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ESPEN Guideline

ESPEN practical guideline: Clinical Nutrition in cancer

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SUMMARY

Background: This practical guideline is based on the current scientific ESPEN guidelines on nutrition in cancer patients.
Methods: ESPEN guidelines have been shortened and transformed into flow charts for easier use in clinical practice. The practical guideline is dedicated to all professionals including physicians, dieticians, nutritionists and nurses working with patients with cancer.
Results: A total of 43 recommendations are presented with short commentaries for the nutritional and metabolic management of patients with neoplastic diseases. The disease-related recommendations are preceded by general recommendations on the diagnostics of nutritional status in cancer patients.
Conclusion: This practical guideline gives guidance to health care providers involved in the management of cancer patients to offer optimal nutritional care.

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Abbreviations

BMI	body mass index
EN	enteral nutrition
ERAS	enhanced recovery after surgery
GI	gastrointestinal
HMB	β-Hydroxy-β-methyl butyrate
HSCT	hematopoietic stem cell transplantation
NSAID	Non-steroidal anti-inflammatory drug
ONS	oral nutritional supplements
PEG	percutaneous endoscopic gastrostomies
PN	parenteral nutrition
RCT	randomized controlled trial
REE	resting energy expenditure
RIG	radiologically inserted gastrostomies
TEE	total energy expenditure
THC	Tetrahydrocannabinol

1. Introduction

Neoplastic diseases represent the second leading cause of death worldwide and the number of new cases is expected to rise significantly over the next decades. Malnutrition is a common feature in cancer patients and is the consequence of both the presence of the tumor and the medical and surgical anticancer treatments. Malnutrition negatively impacts on quality of life and treatment toxicities, and it has been estimated that up to 10–20% of cancer patients die due to consequences of malnutrition rather than for the tumor itself. Thus, nutrition plays a crucial role in multimodal cancer care. Robust evidence indicates that nutritional issues should be taken into account since the time of cancer diagnosis, within a diagnostic and therapeutic pathway, and should be running in parallel to antineoplastic treatments. However, worldwide, cancer-related malnutrition is still largely unrecognized, underestimated and undertreated in clinical practice,. These evidence-based guidelines were developed to translate current best evidence and expert opinion into recommendations for multi-disciplinary teams responsible for the identification, prevention, and treatment of reversible elements of malnutrition in adult cancer patients.

2. Methodology

The present practical guideline consists of 43 recommendations and is based on European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients [1]. The original guideline was shortened by restricting the commentaries to the gathered evidence and literature on which the recommendations are based on. The recommendations were not changed but the presentation of the content was transformed into a graphical presentation consisting of decision-making flow charts wherever possible. The original guideline was developed based on the ESPEN framework for disease-specific guidelines [2] and topics to be covered were decided through several rounds of discussion and modification, searching for meta-analyses, systematic reviews and comparative studies based on clinical questions according to the PICO format. The evidence was evaluated and merged to develop clinical recommendations using the GRADE method. All recommendations were not only based on evidence but also underwent a consensus process, which resulted in a percentage of agreement (%). Whenever possible, representatives from different professions (physicians, dieticians, nurses, others) as well as patient representatives were involved. Members of the guideline group were selected by ESPEN to include a range of professions and fields of expertise. The guideline process was commissioned and financially supported by ESPEN and by the European Partnership for Action Against Cancer (EPAAC), an EU level initiative. The guideline shortage and dissemination was funded in part by the United European Gastroenterology (UEG) society, and also by the ESPEN society. For further details on methodology, see the full version of the ESPEN guideline [1] and the ESPEN framework for disease-specific guidelines [2]. The ESPEN practical guideline “Clinical Nutrition in Cancer” has been structured according to a flow chart covering all nutritional aspects of cancer (Fig. 1).

3. General concepts of treatment relevant to all cancer patients

3.1. Screening and assessment (Fig. 2)

1) To detect nutritional disturbances at an early stage, we recommend to regularly evaluate nutritional intake, weight change, and body mass index (BMI), beginning with cancer diagnosis and repeated depending on the stability of the clinical situation. (Recommendation B1-1; strength of recommendation strong – level of evidence very low – strong consensus)
2) In patients with abnormal screening, we recommend objective and quantitative assessment of nutritional intake, nutrition impact symptoms, muscle mass, physical performance and the degree of systemic inflammation. (Recommendation B1-2; strength of recommendation strong – level of evidence very low – consensus)

3.2. Energy and substrate requirements

3) We recommend that the total energy expenditure (TEE) of cancer patients, if not measured individually, be assumed to be similar to healthy subjects and generally ranging between 25 and 30 kcal/kg/day. (Recommendation B2-1; strength of recommendation strong – Level of evidence low – consensus)

Commentary

It is well known that an insufficient diet leads to chronic malnutrition. To maintain a stable nutritional state, the diet has to meet the patient's energy requirements which are the sum of the resting energy expenditure (REE), physical activity, and, in a small percentage, of diet-induced thermogenesis. In cancer patients, REE determined by indirect calorimetry, the gold standard, has been reported to be unchanged, increased, or decreased in relation to non-tumor bearing controls [3]. In a large study from the group at Lundholm [4], approximately 50% of all cancer patients who were losing weight were hypermetabolic when compared to appropriate controls allowing for similarity in physical activity, body composition, age, and weight loss. Similarly, in newly diagnosed cancer patients 47% were hypermetabolic and displayed a higher ratio of measured versus predicted REE per kg of fat-free mass [5]. While REE is increased in many cancer patients, when TEE is considered, this value appears to be lower in patients with advanced cancer when compared to predicted values for healthy individuals the main cause appears to be a reduction in daily physical activity [6,7]. In conclusion, it appears sensible to initiate nutrition therapy assuming TEE to be similar to healthy controls. TEE may be estimated from standard formulas for REE and standard values for physical activity level [7].

4) We recommend that protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day. (Recommendation B2-2;

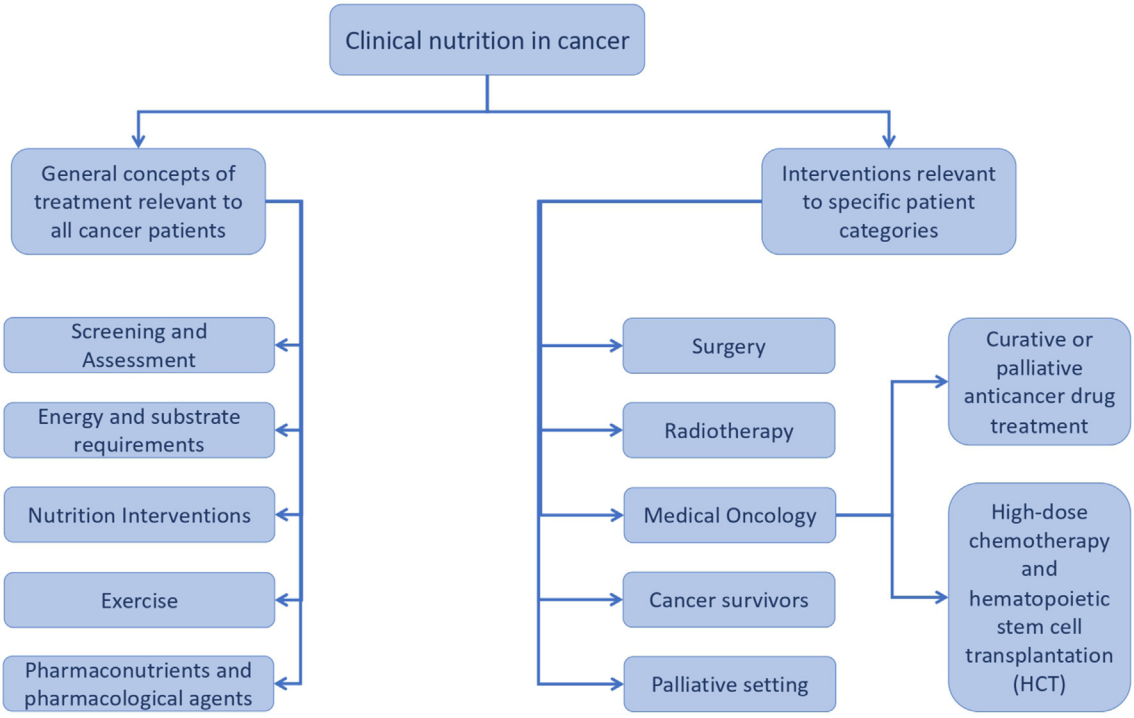

Fig. 1. Structure of the ESPEN practical guideline: "Clinical nutrition in cancer".

