Module 26.2

Nutritional Treatment Strategies in Cancer Patients

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Learning Objectives

- To understand the role of nutrition in relation to metabolism, nutritional status, functioning, treatment tolerance, and quality of life;
- To discuss indications for starting and ending nutritional treatment;
- To understand indications for dietary counselling, food modification, oral nutritional supplements, tube feeding, and parenteral nutrition;
- To discuss nutrition/diet/dietary patterns for cancer survivors.

Contents

Key Messages

- Dietary counselling by a trained nutrition professional (registered/accredited dietitian/nutritionist) is regarded as the 1st line of nutritional treatment;

- Several RCTs have demonstrated that individualized dietary counselling by a trained professional compared to conventional food without dietary education improves nutritional intake, body weight, and quality of life, but not mortality;
- Since malnutrition is associated with poorer clinical outcomes, including decreased survival, and because it is difficult to reverse overt malnutrition in cancer patients with metabolic derangements, nutritional treatment should preferably be initiated when patients are not yet severely malnourished and when the goals of care include maintaining or improving nutritional status;
- Whereas energy expenditure in cancer patients is considered to be similar to healthy subjects, protein requirements are increased;
- Prospective and retrospective observational trials in patients with inadequate food intake have demonstrated that tube feeding compared to oral feeding reduces weight loss, as well as the frequency and duration of cancer treatment interruptions, and rehospitalizations;
- In patients with upper gastrointestinal cancer undergoing surgical resection, oral/enteral immunonutrition is recommended to decrease risk of postoperative infective complications;
- The role of nutrition in palliative care is related to the phase of palliative care;
- As cancer survivors are at higher risk for developing second primary cancers and other chronic diseases, a diet rich in vegetables, fruits, and whole grains, and low in fats, red meats, and alcohol is recommended for cancer survivors.

1. Introduction

The aim of nutritional treatment depends on the cancer prognosis and expected survival. Patients with cancer with a comparably good prognosis and an expected overall survival of at least several months (1,2) should receive adequate dietary counselling and support, including oral, enteral or, if required, parenteral nutrition, or combinations. In these patients, nutritional treatment aims to secure an adequate intake of energy and protein as well as other macro- and micro-nutrients. The aim of nutritional treatment in these patients is to diminish metabolic disturbances and impediments to oral intake (i.e., "nutrition impact symptoms"), to optimize nutritional status (i.e., maintenance of or increase in lean body mass (skeletal muscle mass)), and to optimize performance status and quality of life (3). Moreover, if a patient is undergoing anti-cancer treatment, nutritional interventions aim to enable him/her to undergo the planned treatment and to reduce the risk of reductions or interruptions of scheduled anti-cancer treatments.

In patients with advanced cancer, nutritional treatment should be offered and started after careful consideration of the cancer prognosis (1,4), the expected benefit on quality of life and potentially on survival, as well as the potential burden associated with nutritional care, taking into account expectations and wishes of the patient and close relatives or partners (5).

If patients are receiving palliative anti-cancer treatment, nutritional support should receive special consideration. There is agreement that *unconditional* artificial nutrition in all patients undergoing anticancer therapy is associated overall with more harm than benefit and should be avoided. However, treatment-induced and thus iatrogenic deterioration of nutritional status should initiate adequate prophylactic or symptomatic supportive care, including "permissive" nutritional support (3).

In patients who, despite anti-cancer therapy, have rapidly progressive disease, activated systemic inflammation, and/or an ECOG performance status of 3, nutritional support is not likely to affect nutritional status positively. 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, and should support minimizing nutrition impact symptoms.
To prevent or treat malnutrition, the patient needs to be anabolically competent, i.e., in that state which optimally supports protein synthesis and lean body mass, global aspects of muscle and organ function, and immune response (6,7). Optimal intake of macro- and micronutrients is essential for maintenance of metabolic equilibrium. Hence, nutritional interventions form the core of treatment strategies aimed at promoting anabolism and/or counteracting tissue lean body mass catabolism. However, additional anabolic or anti-catabolic factors should also be addressed to stimulate the utilization and efficacy of nutrients. These factors include physical (in)activity, inflammatory state, and the internal milieu, and are included in the multimodality approach recommended in patients with cancer (See also Module 26.3 and Module 26.4).
As part of routine practice, reasonable short- and medium-term outcomes of nutritional treatment should be defined together with the patient. These outcomes include changes in physical function and perceived quality of life. Chosen outcomes, as well as presence of nutrition impact symptoms, should be monitored to estimate stabilization or improvement. The chosen outcomes should serve to decide on continuing, adapting or ending the nutritional treatment (3).

