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Narrative Review

Management of Cancer-Related Malnutrition

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A B S T R A C T

Background: Cancer-related malnutrition is a common complication that negatively affects treatment response, prognosis, and quality of life. Its development involves complex interactions between reduced nutritional intake, systemic inflammation, metabolic alterations, and adverse effects of cancer treatment. **Aim:** This review aims to describe the pathophysiology, nutritional assessment, and comprehensive management of cancer-related malnutrition. **Methods:** This narrative literature review synthesizes published literature and clinical guidelines concerning the mechanisms, diagnosis, and therapeutic approaches to cancer-related malnutrition. **Results:** Cancer-related malnutrition is characterized by anorexia, inflammatory and metabolic disturbances, increased protein turnover, and progressive muscle wasting. Early nutritional assessment through clinical evaluation, anthropometric measurements, laboratory investigations, and validated screening tools, including the Malnutrition Screening Tool (MST), Patient-Generated Subjective Global Assessment (PG-SGA), Mini Nutritional Assessment (MNA), and Nutritional Risk Screening 2002 (NRS-2002), is essential. Management involves individualized nutritional interventions, adequate energy and protein intake, physical activity, and selected pharmacological therapies. Oral nutritional support is preferred whenever possible, while enteral and parenteral nutrition are considered according to gastrointestinal function and nutritional requirements. Pharmacological interventions may improve appetite and alleviate associated symptoms, although potential adverse effects should be considered. **Conclusion:** Early identification and comprehensive, individualized nutritional management are essential to prevent further nutritional deterioration, optimize cancer treatment, and improve clinical outcomes and quality of life.

INTRODUCTION

Nutrition is an important component of cancer care, whether patients are undergoing treatment, recovering from treatment, in remission, or seeking to prevent recurrence. Patients with cancer are generally at high risk of malnutrition because both the underlying disease and its treatment may compromise nutritional status. Nutritional status in patients with cancer is associated with treatment response, prognosis, and quality of life. Approximately 30–87% of patients experience cancer-related malnutrition before treatment. Malnutrition is a nutritional state involving a deficiency or excess (imbalance) of energy, protein, and other nutrients that produces measurable effects on tissue/body form (body

shape, size, and composition), function, and clinical outcomes.[1,2]

Cancer-related malnutrition has four main characteristics: anorexia; changes in inflammatory, metabolic, and endocrine processes; increased tissue protein turnover; and loss of muscle mass. The terms 'malnutrition,' 'weight loss,' and 'cachexia' have been used for many years in patients with cancer. However, 'cancer-related malnutrition' is considered more appropriate because cachexia tends to describe a terminal condition in these patients. The cause of cancer-related malnutrition remains uncertain and is thought to be multifactorial. In addition to anorexia, increased energy expenditure, metabolic changes, tumor type and location affecting the gastrointestinal tract, and the type of cancer treatment are believed to contribute. Various cytokines have also been implicated in anorexia and metabolic disturbances underlying cancer-related malnutrition. Cancer-related malnutrition also affects the success of medical treatment, including radiotherapy and chemotherapy.[1,2,3,4,5,6,7]

The relationship between nutrition and cancer has two aspects: nutrition may contribute to cancer development (the negative aspect), while also playing an important role in cancer treatment (the positive aspect). The general objectives of nutritional management in patients with cancer are to provide adequate calories and protein, correct nutritional deficits, prevent immunosuppression, and minimize weight loss, as substantial weight loss indicates a poor prognosis. Several pharmacological treatments for cancer-related malnutrition are now available. Early nutritional support, before clinical signs of malnutrition develop, is essential for improving prognosis; once malnutrition has occurred, nutritional support helps prevent disease progression. Therefore, early identification of nutritional problems and appropriate management can improve treatment response and reduce treatment complications. Against this background, this literature review aims to improve understanding of the management of cancer-related malnutrition.[1,4,5,6,7]

DEFINITION OF CANCER-RELATED MALNUTRITION

Malnutrition is a nutritional state involving a deficiency or excess (imbalance) of energy, protein, and other nutrients that produces measurable effects on tissue/body form (body shape, size, and composition), function, and clinical outcomes. Inadequate intake is a common problem in malnutrition and also occurs in cachexia. Importantly, not all malnutrition is cachexia, but all patients with cachexia are malnourished. The terms 'malnutrition,' 'weight loss,' and 'cachexia' have been used for many years. However, 'cancer-related malnutrition' is considered more appropriate for patients with cancer because cachexia tends to describe a terminal condition.[1,7]

Cancer-related malnutrition is defined as a complex, multifactorial process characterized by weight loss and changes in body composition, including loss of bone and muscle mass with relative preservation of visceral protein mass, which cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The four main characteristics of cancer-related malnutrition are anorexia; changes in inflammatory, metabolic, and endocrine processes; increased tissue protein turnover; and loss of muscle mass.[7]

Cancer cachexia is a syndrome characterized by weight loss, anorexia, asthenia, and anemia. Cachexia is diagnosed when three of five conditions are present: weight loss of at least 5% over the preceding 12 months (or body mass index (BMI) <20 kg/m^2), reduced muscle strength, fatigue, anorexia, a low fat-free mass index, and abnormal biochemical laboratory findings (elevated inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), anemia, and low albumin). Cancer cachexia was previously considered a consequence of energy imbalance, namely reduced food intake and increased energy consumption. Current explanations of malnutrition in patients with cancer place greater emphasis on cytokines that cause anorexia and alter fat, protein, and carbohydrate metabolism. Relevant mediators may be produced by the host (interleukin-1/IL-1, IL-6, tumor necrosis factor (TNF-α), interferon-gamma (IFN-γ)) or by cancer cells

(PIF/proteolysis-inducing factor and LMF/lipid-mobilizing factor).[1,2]

EPIDEMIOLOGY OF CANCER-RELATED MALNUTRITION

Malnutrition is common in patients with cancer and is a major cause of morbidity and mortality. Overall, the prevalence of cancer-related malnutrition ranges from 40% at diagnosis to 70–80% in advanced disease, depending on tumor type, location, disease stage, treatment received, and the nutritional assessment method used. Reported prevalence is approximately 83–85% in pancreatic and gastric cancer, 54–60% in lung, prostate, and colorectal cancer, and 32–48% in breast cancer, sarcoma, lymphoma, and leukemia. The incidence of malnutrition in patients with cancer generally ranges from 40–80%. A study in Turkey reported a prevalence of 16.2%; by tumor location, the rates were 45% for respiratory tract cancer, 18.8% for genitourinary cancer, 5.5% for breast cancer, and 23.5% for gastrointestinal cancer. A study by Saka and colleagues in 2018 found that 89% of hospitalized patients with cancer were at risk of malnutrition. In the 2018 study by Korfali and colleagues, 43.4% of patients with cancer were at risk.[4,7,8]