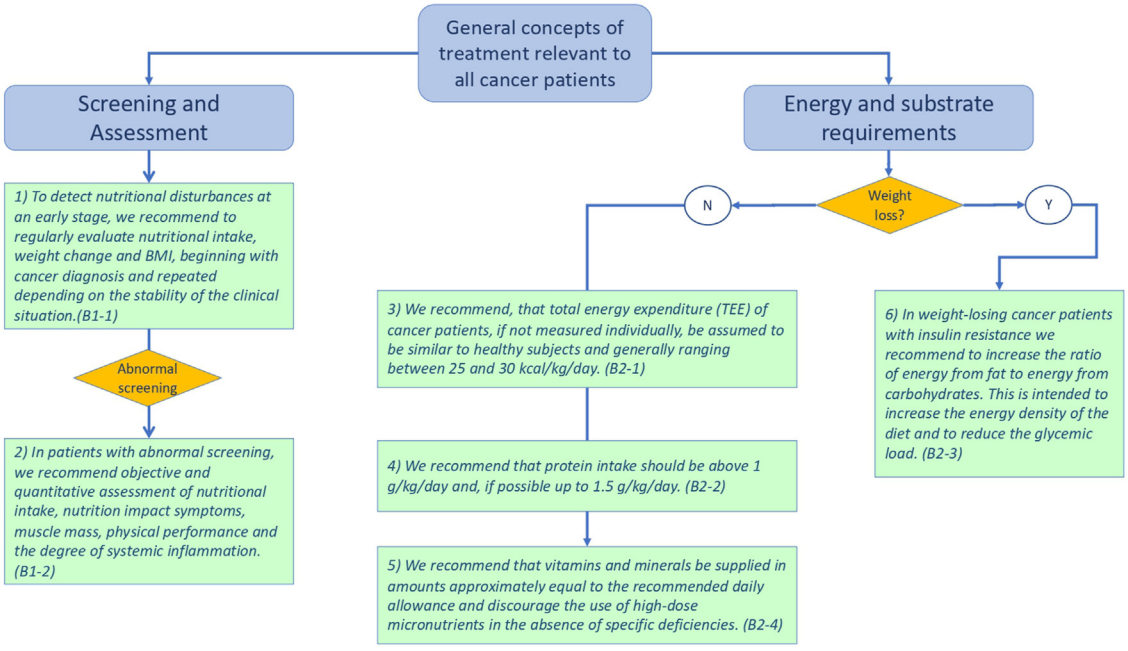

Fig. 2. General concepts of treatment relevant to all cancer patients: screening and assessment; energy and substrate requirements.

strength of recommendation strong – Level of evidence moderate – strong consensus)

Commentary

Muscle protein synthesis is not blunted in patients with cancer. Several studies suggest that this process is not impaired and remains responsive to the dietary supply of amino acids, albeit a somewhat higher quantity amino acids (proteins) than in young, healthy individuals [8]. Data regarding the nutritional quality of proteins in cancer patients are very scarce [9–11].

5) We recommend that vitamins and minerals be supplied in amounts approximately equal to the recommended daily allowance and discourage the use of high-dose micronutrients

in the absence of specific deficiencies. (Recommendation B2-4; strength of recommendation strong – Level of evidence low – strong consensus)

Commentary

An estimated 50% of all cancer patients consume complementary or alternative medical products [12]; a large fraction of this is accounted for by multivitamin supplements.

Deficiency of vitamin D has been associated with cancer incidence [13] but a meta-analysis of 40 randomized controlled trials (RCTs) reported that vitamin D supplementation with or without calcium did not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15% [14]. Other systematic reviews arrived at a similar conclusion [15].

In an RCT 14,641 US physicians combined supplementation with vitamin E (400 IU/day) and vitamin C (500 mg/day) for an average of ten years was without any effect on cancer incidence [16]. Neither long-term supplementation with vitamin E (400 IU/day) nor selenium (200 μg from selenomethionine) had a beneficial effect on the incidence of prostate cancer [17].

6) In weight-losing cancer patients with insulin resistance, we recommend to increase the ratio of energy from fat to energy from carbohydrates. This is intended to increase the energy density of the diet and to reduce the glycemic load. (Recommendation B2-3; strength of recommendation strong – Level of evidence low – consensus)

Commentary

In patients with insulin resistance, uptake and oxidation of glucose by muscle cells are impaired; however, utilization of fat is normal or increased thus suggesting a benefit for a higher fat to carbohydrate ratio. Fat is efficiently mobilized and utilized as a fuel source in cancer patients [18]. Compared to healthy subjects the metabolic clearance of different lipid emulsions was increased in weight-stable and even more in weight-losing cancer patients [19]. Furthermore, there are additional advantages to replacing glucose with lipids in parenteral nutrition (PN) regimens. It appears prudent to try to limit the infectious risks associated with hyperglycemia, which, albeit mainly reported in the non-oncologic setting, may be similarly expected in cancer patients with insulin resistance.

There have been no clinical studies comparing the effects of different fat emulsions on outcomes in cancer patients, the role of these alternative emulsions is still not clearly defined.

3.3. Nutrition interventions (Fig. 3)

7) We recommend nutritional intervention to increase oral intake in cancer patients who are able to eat but are malnourished or at risk of malnutrition. This includes dietary advice, the treatment of symptoms and derangements impairing food intake (nutrition impact symptoms), and offering oral nutritional supplements (ONS). (Recommendation B3-1; strength of recommendation strong – Level of evidence moderate – consensus)

Commentary

Nutritional therapy should preferably be initiated when patients are not yet severely malnourished. The first form of nutritional support should be nutrition counseling to help manage symptoms and encourage the intake of protein- and energy-rich foods and fluids that are well tolerated; a diet enriched in energy and protein is the preferred way to maintain or improve nutritional status. The additional use of ONS is advised when an enriched diet is not effective in reaching nutritional goals. Medical nutrition is indicated if patients are unable to eat adequately (e.g. less than 50% of the requirement for more than one week or only 50–75% of the requirement for more than two weeks). If a decision has been made to feed a patient, we recommend enteral nutrition (EN) if oral nutrition remains inadequate despite nutritional interventions (counseling, ONS), and PN if EN is not sufficient or feasible. Nutritional therapy in cancer patients who are malnourished or at risk of malnutrition has been shown to improve body weight and energy intake but not survival [20,21]. In patients undergoing (adjuvant) radiotherapy, there is good evidence that nutritional support improves also some aspects of quality of life [22], but these results have not yet been confirmed in patients undergoing chemotherapy [20,23].

8) We recommend not to use dietary provisions that restrict energy intake in patients with or at risk of malnutrition. (Recommendation B3-2; strength of recommendation strong – Level of evidence low – strong consensus)

Commentary

We recommend against all forms of diets that are not based on clinical evidence, have no proven efficacy, and that potentially could be harmful. There are no diets known to reproducibly cure cancer or prevent cancer recurrence. In many cases, the supporting arguments are neither based on scientific reasoning nor solid evidence and the supporting information is derived from anecdote and unverifiable sources in the popular literature and Internet rather than peer-reviewed literature [24]. These diets increase the risk of insufficient intake of energy, fat, and protein, as well as the general risk of micronutrient deficiency.