2. Nutritional Requirements

Nutritional treatment, which may include oral nutritional supplements, enteral or parenteral nutrition, or combinations, should be started according to the patient's energy and protein needs, and the ability to eat and utilize the digestive tract (3). Nutritional treatment should always be tailored to the individual patient’s possibilities and preferences.

2.1 Energy Requirements

Total energy requirements are the sum of the resting energy expenditure (REE), expenditure from physical activity (PAL), and, in a small percentage, of diet-induced thermogenesis. Only a few studies, including only a small number of patients, have assessed total energy expenditure (TEE) in cancer, because accurate measurement of TEE is challenging (8). Total energy expenditure of cancer patients, even if not measured individually, can be assumed to be similar to healthy subjects. The REE tends to be increased in patients with advanced stages of cancer, which has been associated with tumor-induced futile substrate cycles resulting in increased glucose turnover and increased energetic demand by liver metastases, inflammation, and brown adipose tissue (BAT) activation (8). However, patients with advanced cancer also experience increasing fatigue and decreasing physical activity, therefore decreasing TEE (9). Moreover, instead of hypermetabolism, also hypometabolism has been reported, which has been suggested to be the result of underfeeding (8).
The use of standard formulas for the calculation of energy requirements may be inaccurate given the altered energy metabolism and metabolic differences in patients with different cancer types. In about 25% of patients with active cancer, REE as measured by indirect

calorimetry is more than 10% higher than estimated REE. In another 25%, measured REE is more than 10% lower than estimated REE. Unfortunately, the extent or direction of the difference between measured and estimated REE cannot be predicted for the individual patient (8). However, it has been relatively consistently reported that patients with pancreatic and lung cancer have increased REE, which has been associated with systemic inflammatory activity (10–12). There are few and inconsistent data regarding the effects of cancer treatments on REE (3).

In patients with advanced cancer, TEE appears to be lower when compared to predicted values for healthy individuals (11,13), due to reduction in daily physical activity. Using hypercaloric feeding in cancer patients with metabolic derangements who are losing weight may fail to increase body weight, but rather lead to overfeeding with undesired metabolic effects. Therefore, energy provision should be based on measured, or alternatively, estimated total energy requirements.

To measure TEE, REE ideally is measured by indirect calorimetry and PAL can be measured by wearable devices (e.g., SenseWear, Fitbit). If indirect calorimetry is not feasible, TEE may be estimated from standard formulas for REE, and if no wearable device is available then standard values for physical activity level (PAL) can be consulted (13). Alternatively, TEE may be estimated roughly using a rule of thumb, assuming TEE to range between 25 and 30 kcal/kg/day, depending on the patient's performance status, although it is important to take into account that such rough estimates are accompanied by substantial error (3,14,15).

After initial determination or estimation of total energy requirements, it is subsequently essential to adapt provision of energy during the course of treatment and rehabilitation, according to clinical effects on body weight and muscle mass (3).

In weight-losing cancer patients with insulin resistance, uptake and oxidation of glucose by muscle cells is impaired, whereas utilization of fat is normal or increased (16). Therefore, in these patients it is recommended to increase the energy from fat to energy from carbohydrates ratio, with the aim of increasing the energy density of the diet and reducing the glycaemic load.

2.2 Protein Requirements

Protein requirements vary in the individual cancer patient. However, protein requirements of patients with cancer are higher than those of healthy individuals, due to increased protein turnover and 'anabolic resistance', i.e., decreased responsiveness of protein synthesis to anabolic stimuli, caused by systemic inflammation, decreased physical activity, and ageing (17). Research has demonstrated that higher intake of protein intake promotes muscle protein anabolism in patients with cancer (18). Therefore, generally, protein intake should be more than 1 g/kg/day and, if possible up to 1.5 g/kg/day. For chronically ill older patients, a protein intake of 1.2-1.5 g/kg/day is recommended (19).

Based on studies on intravenous provision of amino acids, it has been suggested that intravenous provision of about 2 g amino acids/kg/day can result in a positive protein balance in cancer patients (20). In patients with normal kidney function, intake of protein in doses up to and above 2 g/kg/d are safe (21), whereas in patients with acute or chronic renal failure protein supply should not exceed 1.0 or 1.2 g/kg/d, respectively (22) (but see also Module 15.2 as stricter limitation may be necessary). To further quantify increased protein requirements of the individual patient, nitrogen balance measurement may be helpful.

To meet the protein requirements, good quality protein from animal, fish, dairy, and plant sources is recommended (15).
There are insufficient consistent clinical data to recommend the supplementation with branched-chain or other amino acids or metabolites, e.g., ß-Hydroxy-ß-methyl butyrate (HMB) to improve fat-free mass (3).
Although glutamine is semi-essential in catabolic conditions, the role of supplementation with glutamine is still controversial, due to inconclusive results of studies with parenteral supplementation of glutamine (23).

