Nutritional Support in Cancer Topic 26

Module 26.4

Multimodal Care

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Learning Objectives

- Know the relevant therapeutic problems in cancer cachexia;
- Know the importance of a multi-targeted and multi-professional approach for treatment of cachexia;
- Know pharmacological agents proposed and approved to treat cancer cachexia;
- Know other important components of anti-cachexia treatment.

Contents

Key Messages

- A multitude of pathological factors may promote malnutrition and cachexia;
- Frequently, several factors are acting simultaneously and reinforce each other;
- To treat cachexia, all relevant impairements need to be considered and treated;
- Nutritional interventions and muscle training are basic components of treatment;
- To improve appetite, psychological and social distress as well as chronic pain have to be alleviated;
- Debilitating symptoms interfering with food intake need to be treated;

- Pharmacological agents may help to relieve nausea and gastrointestinal dysfunction;
- To stimulated appetite, corticosteroids and progestins are best established; both have unwanted side-effects that need to be considered;
- Anti-inflammatory agents, like NSAIDs and N-3 fatty acids may be used to counteract chronic inflammatory states in cancer patients;
- A large number of other anti-inflammatory and anabolic agents have been studied but none has yet been approved to treat cancer cachexia;
- Trials are ongoing to establish the benefit of combining complex multi-targeted anti-cachexia interventions.

1. Introduction

Weight loss and loss of body cell mass are frequent and complex problems in cancer patients. Major factors leading to malnutrition and compromised prognosis are anorexia, gastrointestinal (GI) dysfunction, systemic inflammatory processes and a prevalence of catabolic signals. These factors interact and may aggravate each other.
Body resources are endangered by a number of factors, often acting simultaneously and synergistically during progression and treatment of a malignant tumor. Under normal conditions, to remain stable, our bodies require 1) a constant supply of energy and nutrients to compensate for ubiquitous and inevitable losses; 2) a stable metabolic milieu balancing anabolic against catabolic factors; and 3) regular activity of all organs and tissues to avoid atrophy **(Fig. 1**). The last point is exemplified most prominently by the growth and strengthening of skeletal muscle induced by training, and loss of muscle mass associated with inactivity.

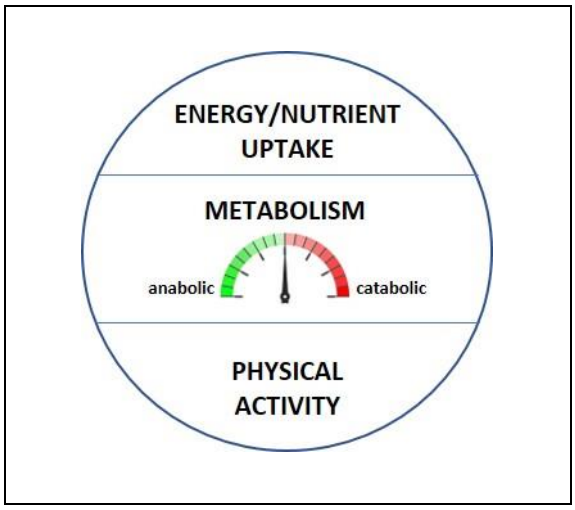

Fig. 1 Determinant of body resources are
1) energy/nutrient uptake balancing continuous losses,
2) overall metabolic balance between anabolic and catabolic processes,
and 3) physical activity to counteract trends towards atrophy

The balance of these basic equilibria is threatened by a large number of factors activated during the emergence and progression of a malignant tumor, and induced by all anti-cancer treatment modalities as well as by intercurring infections and other complications (see **Fig. 2**). A beneficial balance and a relevant benefit for the patient may only be achieved if all or at least most derangements are resolved or at least alleviated. It is easily apparent

then, that treatment of these complex and interacting derangements requires a multi-targeted, multi-modal and multi-professional approach based on close interaction of all members of the treatment team, caregivers and the patient.