There are no clinical trials demonstrating a benefit of a ketogenic diet in cancer patients [25,26]. Due to their low palatability, ketogenic diets may lead to insufficient energy intake and weight loss [25]. A small observational series and a small randomized trial reported good tolerability of fasting in humans [27,28], but without evidence of a benefit of fasting during chemotherapy, we do not recommend the use of this approach before, during or after the application of anticancer agents The reason for this recommendation is also due to the known risks of malnutrition and because patients might be tempted to prolong fasting episodes.

9) If a decision has been made to feed a patient, we recommend EN if oral nutrition remains inadequate despite nutritional interventions (counseling, ONS), and PN if EN is not sufficient or feasible. (Recommendation B3-3; strength of recommendation strong – Level of evidence moderate – strong consensus)

Commentary

In cancer patients who are unable to eat, digest or absorb food, medical nutrition may stabilize nutritional status. In patients with tumors that impair oral intake or food transport in the upper gastrointestinal (GI) tract, nutritional status can be stabilized by EN [29,30]. In cases of severe intestinal insufficiency due to radiation enteritis, chronic bowel obstruction, short bowel syndrome, peritoneal carcinosis, or chylothorax, nutritional status can be maintained by PN [31–33]. It has been reported that in head and neck cancer patients complication rates were lower with nasogastric tubes compared to feeding via PEG while success rates were high [34]. We recommend increasing the invasiveness of the nutritional approach only after carefully assessing the inadequacy of the more

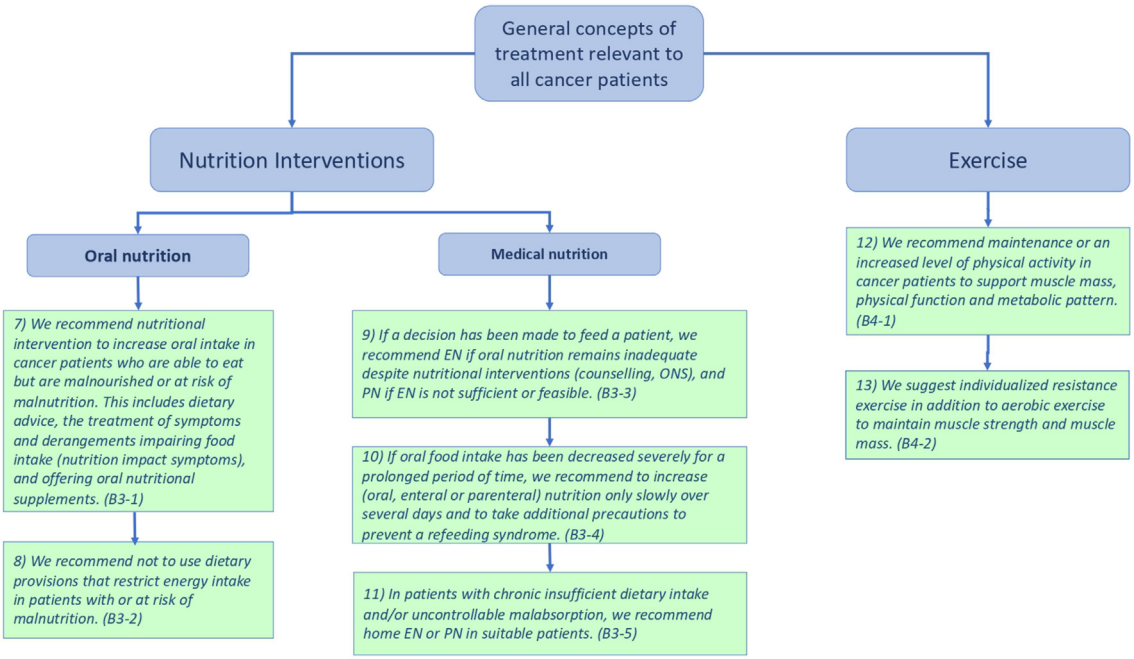

Fig. 3. General concepts of treatment relevant to all cancer patients: types of nutrition intervention; exercise.

physiological oral route. Clinical practice, contraindications, complications, and monitoring of EN and PN do not differ between cancer patients and patients with benign diseases [35]. The risks and detriments, as well as the possible futility of medical nutrition, must be weighed against possible physiologic and or psychological benefits, for a given patient and family. As a general rule, the risks of PN are regarded to outweigh its benefits for patients with a prognosis of fewer than two months.

10) If oral food intake has been decreased severely for a prolonged period, we recommend to increase (oral, enteral or parenteral) nutrition only slowly over several days and to take additional precautions to prevent a refeeding syndrome. (Recommendation B3-4; strength of recommendation strong – Level of evidence low – consensus)

Commentary

The classic biochemical feature of refeeding syndrome is hypophosphatemia, but it may also feature abnormal sodium and fluid balance, changes in glucose, protein, and fat metabolism, thiamine deficiency, hypokalaemia, and hypomagnesemia. Before and during nutritional repletion it is prudent to supply vitamin B1 in daily doses of 200–300 mg as well as a balanced micronutrient mixture. The following electrolytes should be monitored and substituted, if necessary, by the oral, enteral, or parenteral route: potassium (requirement approximately 24 mmol/kg/day), phosphate (requirement approximately 0.3–0.6 mmol/kg/day) and magnesium (requirement approximately 0.2 mmol/kg/day if supplied intravenously or 0.4 mmol/kg/day if supplied orally).

11) In patients with chronic insufficient dietary intake and/or uncontrollable malabsorption, we recommend home EN or PN in suitable patients. (Recommendation B3-5; strength of recommendation strong – Level of evidence low – strong consensus)

Commentary

Withdrawal of medical nutrition or deciding not to initiate medical nutrition in a patient who is unable to consume food is usually considered only in an end-of-life setting. There are data showing benefits of home EN or PN in cancer patients with chronic defects of dietary intake or absorption even in advanced cancer as long as there is a survival of more than a few weeks [36,37]. A benefit may be inferred by the fact that some cancer patients survive many months and even years exclusively on PN, i.e. time frames over which any person without food would have otherwise succumbed to starvation [31,38]. It is important to evaluate the patient's cognitive and physical abilities before starting a home PN training program.

3.4. Exercise

12) We recommend maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function, and metabolic pattern. (Recommendation B4-1; strength of recommendation strong – Level of evidence high – consensus)

Commentary

Physical activity is well-tolerated and safe at different stages of cancer and also patients with advanced stages of the disease are able and willing to engage in physical activity [39,40]. This consists of supervised or home-based moderate-intensity training (50–75% of baseline maximum heart rate or aerobic capacity), three sessions per week, for 10–60 min per exercise session. Physical activity in cancer patients is associated with maintenance or significant improvements in aerobic capacity, muscle strength, health-related quality of life, self-esteem, and a reduction in fatigue and anxiety [41–43]. For some patients, recommendations for physical activity should consist of motivating patients to take a daily walk in order to reduce risks of atrophy due to inactivity.

13) We suggest individualized resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass. (Recommendation B4-2; strength of recommendation weak – Level of evidence low – strong consensus)

Commentary

Cancer patients, in general, report low levels of physical activity and both inactivity and cancer treatment [44,45] have serious adverse effects on muscle mass [46]. A recent systematic review concluded that both aerobic and resistance exercise improves upper and lower body muscle strength more than usual care, and there is some indication that resistance exercise perhaps is more effective for improving muscle strength than aerobic exercise [43].