ETIOPATHOGENESIS OF CANCER-RELATED MALNUTRITION

The causes of malnutrition in patients with cancer are multifactorial and can generally be grouped into reduced food intake, malabsorption, and metabolic disturbances. Cancer can adversely affect nutritional status. Cancer cells draw nutrients from the patient's body, while treatment and the physiological consequences of cancer can also interfere with adequate nutrition. Another classification of factors contributing to cachexia includes psychological and central nervous system factors (anorexia, altered taste perception, psychological stress); tumor effects (mechanical obstruction, substrate/nutrient utilization by the tumor, cytokine production by tumor cells); treatment-related effects (chemotherapy, radiotherapy, surgery, nausea, stomatitis, xerostomia, pain, ileus); and patient-related effects (increased resting energy expenditure/REE), metabolic disturbances, cytokine production by macrophages, autonomic dysfunction, and delayed gastric emptying. Cytokines thought to contribute to cancer cachexia include TNF-α, TNF-β, cachectin, IL-1, IL-6, and interferon-α. Their physiological activities overlap, making them individual contributing factors in cachexia. Antibodies, anticytokine agents, and other cytokine inhibitors are considered potential interventions for cancer cachexia. The etiopathogenesis of cancer-related malnutrition is shown in Figure 1.[1,2,4,9,10,11,12]

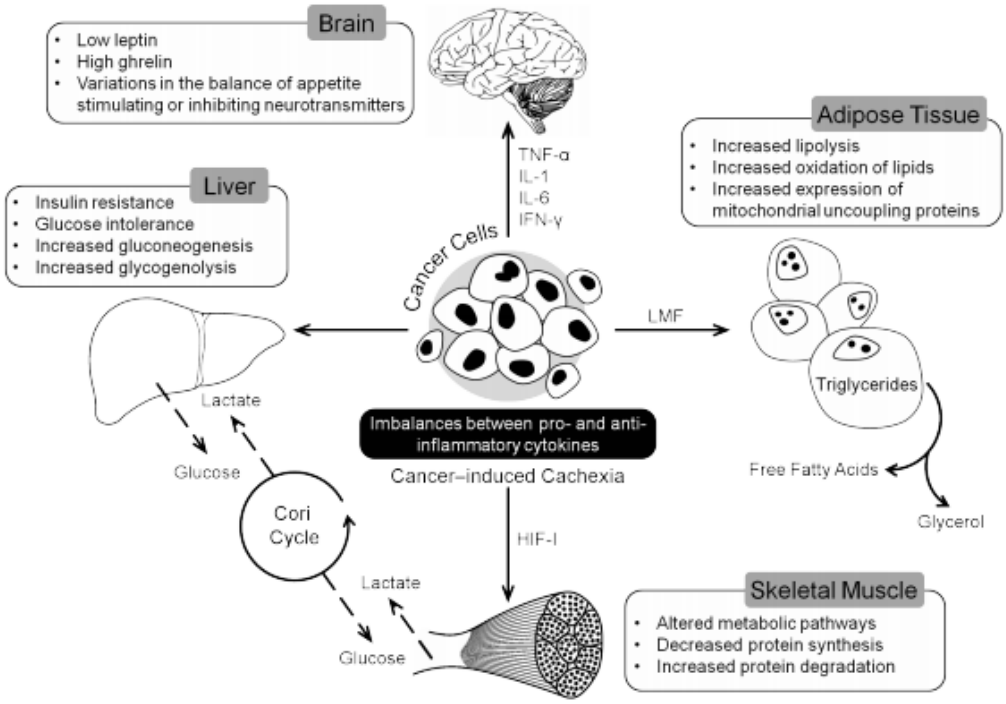


Figure 1. Etiopathogenesis of Cancer-Related Malnutrition[9]

The initial cause of malnutrition in patients with cancer is molecular alteration arising from tumor–host interactions. Tumor cells have greater nutritional requirements than normal cells. Tumor-driven mobilization of metabolites supports tumor growth and has systemic effects across the organism's metabolism, leading to cancer anorexia-cachexia syndrome (CACS). CACS results from several factors, including mechanical changes associated with tumor location, systemic inflammation causing catabolic changes, anorexia, and tumor-associated neuroendocrine alterations. Loss of muscle and adipose tissue in cancer results from reduced protein synthesis, increased protein degradation, and increased lipolysis. Increased inflammatory cytokines also regulate metabolic responses leading to cachexia and anorexia.[9]

Anorexia

Anorexia is a reduced desire to eat and is one of the most common symptoms of cancer-related malnutrition. Its incidence at cancer diagnosis is 15–40%. Anorexia is a major cause of cancer-related malnutrition, although its causes and mechanisms remain incompletely understood. Cancer metabolites may cause anorexia and alter taste perception. Psychological stress also plays an important role. Mechanical gastrointestinal obstruction, pain, depression, constipation, malabsorption, and adverse effects of treatments such as opioids, radiotherapy, and chemotherapy may reduce food intake. Anticancer treatment is also a frequent cause of malnutrition. Chemotherapy can cause nausea, vomiting, abdominal cramps and bloating, mucositis, and paralytic ileus. Several antineoplastic agents, including fluorouracil, adriamycin, methotrexate, and cisplatin, induce severe gastrointestinal complications.[1,2,9,10]

Cancer anorexia involves changes in pathways regulating energy intake, mediated by hormones (such as leptin), neuropeptides (such as neuropeptide Y/NPY), inflammatory cytokines (such as IL-1, IL-6, and TNF-α), and neurotransmitters (such as serotonin and dopamine). Peripheral signals, including hormones and inflammatory cytokines, are transmitted to the hypothalamic arcuate nucleus and alter the balance between appetite-stimulating neurotransmitters (such as NPY and agouti-related peptide/AGRP) and appetite-inhibiting neurotransmitters (opiomelanocortin and cocaine-amphetamine-related factor), thereby changing food intake. Persistent activation of the melanocortin system has been reported in patients with CACS. Tools commonly used to diagnose anorexia in patients with cancer include the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) and the North Center Cancer Treatment Group (NCCTG) questionnaire, which assess appetite and appetite-related symptoms.[9]

Inflammatory Response

Proinflammatory cytokine activity increases during cancer progression, and systemic inflammation is a hallmark of cancer cachexia, reflected by the production of acute-phase response (APR) proteins such as CRP and fibrinogen. Increased APR protein production may increase amino acid requirements, compensated for by increased muscle catabolism. Cachexia frequently accompanies anorexia because of an imbalance between proinflammatory cytokines (e.g., TNF-α, IL-1, IL-6, IFN-γ) and anti-inflammatory cytokines (e.g., interleukin-4/IL-4, interleukin-12/IL-12, interleukin-15/IL-15). Proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IFN-γ cross the blood–brain barrier and interact with brain endothelial cells, causing the release of substances that influence appetite.

