The SCWD (task force of the Society for Sarcopenia, Cachexia and Wasting Disorders) recommends to screen for sarcopenia using a simple tool like the SARC-F. It is necessary to diagnose sarcopenia using following examinations: grip strength or chair stand and—if possible—a measurement of fat-free mass [18]. DXA (dual X-ray absorptiometry), MRI (magnetic resonance imaging), CT (computed tomography), US (ultrasound) and BIA (bioelectrical impedance analysis) can be used to determine fat-free mass and to monitor muscle depletion. DXA seems to be the most valid method but the BIA method is widely used due to its simplicity and low cost ([13, 19]; Fig. 1).

Treatment of malnutrition and cachexia

If risk of malnutrition is present, nutritional assessment is required to improve physical performance, metabolism, tolerability of antitumor therapies, quality of life, and course of disease. Nutritional counselling includes a recording of food intake (computer-aided evaluation of food log), nutritionally relevant symptoms, body and muscle mass, systemic inflammation, and performance status [4].

If the caloric intake is less than 60% of the estimated requirements over a period of 1–2 weeks, or if eating is not possible for a week, insufficient nutritional intake is validated [2]. High-quality medical nutritional intervention is provided by dieticians. The structure of the therapeutic interventions is shown by the following scheme described by Valentini et al. ([6]; Fig. 2):

Enteral or parenteral nutrition is indicated in case of inadequate nutritional intake (less than 500 kcal/day for a couple of days or oral nutritional intake of less than 75% of TEE for 1–2 weeks), and if an improvement of quality of life, increased longevity and greater patient comfort can be expected ([1, 4]; Table 1).

The main goals in the treatment of cachexia are improvements in lean body mass, resting energy expenditure, fatigue, anorexia, quality of life, and performance status as well as a reduction of the tumor-associated inflammation [13]. Appetite stimulants,

Table 1 Recommended energy and nutrient intake of malnourished cancer patients

Energy	Use indirect calorimetry to determine resting energy expenditure if available, or estimate REE with formulas like Harris–Benedict, Schofield or WHO. Assume a physical activity level of 1.0–1.5 [4]	
Protein	1.2–1.5 g/kg body weight per day to maintain or restore lean body mass [4] Protein amounts of more than 2 g/kg body weight per day are of no benefit [4]	Enrich with supplements (e.g. protein powder, ONS) Choose foods with a high biological value Offer immunomodulatory enteral formulas containing arginine and nucleotides to patients undergoing cancer surgery [2]
Fat	Intake should amount to at least 35% of TEE [4] In case of insulin resistance or if a higher energy density is required, up to 50% of TEE may be considered [4]	Enrich with high-quality vegetable oils as well as butter, cream or other fatty dairy products Fish oil (omega-3 fatty acids) is suggested to improve appetite, oral intake, lean body mass and body weight [2]

REE resting energy expenditure, *WHO* World Health Organization, *ONS* oral nutritional supplement, *TEE* total energy expenditure

Table 2 Pharmacological treatment options

Drug	Effects	Side effects
Prokinetics	Appetite stimulating, Reduced sickness [7]	No effects on body weight [7]
Gestagenes	Appetite stimulating Weight gain [4, 7]	Adrenal insufficiency Thromboembolism Impotence [4, 7]
Glucocorticoids	Appetite stimulating Reduced systemic inflammation Increase in ingestion, quality of life, physical performance and well-being [4, 7, 13]	Cushing syndrome Short-lived positive effects [4, 7, 13]
Cannabinoids	Appetite stimulating Reduced dysgeusia [4, 7, 13]	Neuropsychological side effects [4, 7, 13]
Eicosapentaenoic acid	Appetite stimulating Reduced systemic inflammation Weight gain Increase in ingestion and quality of life [7]	Under high-dose therapy reduced blood coagulation [7]
Nonsteroidal antirheumatics	Reduced systemic inflammation, Weight gain Increase of physical performance [7, 13]	Gastroenteral bleeding Kidney insufficiency Platelet inhibiting [7, 13]

anticytokine-acting or metabolic change-affecting drugs and anabolic steroids can be used to counteract anorexia, inflammation, and muscle loss. However, the potential positive effects of the pharmaceutical substances are offset by undesirable side effects ([7]; Table 2).

Physical training programs that are based on the individual performance should be integrated into the treatment, as exercise has been shown to have many positive effects (e.g., anti-inflammatory effects, counter insulin resistance, decrease oxidative stress, reduce depressive symptoms, increase anabolic hormones) [1].

Regular dietary consultations and check-ups as well as measuring of muscle mass should be carried out. In end-of-life care, symptoms such as hunger or thirst must be treated, while continued normal food intake lacking allowances for end-of-life care would put an unacceptable burden on the dying person [1, 2].

Take-Home Message

- Every cancer patient should be screened for malnutrition.
- Adequate nutritional therapy and regular dietetic counselling should be offered.
- Cachectic patients should receive additional support.

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