4.1. Pharmaconutrient and pharmacological agents (Fig. 4)

14) We suggest considering corticosteroids to increase the appetite of anorectic cancer patients with advanced disease for a restricted period (1–3 weeks) but to be aware of side effects (e.g. muscle wasting, insulin resistance, infections). (Recommendation B5-1; strength of recommendation weak – Level of evidence high – consensus)

Commentary

In a systematic review of pharmacological therapies for cancer-associated anorexia and weight loss in adult patients with non-hematological malignancies, Yavuzsen et al. (2005) found only two classes of drugs (progestins and corticosteroids) to have sufficient evidence, about efficacy and safety of appetite stimulants, to support their use in cancer patients. The antianorectic effect of corticosteroids is transient and disappears after a few weeks [47] when myopathy and immunosuppression become manifest; insulin resistance is an early metabolic adverse effect, osteopenia is a long-term effect. Due to these adverse effects, particularly with longer duration of use, corticosteroids may be more suitable for patients with a short life expectancy, especially if they have other symptoms that may be alleviated by this class of drugs such as pain or nausea.

15) We suggest considering progestins to increase the appetite of anorectic cancer patients with advanced disease but to be aware of potentially serious side effects (e.g. thromboembolism). (Recommendation B5-2; strength of recommendation weak – Level of evidence high – consensus)

Commentary

Progestins (megestrol acetate and medroxyprogesterone acetate) increase appetite and body weight but not fat-free mass; they may induce impotence, vaginal spotting, thromboembolism and in some case death [48–50].

16) In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest using supplementation with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass, and body weight. (Recommendation B5-7; strength of recommendation weak – Level of evidence low – strong consensus)

Commentary

Despite some systematic reviews, like Dewey et al. 2007, which concluded that there was insufficient evidence to support a recommendation for long-chain omega-3 fatty acids to treat cancer cachexia [51], two recent reviews demonstrate that long-chain fatty acids improved appetite, body weight, post-surgical morbidity, and quality of life in weight-losing cancer patients [52] and long-chain N-3 fatty acids in similar population during chemo- and/or radiotherapy and reported beneficial effects when compared to a control arm, most prominently conservation of body composition [53]. Interestingly, there are several reports on the

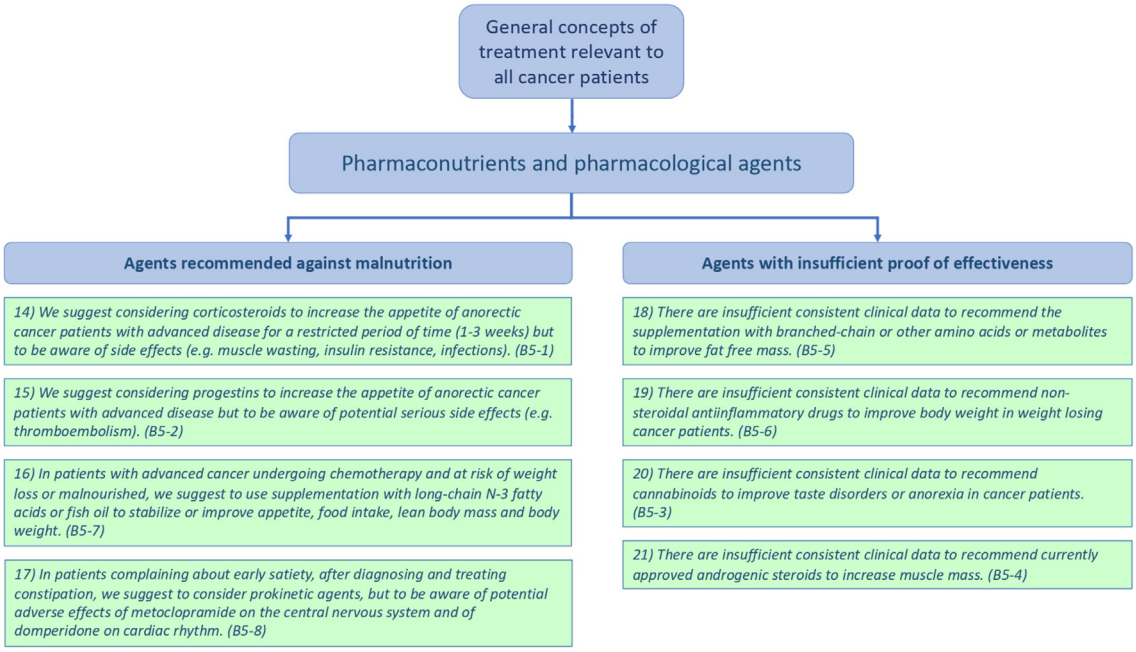

Fig. 4. General concepts of treatment relevant to all cancer patients: pharmaconutrients and pharmacological agents.

protective effects of fish oil on chemotherapy-induced toxicities like peripheral neuropathy [54,55].

When supplemented in usual doses fish oil and long-chain N-3 fatty acids are mostly well-tolerated. Mild GI effects were reported; the taste, a fishy aftertaste or fish belching, may impair compliance [56]. Recently ibrutinib has been associated with epistaxis in patients taking fish oil supplements; therefore, patients receiving ibrutinib should be counseled to avoid fish oil supplements.

Due to the inconsistencies in the reported effects but with several positive trials published during the last few years reporting nutritional benefits, a plausible biological rationale, only mild side effects and no convincingly serious safety issues a weak recommendation for the use of fish oil and long-chain N-3 fatty acids has been made.

17) In patients complaining about early satiety, after diagnosing and treating constipation, we suggest to consider prokinetic agents, but to be aware of potential adverse effects of metoclopramide on the central nervous system and domperidone on cardiac rhythm. (Recommendation B5-8; strength of recommendation weak – Level of evidence moderate – consensus)

Commentary

Pro-kinetic agents such as metoclopramide or domperidone stimulate gastric emptying and they are frequently used to improve early satiety [57]. Two RCTs compared metoclopramide in doses of 40 or 80 mg/day with placebo in patients with advanced cancer and chronic nausea and observed an improvement in nausea but not in appetite or caloric intake [58,59].

18) There are insufficient consistent clinical data to recommend the supplementation with branched-chain or other amino acids or metabolites to improve fat-free mass. (Recommendation B5-5; strength of recommendation none – Level of evidence low – strong consensus)

Commentary

Muscle protein depletion is a hallmark of cancer cachexia and, due to the frequent presence of anabolic resistance, dietary amino acid incorporation is impaired. Data suggest that in cancer cachexia-impaired protein balance and anabolic resistance in muscle may be overcome by simultaneously supplementing insulin and amino acids [60]. Long-term insulin treatment at bed-time, however, was without effect on lean body mass. In a randomized study in 338 patients with cancer cachexia, daily insulin treatment (0.11 IU/kg/d) in addition to basic supportive care increased whole-body fat but not lean body mass [61].

β-Hydroxy-β-methyl butyrate (HMB), a metabolite of leucine, at the usual dose of 3 g/day has been claimed to be an anti-catabolic agent that minimizes protein breakdown. A larger RCT in 472 cachectic cancer patients tried to compare an oral mixture of HMB, glutamine, and arginine with an isonitrogenous control mixture but failed because of the difficulties in compliance with such a regimen over eight weeks; only 37% of the patients completed the protocol and no statistically significant differences were observed between the study groups [62].

19) There are insufficient consistent clinical data to recommend non-steroidal anti-inflammatory drugs to improve body weight in weight-losing cancer patients. (Recommendation B5-6; strength of recommendation none – Level of evidence low – strong consensus)

Commentary

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the release of acute-phase proteins and cytokines by the tumor and host tissues. The evidence is too limited to recommend NSAIDs or other anti-inflammatory drugs for the treatment of cachexia outside of clinical trials. NSAIDs may improve weight in cancer patients with cachexia, and there is some evidence of their effect on physical performance, self-reported quality of life, and inflammatory parameters [63–65]. The reason for not recommending NSAIDs with the intention of treating cachexia outside clinical trials is based on the inconsistency of the trials and the low quality of the trials [66], but it is also supported by the known potentially severe side effects of NSAIDs, even though the reviewed literature on use in cachexia reports only almost negligible toxicity [67].