These cytokines alter metabolic pathways in muscle, liver, and adipose tissue, collectively contributing to cancer cachexia. TNF-α has been implicated in several cachexia-related mechanisms, including protein and lipid synthesis and degradation, gluconeogenesis, and uncoupling protein expression. It may cause skeletal muscle wasting by activating the NF-κB pathway. Circulating IL-6 levels are elevated in patients with cancer cachexia and can activate signal transducer and activator of transcription 3 (STAT3), which is involved in muscle wasting. Leukemia inhibitory factor, a member of the IL-6 family, is also implicated in cachexia pathogenesis. Unlike patients with anorexia, however, patients with cachexia have low leptin levels (which inhibit appetite) and high ghrelin levels (which stimulate appetite).[9]

Metabolic Changes in Patients with Cancer

Metabolism involves carbohydrates, proteins, and fats. In patients with cancer,

metabolism of these nutrients changes and contributes to weight loss. Hypermetabolism is common, with metabolic rates up to 50% higher than in patients without cancer, although this does not occur in all patients. Several studies have associated increased metabolism with deteriorating nutritional status and tumor type and size. Increased metabolism in cancer may reflect an inability to adapt to low food intake. In healthy individuals, metabolic rate decreases during starvation as a normal adaptive response, whereas this response does not occur in patients with cancer. Differences between starvation-related metabolic disturbances and cancer cachexia are presented in Table 1. Changes in carbohydrate, protein, and fat metabolism are presented in Table 2.[1,2,9,10]

Table 1. Differences between Starvation-Related Metabolic Disturbances and Cancer Cachexia [1,2]

	Starvation	Cancer Cachexia
Basal metabolism	N/ ↓	N/↑/↓
Role of mediators	-	+++
Hepatic ureagenesis	+	+++
Negative nitrogen balance	+	+++
Gluconeogenesis	+	+++
Proteolysis	+	+++
Hepatic protein synthesis	+	+++

Table 2. Metabolic Changes in Patients with Cancer[1]

Protein	Carbohydrates	Fat
- ↑ Turnover - ↓ Muscle synthesis - ↑ Muscle proteolysis - ↑ Hepatic synthesis - Abnormal amino acids	- Glucose intolerance - Insulin resistance - Impaired insulin secretion - ↑ Glucose production - ↑ Cori cycle activity	- ↑ Lipolysis - ↓ Lipogenesis - Hyperlipidemia - ↑ Free fatty acids - ↓ Lipoprotein lipase activity

DIAGNOSIS OF CANCER-RELATED MALNUTRITION

Nutritional assessment in patients with cancer determines nutritional status so that adequate interventions can reduce morbidity and mortality. One study found that almost 52% of malnourished patients were not identified, indicating that clinicians often overlook nutritional problems. The first strategy is therefore routine nutritional screening of all patients with cancer to identify those at risk of malnutrition. Screening may include history-taking and physical examination, while laboratory investigations are required for further assessment. Several instruments are also available for cancer-specific nutritional screening and assessment, including the Malnutrition Screening Tool (MST), Mini Nutritional Assessment (MNA), Patient-Generated Subjective Global Assessment (PG-SGA), and Nutritional Risk Screening (NRS-2002).[1,3,6,12,13,14,15,16,17,18]

Jensen et al. distinguished starvation-related malnutrition (chronic starvation without inflammation), chronic disease-related malnutrition (chronic mild-to-moderate inflammation), and acute disease- or injury-related malnutrition (severe acute inflammation). Starvation-related malnutrition results from chronic undernutrition in patients without signs of inflammation. General diagnostic criteria for disease-related malnutrition are BMI <18.5 kg/m^2, unintentional weight loss >10% in the preceding 3–6 months, or BMI <20 kg/m^2 together with unintentional weight loss >5% in the preceding 3–6 months. Evans et al. described cachexia criteria as 5% weight loss over $\leq$12 months due to a pre-existing condition, plus three of the following: reduced muscle strength, fatigue, anorexia, a low fat-free mass index, or abnormal blood chemistry (CRP >5.0 mg/L, IL-6 >4.0 pg/mL, anemia with Hb <12 g/dL, and albumin <32 g/L). Fearon et al. described cachexia as the presence of two of three criteria: weight loss ≥10%, low food intake ≤1,500 kcal/day, and systemic inflammation (CRP ≥10 mg/L). [19]

History-Taking

Patients should be asked about cancer type and stage, anticancer treatment, and treatment-related adverse effects to establish the disease history. Nutritional history should include weight change, its duration and magnitude, changes in appetite, nausea, vomiting, and taste disturbances. Dietary patterns and habits, food intolerance, and dietary intake should be assessed to determine the proportions of calories, protein, carbohydrates, and fat, along with changes in gastrointestinal function, difficulty eating, malabsorption, and altered bowel habits.

Unintentional weight loss is a key indicator of cancer-related malnutrition. Premorbid weight should be established, particularly when unintentional weight loss or reduced appetite is reported. Weight loss exceeding 5% over 6 months raises suspicion of cachexia, especially when accompanied by muscle wasting. Unintentional weight loss of 10% indicates severe malnutrition and supports a diagnosis of anorexia-cachexia syndrome.