2.3 Requirements of Vitamins and Minerals

In all forms of malnutrition, the patient may be at risk of micronutrient deficiency, especially of, but not limited to, water soluble vitamins (24). However, patients with cancer frequently use supplements with vitamins/ minerals, even when micronutrient requirements are met already (25).
To prevent or treat nutrient deficiencies, the use of a multivitamin-multimineral supplement in physiological doses, i.e., nutrient amounts that approximately
equal the recommended daily allowance, is considered useful and safe, even for cancer patients during chemo- and radiation therapy (26,27). Since supplemen-tation with high doses of vitamins and/or minerals may affect tumour growth, may interact with anti-cancer treatment such as chemotherapy, and may increase mortality (28), the use of high-dose micronutrients in the absence of specific deficiencies should be discouraged (3).
For oral and enteral feeding, daily requirements for micronutrients may be taken from recommendations of WHO/FAO or from national and international nutrition societies (29).
Vitamins and trace elements should be generally substituted in parenteral nutrition unless there are contraindications: thiamine is particularly important. After provision of parenteral nutrition during for more than one week, supplementation of trace elements too becomes obligatory (3).
Quite frequently, deficiency of vitamin D is observed in cancer patients (30), which has been associated with cancer incidence and prognosis (31,32). However, a causal relationship has not clearly been demonstrated (33). Therefore, it remains unclear whether using vitamin D supplements to normalize vitamin D levels in states of deficiency will improve prognosis in cancer patients (3).

2.4 Fluid Requirements

For patients with cancer, the recommended daily fluid intake is at least 1500 ml from liquids. Since solid foods also contain fluids, the total recommended fluid intake is higher if a patient is not using solid foods. For patients with adequate renal function, this amount of fluid is considered sufficient during radiotherapy or chemotherapy to eliminate waste products from the body and to flush chemotherapy chemicals out via the kidneys. However, for older patients with cancer, a fluid intake of at least 1700 ml is advised, given the more vulnerable renal function and increased permeability of the skin in older adults (34).
Higher amounts of fluids, i.e., at least 2000 ml are recommended in patients receiving a combination of chemotherapy and radiotherapy, nephrotoxic cytostatic agents (cisplatin and carboplatin), patients with fever, and in patients with compromised bladder and renal

function. Other indications for increased fluid intake include increased losses from drains, fistulae, ileostomies, vomiting, and diarrhoea (34).

3. Nutritional Treatment Options

Dietary counselling by a trained nutrition professional (registered/accredited dietitian/nutritionist) on the basis of the nutrition care process is regarded as the 1st line of nutritional treatment (3). Dietary counselling includes a dietary history, dietetic/nutrition diagnosis, and dietary interventions. Rather than brief and casual nutritional "advice", dietary counselling is a dedicated and repeated professional communication process that aims to provide patients with a thorough understanding of nutritional topics that can lead to lasting changes in eating habits. Therefore, critical components of dietary counselling are to: 1) convey to the patient the reasons and goals for nutritional recommendations, and 2) motivate the patient to adapt to the altered nutritional demands of their disease (35).

Next to supporting health, food and eating have important roles in psychological stabilization and social integration, and may have a major impact on quality of life. Dietary counselling should consider and aim to maintain or improve all of these aspects. This will require ascertaining individual habits and preferences and adequate communication skills to ensure high compliance with the individualized dietary advice given (3).

Dietary counselling can be initiated upon standard referral by protocol, or after nutritional screening and/or assessment, to ensure referral of patients at risk of malnutrition or who are already malnourished. In severely malnourished patients who are undergoing active treatment, nutritional treatment should be offered immediately (3).

Since malnutrition is associated with poorer clinical outcomes, including decreased survival, and because it is difficult to reverse overt malnutrition in cancer patients with metabolic derangements (36), dietary counselling should preferably be initiated when patients are not yet severely malnourished and when the goals of care include maintaining or improving nutritional status (3).

3.1 Feeding Routes

Nutritional treatment options for patients with cancer include (combinations of) the following:

1. Oral feeding:
    a. Normal/regular foods, including fortified foods, modifying of texture or nutrient content, and "selective taste steering";
    b. Oral nutritional supplements (ONS).
2. Enteral nutrition (EN; tube feeding).
3. Parenteral nutrition (PN).

EN and PN are also referred to as "artificial nutrition" (3,37), whereas the term "medical nutrition" includes ONS, EN, and PN (37).