20) There are insufficient consistent clinical data to recommend cannabinoids to improve taste disorders or anorexia in cancer patients. (Recommendation B5-3; strength of recommendation none – Level of evidence low – consensus)

Commentary

Tetrahydrocannabinol (THC) is the principal psychoactive constituent of cannabis and commercially available as dronabinol. In a prospective randomized placebo-controlled multi-center trial in 164 patients with advanced cancer and anorexia-cachexia syndrome cannabis extract or THC provided at a fixed dose of 5 mg per day for six weeks did not improve appetite or quality of life [68]. However, in a small pilot RCT in patients with advanced cancer, poor appetite, and chemosensory alterations, THC (2.5 mg bid) for 18 days resulted in improved chemosensory perception, better taste perception of foods, and improved pre-meal appetite compared to placebo [69].

Thus, although dronabinol may have the potential to improve chemosensory perception and appetite in patients with cancer anorexia, the limited and inconsistent evidence does not support a recommendation.

21) There are insufficient consistent clinical data to recommend currently approved androgenic steroids to increase muscle mass. (Recommendation B5-4; strength of recommendation none – Level of evidence low – consensus)

Commentary

Endogenous and exogenous agents have been investigated and used to diminish muscle loss (proteolysis) or to stimulate protein synthesis. Among them, anabolic or anabolic-androgenic steroids were addressed because they mimic the male sex hormones (testosterone and dihydrotestosterone and the less potent androstenedione) increasing protein synthesis. In patients with advanced cancer, decreased free testosterone levels are frequently observed [70]. Typical representatives of androgens investigated in cancer patients include nandrolone decanoate (for i. m. use 200 mg per week) and oral oxandrolone or fluoxymesterone (20 mg per day).

In a randomized trial of 37 patients with non small cell lung carcinoma undergoing chemotherapy, nandrolone decanoate (200 mg per week) was compared to no additional therapy; the nandrolone-treated group showed a trend toward a smaller loss of body weight [71]. An RCT that included 475 cachectic cancer patients compared a steroid, a progestin, and fluoxymesterone. Fluoxymesterone (20 mg/day) resulted in less appetite stimulation compared to megestrol acetate (800 mg/day) and dexamethasone

(3 mg/day), while the discontinuation rate due to toxicity was similar among the three treatment arms [72].

5. Interventions relevant to specific patient categories

5.1. Surgery (Fig. 5)

22) For all cancer patients undergoing either curative or palliative surgery, we recommend management within an enhanced recovery after surgery (ERAS) program; within this program, every patient should be screened for malnutrition and if deemed at risk, given additional nutritional support. (Recommendation C1-1; strength of recommendation strong – Level of evidence high – consensus)

Commentary

In the current surgical environment, cancer patients undergoing surgery should be managed within an ERAS program that seeks to minimize surgical stress, maintain nutritional status, reduce complications and optimize rate of recovery. Nutritional components of ERAS include avoiding fasting, pre-operative fluid and carbohydrate load, and recommencement of oral diet on the first post-operative day. Data suggest that when all patients receive such optimized nutritional and metabolic care, the metabolic response to surgery can be minimized.

23) For a patient undergoing repeated surgery as part of a multimodal oncological pathway, we recommend the management of each surgical episode within an ERAS program. (Recommendation C1-2; strength of recommendation strong – Level of evidence low – consensus)

Commentary

Patients undergoing multimodal oncological care are at particular risk of progressive nutritional decline. In order to minimize a stepwise decline in nutritional status during such arduous anti-cancer therapy, it is essential to minimize the nutritional/metabolic impact of repeated surgery and manage each surgical episode within the context of an ERAS pathway.

24) In surgical cancer patients at risk of malnutrition or who are already malnourished, we recommend appropriate nutritional support both during hospital care and following discharge from the hospital.(recommendation C1-3; strength of recommendation strong – Level of evidence moderate – consensus)

Commentary

Patients at moderate or severe nutritional risk (especially those undergoing upper GI cancer surgery) should be considered for routine post-operative nutritional support (where relevant by oral or enteral route) and consideration should be given to the extending such support when the patient is discharged into the community [73,74].

25) In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care, we recommend oral/enteral immunonutrition (arginine, n-3 fatty acids, nucleotides). (Recommendation C1-4; strength of recommendation strong – Level of evidence high – strong consensus)

Commentary

Upper GI cancer patients predicted to be at severe nutritional risk experienced reduced complications from pre-operative PN [75]. Subsequently, it was demonstrated that upper GI cancer patients managed within a traditional pattern of peri-operative care experienced a reduction in post-operative infective complications when given oral/enteral so-called “immune-modulating nutrition” in the peri-operative period [76]. The term “immune-modulating nutrition” or “immunonutrition” refers to liquid nutritional supplements enriched with specific nutrients (arginine, n-3 fatty acids, nucleotides).

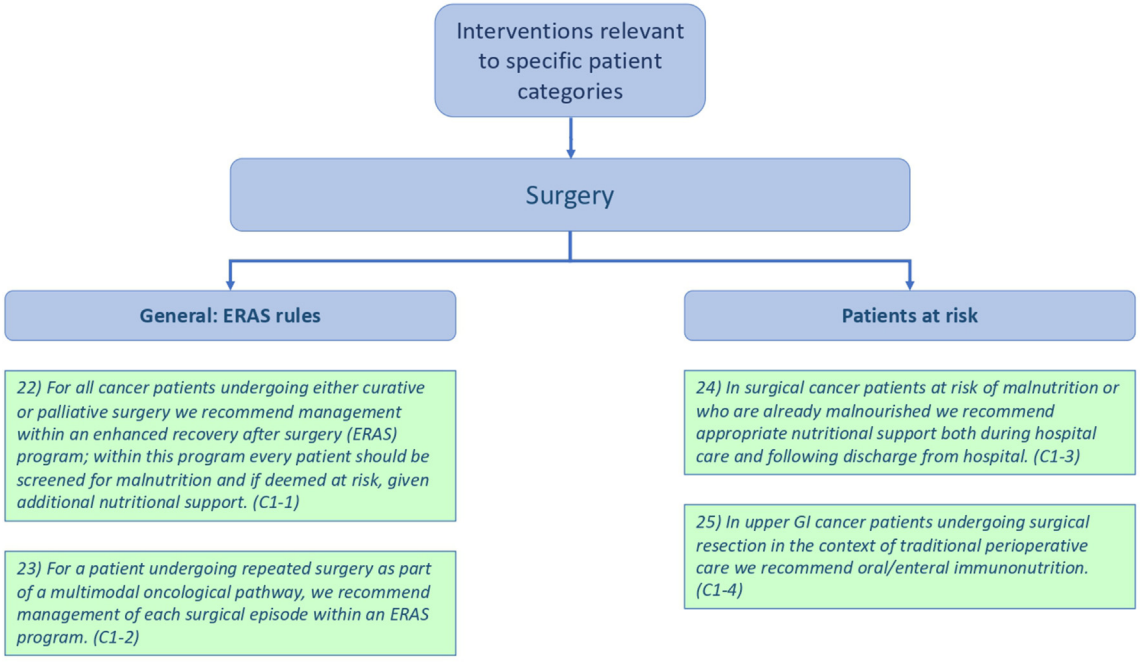

Fig. 5. Interventions relevant to specific patient categories: surgery.

5.2. Radiotherapy (Fig. 6)

26) We recommend that during radiotherapy – with special attention to radiotherapy of the head and neck, thorax and GI tract - an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of ONS, in order to avoid nutritional deterioration, maintain intake and avoid radiotherapy interruptions. (Recommendation C2-1; strength of recommendation strong – Level of evidence moderate – strong consensus)

Commentary

Radiotherapy to the head and neck or esophagus induces mucositis, decreased food intake, and weight loss in up to 80% of patients [77–88]. Similarly, radiotherapy of the pelvic region is associated with GI symptoms in up to 80% of patients [89]. For those reasons all patients undergoing radiation of the GI tract or the head and neck region should receive thorough nutrition assessment, adequate nutritional counseling and, if necessary, nutritional support according to symptoms and nutritional status [22,90]. If nutritional support is required, this should be initiated early and if energy intake is inadequate ONS are recommended [79] or EN [78] should be offered.