Dietary assessment includes recent food and fluid intake, previous intake, and any changes. This can be established by asking about subjective appetite loss and reduced food intake. Quantitative data can be obtained using an appetite score from 0 to 7 (0=no appetite, 1=very poor appetite, 2=poor appetite, 3=fair appetite, 4=good appetite, 5=very good appetite, 6=excellent appetite, 7=always hungry).[1,6]

Physical Examination

A comprehensive general physical and anthropometric examination includes body weight, height, BMI, mid-upper arm circumference, subcutaneous fat thickness, tissue wasting, edema or ascites, signs of vitamin and mineral deficiencies, and functional status. Muscle wasting and loss of adipose tissue should be noted as late signs of malnutrition. Body composition can be assessed using bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), and body densitometry.[1,6,17,18]

A commonly used anthropometric measure is BMI, calculated as body weight in kilograms divided by height in meters squared. BMI is an indicator of chronic malnutrition. A BMI <18.5 kg/m^2 is considered low and is associated with poor outcomes and higher mortality in patients with cancer, as is a BMI >30 kg/m^2 (obesity). In older adults, the threshold for underweight is higher, at <22 kg/m^2. BMI has limitations: fluid overload and edema can cause bias, and it does not describe body composition (for example, a high BMI in individuals with obesity and muscular athletes). Unintentional weight loss is particularly important in nutritional assessment because it indicates a catabolic metabolic state and is associated with greater morbidity and mortality.[18]

One of the simplest and least expensive noninvasive methods is measurement of limb circumference (such as mid-upper arm or calf circumference) and skinfold thickness (SFT). Subcutaneous adipose tissue generally represents half of total body fat, and SFT provides information about energy stores, particularly fat (triglycerides). To estimate total body fat, four skinfolds should be measured: 1) biceps; 2) triceps; 3) subscapular; and 4) suprailiac.[18]

Other anthropometric methods include BIA and DEXA. BIA assesses body composition, including water, musculoskeletal mass, and particularly body fat. It is one of the most popular methods for estimating body fat. BIA is a noninvasive, rapid, simple, inexpensive, and consistent examination available in hospitals to assess body tissues and estimate total body water and fat-free mass. BIA is not recommended in patients with fluid overload, extreme BMI (<16 or >34 kg/m^2), intensive care patients, or older people. DEXA is currently considered the gold standard for measuring body composition. Its use in clinical practice and research is increasing despite radiation exposure. DEXA relies on analysis of radiological density (usually at the hip and spine) and is a useful indirect method for measuring fat mass, fat-free mass, and bone mineral mass.[18]

Laboratory Investigations

Laboratory investigations include albumin, prealbumin, 24-hour nitrogen balance, iron levels, immune assessment through total lymphocyte count, liver and kidney function, electrolytes, and serum minerals. Baseline serum CRP may identify patients with deteriorating nutritional status. This is associated with an active inflammatory response and is recognized as a precursor to cachexia.[1,6,18]

Identifying biomarkers that accurately diagnose cancer-related malnutrition at an early stage and predict progression and outcomes would significantly affect treatment and survival in patients with cancer. Potential diagnostic and prognostic biomarkers in CACS include IL-1β, IL-6, IL-8, ghrelin, leptin, angiotensin II, and growth differentiation factor 15 (GDF-15).[9]

Nutritional Screening and Assessment in Patients with Cancer

Patients with cancer at high risk of malnutrition can be identified using simple,

noninvasive instruments sufficiently sensitive to predict current and potential future nutritional deterioration related to the disease process. Nutritional screening should ideally be performed before anticancer treatment begins so that dietary recommendations can be aligned with the treatment schedule. Common tools in oncology include NRS-2002, MST, PG-SGA, and MNA.

Wilkes and Allen (2018) strongly recommended PG-SGA for nutritional assessment in patients with cancer because it is designed to measure cancer-related effects or adverse effects; most patients undergo chemotherapy, which can cause anorexia, nausea, and vomiting. In addition to PG-SGA, Shiroyama et al. (2017) recommended MNA for older patients with cancer receiving palliative care because it is simple, comprehensively assesses factors affecting nutritional status, and has been validated in many countries. In Indonesia, MNA is more commonly used to assess nutritional status in older adults.[1,3,9,12,13,14,15,16,17,18,19,20,21]

MANAGEMENT OF CANCER-RELATED MALNUTRITION

Nutrition is important in cancer prevention and recovery. Factors influencing nutritional therapy include the locations of the primary tumor and metastases, clinical symptoms, treatment type, potential adverse effects, and the effects of malignancy on food intake, nutrient absorption, and utilization. General nutritional management aims to provide sufficient calories and protein, correct nutritional deficits, prevent immunosuppression, and minimize weight loss. The European Society for Clinical Nutrition and Metabolism (ESPEN) practical guideline on 'Clinical Nutrition in Cancer' provides recommendations for identifying, preventing, and treating malnutrition in patients with cancer, covering general and specific therapies, as shown in Figure 2.[1,5,22,23]

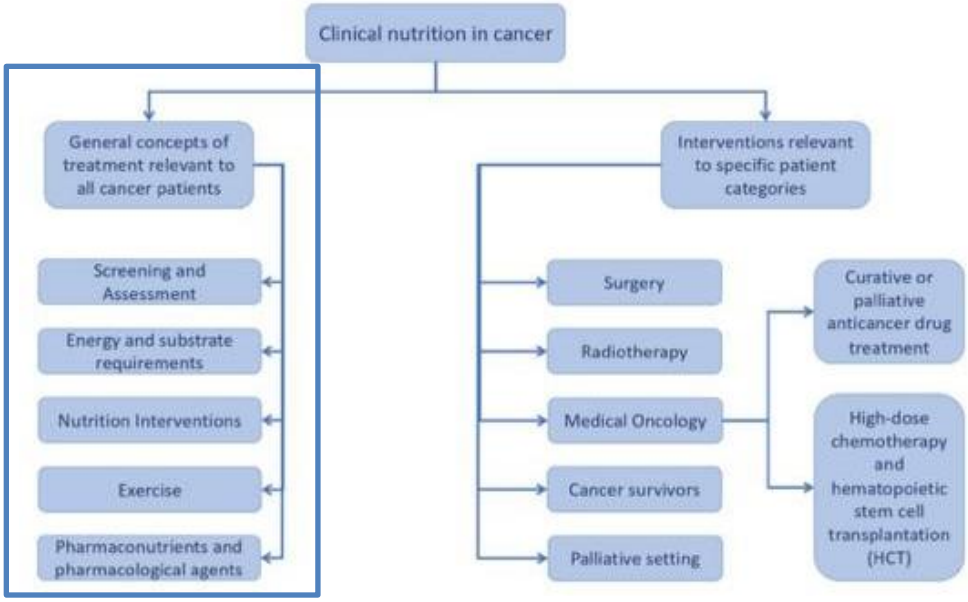


Figure 2. Clinical Nutrition in Cancer[23]