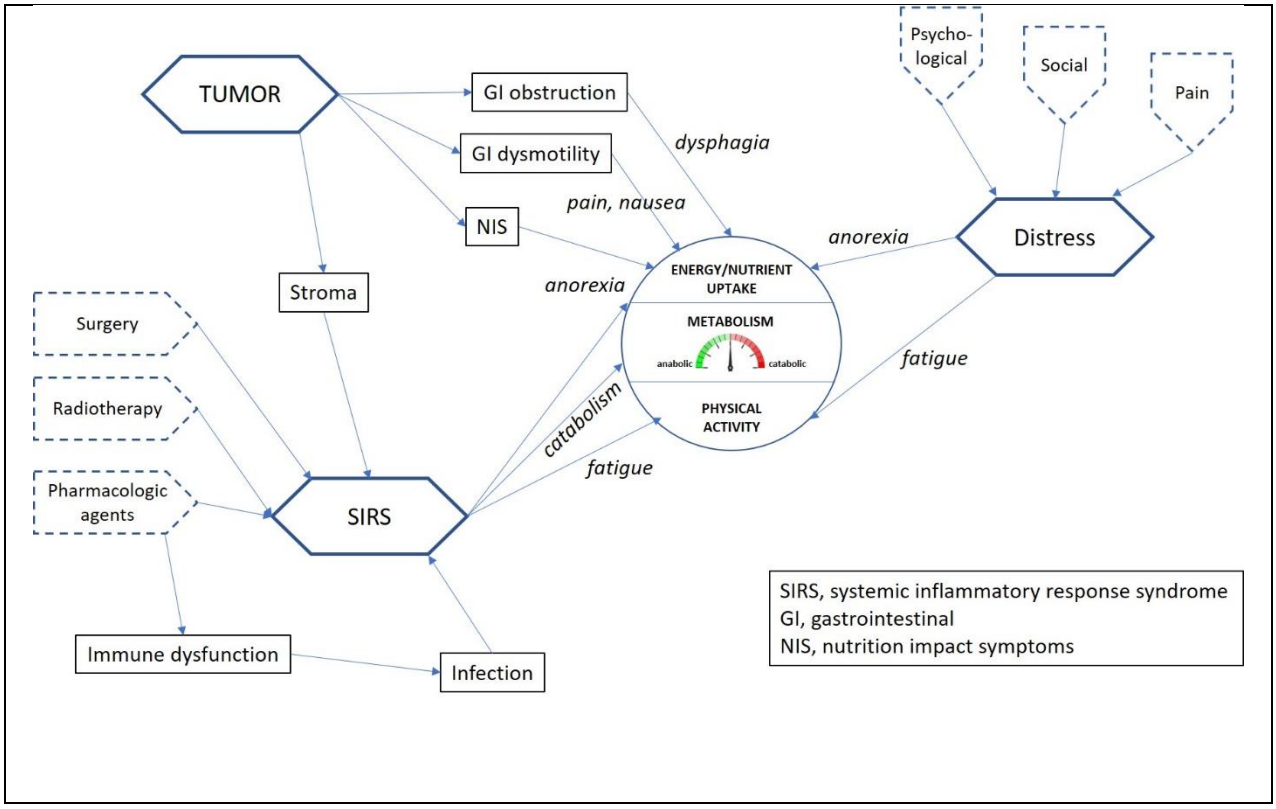

Fig. 2 Examples of possible cause-effect relationships impairing body resources in patients with cancer

2. Team Approach

Due to the complex and multi-faceted contributors to cachexia, anti-cachexia treatment by necessity needs to target all relevant factors active in an individual patient. Cachexia treatment thus has to be based on a comprehensive assessment of the patient's situation and an evaluation of reasonably available treatment options, resulting in a personalized multi-targeted multi-modal supportive therapy. This refers to assessing and treating inadequate food intake, metabolic derangements, pain and psycho-social distress as well as motivating to and guiding muscle training. To be effective, this requires the expertise of several different specialties and a close and respectful collaboration of the experts assigned to be members of the treatment team.

It is advisable for a cachexia clinic or team to include the expertise and consulting services of a nutritionist, pharmacist, nurse, physiotherapist, oncologist, hematologist, supportive and palliative care physician, gastroenterologist, surgeon, head&neck cancer specialist, speech therapist, pain expert, psychologist, social worker.

An important point is prioritizing the available multimodal treatment components. In patients with advanced cancer, educating patients to understand their experience can alleviate distress and foster self-management. If anticancer treatment is applied to a cachectic patient, the intensity of multimodal management needs to be enhanced. In these patients, both a rehabilitative approach with education and empowerment of patients (1)

with nutritional, physical activity, and psychosocial support and early integrated supportive with palliative interventions (2) should be offered to patients and family members.
In patients physically unfit for further oncological therapy, it is of major importance to ensure that supportive interventions are safe and do not add unnecessary burdens to the suffering patient. Palliative interventions for both patient and family members may encompass relief of eating- and weight loss-related distress, strategies to cope with proximity of death, and enhancing communication with patients and family. This may also include alleviating metabolic derangements, providing cautious nutritional support, especially by counselling, and physical exercises, while carefully monitoring individual goals and QoL.

3. Pharmacological Agents

In cachexia, catabolic drivers are frequently activated, represented most prominently by the activation of the systemic inflammatory response syndrome, while anabolic factors are diminished, including reduced intake of energy and protein, reduced physical activity and thus inadequate muscle training, and the evolution of insulin resistance (3) and anabolic resistance (4). This impairs the ability to maintain whole body muscle mass. Pharmacological interventions to decrease catabolism and to increase anabolic pathways include efforts to normalize energy and nutrient intake by increasing appetite, to inhibit pro-inflamatory actions and to increase muscle mass.
Many different pharmacological approaches have been proposed to treat components of this cachexia network (**Table 1**). Several agents are used frequently in standard supportive and palliative care of cancer patients. However, of the numerous substances tested to correct or antagonize deranged metabolic pathways, only a few have so far been proven effective. Unfortunately, today there are still many more theoretical options than established treatments against cancer cachexia.