27) We recommend to screen for and manage dysphagia and to encourage and educate patients on how to maintain their swallowing function during EN. (Recommendation C2-3; strength of recommendation strong – Level of evidence low – strong consensus)

Commentary

A consensus group recently recommended assessment of all patients at risk for swallowing difficulties before and during treatment and regularly during follow-up, and that all patients with dysphagia be prescribed professionally supervised swallowing exercises. Therefore, dysphagia assessment and prophylactic as well as therapeutic interventions should be used regularly.

28) We recommend EN using nasogastric or percutaneous tubes (e.g. percutaneous endoscopic gastrostomies (PEG)) in radiation-induced severe mucositis or obstructive tumors of the head-neck or thorax. (Recommendation C2-2; strength of recommendation strong – Level of evidence low – strong consensus)

Commentary

Patients with obstructing head and neck or esophageal cancers and in settings with expected severe radiation-induced oral or esophageal mucositis, there is a high risk for weight loss, decreased physical performance, dehydration, decreased treatment tolerance, and increased treatment interruptions. In high-risk situations, e.g. hypopharyngeal primary site, T4 tumor, female sex, or combined radiochemotherapy [91], prophylactic EN (as opposed to enteral feeding initiated after development of dysphagia) may maintain nutritional status and avoid interruption of treatment. Several, mostly retrospective observational, studies observed improved body weight and lower incidences of rehospitalization and treatment interruptions for patients treated with early compared to later or no EN [78,92]. PEG compared to radiologically inserted gastrostomies (RIG) appear to be associated with a lower risk of peritonitis and mortality [93]. PEG, in comparison with nasogastric tubes, show that body weight may be maintained similarly [94], risk of tube dislodgement is lower [94] and quality of life is possibly better [95], while nasogastric tubes are associated with less dysphagia [94] and earlier weaning after completion of radiotherapy [94]. Risks of pneumonia and other infections are similar [94].

29) We do not recommend PN as a general treatment in radiotherapy but only if adequate oral/enteral nutrition is not possible, e.g. in severe radiation enteritis or severe malabsorption. (Recommendation C2-6; strength of recommendation strong – Level of evidence moderate – consensus)

Commentary

Radiotherapy of the head and neck or pelvic region is associated with GI symptoms and weight loss in up to 80% of patients [80,83,96]. The use of PN is indicated if oral/enteral food tolerance is insufficient to supply the required amounts of energy and

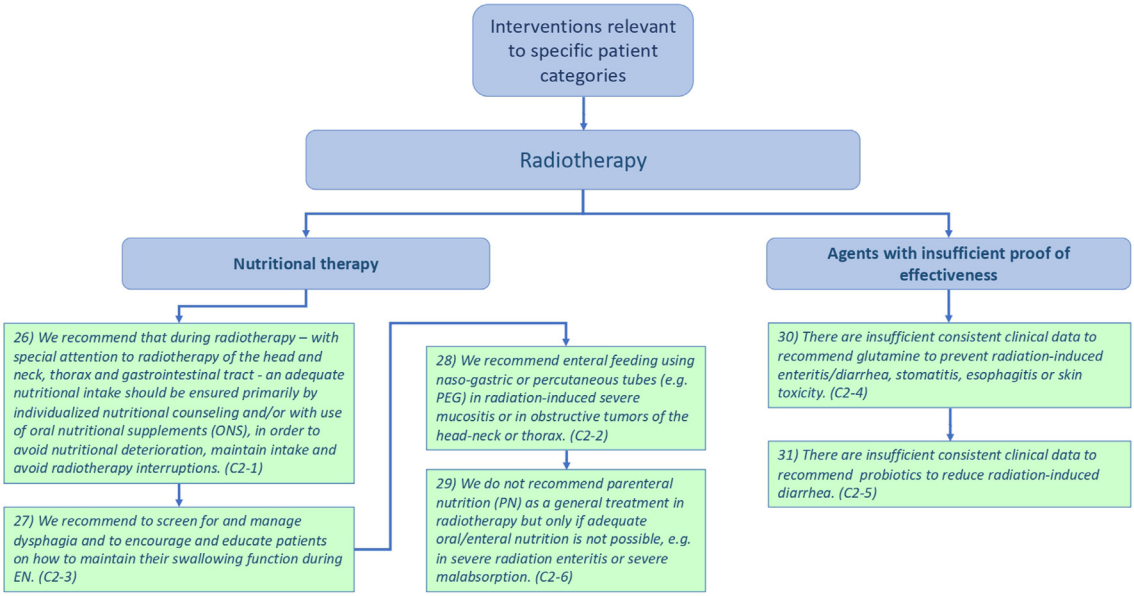

Fig. 6. Interventions relevant to patients undergoing radiotherapy.

nutrients. This is the case with chronic severe enteral food intolerance (like untreatable nausea, vomiting, abdominal pain, malabsorption, or diarrhea) that cannot be overcome by EN. Intestinal failure develops in approximately 5% [31] and in these patients HPN appears to be a reasonable treatment option possibly superior to surgical intervention [97].

30) There are insufficient consistent clinical data to recommend glutamine to prevent radiation-induced enteritis/diarrhea, stomatitis, esophagitis or skin toxicity. (Recommendation C2-4; strength of recommendation none – Level of evidence low – strong consensus)

Commentary

There is some evidence for potential beneficial effects of glutamine against radiation-induced mucositis and skin toxicity. Two small randomized trials reported that either mouthwashes with glutamine (16 g/day; 17 patients) [98] or intravenous glutamine (0.3 g/kg/day; 29 patients) [99] when compared to placebo (sodium chloride), decreased the incidence, severity, and duration of radiation-induced mucositis. Glutamine has been associated with higher tumor relapse rates in hematopoietic stem cell transplantation (HSCT) patients [100]; thus, recommending glutamine will require solving this safety issue and more robust efficacy data [101].

31) There are insufficient consistent clinical data to recommend probiotics to reduce radiation-induced diarrhea. (Recommendation C2-5; strength of recommendation none– Level of evidence low – strong consensus)

Commentary

There is some indication for protective effects of probiotics, due to the heterogeneity of the data and the limited study quality no recommendation can be made. In addition, the safety of using probiotics has to be reliably addressed, before these products can be recommended in immunocompromised patients [102–104].

5.3. Medical oncology: curative or palliative anticancer drug treatment (Fig. 7)

32) During anticancer drug treatment, we recommend to ensure an adequate nutritional intake and to maintain physical activity. (Recommendation C3-1; strength of recommendation strong – Level of evidence very low – strong consensus)

Commentary

Weight loss is a common side effect of targeted therapies and multikinase inhibitors have been reported to result in skeletal muscle wasting [44]. In addition, low muscle mass has been shown to be a risk factor for toxicity in these patients [105]. Indeed weight stabilization for patients with GI and lung cancers is correlated with significant improvements in survival [106,107]. So far there is a paucity of studies showing if this is attributed to improved nutritional intake or cancer treatment alone.

33) In a patient undergoing curative anticancer drug treatment, if oral food intake is inadequate despite counseling and ONS, we recommend supplemental EN or, if this is not sufficient or possible, PN. (Recommendation C3-2; strength of recommendation strong – Level of evidence very low – consensus)

Commentary Data on medical nutrition supplied according to caloric demand during standard cytostatic therapies are scarce. Studies comparing EN to PN showed that EN is feasible and, compared to PN, may be associated with a lower rate of neutropenia [108].