In general, oral intake is the preferred route of feeding. 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 (3). Food fortification may help to increase intake of protein and energy. Moreover, texture modification may help to continue or improve oral intake in patients having nutrition impact symptoms like dysphagia and/or chewing problems, whereas "selective taste steering", i.e., an innovative method to enable individual tailored recipe modification, can be used in patients with alterations in taste and smell.
However, for patients with cancer it is often very challenging to meet increased nutritional requirements with normal/regular foods alone. Meeting nutritional requirements may especially be challenging when the patient has nutrition impact symptoms due to the disease or its treatment (38,39), or if (s)he experiences other barriers to realize adequate oral intake, like not being able to shop, cook and prepare food, or having insufficient money to buy additional snack items.
In patients with cancer, especially those undergoing intensive anti-cancer treatment, proactive interventions are required in anticipation of further short-term decreases in oral intake. Depending on adequacy of the current dietary intake, presence of nutrition impact symptoms, expected short-term ability to continue and improve oral intake, and availability of the digestive tract, additional food or (partial) replacement by medical nutrition (ONS, EN, and/or PN) is often required.
In particular radiotherapy to the head and neck or oesophagus induces mucositis, decreases food intake, and results in weight loss in up to 80% of patients (3,40). Similarly, radiotherapy of the pelvic region is associated with gastrointestinal symptoms in up to 80% of patients (41). Therefore, in patients undergoing radiotherapy of the head and neck, thorax or gastrointestinal tract, the combination of intensive individualized dietary counseling (i.e., weekly contacts by a trained dietitians/nutritionist during radiotherapy of head and neck cancers and follow-up every two weeks for at least six weeks (42)) and ONS is required to prevent nutritional deterioration, maintain intake, and avoid radiotherapy interruptions. Several RCTs have demonstrated that individualized dietary counselling by a trained professional compared to conventional food without dietary education improves nutritional intake, body weight, and quality of life (43–47).
A systematic review with 13 studies showed that oral nutritional interventions in patients with cancer who are malnourished or at risk of malnutrition had a beneficial effect on some aspects of quality of life, but not convincingly on dietary intake, body weight, and survival (48). However, a more recent RCT in older patients at risk for malnutrition during chemotherapy showed that early dietary counselling was efficient in increasing intake, but had no beneficial effect on mortality or secondary outcomes (49).
In patients undergoing (adjuvant) radiotherapy there is good evidence that nutritional support improves intake and weight, and some aspects of quality of life (43,44,50). In patients undergoing chemotherapy, results are less conclusive (3).
The systematic review by Baldwin et al. studied the effect of dietary intervention (dietary advice, i.e., instruction to modify food intake given with the aim of improving nutritional intake, or ONS, or both) in cancer patients who were malnourished or were at risk of malnutrition, and showed no difference in survival. However, this systematic review did show significant improvement in quality of life in those studies in which the patients received (adjuvant) radiotherapy (no more tumour in situ), in contrast to studies that included patients undergoing systemic chemotherapy. The dietary interventions were associated with statistically significant improvements in body weight (mean difference in

weight 1.86 kg, 95% confidence interval (CI) 0.25-3.47, p=0.02), but there was statistically significant heterogeneity. Groups receiving nutritional treatment had a significantly higher energy intake than groups receiving routine care, again with high heterogeneity. A post-hoc analysis found that studies that offered both dietary advice and ONS had the greatest beneficial effect (48).

In general, artificial nutrition, i.e. EN or PN, is indicated if patients are unable to eat adequately (e.g., no food for more than one week or <60% of requirement for >1-2 weeks), or to digest or absorb food. In these patients, artificial feeding may stabilize nutritional status. If oral nutrition remains inadequate despite dietary interventions including ONS, tube feeding is indicated (3).

Patients with obstructing head and neck or oesophageal cancers, and with expected severe radiation-induced oral or oesophageal mucositis, have a high risk for weight loss, decreased physical performance, dehydration, decreased treatment tolerance, and increased treatment interruptions (45,51–54). Tube feeding is indicated in cases of severe dysphagia and inadequate energy intake. Prospective and retrospective observational trials in patients with inadequate food intake have demonstrated that tube feeding compared to oral feeding reduces weight loss, and the frequency and duration of treatment interruptions and rehospitalizations (40,45,52).

While sufficient evidence to determine the optimal method of enteral feeding for patients with head and neck cancer receiving radiotherapy and/or chemoradio-therapy is lacking, gastrostomy placement should be considered if an (expected) duration of required tube feeding is >6 weeks. A systematic review with 22 studies in head and neck cancer patients undergoing chemoradiation showed that gastrostomy placement prior to chemoradiation ("prophylactic gastrostomy placement") reduces the number of malnourished patients (defined as >10% weight loss), but average weight loss at various time points following treatment is similar to that in patients who receive the gastrostomy during treatment (55). Prophylactic gastrostomy placement is also associated with improved quality of life at 6 months, but greater long-term gastrostomy dependence, which stresses the importance of speech therapy to maintain swallowing function during feeding by tube.