NUTRITIONAL THERAPY FOR CANCER-RELATED MALNUTRITION

Energy Requirements

Energy requirements are determined by calculating basal energy expenditure or basal metabolic rate using the Harris–Benedict equation multiplied by activity and stress factors. Energy and protein requirements are generally recommended to correspond to moderate stress, with approximately 0–20% for solid tumors. A simpler approach recommends 25–35 kcal/kg body weight to maintain nutritional status and 40–50 kcal/kg body weight to replenish body reserves in underweight patients. Additional calories are required during infection according to its severity. Calories should be increased slightly more than protein intake; if weight loss continues despite a high protein intake, protein will be used for energy rather than structural repair. Therefore, caloric provision should be considered alongside protein intake.[1,2,4,6,22,23]

Protein Requirements

Most patients with cancer have a negative nitrogen balance. Nutritional support should therefore meet requirements for protein synthesis and reduce protein degradation. Suggested protein intakes are 0.8–1.0 g/kg body weight to maintain normal levels, 1.0–1.5 g/kg body weight as a safe intake in patients without stress, and 1.5 g/kg body weight after bone marrow transplantation. Patients with increased requirements, hypermetabolism, or severe wasting are advised to receive 1.5–2 g/kg body weight. Higher protein intake may be contraindicated in kidney or liver disease. An average of 250 additional calories per day may be added to achieve weight gain within 2 weeks, or 500 additional calories per day to achieve weight gain within 1 week.[1,2,4,6,22,23]

Fat Requirements

Fat may provide 30–50% of total caloric requirements. A greater proportion of food should be offered in the morning, using small, frequent portions. As appetite often declines during cancer treatment, increasing fat is an effective way to maximize caloric intake. Monounsaturated or 'heart-healthy' fats, such as olive, nut, or fish oils, may be recommended to increase caloric density. Each teaspoon of oil, butter, or margarine contains 45–50 calories. Adding a teaspoon of fat to each meal and snack increases intake by approximately 250 calories daily without increasing food volume. Another strategy is to add a tablespoon of heavy cream to each milk-containing food or beverage, increasing its caloric content by approximately 50 calories. Higher fat intake may also help patients with dyspnea because fat requires less oxygen during digestion; higher-fat foods may therefore minimize oxygen requirements.[1,2,4,6,21,23]

Fluid Requirements

Some patients with cancer, particularly those receiving chemotherapy or radiotherapy, are prone to dehydration. Chemotherapy frequently causes nausea, vomiting, and diarrhea, while radiotherapy, especially to the head and neck, may cause dysphagia, pain, edema, and other problems that limit fluid intake. Patients receiving enteral nutrition are also at risk of dehydration if fluid intake is inadequate, whereas fluid overload may occur with parenteral nutrition or oral supplemental fluids. Energy-dense formulas contain less fluid, so adequate additional fluid is necessary. Fluid requirements in patients with cancer are comparable to those in patients without cancer who have no kidney dysfunction (30–35 mL/kg body weight). Fluid balance should be monitored daily.[4,6]

Micronutrient Requirements

Micronutrient deficiencies in patients with cancer may impair immune function, particularly deficiencies of zinc, selenium, vitamin C, vitamin A, vitamin B6, and folate. These may arise from direct tumor effects, cytokines, infection, treatment, or inadequate intake. Vitamin and mineral supplementation is provided when daily dietary intake cannot meet requirements or when treatment-related adverse effects compromise intake. Supplementation may be given at <150% of the recommended daily allowance (RDA).

According to the American Institute for Cancer Research (AICR), patients receiving radiotherapy and chemotherapy should not take antioxidant vitamin and mineral supplements above the upper safe intake levels: vitamin C 2,000 mg/day, vitamin E 250 mg/day, and selenium 400 µg/day. Recommended intakes of potassium, sodium, and chloride are each 45–145 mEq/day, calcium 60 mEq/day, magnesium 35 mEq/day, and phosphate 23 mmol.[4,6,23]

PHYSICAL ACTIVITY

Increasing physical activity in patients with cancer helps maintain muscle mass, physical function, and metabolic patterns. Physical activity is generally well tolerated and safe across different cancer stages, including advanced disease in patients who are able and willing to exercise. Activities may include home-based or supervised moderate-intensity training (50–75% of baseline maximum heart rate or aerobic capacity), performed three times weekly for 10–60 minutes per session. Physical activity is associated with maintenance or improvement of aerobic capacity, muscle strength, health-related quality of life, and self-esteem, as well as reduced fatigue and anxiety. For some patients, encouraging daily walking may help reduce the risk of inactivity-related muscle atrophy. In addition to aerobic exercise, individualized

resistance training is recommended to preserve muscle strength and mass.[23]

PHARMACOLOGICAL THERAPY FOR CANCER-RELATED MALNUTRITION

Current treatment and prevention strategies for cancer-related malnutrition include nutritional interventions, appetite stimulation, anti-inflammatory agents, growth factors, anabolic agents, and pharmaconutrients. In recent years, several potential pharmacological agents have been investigated through mechanisms including: (1) inhibition of cytokine and other factor production/release; (2) gastroprokinetic activity with or without antiemetic effects; (3) inhibition of the Cori cycle; (4) inhibition of fat and tissue wasting; (5) appetite stimulation with or without antiemetic effects; and (6) anxiolytic/antidepressant effects. On this basis, pharmacological interventions are classified as first-line agents (glucocorticoids and progestational agents) and second-line agents (unproven or under investigation), including cannabinoids, nonsteroidal anti-inflammatory drugs (NSAIDs), omega-3 fatty acids (EPA and DHA), cyproheptadine, branched-chain amino acids, metoclopramide, 5′-deoxy-5-fluorouridine, melatonin, thalidomide, β2-adrenoceptor agonists, other anabolic steroids, pentoxifylline, hydrazine sulfate, statins, angiotensin-converting enzyme inhibitors, and selective androgen receptor modulators. Agents are selected individually according to the cause of cancer-related malnutrition. Their mechanisms and pharmacological interventions are shown in Figure 3.[7]