Table 1

Appetite stimulants	**Gastrointestinal Modulators and other Supportive Agents**	**Anti-inflammatory Agents**	**Anti-catabolic and Anabolic Agents**
Corticosteroids	Prokinetic drugs	Steroids, cannabinoids	Insulin and insulin sensitivity modulators
Progestins	Inhibitors of GI motility	NSAID	Growth hormone and secretagogues
Cannabinoids	Proton pump inhibitors	N-3 fatty acids	Anabolic-androgenic steroids and SARMs
Ghrelin and analogues	Parasympathomimetics	Anti-interleukin 6 antibodies	Amino acids, metabolites
Melanocortin 4 receptor antagonists	Antiemetics	Anti-cytokine agents	Experimental agents (anti-myostatin, selumetinib, IL 15)
Cyproheptadine	Analgesics	Antibiotics (clarithromycin)	Proteasome inhibitors
BCAA	Psychotropic drugs	Melatonin	ß-receptor modulators
Herbal medicine, bitters		Antioxidants	Hydrazine sulfate
			ATP

BCAA: branched-chain amino acids
NSAID: non-steroidal anti-inflammatory drug
SARM: selective androgen receptor modulator
ATP: adenosine 5'-triphosphate

Anorexia is a hallmark sign of many cancers and may appear early and even before cancer is diagnosed. It is the result of complex neuro-hormonal interactions that lead to a declining or absent desire to eat (5). Chronic pain even at a low level may contribute to anorexia as may psychological and social stressors which often are present during the course of a cancer disease and may peak during critical phases. Nausea and defects in smelling or tasting will similarly reduce or block any urge to eat.
Physiological function of the gastrointestinal tract is essential to the efficient intake, transport, breakdown and absorption of foods and nutrients. Dysfunction may occur at many different sites and be of diverse nature. To alleviate or correct disturbed GI functions targeted pharmacological treatments should be applied.
Systemic inflammation is present in many patients with advanced tumours. The associated immunological, endocrine, paracrine and metabolic changes will inhibit appetite and physical activity while increasing fatigue, lethargy and exhaustion. Resting energy expenditure is increased and inter-organ nutrient fluxes are redistributed. Anti-inflammatory agents may antagonize some of these effects.
Reduced energy intake and inflammation activate catabolic reactions leading to loss of protein and fat and body cell mass. At the same time water is retained in the extracellular compartment resulting in subclinical and clinical edema. Antagonizing catabolic pathways and activating anabolic processes may improve protein and performance status, vitality and quality of life.
When studying the effects of biologically active substances to treat anorexia or cachexia it is essential to understand that no agent will make muscles grow if they are not stimulated to work. Therefore, any pharmacological treatment in cancer patients should invariably be combined with exercise training.

3.1 Appetite Stimulants

Anorexia is a psychological burden for the patient and close relatives. Families may push patients to eat against their wishes. Anorexia is a primary cause of reduced food intake and thus of weight loss. A number of agents has been proposed and studied to counteract anorexia and to increase appetite (**Table 2**).

Table 2

Appetite stimulants
Corticosteroids
Progestins
Cannabinoids
Ghrelin and analogues
Melanocortin 4 receptor antagonists
Cyproheptadine
Branched-chain amino acids
Herbal medicines, bitters

Corticosteroids

This group of drugs includes dexamethasone (DEX), prednisolone (PRED), methylprednisolone (MP) and hydrocortisone. These agents stimulate the appetite, they have an antiemetic activity and they are able to reduce asthenia. In addition, they may increase general well-being. The mechanism of action on appetite is not well understood but may involve suppression of production or release of prostaglandins and proinflammatory cytokines such as IL-1 and TNF-α. The effects on appetite and well-being are usually temporary and limited to a few weeks.

Corticosteroids have been investigated in randomized controlled studies (RCT) since the 1970s. A systematic review (6) analyzed 6 studies involving a total of 647 patients. Intravenous or oral corticosteroids significantly improved appetite, pain, quality of life (QoL) scores, vomiting, well-being and performance status. Doses used were PRED 10 mg/d, MP 32-125 mg/d, DEX 3-8 mg. Improvements could be observed for several weeks; in one study, however, beneficial effects present after 2 weeks of treatment disappeared after 4 weeks.

Corticosteroids produce a number of unwanted effects if taken for prolonged periods, including myopathy, osteoporosis, immune suppression, susceptibility to infections, skin frailty, accumulation of extracellular water, edema, insulin resistance and increase of blood glucose, gastrointestinal ulcers and mood abnormalities.

Since beneficial effects are usually limited to a few weeks and prolonged treatment is associated with increasing side-effects, the use of corticosteroids should be restricted to patients with an expected survival of short duration.

Progestins

When progestins were used to treat hormone-responsive breast cancer, weight gain was observed as an unexpected side effect. Two synthetic progestins have been studied to assess effects on appetite in cancer-associated anorexia: Megestrol acetate (MA) and medroxyprogesterone acetate (MPA). Yavuszen reviewed 23 RCTs using MA at doses from 160 to 1600 mg/d and 6 RCTs using MPA at doses from 300 to 1200 mg/d (6) including a total of 4139 patients.

Side effects of both MA and MPA were found to be acceptable. The optimal dose of MA was reported to lie between 480 and 800 mg, while there are no data for an optimal MPA dose. Compared to placebo both MA and MPA increased appetite and less reliably body weight, while there were only minimal effects on QoL. In increasing appetite, MA was similarly effective to corticosteroids, but MA was more effective than the cannabinoid dronabinol and the anabolic steroid fluoxymestrone.

A Cochrane meta-analysis of 31 RCT and a total of 4123 patients showed a benefit of MA compared with placebo, particularly with regard to appetite improvement and weight gain in cancer patients, while again there was insufficient information to define the optimal dose of MA (7). A more recent meta-analysis (8) concluded that MA was able to reduce the symptoms of cancer cachexia with no effect on survival or quality of life.