34) There are insufficient consistent clinical data to recommend glutamine supplementation during conventional cytotoxic or targeted therapy. (Recommendation C3-3; strength of recommendation none – Level of evidence low – strong consensus)

Commentary

Beneficial effects of oral and parenteral supplementation of glutamine have been reported on chemotherapy-induced mucosal inflammation [99], vomiting and diarrhea [109,110] and cytopenia [111]. A more recent systematic review analyzing 15 prospective and retrospective trials in cancer patients undergoing chemo-, radio or radio-chemotherapy [112] found positive effects of oral glutamine on mucositis in 11 of these 15 trials. Among the six prospective and placebo-controlled trials, however, two trials reported a benefit of glutamine while in four trials no effect was observed [112]. Considering the heterogeneity of these data and the lack of information on glutamine effects on tumor response, no recommendation on the therapeutic use of glutamine is possible.

5.4. Medical oncology: high-dose chemotherapy and HSCT

35) During intensive chemotherapy and after stem cell transplantation we recommend maintaining physical activity and to ensure an adequate nutritional intake. This may require EN and/or PN. (Recommendation C4-1; strength of recommendation strong – Level of evidence very low – strong consensus)

Commentary

Many patients referred for autologous and especially those referred for allogeneic HSCT are malnourished at admission. The high-dose radio-/chemotherapy associated with the treatment and its typical spectrum of side effects, including nausea, vomiting, mucositis, diarrhea, and infections, further impacts oral food tolerance and patients lose weight particularly in the first 40 days after admission [113]. Therefore, patients should be screened and assessed for impending or overt malnutrition at admission and after that monitored weekly during their HSCT for adequate nutrient intake, metabolism, and physical activity. If deficits are observed, nutrition support, including counseling, ONS, EN and/or PN, should be initiated early to avoid or minimize further loss of weight and body cell mass.

PN may have specific benefits by providing the option to supply selected nutrient mixtures. In patients undergoing allogeneic bone marrow transplantation for hematologic malignancies, reduced rates of lethal acute graft-versus-host disease were observed with PN regimens containing a high content of long-chain fatty acids [114].

Since a number of factors is responsible for muscle weakness and muscle loss (underlying malignant disease, pre-HSCT therapy, immobilization during HSCT, and side-effects of drugs like corticosteroids) it is recommended that patients be encouraged and supported to perform muscle training and to increase their physical activity before, during, and after HSCT [115,116].

36) If oral nutrition is inadequate we suggest preferring EN to PN, unless there is severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic GI graft versus host disease. (Recommendation C4-2; strength of recommendation weak – Level of evidence low – strong consensus)

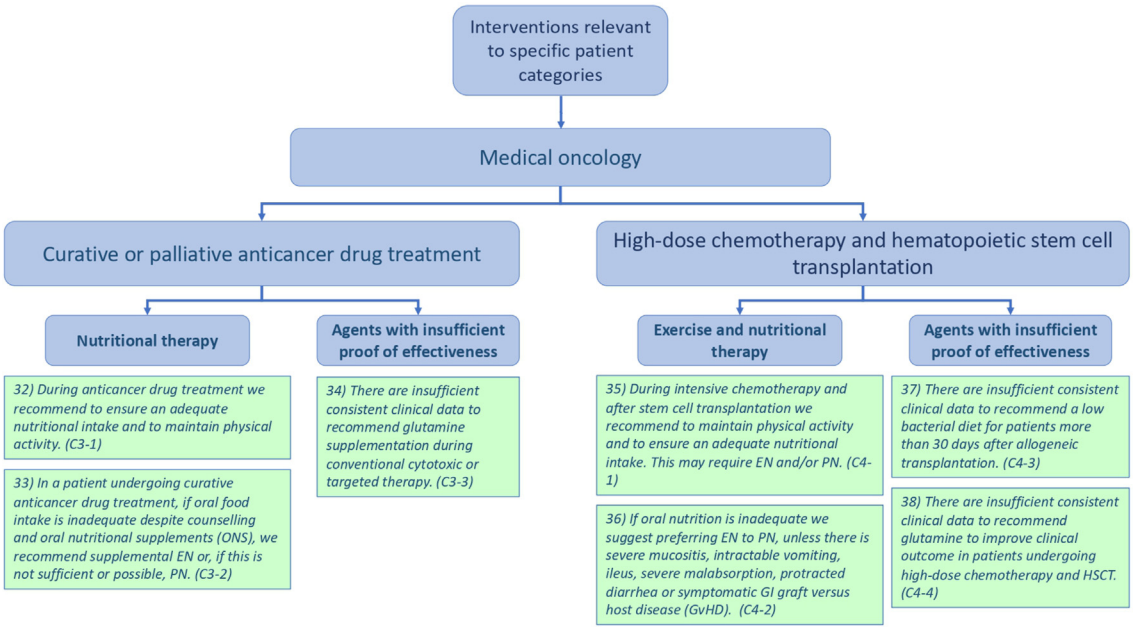

Fig. 7. Interventions relevant to medical oncology patients.

Commentary

Medical nutrition is indicated if a patient cannot be fed adequately by the oral route. If the intestinal tract is not severely compromised, EN generally should be preferred. Several recent studies support preferring EN over PN in allogeneic HSCT [117]. Data show a trend toward fewer complications using enteral compared to PN during this procedure especially for infectious complications [117]. After autologous HSCT, PN will be necessary only in a few cases. After allogeneic HSCT PN will be necessary more frequently and for prolonged periods because of severe toxic mucositis, GI infections, and GI graft vs host disease.

37) There are insufficient consistent clinical data to recommend a low bacterial diet for patients more than 30 days after allogeneic transplantation. (recommendation C4-3; strength of recommendation none – Level of evidence low – strong consensus)

Commentary

Due to the severe, and sometimes protracted, immunosuppression induced by chemotherapy there is a risk of foodborne infections In the 1980s the use of neutropenic diets after HSCT was instituted as a means of preventing infection from organisms colonizing the GI tract [118]. A Cochrane database review identified 619 studies investigating low bacterial diets during chemotherapy-induced neutropenia but found only three RCTs among these studies, each with methodological limitations and none considered the post-neutropenia phase [119]. The authors concluded that there was no evidence to support the use of a low bacterial diet for the prevention of infection and related outcomes [119].

38) There are insufficient consistent clinical data to recommend glutamine to improve clinical outcome in patients undergoing high-dose chemotherapy and HSCT. (Recommendation C4-4; strength of recommendation none – Level of evidence low – strong consensus)

Commentary

Some nutritional substrates, such as glutamine, may influence physiological mechanisms and have been proposed to protect the intestinal mucosa from the impact of aggressive chemotherapy and radiotherapy, support recovery of the hematopoietic and immune system after cytoreductive therapies, optimize nitrogen balance and muscle protein synthesis, and improve antioxidant systems [120]. One RCT comparing PN supplemented with glutamine with glutamine-free PN in autologous transplant patients reported more severe oral mucositis and more relapses in the glutamine group [100]. In recent years, only one further RCT has been published that compared glutamine supplementation of PN to standard PN in 120 children with hematological malignancies and HSCT did not affect the severity or duration of mucositis, engraftment, graft versus host disease, relapse rate, or mortality [121]. Based on this information, the use of glutamine in HSCT is not recommended.

5.5. Cancer survivors (Fig. 8)

39) We recommend that cancer survivors engage in regular physical activity. (Recommendation C5-1; strength of recommendation strong – Level of evidence low – consensus)

Commentary

There is a strong theoretical background for advising cancer survivors to engage in physical activity. Physical activity is an effective strategy to improve aerobic capacity, physical fitness, and function in cancer survivors [42,122,123] (RCT and meta-analysis; high-grade evidence). Several observational studies have shown that physical activity is associated with reduced recurrence and mortality among breast and colon cancer survivors, however, there is currently insufficient evidence regarding the association between physical activity and mortality for survivors of other cancers [124–126] (Overall survival: low-grade evidence). Preliminary results from randomized trials of physical activity suggest beneficial changes in the circulating levels of insulin, insulin-related pathways, and inflammation parameters [126].