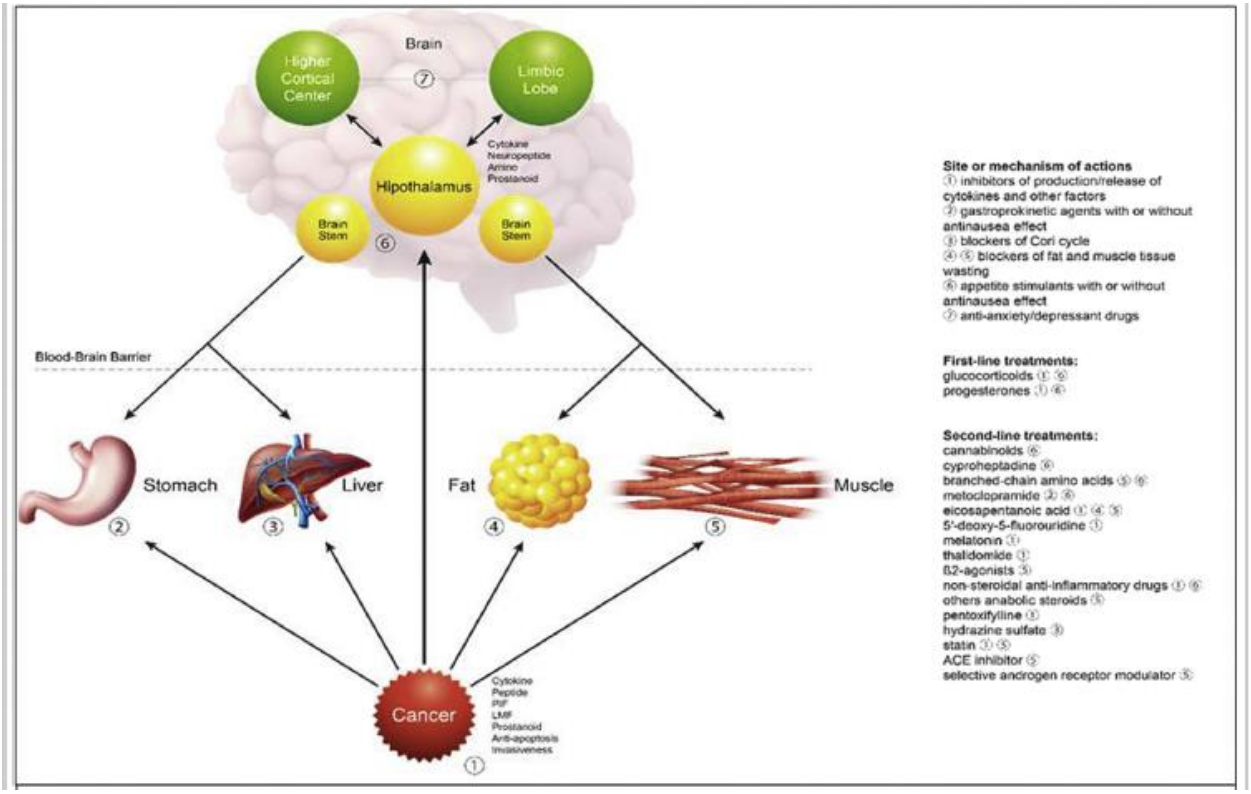


Figure 3. Mechanisms of Action and Pharmacological Interventions for Cancer-Related Malnutrition[7]

Progestogens were the first agents used to treat cancer cachexia and are currently among the treatments approved in Europe. Megestrol acetate and medroxyprogesterone acetate (MPA) have comparable efficacy. Positive effects of oral megestrol acetate on body weight and health have been observed at 160–1,600 mg/day. MPA is used at 300–4,000 mg/day. Both agents have adverse effects, including increased risks of thromboembolic events, peripheral edema, bleeding, hyperglycemia, hypertension, and Cushing syndrome.[12,23,24]

The ESPEN guideline provides several pharmacological recommendations for cancer-related malnutrition: 1) Corticosteroids are recommended to improve appetite in patients with advanced cancer and anorexia for a limited period (1–3 weeks), with caution regarding adverse effects such as muscle wasting, insulin resistance, and infection. Their antianorectic

effect is temporary and disappears after several weeks, when myopathy and immunosuppression become apparent. Insulin resistance is an early metabolic adverse effect, whereas osteopenia is a long-term effect. Because adverse effects develop with prolonged use, corticosteroids are more suitable for patients with a short life expectancy; 2) Progestins are recommended to improve appetite in advanced cancer with anorexia, but may cause serious adverse effects such as thromboembolism. Megestrol acetate and MPA increase appetite and body weight, but not fat-free mass, and may also cause impotence, thromboembolism, and death; 3) Long-chain n-3 fatty acids or fish oil may stabilize or improve appetite, lean body mass, and weight in patients with advanced cancer receiving chemotherapy who are at risk of weight loss. They are generally well tolerated, although mild gastrointestinal effects, such as a fishy taste or fishy belching, may reduce adherence; 4) Prokinetic agents may be suggested for early satiety, while considering the potential central nervous system adverse effects of metoclopramide and cardiac rhythm effects of domperidone; 5) Branched-chain amino acids or other metabolites may be supplemented to increase fat-free mass. Data indicate that impaired protein balance and muscle anabolic resistance in cancer may be overcome by simultaneous insulin and amino acid administration. In a randomized study of 338 patients with cancer cachexia, daily insulin (0.11 IU/kg/day) in addition to basic supportive care increased whole-body fat, but not lean body mass. β-Hydroxy-β-methylbutyrate (HMB), a leucine metabolite, at a usual dose of 3 g/day may act as an anticatabolic agent that minimizes protein breakdown; 6) NSAIDs may reduce tumor release of acute-phase proteins and cytokines. They may increase weight, with some evidence of effects on physical performance, quality of life, and inflammatory parameters; 7) Cannabinoids may improve taste disturbances or anorexia, but clinical evidence is insufficiently consistent to recommend their use in cancer-related malnutrition; 8) Androgenic steroids may increase muscle mass, but consistent clinical evidence is currently insufficient to recommend them. Free testosterone is often reduced in advanced cancer. A randomized trial of 37 patients with non-small cell lung cancer (NSCLC) receiving chemotherapy compared nandrolone decanoate (200 mg/week) with no additional treatment; the nandrolone group showed a tendency toward less weight loss. An RCT of 475 patients with cancer cachexia compared steroids, progestins, and fluoxymesterone. Fluoxymesterone (20 mg/day) produced less appetite stimulation than megestrol acetate (800 mg/day) and dexamethasone (3 mg/day), while discontinuation rates due to toxicity were similar across the three groups.[23]