The mechanism of action of progestins is still unclear. Progestins have been shown to reduce production of proinflammatory cytokines IL-1, IL-6 and TNF-α by peripheral blood mononuclear cells (9) and they may stimulate appetite via the neuropeptide Y orexigenic network in the ventromedial hypothalamus (10). Unfortunately, weight gain generally is not accompanied by an increase in lean body mass (11); thus weight gain is based on fat gain and accumulation of water. Progestins under certain conditions may even decrease muscle mass by reducing circulating androgen levels. On the other hand, very recent data

in cachectic tumour-bearing rats show an improvement in muscle mass after administration of MA.
Side effects of progestins include thromboembolism (reported in up to 5% of cases (12)), impotence in males and vaginal spotting or bleeding in females, hyperglycaemia, hypertension, peripheral oedema, alopecia, and adrenal insufficiency.
Progestins should not be offered to patients with a history or a high risk of thromboembolism. If side effects are acceptable, progestins may induce a long-term increase in appetite and weight. It has been suggested that the daily dosage should be started low and be increased only if the expected effect on appetite does not occur after a trial period of two weeks.

Cannabinoids
Anecdotal reports and numerous small studies suggest that marijuana stimulates appetite (13). Cannabis extracts and the most active ingredient tetrahydrocannabinol (THC) have been studied. The mechanism by which cannabinoids exert their effects has yet to be clarified. They bind to receptors of the endocannabinoid system in the central nervous system; they might act by inhibiting prostaglandin synthesis or by inhibiting cytokine production and/or secretion.
An effect on appetite and mood is obtained from administration of THC 5 mg/day, with about 2/3 of patients reporting that their appetites are stimulated. Neuropsychological effects are not uncommon, including nausea and slurred speech. Approximately 50% of patients tolerate 10 mg twice daily.
There are only few valid studies reporting on cannabinoid effects on appetite. A RCT by Strasser et al. (14) did not observe any benefit of oral administration of cannabis extract or THC (2.5 mg/d) on appetite or quality of life when compared with placebo. The dose used in the study, unfortunately, was fairly low. A 3-arm study compared THC (5 mg/d) with MA (800 mg/d) and a combination of both. MA improved appetite and QoL better than THC, but the combination of dronabinol with megestrol acetate did not offer any advantage over treatment with megestrol acetate alone (15).
Cannabinoids thus may be offered to individual patients, if other orexigenics are unsuitable; the dose should be carefully increased to at least 5 mg and if possible up to 15 or 20 mg/d, while carefully observing an effect on appetite as well as potential side effects.

Other available agents
Branched-chain amino acids (BCAA)
It has been proposed that increased ventromedial hypothalamic serotonin levels might play a role in the development of anorexia. Since BCAA compete with tryptophan for the same transport system across the blood-brain barrier, it has been suggested that BCAA might slow down the entry of this serotonin precursor into the brain, lead to decreased brain tryptophan concentration and reduced serotoninergic activity and finally to decreased anorexia. In a randomized controlled study in 28 cancer patients BCAA (15 g/d) consumed for 7 days prior to planned surgery resulted in reduction of anorexia in the BCAA group which was not seen in the controls (16).
In a randomized study in 84 patients undergoing chemoembolisation for hepatocellular carcinoma 41 patients received BCAA (11 g/d) for 1 year. These patients had lower rates of ascites and oedema, higher serum albumin levels and better quality of life than the control group (27).

These data are not sufficient to recommend BCAA as appetite stimulants.

Herbal medicines, bitters

Herbal bitters and other herbal remedies have been used in many countries to increase or stabilize appetite (17). Clinical evidence to support the use of herbal medicine is very sparse. Data from preclinical studies suggest a stimulatory effect of the herbal medicine rikkunshito on ghrelin signaling (18); this might contribute to a postulated orexigenic effect. A recent systematic review reported on 2 small randomized studies using rikkunshito in combination with anticancer chemotherapy drugs; these studies reported significant beneficial effects of rikkunshito on nausea, anorexia and food intake (19).

Experimental agents

Ghrelin and analogues

Ghrelin is a peptide hormone produced mainly in the stomach from a distinct group of endocrine cells located within the gastric oxyntic mucosa. Ghrelin stimulates food intake and adiposity. It stimulates growth hormone (GH) secretion via the GH secretagogue receptor, but it also promotes food intake via the orexigenic neuropeptide Y system and decreases sympathetic nerve activity. It also influences glucose and lipid metabolism (20). In a small randomized, placebo-controlled, cross-over trial 7 anorectic cancer patients reported a marked increase in energy and food intake during a 3-hour ghrelin infusion compared with saline control, with all patients reporting a benefit (21). Strasser et al. (22) studied 21 adult patients in a randomized cross-over design to receive 60-minute ghrelin infusions or placebo. Nutritional intake and eating-related symptoms did not differ between ghrelin and placebo. In a RCT in 21 patients after total gastrectomy twice daily ghrelin infusions for 10 days induced higher appetite and food intake compared with placebo. Loss of body weight was less in the ghrelin group and lean body mass remained stable with ghrelin but decreased in the placebo group (23). In a randomized double-blind 8-week trial in 31 weight-losing cancer patients comparing two doses of daily subcutaneous ghrelin injections, high-dose ghrelin reduced the loss of body fat and showed a trend for improved energy balance; serum levels of tumour markers did not change and no adverse events were reported (24).