If a patient with an expected survival of several months or years is unable to eat, artificial nutrition may improve survival (5,56,57). In contrast, several systematic reviews analyzing "routine" (i.e., not triggered by severe malnutrition and/or a relevant caloric deficit) artificial nutrition in cancer patients during chemotherapy concluded that tube feeding (58) or PN (59) does not have a beneficial effect on survival.

PN as a general treatment in radiotherapy is not recommended. If intestinal functions are preserved, enteral feeding may be as efficient as parenteral feeding (51), and has the advantages of maintaining the gut barrier, decreasing risk of infectious complications, and has lower costs. However, PN is indicated if tube feeding is not sufficient or feasible, for example in patients with intestinal insufficiency due to radiation enteritis, chronic bowel obstruction, short bowel syndrome, peritoneal carcinomatosis, or chylothorax. Chronic radiation enteritis has been reported in up to 20% of patients receiving pelvic radiotherapy (60), intestinal failure develops in approximately 5% (56) and in these patients home PN appears to be a reasonable treatment option (61) possibly superior to surgical intervention (62).

In allogeneic haematopoietic cell transplantation (HCT), several recent studies support a preference for EN over PN (63,64). Data show a trend toward fewer complications using enteral compared to parenteral nutrition during this procedure especially with respect to infectious complications (64). However, an increased risk of local bleeding and/or infection

in these patients has to be considered. After autologous HCT, PN will be necessary only in a few cases. After allogeneic HCT, PN will be necessary more frequently and for prolonged periods because of severe toxic mucositis, gastrointestinal infections, and gastrointestinal graft versus host disease. PN should be performed by experienced experts to avoid side effects and to obtain the best clinical results.
If oral food intake has been decreased severely for a prolonged period of time,
oral nutrition, EN, or PN should be introduced only slowly and incrementally over several days, and additional precautions should be taken to prevent a refeeding syndrome.

3.2 N-3 Fatty Acids

Evidence on the effects of long-chain N-3 fatty acids on body composition, quality of life and clinical outcomes in cancer patients undergoing anti-cancer treatment or cancer patients with cachexia is not conclusive. Beneficial effects of fish oil were observed especially in trials studying patients undergoing chemotherapy, which included improvements in physical activity and quality of life (65), appetite, intake of energy and protein (66), body weight (67), and lean body mass (66).
Supplemental intakes of EPA and DHA combined at doses up to 5 g/day, and supplemental intakes of EPA alone up to 1.8 g/day are considered safe for adults (68). Furthermore, supplementation of fish oil and long-chain N-3 fatty acids in these doses are mostly well-tolerated, although mild gastrointestinal effects have been reported. The taste, a fishy aftertaste or fishy belching, may impede compliance.
There are no clinical data to indicate decreased efficacy of chemotherapy by N-3 fatty acids. Rather, some clinical data reported increased efficacy of several cytotoxic agents when N-3 fatty acids are given (69).
Given the inconclusive 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, it is suggested to use supplementation (at least 2 g/day) with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight in patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished (70–72).

3.3 Immunonutrition

Immunonutrition, also referred to as immune-modulating nutrition, refers to liquid nutritional supplements enriched with specific nutrients. The role of the individual constituents of immunonutrition regimens remains to be resolved.
Oral/enteral immunonutrition is recommended in upper GI cancer patients undergoing surgical resection, to decrease risk of postoperative infective complications (3).
Beneficial effects of oral and parenteral supplementation of glutamine have been reported in chemotherapy-induced mucosal inflammation (73,74), vomiting and diarrhoea (75), and cytopenia (76). However, glutamine supplementation during conventional cytotoxic or targeted therapy, high-dose chemotherapy, and hematopoetic stem cell transplantation is not recommended, since sufficient consistent clinical data are lacking.

3.4 Energy Restricting and Ketogenic Diets

There are no diets known to reproducibly cure cancer or prevent cancer recurrence (3). Theoretical arguments that nutrients "feed the tumor" are not supported by evidence related to clinical outcome and should not be used to refuse, diminish, or stop feeding (77,78).

Dietary interventions that restrict energy intake in patients with or at risk of malnutrition should be avoided. While studies are being conducted to determine the role of short-term (24-72 h) fasting before, during and after the application of cytotoxic agents on tolerability and effects of cytotoxic treatment (79), currently evidence is lacking to recommend fasting during chemotherapy (3).

In recent years, ketogenic diets have gained growing attention as a broad-spectrum approach to lower blood glucose and insulin levels and target the Warburg effect, i.e., the observation that cancer cells tend to favor metabolism via aerobic glycolysis rather than the much more efficient oxidative phosphory-lation pathway, and its underlying genetic alterations. As such, this dietary approach exploits the main metabolic differences between normal and cancer cells (80).