ROUTES OF NUTRITIONAL SUPPORT

Oral and Enteral Nutrition

Oral nutrition is the preferred route of nutritional support. However, anorexia, nausea, taste changes, and dysphagia may complicate oral feeding and require particular attention. Most patients tolerate small, frequent meals. High-calorie foods and beverages are recommended to increase intake. For patients with swallowing difficulties, soft or liquid foods may be offered at room temperature or chilled. Enteral nutrition is indicated when intake remains below 60% of requirements for 10–14 days. Nutritional interventions in patients with cancer are shown in Figure 4.[1,2,6,7,10,14,19,23,25,26,27,28,29,30]

Enteral nutrition is indicated for patients unable to eat because of mechanical obstruction or prolonged anorexia, or unable to eat orally because of treatment-related adverse effects such as odynophagia, mucositis, or esophagitis. In patients with adequate gastrointestinal function, enteral nutrition may be delivered through nasogastric, gastric, duodenal, or jejunal access according to tumor location, using bolus, intermittent, or continuous administration. Enteral nutrition helps normalize intestinal function and is less expensive, less invasive, and associated with fewer risks than parenteral nutrition. Short-term enteral nutrition (<4–6 weeks) may use a nasogastric tube (NGT), whereas long-term feeding (>4–6 weeks) uses percutaneous endoscopic gastrostomy (PEG). Nasogastric feeding does not affect tumor response or cause adverse effects related to chemotherapy. Routine nasogastric tube placement is unnecessary unless ileus is threatened or nutritional intake is inadequate.[1,2,6,7,10,14,19,23,25,26,27,28,29,30]

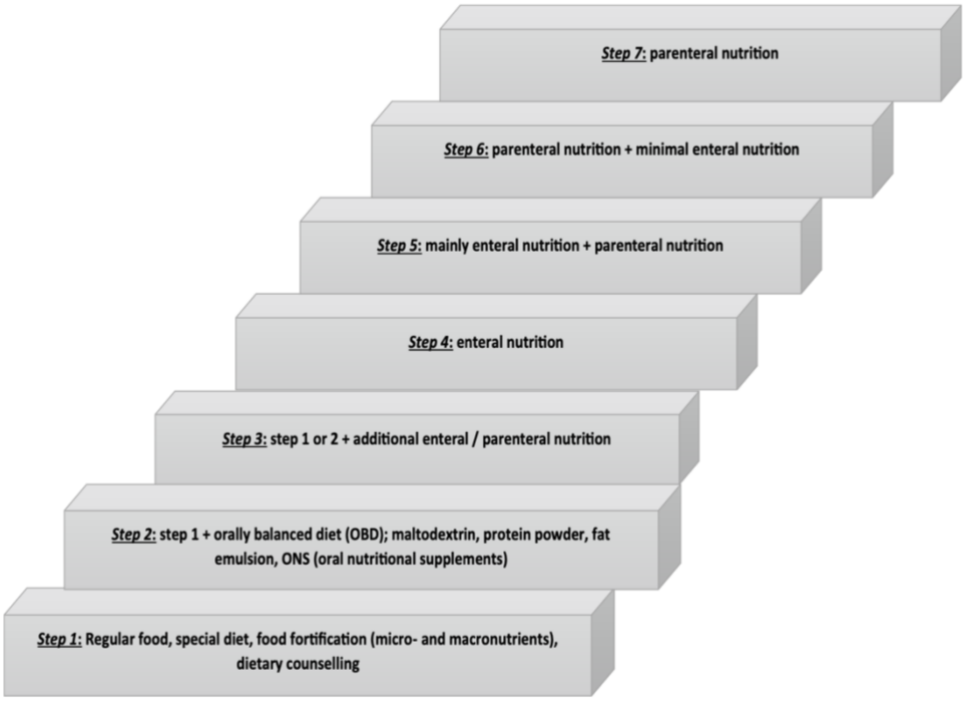


Figure 4. Nutritional Interventions in Patients with Cancer[19]

Parenteral Nutrition

Parenteral nutrition is primarily indicated as specific nutritional support when patients with cancer have gastrointestinal dysfunction and/or inadequate oral or enteral nutrition. Indications include: a) gastrointestinal feeding is contraindicated; b) gastrointestinal feeding is not feasible; c) the gastrointestinal tract is ineffective; and d) oral and/or enteral nutritional intake is inadequate.[31]

The composition of parenteral nutrition depends on each patient's requirements. Long-term parenteral nutrition is recommended for severe radiation-induced mucositis or enteritis. It is also needed when patients cannot tolerate gastrointestinal feeding because of nausea, vomiting, severe diarrhea, complete or mechanical bowel obstruction, or malabsorption. Close monitoring is required to prevent complications, including fluid overload, hyperglycemia, electrolyte disturbances, and infection. Access routes are the same in patients with and without cancer and are shown in Table 3; complications are shown in Table 4.[1,2,6,7,10,14,19,23,25,26,27,28,29,30,31,32]

Table 3. Access Routes for Parenteral Nutrition[29]

Routes	Characteristics
Peripheral	It will be used if central access is not available and a short-term duration (less than 7–10 days) is expected. It is percutaneously inserted peripherally. It is inexpensive, simple to use, and has a low incidence of infection associated with a catheter. The drawbacks are that the osmolarity of the mixture should not exceed 800 mOsm/L and should be rotated every 48–72 h due to the incidence of phlebitis.
Central	They can be of four types :
a. Central percutaneous catheter	Implanted by a physician in the subclavian, jugular, or femoral vein. It is economical and easily replaceable. It is only used for short-term parenteral support, requires suture for fixation, and has a high incidence of infection.
b. Peripherally inserted central catheter (PICC)	It has the advantage that it can be implanted by graduates in nursing. It admits any composition and osmolarity of the mixture. It can be somewhat more complicated to handle for the patient with ulnar access in case of home support.
c. (Hickman-type) tunneled catheter	It is implanted in the subclavian or jugular vein in the operating room by vascular radiologists or surgeons. The single-lumen one is preferable as it minimizes the possibility of infection. It is easily manageable by the patient in case of home support, so it is the most advisable in such cases. It has the cosmetic disadvantage that it is visible from the outside.
d. Reservoir or port-a-cath	It consists of a subcutaneous reservoir or port that is radiopaque and usually made of titanium, with a very resistant self-sealing silicone membrane. It is implanted in the subclavian or jugular vein in the operating room by vascular radiologists or surgeons. The body image is not altered since it is subcutaneous, and it lacks external elements that can be damaged. It is preferred in cancer patients who require repeated or continuous vascular access for the administration of chemotherapy, blood, or medications. The disadvantage is the need for a special needle called a Gripper or Huber needle that must be changed weekly.