The orally active growth hormone secretagogue receptor agonist anamorelin (RC-1291) produces a dose-related increase in body weight in healthy volunteers (25). When administered in a randomized, placebo-controlled trial over 12 weeks to patients with a variety of cancers RC-1291 produced an increase in body mass and grip strength and a trend towards increased lean mass but no benefit in quality of life (26).

Two large multi-centered phase 3 trials compared oral anamorelin to placebo in more than 900 patients with non-small cell lung cancer and cachexia, defined from weight loss (5% in 6 months) or low BMI (<20 kg/m²). Over 12 weeks, anamorelin significantly improved lean body mass but not handgrip strength and did not gain approval by the FDA or EMA. Further clinical trials are being planned.

At this time, ghrelin and anamorelin are still experimental agents and are not available for clinical use.

Melanocortin 4 receptor (MC4R) antagonists

Systemic cytokines lead to the stimulation of the central melanocortin system in the hypothalamus and result in anorexia, increased energy expenditure and loss of lean body mass. Signaling involves the MC4 receptor. Antagonists for the melanocortin type 4 receptor are being developed and tested to inhibit inflammation-associated anorexia (27). Preclinical data obtained with the MC4R antagonist BL-6020/979 show positive

effects on food intake, body weight, energy expenditure, body composition and fatigue (28). At this time no clinical trials using these substances to treat cancer-associatred anorexia have been reported.

Cyproheptadine
Cyproheptadine is a serotonin antagonist acting as a 5-HT2 receptor antagonist.
Cyproheptadine improved diarrhoea and promoted weight gain in patients with carcinoid tumours (29). In an early study in anorexic adults cyproheptadine yielded a significant improvement in appetite and body weight (30). In a randomized double-blind trial in cancer patients with anorexia or cachexia, however, it failed to prevent weight loss compared with the placebo group, while patients receiving cyproheptadine (24 mg/d) had less nausea but also less energy and more sedation and dizziness (31). A recent study demonstrated that cyproheptadine was able to enhance body weight in children with cancer-associated cachexia; the most prominent side effect was drowsiness (32).
Thus, cyproheptadine is not recommended in adult patients with cancer cachexia except in patients with carcinoid tumour.

3.2 Anti-inflammatory Agents

Systemic inflammation is a frequent and prognostically relevant phenomenon in patients with advanced cancer (33). An array of anti-inflammatory agents has been studied (**Table 3**).

Table 3

Anti-inflammatory agents
Corticosteroids, progestins, cannabinoids
NSAID
N-3 fatty acids
Anti-interleukin 6 antibodies
Anti-cytokine agents
Antibiotics (clarithromycin)
Melatonin
Antioxidants

Steroids (corticosteroids and progestins) and cannabinoids
See 3.1.

Non-steroidal anti-inflammatory drugs (NSAID)
NSAIDs like indomethacin, ibuprofen and celecoxib inhibit prostaglandin production via the rate-limiting enzymes cyclo-oxygenases-1 and-2 (COX-1 and COX-2). While COX-1 is expressed constitutively in most tissues and appears to be responsible for the regulation of physiological functions, COX-2 is induced by cytokines, growth factors, and oncogenes, and it contributes to the synthesis of prostaglandins in inflamed and neoplastic tissues.

In 135 cancer patients with weight loss, indomethacin (100 mg/d) compared to prednisolone (20 mg) or placebo had no effect on body weight loss but prolonged the mean survival time considerably (34). In a single arm study ibuprofen (1200 mg/d) reduced elevated resting energy expenditure and C-reactive protein levels in 16 weight losing pancreatic cancer patients (35). A randomized study in patients with gastrointestinal cancers and weight loss showed that ibuprofen combined with megestrol acetate (MA) increased quality of life (QoL) and body weight after 12 weeks, while patients treated with MA alone lost body weight and had no improvement in QoL (36).
Mantovani et al. studied the efficacy and saftety of celecoxib (300 mg/d) for 4 months in 24 patients with cancer cachexia (37). There was no grade 3-4 toxicity and all patients could maintain the NSAID dose. There were significant improvements in lean body mass, grip strength, quality of life and performance status; TNF-α levels decreased significantly. In a small placebo-controlled study celecoxib (400 mg/d) given for 3 weeks to 11 cachectic patients with head and neck or gastrointestinal cancer significantly increased body weight and quality of life compared to placebo (38).
In a systematic review Solheim evaluated 13 clinical studies using NSAID to treat cancer cachexia (39). 7 of the 13 studies were one-arm studies without a comparator and most studies had serious limitations to study quality; however, 11 of the 13 studies reported beneficial effects on weight or lean body mass and only negligible side effects. Solheim et al. concluded that NSAID may improve weight in cancer patients with cachexia but that evidence is too frail to recommend these drugs for the treatment of cachexia outside clinical trials.