Ketogenic diets are high fat, adequate protein (~1.5 g/kg body weight) and low-carbohydrate (≤50 g/day) diets that do not necessarily induce weight loss or micronutrient limitations. Instead, these diets mimic fasting to some extent, mainly through decreasing and stabilizing insulin levels, mildly increasing cortisol levels, and increasing fatty acid oxidation. These metabolic changes promote hepatic ketogenesis, which increases concentrations of the ketones acetoacetate and D-b-hydroxybutyrate (80).

Ketogenic diets in cancer treatment are considered safe, but are challenging in terms of compliance, due to practical aspects (e.g., shopping and preparation of meals), social aspects, and financial aspects. Especially extreme forms of the ketogenic diet, such as those relying heavily on artificial foods or the classic ketogenic diet have been used in the past and may partially account for the overall low adherence rate among cancer patients in published studies, which a recent systematic review estimated as only 49% (81). However, even the less strict versions of the ketogenic diet, like MCT-supplemented ketogenic diets, the modified Atkins diet, or the paleolithic ketogenic diet, restrict many food types from modern-day standard diets, which implies major dietary challenges for patients (80). Ketogenic diets may also lead to insufficient energy intake and weight loss due to their low palatability (82).

Most animal studies provide evidence for anti-tumor effects of ketogenic diets, although more recently some tumor models not responding have been described (80,83). The most recent case and cohort studies have shown promising results for ketogenic diets in relation to antitumor effects, body composition, physical functioning and metabolic parameters. However, further research on the effects of ketogenic diets in combination with other treatments on 'hard' endpoints, such as tumor control and overall survival, both in advanced cancer patients and in early stage patients, is needed (80).

3.5 Probiotics

Radiotherapy of the pelvic region is associated with gastrointestinal symptoms in up to 80% of patients, which include altered bowel habit (94%), loose stools (80%), increased stool frequency (74%), urgency (39%), and faecal incontinence (37%) (41); and these

often continue after the end of the treatment (84). Symptoms after radiotherapy may be manifestations of new onset gastrointestinal physiological deficits induced by the radiotherapy, including changes in gut microbiota (85).
Although there is some indication for protective effects from probiotics, data are heterogeneous and the quality of studies is limited. Therefore, reviews have concluded cautiously that there is inconclusive evidence supporting a prophylactic effect of probiotics against radiation-induced diarrhoea (86).

4. The Role of Nutrition in Palliative Care

Palliative care can be divided into three phases:
1. Predominantly disease-focused palliation aimed at prolonging survival;
2. Predominantly symptom-focused palliation aimed at alleviating symptoms;
3. The phase of dying.
The characteristics and aim of nutritional intervention are related to the phase of palliative care, as visualized in **Fig. 1** (87).