40) In cancer survivors, we recommend maintaining a healthy weight (BMI 18.5–25 kg/m^2) and to maintain a healthy lifestyle, which includes being physically active and a diet

based on vegetables, fruits, and whole grains and low in saturated fat, red meat, and alcohol. (Recommendation C5-2; strength of recommendation strong – Level of evidence low – strong consensus)

Commentary

Cancer survivors should strive to maintain a healthy weight and avoid excessive weight gain throughout life by balancing calorie intake with physical activity. Survivors who are overweight or obese should strive to reduce weight and, referably until a healthy BMI has been reached. Obesity and metabolic syndrome might be independent risk factors for recurrence and reduced survival in breast and gastric cancer patients [127]. High consumption of red meat (beef, pork, mutton) is associated with an increase in the risk of breast cancer [128], and overall cancer mortality [129]. It is unclear whether plant-based foods affect cancer recurrence rates, in particular, consumption of vegetables and fruits exerts limited protective effects against cancers associated with smoking or drinking [130]. Therefore, a fruit- and vegetable-rich diet should be recommended to cancer survivors. Pierce et al. reported decreased rates of breast cancer recurrence only in women who had a high intake of plant-based foods in combination with regular moderate physical activity when compared to women with either less physical activity and/or lower intake of vegetables and fruits [131].

5.6. Patients with advanced cancer receiving no anticancer treatment (palliative situation)

41) We recommend to routinely screen all patients with advanced cancer for inadequate nutritional intake, weight loss, and low BMI, and if found at risk, to assess these patients further for both treatable nutrition impact symptoms and metabolic derangements. (Recommendation C6-1; strength of recommendation strong – Level of evidence low – consensus)

Commentary

Patients with advanced cancer may have a life expectancy of several months to several years. In these patients, deficits in nutritional status may impair performance status, quality of life, tolerance to anticancer treatments, and survival. In patients with shorter expected survival, alleviating nutrition impact symptoms may relieve the burden of the disease [132]. It is recommended to proceed with screening and assessment in patients with advanced cancer as outlined in section 3.1.

42) We recommend offering and implementing nutritional interventions in patients with advanced cancer only after considering together with the patient the prognosis of the malignant disease and both the expected benefit on quality of life and potentially survival as well as the burden associated with nutritional care. (Recommendation C6-2; strength of recommendation strong – Level of evidence low – consensus)

Commentary

The benefit of nutritional support in patients with advanced cancer should be carefully considered, taking into account all relevant aspects, including the cancer prognosis [133,134]. Expected survival is most important. If expected survival is several months or years nutrition therapy should be given with the aim to secure an adequate intake of energy and protein, to diminish metabolic disturbances, and to maintain an adequate performance status and subjective quality of life. If a patient in this prognostic group is unable to eat, medical nutrition may improve survival [31], but the evidence is weak (ref Tobberup R et al. 2019). If expected survival is in the range of few to several weeks, interventions should be non-invasive and primarily aimed at psychosocial and existential support. Patients with a comparably good prognosis and an expected overall survival of at least several months [134]as well as patients with low tumor activity and no inflammatory reaction (CRP <10 mg/dl) [133] should receive adequate nutritional counselling and support including oral, enteral or, if required, PN, or

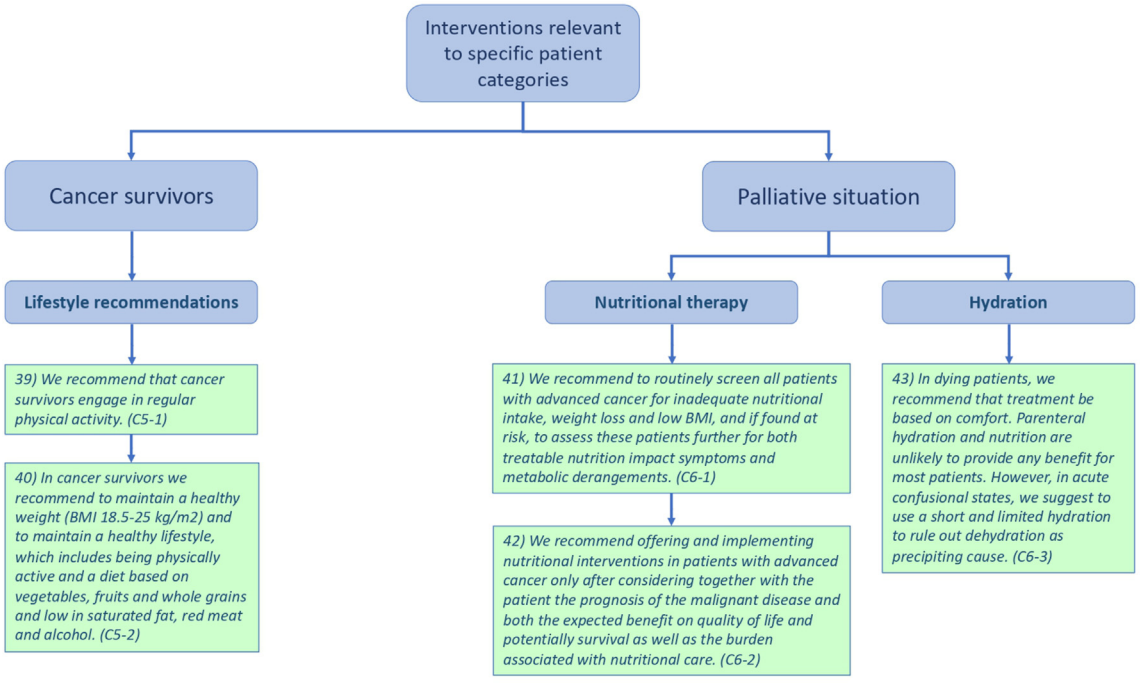

Fig. 8. Interventions relevant to cancer survivors and palliative care advanced cancer patients.

combinations. Performance status should not influence decision making for or against nutritional support in these patients if performance status is considered low due to reduced nutritional intake and not rapidly progressive disease. Patients, who, despite oncologic therapy, have rapidly progressive disease, activated systemic inflammation, and/or an Eastern Co-operative of Oncology Group (ECOG) performance status of ≥3, are less likely to benefit from nutritional support. There is an agreement that unconditional medical nutrition in all patients undergoing anticancer therapy is associated overall with more harm than benefit [135,136].

43) In dying patients, we recommend that treatment be based on comfort. Parenteral hydration and nutrition are unlikely to provide any benefit for most patients. However, in acute confusional states, we suggest using a short and limited hydration to rule out dehydration as precipitating cause. (Recommendation C6-3; strength of recommendation strong − Level of evidence low − strong consensus)

Commentary

There is little or no benefit from nutritional support in the last weeks of life since it will not result in any functional or comfort benefit for the patient. In fact, during terminal hypometabolism, normal amounts of energy and substrates may be excessive and induce metabolic distress. Still, not infrequently, relatives and caregivers may demand medical nutrition or hydration for terminally ill patients [137]. It is mandatory to explain that the goal is comfort and to explain and communicate the pros and cons of continued nutritional treatment with patients, family members, and the care team [138]. Hunger is rare in imminently dying patients and minimal amounts of desired food may provide appropriate comfort [139]. A patient who has been classified as imminently dying but is awake and is hungry may have been misdiagnosed. In such cases, the patient should be reassessed and may require treatment. Routine hydration showed no improvement in [137] or only limited effects [138,140] on symptoms and quality of life in cancer patients who are imminently dying [138,140,141]. In the imminently dying patient, parenteral hydration may be tried in the attempt to improve or maintain cognition. Parenteral hydration should not be used for thirst palliation or mouth dryness (often caused by medications like opioids) [138]; oral care measures are effective to comfort these patients [139].

Conflicts of interest

No conflict of interest.

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