Omega-3 (N-3) long-chain fatty acids (EPA, DHA)
Fish oil is particularly rich in long-chain N-3 polyunsaturated fatty acids including eicosapentaenoic (EPA; C20:5; n-3) and docosahexaenoic (DHA; C22:6; n-3) acids. These undergo biological transformation by cyclooxygenases (COX) to produce eicosanoids, which alter the balance in the production of inflammatory mediators including cytokines. EPA is a competitive antagonist of arachidonic acid and is transformed to less pro-inflammatory eicosanoids. Thus, EPA may decrease inflammatory status.
Several RCT have studied the effects of N-3 fatty acids on cancer cachexia. In 2007 2 systematic reviews were published on 5 RCT (40) and on 17 clinical trials and prospective studies (41). The Cochrane Review concluded that there were insufficient data to conclude that oral EPA was better than placebo. The analyzed RCT, however, were hampered by poor patient compliance and short trial durations. The other review concluded, that oral n-3 fatty acids at a dose above 1.5 g/d increase body weight and appetite, improve QoL and reduce post-surgical morbidity. The levels of evidence for these conclusions, however, were grade B and C.
More recently, results from three further prospective trials have been reported. Van der Meij et al. in a randomized double-blind 4 week study compared two oral nutritional supplements with or without n-3 fatty acids (2 g/d of EPA plus 0.9 g/d DHA) in 40 patients with stage III non-small cell lung cancer undergoing multimodal cancer therapy (42). Patients receiving n-3 fatty acids lost significantly less weight and lean body mass; had lower resting energy expenditure and a higher energy and protein intake.
Murphy et al. used a non-randomized design and offered fish oil supplements (2.2 g/d EPA) to 40 patients with advanced non-small cell lung cancer undergoing first-line chemotherapy. 16 patients who accepted the offer to take fish oil maintained weight and muscle mass, while 24 patients who declined the offer lost weight (43). In a second study, of 46 patients with advanced non-small cell lung cancer undergoing chemotherapy 15

patients accepted the offer to consume fish oil (2.5 g/d of EPA+DHA); these patients had significantly better response rates to chemotherapy when compared to patients who chose not to take fish oil (44).
While there are few well designed clinical trials reporting on effects of n-3 fatty acids on clinical outcome in cachectic cancer patients, the partially positive results of the available trials may be weighed against the only mino side effects of fish oil and n-3 fatty acids. Thus, the decision to recommend supplements of n-3 fatty acids needs at present to be made on an individual basis.

Other available agents

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring compound found in animals, plants and microbes. In mammals, melatonin is secreted into the blood by the pineal gland with a diurnal rhythm. It has effects on the circadian rhythm and on both innate and adaptive immune functions. Many biological effects are produced through activation of melatonin receptors, while others effects are due to its role as a powerful antioxidant (45).
Melatonin has been implicated in cancer prevention and in reducing the risk of death in cancer patients (46). In a randomized study of 100 patients with advanced cancer supportive care was compared to supportive care plus melatonin (20 mg/d at night) for 3 months (47). In 86 evaluable patients weight loss ≥10% occurred less often with melatonin treatment, while there was no difference in food intake. In the melatonin group TNF-α levels decreased significantly during the study period.
The same centre subsequently studied overall survival in patients with metastatic non-small cell lung cancer. 100 consecutive patients were randomized to either chemotherapy or chemotherapy plus melatonin (20 mg/d at night). Chemotherapy response rates were improved and 5-year survival was significantly better with melatonin (6%) than without melatonin (0%) (48).
A systematic review and meta-analysis included 10 RCT (with a total of 643 patients) of melatonin in solid tumour cancer patients (46). All studies were performed in the same hospital network and all trials were unblinded. Melatonin significantly reduced the risk of death at 1 year by 34%. Effects were consistent across melatonin dose and tumor type. No severe adverse events were reported.
Unfortunately, all these trials in advanced cancer patients were from the same institution. Since confirmatory reports are still lacking, melatonin has not entered standard treatment protocols.

Antioxidants

Oxidative stress has been implicated in cancer initiation and progression (49). In addition, cancer-associated inflammation promotes production of reactive oxygen species. Thus, antioxidants have been proposed to be beneficial in states of advanced cancer (50). However, no reliable randomized studies have been published from which to judge the effect of antioxidants in cancer.

Anti-cytokine agents

Pro-inflammatory cytokines mediate many of the metabolic derangements observed in cancer cachexia (51-53). Different strategies to suppress or block cytokines have been followed.

TNF-binding agents: infliximab, etanercept

Tumour necrosis factor alpha (TNF-α) is a prominent pro-inflammatory cytokine involved both in survival and inducing cachexia (54, 55). In a randomized controlled study 89 patients with pancreatic cancer cachexia were treated for 8 weeks, in addition to gemcitabine, with 2 different doses of the anti-TNF-α monoclonal antibody infliximab or with placebo (56). At 8 weeks no significant differences were observed for changes in lean body mass or any of the secondary endpoints of overall or progression-free survival, performance status or quality of life.

The dimeric fusion protein etanercept binds to and neutralizes TNF-α. In a randomized controlled study 63 anorectic or weight losing cancer patients were treated with etanercept or placebo for up to 3 months. Medication was injected twice weekly. Treatment with etanercept was associated with higher rates of neurotoxicity but lower rates of neutropenia or thrombocytopenia. Weight gain and changes in appetite were minimal and similar in both groups; median survival did not differ between the groups (57).

Thus, use of TNF-binding agents currently cannot be recommended.

Pentoxifylline

The methylxanthine derivative pentoxifylline is a competitive non-selective phosphodiesterase inhibitor that suppresses TNF synthesis by decreasing gene transcription. In a double-blind placebo-controlled randomized study pentoxifylline (1200 mg/d) was compared to placebo in 70 anorectic or weight losing cancer patients (58). Pentoxifylline failed to improve appetite, weight or subjective perception of benefit.