Table 4. Complications of Parenteral Nutrition[31]

	Types of Complications
Mechanical	These complications are related to the placement, but especially the maintenance, of the catheter. With OPN, catheter occlusion and venous thrombosis are particularly common.
Infectious	These are the complications most commonly seen in patients with PN, and mainly include catheter-related bacteremia and/or sepsis.
Metabolic	These are acute metabolic complications such as hyperglycemia/ hypoglycemia, water and electrolyte changes, and refeeding syndrome, and long-term complications resulting from the effects of TPN on liver and bone. Liver disease occurs as steatosis, intrahepatic cholestasis, biliary sludge, or cholelithiasis. To prevent this complication, ESPEN recommends not supplying more than 1 g/kg of fat, adjusting calorie supply, and infusing PN cyclically (grade of recommendation B). Metabolic bone disease is characterized by the presence of osteomalacia, osteoporosis, pain, or bone fractures. Factors related to PN such as hypercalciuria, aluminum toxicity, vitamin D deficiency or toxicity, and protein overload are involved in this condition.
Psychosocial	PN may impact on patient quality of life.

Parenteral nutrition is intravenous provision of nutrients outside the gastrointestinal tract. Total parenteral nutrition (TPN) is used when intravenous nutrition is the patient's sole source of nutrition. TPN is used in the management and treatment of malnutrition. Enteral nutrition is usually preferred because it is less expensive and associated with fewer complications, but requires a functioning gastrointestinal system. TPN combines lipid emulsions, dextrose, amino acids, vitamins, electrolytes, and minerals. Its composition must be individualized. The three main macronutrients are lipid emulsions, protein, and dextrose.[31,32]

Lipid emulsions provide calories and prevent fatty acid deficiency. Essential fatty acid deficiency may develop within 3 weeks of lipid-free TPN. Lipids may provide 25–30% of total calories. **Protein** consists of essential and nonessential amino acids, except arginine and glutamine. Healthy adults require 0.8–1 g/kg/day, adjusted according to clinical condition. Critically ill patients require 1.5 g/kg/day; patients with chronic kidney failure receive 0.6–0.8 g/kg/day; acute hepatic encephalopathy requires temporary protein restriction to 0.8 g/kg/day; and patients receiving hemodialysis require 1.2–1.3 g/kg/day. **Carbohydrates** are administered as dextrose monohydrate at various concentrations, most commonly 40%, 50%, and 70%. The maximum glucose utilization rate is 5–7 mg/kg/minute. Excessive carbohydrate supplementation may cause hyperglycemia and hypertriglyceridemia. **Electrolytes and vitamins** are micronutrients whose doses can be adjusted to recommended daily requirements. Recommended electrolytes per liter of parenteral nutrition are sodium 100–150 mEq, magnesium 8–24 mEq, calcium 10–20 mEq, potassium 50–100 mEq, and phosphorus 15–30 mEq.[31,32]

Total nutrient admixtures are 3-in-1 solutions containing three macronutrients: dextrose, amino acids, and lipid emulsions. A 3-in-1 solution incorporates intravenous lipid emulsion together with electrolytes, vitamins, and water. Parenteral nutrition containing only dextrose and amino acids, with a separate intravenous lipid infusion, may also be administered as a 2-in-1 solution. Current TPN amino acid mixtures remain incomplete, containing only 19 amino acids. Glutamine, a nonessential amino acid, has been used to supplement TPN (glutamine at 8–10% in parenteral nutrition is supplemental).[31,32]

Total parenteral nutrition is not administered through a peripheral intravenous catheter as peripheral parenteral nutrition (PPN) because of its high osmolarity. PPN osmolarity should be below 900 mOsm. Lower concentrations require larger volumes and a high lipid content. High osmolarity may irritate peripheral veins, so TPN should preferably use central venous access. PPN provides supplemental nutrition for patients with a functioning gastrointestinal tract and as an addition to enteral nutrition.[31,32]

According to American Society for Parenteral and Enteral Nutrition (ASPEN) guidance, TPN monitoring includes: a) Patients newly receiving TPN should be monitored daily until stable, with more frequent monitoring if metabolic abnormalities occur or refeeding syndrome is a risk. Refeeding syndrome can occur when severely malnourished or cachectic individuals resume feeding and may cause severe electrolyte instability. Classic biochemical

features include hypophosphatemia, abnormal sodium and fluid balance, altered glucose, protein, and fat metabolism, thiamine deficiency, hypokalemia, and hypomagnesemia. Before and during nutritional replenishment, vitamin B1 should be given at 200–300 mg/day with a balanced micronutrient mixture. The following electrolytes should be monitored and replaced if necessary by oral, enteral, or parenteral routes: potassium (approximately 24 mmol/kg/day), phosphate (approximately 0.3–0.6 mmol/kg/day), and magnesium (approximately 0.2 mmol/kg/day intravenously or 0.4 mmol/kg/day orally). Refeeding syndrome may be associated with hypophosphatemia, respiratory disturbances, rhabdomyolysis, and acute kidney injury. Prevention is essential and may involve starting TPN at a slower infusion rate; b) Unstable and critically ill patients should be monitored daily until stable; c) Stable inpatients without formulation changes for 1 week should be monitored every 2–7 days; d) Stable inpatients, home-care patients, or long-term care patients without formulation changes for 1 week should be monitored every 1–4 weeks if clinically stable.[23,30]

CONCLUSION

Cancer-related malnutrition has four main characteristics: anorexia; changes in inflammatory, metabolic, and endocrine processes; increased tissue protein turnover; and muscle mass loss. Its causes are multifactorial and include reduced food intake, malabsorption, an inflammatory response, and altered or disturbed metabolism.

Cancer-related malnutrition is diagnosed through history-taking, physical examination, and laboratory investigations. Instruments used to assess nutritional status include MST, MNA, NRS-2002, and PG-SGA. Management comprises general nutritional care, physical activity, and pharmacological therapy. Early nutritional support before signs of malnutrition develop may improve prognosis, whereas support after malnutrition has occurred helps prevent disease progression.

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