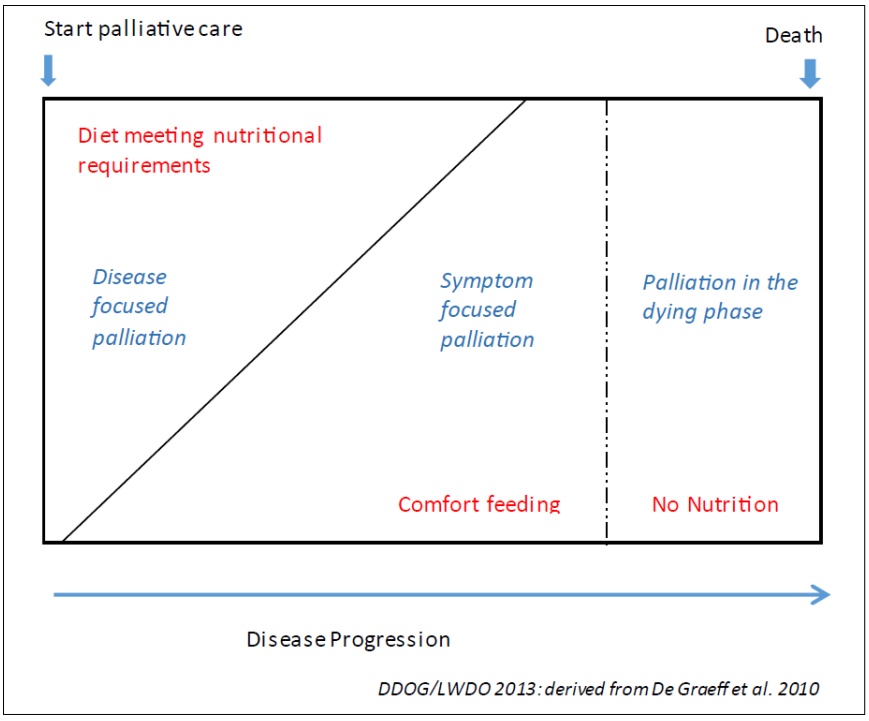

Fig.1. Nutrition care spectrum in palliative care

Two types of diet relevant to the trajectory of palliative care have been defined: a diet meeting nutritional requirements for patients with cancer, indicated in phase 1, and comfort feeding, indicated in phase 2. The transition of a diet meeting nutritional requirements to comfort feeding is not abrupt, but progresses gradually (see Figure 1). In phase 3, the patient gradually loses interest in food and drinks and may spontaneously stop eating and drinking at any moment (87).
It must be emphasized that life expectancy may be difficult to estimate due to the lack of clear criteria to ascertain the beginning of the dying phase. However, recent research in this area has shown that the combination of weight loss and body mass index (BMI) (88)

or a composite oncologic-inflammatory nomogram (56,89) may be of help in uncertain situations.

A diet meeting nutritional requirements is tailored dietary advice to meet an individual's energy, protein and other macro- and micronutrient requirements (90). Such diet is indicated if the incurable cancer patient is otherwise expected to die from starvation prior to tumour progression, and the quality of life of the patient is (still) acceptable or potentially susceptible to improvement. However, if the quality of life is not satisfying the patient, any decision on using a diet meeting nutritional requirements should be first agreed with the palliative care team and then negotiated with the patient (91).

During phase 1, preserving nutritional status may still be important for some time. Even when the disease can no longer be cured, the patient may still live for a reasonable amount of time and may benefit from a diet meeting energy and protein requirements. However, when life prolonging treatment is no longer available and care shifts towards symptom focused palliation (phase 2), meeting nutritional requirements correctly gets less and less priority (90).

Comfort feeding aims to make the patient feel physically, socially, emotionally and spiritually comfortable (87), and is indicated when the incurable cancer patient is expected to die from tumour progression rather than from starvation (91). The underlying assumption is that survival after total macronutrient starvation rarely exceeds two months in previously healthy people and much less in advanced cancer patients (91). Comfort feeding also intends to provide a quality of life as best is possible and to alleviate symptoms. The goal of comfort feeding is to recommend food that the patient can tolerate, provides minimal burden, and fits the patient's way of dealing with disease progression. With comfort feeding, inadequate nutritional intake is accepted (87).

Food and artificial nutrition may have social, emotional, and existential significance for the individual patient and family members (92). Also small amounts of food can have a significant meaning for the individual and contribute to a sense of wellbeing, autonomy, and dignity (93). However, in dying patients, treatment should be based on comfort. Therefore, pros and cons of continued nutritional treatment in this phase should be explained and communicated with patients, family members, and the care team (92,94).

There are no clear criteria to ascertain the beginning of the dying phase; therefore, a nutritional intervention in this phase of life should be followed in an individualized manner (5). 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. During terminal hypometabolism, normal amounts of energy and substrates may even be excessive and induce metabolic distress. Artificial hydration and nutrition are unlikely to provide any benefit for most dying patients. Therefore, the burden and risks of artificial nutrition, such as physical attachment to a feeding device, gastrostomy or central venous catheter placement, and complications associated with the feeding device, must be cautiously considered. However, in acute confusional states, it is suggested that use a short period of hydration is used to rule out dehydration as the precipitating cause (3).

Still, not infrequently, relatives and caregivers may demand artificial nutrition or hydration for terminally ill patients (95). Psychosocial distress of and among family members or other proxies should be addressed by communication and educational interventions provided by multiprofessional teams (96), taking into account the religious, ethnic and cultural backgrounds of patients and their families (5).

5. Nutrition/Diet/Dietary Patterns for Cancer Survivors

Cancer survivors are often highly motivated to seek information about food choices, physical activity, and dietary supplements to improve their treatment outcomes, quality of life, and overall survival (3).

As cancer survivors are at higher risk for developing second primary cancers and other chronic diseases, a diet rich in vegetables, fruits, and whole grains, and low in fats, red meats, and alcohol is recommended (3,97,98). This recommend-dation is supported by epidemiological data demonstrating a relationship between healthy dietary patterns and mortality, but not cancer recurrence. Although current evidence also does not support large effects of food choices on cancer incidence (98,99), high consumption of red meat (beef, pork, mutton) is associated with an increased risk of colorectal cancer (98), breast cancer (100), and overall cancer mortality (101).