Thalidomide

Thalidomide is an anti-TNF agent. It inhibits the production of TNF-α by human macrophages by accelerating the degradation of TNF messenger RNA transcripts. In randomized studies thalidomide was shown to halt and reverse weight loss in AIDS associated cachexia (59).

Bruera et al. treated 72 anorectic or weight losing patients with advanced cancer with thalidomide (100 mg/d given at night) for 10 days. In 37 evaluable patients there was an improvement of anorexia, nausea, insomnia and well-being (59).

In an open-label study (60) 10 patients with inoperable oesophageal cancer were observed during 2 weeks on an isocaloric diet and received additional treatment with thalidomide (200 mg/d) during the 2 subsequent weeks. Nine of the 10 patients lost weight during the first 2 weeks, while 8 of the patients gained weight during the second 2 weeks. A similar trend was recorded for lean body mass.

In a placebo-controlled trial 50 patients with advanced pancreatic cancer who had lost ≥10% of their body weight were randomized to receive thalidomide (200 g/d) or placebo for 24 weeks. 33 patients were evaluable at 4 weeks. Patients who received thalidomide had gained weight and arm muscle mass, while controls had lost both weight and arm muscle mass. The difference between groups increased at 8 weeks (61).

However, in 2012 a Cochrane review concluded that there was insufficient evidence to make an informed decision about thalidomide for the management of cancer cachexia (62). Thalidomide is teratogenic and in clinical use is associated with frequent and potentially severe side-effects, including peripheral neuropathy, fatigue and constipation, thromboembolism, pulmonary oedema, atelectasis, aspiration pneumonia, hypotension and renal insufficiency. Thus, despite the promising results with respect to weight and muscle mass thalidomide treatment is not recommended in treatment of cancer cachexia.

Anti-interleukin 6 antibodies: Tocilizumab and others
Interleukin 6 (IL-6) is a major mediator of the acute phase response. IL-6 is associated with poor prognosis in patients with lung cancer and its levels correlate with symptoms such as fatigue and cachexia (63).
The monoclonal antibody ALD518 targets IL-6 and is undergoing clinical testing in phase I and II trials with a focus on non-small cell lung cancer (NSCLC). It appears well tolerated and ameliorates NSCLC-related anaemia and cachexia (63).
Ando described a patient suffering from large-cell lung cancer, severe weight loss and an exaggerated inflammatory response, including elevated levels of IL6 (64). After initiating treatment with tocilizumab anti-IL-6 receptor antibody, CRP levels normalized and appetite improved rapidly; during the following weeks albumin and body weight improved considerably and overall condition could be stabilized for 9 months until the tumor progressed. Hirata et al. reported on 2 further patients with cancer-related cachexia who responded favorably to tocilizumab (65).

Ruxolitinib
The janus kinase (JAK) 1/2 inhibitor ruxolitinib has been used to improve clinical status in patients with myeloid fibrosis. It has a tolerable safety profile, and induced considerable weight gain in most treated patients (66). A potential mechanism for its effects may be an inhibitory effect on a number of proinflammatory cytokines, i.e. TNFalpha, IL-1ra, IL-6, MIP-1ß. The agent has been studied further and compared to placebo when added to oral capecitabine chemotherapy in 127 patients with pancreatic cancer (67). In this trial no overall effect was observed; however, in the subgroup of 60 patients with activated systemic inflammation ruxolitinib resulted in an increase in overall survival. It remains to be seen, whether this agent may find a way into the treatment of cachexia.

Other agents
Some newly developed anti-cytokine agents are undergoing clinical testing (68). The anti-IL-1alpha antibody MABp1 when infused every 3 weeks, has been shown to improve lean body mass and cachexia-associated symptoms and is targeted for further clinical testing (68). A large number of other agents and targets are being studied, primarily in preclinical models, including micro-RNAs, metal ion transporter ZIP14, rapalogs, activin A antagonists, and modulators of BET proteins (69). In addition, gut microbiota may contribute to development of cachexia and are now being investigated as treatment targets (69).

3.3 Anticatabolic and Anabolic Agents

A number of endogenous and exogenous agents have been studied or are being investigated to determine whether they cab inhibit proteolysis or stimulate protein synthesis. The aim is to diminish loss and to initiate gain of muscle and lean body mass (**Table 4**).

Table 4

Anti-catabolic and anabolic agents
Insulin and insulin sensitivity modulators
Growth hormone, GH secretagogues, IGF-1
Anabolic-androgenic steroids and SARMs
Amino acids and metabolites
Anti-myostatin antibodies
Selumetinib
Interleukin 15
Proteasome inhibitors
ß-receptor modulators
Hydrazine sulfate
Adenosine 5'-triphosphate

Amino acids and metabolites

In-vitro and in-vivo work has demonstrated anti-catabolic effects of leucine and its metabolite α-ketoisocaproate (70). Because of discrepancies between in-vitro and in-vivo studies, Abumrad and coworkers postulated that a further leucine metabolite, the ketone body ß-hydroxy ß-methylbutyrate (HMB), may be responsible for the leucine inhibitory effect on protein breakdown (70). HMB inhibits proteolysis in vitro possibly via the mTOR and proteasome pathways (71). In volunteers during resistance exercise training for 2-7 weeks, HMB supplementation (3 g/d) decreased exercise-induced muscle proteolysis and increased fat free mass (70).