A systematic review and meta-analysis of 27 studies, which were mainly cohort studies in the general population in the United States (102), found significant inverse associations between adherence to the Dietary Approaches to Stop Hypertension (DASH) diet (HR: 0.85; 95% CI: 0.79 to 0.91; I^2=81.8%), the Alternative Healthy Eating Index (AHEI) (HR: 0.90; 95% CI: 0.85-0.95; I^2=61.5), the healthy eating index (HEI) (RR: 0.82; 95% CI: 0.75-0.89; I^2=89.5%), Diet Quality Index (DQI) (HR: 0.91; 95% CI: 0.89–0.93; I^2=0.0%), alternative Mediterranean Diet (aMED) (RR: 0.81; 95% CI: 0.78–0.83; I^2=1.7%), and HEI-2010 (HR: 0.82; 95% CI: 0.69–0.98, I^2=0.0%) and cancer mortality. These diets are mostly characterized by higher intake of whole grains, vegetables, fruits, legumes, nuts and low intake of refined grains, red meats, alcohol, and sugar-sweetened products (102).

A systematic review of 38 studies specifically in survivors of common cancers with a 10-year survival rate of ≥50% (bladder, bowel, breast, cervical, kidney, laryngeal, prostate, testicular, uterine cancer, malignant melanoma and (non-)Hodgkin's lymphoma), provided limited evidence that the reduction of dietary fat after breast cancer diagnosis could increase relapse free survival among breast cancer survivors (HR=0.76; 95% CI 0.60-0.98); that adherence to the HEI-2005 score after diagnosis is associated with decreased overall mortality (HR=0.40; 95% CI 0.17-0.94); that adherence to the AHEI diet after diagnosis is associated with decreased death from other causes (RR=0.57; 95% CI 0.42-0.77); and that adherence to a prudent diet (which characteristics overlap with the Mediterranean diet) after diagnosis is associated with decreased death from other causes among breast cancer survivors (HR=0.54; 95% CI 0.31-0.95). In this systematic review, no conclusive evidence could be provided for other survivors than of breast cancer (103).

The findings of this systematic review were in line with findings from an earlier systematic review, in which post-diagnosis adherence to a high-quality diet (RR=0.79; 95% CI: 0.71–0.89; I^2=0%) and postdiagnosis prudent diet (RR=0.77; 95% CI: 0.60–0.99; I^2=56%) were inversely associated with overall mortality (104). The latter systematic review also reported that neither a postdiagnosis prudent/healthy dietary pattern (RR:0.94; 95% CI:0.71–1.24; I^2=19%) nor the 'unhealthy' Western dietary pattern (RR=1.34; 95%CI, 0.61–2.92; I^2=85%) was not associated with cancer recurrence.

Consumption of vegetables and fruits exerts limited protective effects against cancers associated with smoking or drinking (105). However, it is unclear whether plant-based foods have an effect on cancer recurrence rates.

Several recently published reviews indicate that obesity and metabolic syndrome might be independent risk factors for recurrence and reduced overall survival in breast and gastric

cancer patients (106,107). Moreover, it is suggested that diet and exercise can have a positive impact on progressive disease and overall survival (97). Therefore, it is recommended to maintain a healthy weight (BMI 18.5-25 kg/m^2) (3).

6. Summary

Patients with cancer with a comparably good prognosis and an expected overall survival of at least several months should receive adequate dietary counselling and nutritional support including oral, enteral or, if required, parenteral nutrition, or combinations. In these patients, nutritional treatment aims to secure an adequate intake of energy and protein as well as other macro- and micro-nutrients, to diminish metabolic disturbances and nutrition impact symptoms, to optimize nutritional status, i.e., maintain or increase lean body mass (skeletal muscle mass), to optimize performance status, and to optimize quality of life. Moreover, if a patient is undergoing anti-cancer treatment, nutritional interventions aim to enable the cancer patient to undergo the planned treatment and to reduce the risk of reductions or interruptions of scheduled anti-cancer treatments. There are no diets known to reproducibly cure cancer or prevent cancer recurrence. Theoretical arguments that nutrients "feed the tumor" are not supported by evidence related to clinical outcome and should not be used to refuse, diminish, or stop feeding.

Research has demonstrated that dietary counselling improves body weight and quality of life, while effects on mortality are not conclusive. However, nutritional support should receive special consideration if patients are receiving palliative anti-cancer treatment. In the palliative phase, nutritional interventions need to be carefully considered in relation to the patient's prognosis and quality of life.

Nutritional treatment should be started according to the patient's energy and protein needs, taking into account the patient's ability to eat and utilize the digestive tract, as well as the individual patient's preferences.

In general, oral intake is the preferred route of feeding. However, a proactive policy is required to anticipate decreased oral intake due to the disease or its often intensive treatment. If nutritional requirements cannot be met by oral intake, enteral feeding, in particular oral nutritional supplements and/or tube feeding, or, to a lesser extent parenteral feeding may be required. Effects of nutritional treatment on outcomes should be monitored on a regular basis. Moreover, the goals of nutritional treatment should be reconsidered during the various phases of disease and its treatment.

After cancer treatment, a healthy dietary pattern may reduce mortality and therefore should be promoted.

7. References

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