To increase anabolic effects, HMB supplements have been given in combination with glutamine and arginine and this nutrient mixture has been investigated in several randomized trials. In 43 patients with HIV-associated wasting 8 weeks of treatment with HMB (3 g/d) plus L-glutamine (14 g/d) plus L-arginine (14 g/d) resulted in more gain of weight and lean body mass than a placebo added to the feed (72). The same mixture, however, was not more effective than a mixture of 5 other amino acids in 40 patients with rheumatoid cachexia (73).

The same mixture and doses of HMB/glutamine/arginine were compared in a RCT to an isonitrogenous mixture of non-essential amino acids in 32 patients with cancer cachexia; after 4 and after 24 weeks HMB/glutamine/arginine improved lean body mass, while the control group lost lean body mass (74). A subsequent larger RCT including 472 patients with cancer cachexia, however, could not detect any positive effects on lean body mass when comparing the same combination of HMB/glutamine/arginine to an isonitrogenous control mixture (86). Because compliance with the protocol was low, only 37% of the patients completed the planned 8-week course of treatment.

More recently, HMB has been studied in a small group (N=24) of healthy elderly subjects undergoing a 10-day period of bed rest. Using a randomized trial design, daily supplementation with 3 g/d HMB when compared to an inactive placebo powder prevented the decrease of lean body mass induced by bed rest (75).

Deutz et al. have investigated the effect of protein and leucine dose in a randomized clinical trial. In a small group (N=25) of cancer patients in an inflammatory state, consumption of a high-protein (40 g/d, including 4 g/d free leucine) oral nutritional supplement compared to a control supplement (24 g/d protein) resulted in increased plasma leucine levels and an increase in the fractional rate of muscle protein synthesis (76).
Thus, there is accumulating evidence that protein and especially leucine and its metabolite HMB, may support muscle mass by increasing synthetic rate and/or decreasing protein breakdown. Even though these mechanisms appear plausible, more solid evidence from high-quality studies in cancer patients is required before the use of leucine and HMB can be generally recommended.

Endocrine agents

Insulin and insulin sensitivity modulators

Administration of insulin to cancer patients has resulted in a decreased whole body protein breakdown rate (77) and in an appropriate response of muscle protein synthesis (78), while there was resistance to the effect of insulin on glucose metabolism.
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), improved metabolic efficiency during exercise (but not maximum exercise capacity or spontaneous physical activity) and improved overall survival (79).
Metformin activates AMP-activated protein kinase (AMPK) in the liver and in the muscle and thus increases insulin sensitivity (80). Metformin has been suggested as a novel anti-cancer agent (81). In patients with severe burn injury metformin has been shown to increase protein synthesis (82). Therefore, further study of this agent in cancer cachexia with associated systemic inflammation and insulin resistance is warranted.

Growth hormone (GH), GH secretagogues and IGF-1

Growth hormone (GH) is a polypeptide hormone, which stimulates growth, cell reproduction and regeneration in humans and other animals. In recent years, replacement therapies with GH have become popular in the battle against aging and in weight management. Reported effects in GH deficient patients (but not in healthy subjects) include decreased body fat, increased muscle mass, increased bone density, increased energy levels, improved skin tone and texture, increased sexual function and improved function of the immune system. As an anabolic agent, GH has been used by competitors in sports since the 1970s, and it has been banned by the IOC and NCAA.
There is concern regarding the use of growth hormones because of the possible stimulation of tumour growth. Preclinical data have not shown tumour progression (83), but valid clinical data are lacking.
A large randomized clinical trial including 552 critically ill adults demonstrated increased mortality for growth hormone treatment (0.1 mg/kg/d for 21 days) compared to placebo (84). Since GH increases cytokine concentration in normal tissues it has been speculated that GH may complicate conditions in already compromised patients (85).
Ghrelin is a secretagogue, acting via the GH secretagogue receptor, a G protein-coupled receptor. For ghrelin see 3.1.
Insulin-like growth factor 1 (IGF-1) is an anabolic hormone similar in structure to insulin.
IGF-1 is produced primarily by the liver as an endocrine hormone as well as in target tissues in a paracrine/autocrine fashion. Production is stimulated by GH. Recently, IGF-1 has been linked to tumour development and progression (86). Because of its anabolic

effects, IGF-1 has been proposed for cachexia treatment (87), however, most current activities are aimed at introducing ghrelin and its oral analogues into cachexia treatment.

Anabolic-androgenic steroids and SARMs (selective androgen receptor modulators)
Anabolic steroids or anabolic-androgenic steroids (AAS) are drugs which mimic the effects of the male sex hormones testosterone and dihydrotestosterone. They increase protein synthesis within cells, especially in muscles. Anabolic steroids also have androgenic and virilizing properties. In patients with advanced cancer decreased free testosterone levels are frequently observed.
In a randomized study 37 patients with advanced non-small cell lung cancer undergoing chemotherapy were treated with nandrolone decanoate (200 mg/week) or no additional steroid for 4 weeks. A trend for less weight loss was observed in the nandrolone group (88). Fluoxymesterone (20 m/d) was compared to megestrol acetate (800 mg/d) and dexamethasone (3 mg/d) in a RCT including 475 patients with cancer cachexia (12). The androgenic steroid resulted in less appetite stimulation than the other agents, while the rate of drug discontinuation because of toxicity was similar. Treatment with oxandrolone (20 mg/d) was compared to megestrol acetate (800 mg/d) in a randomized phase III study including 155 weight losing patients with solid tumours receiving chemotherapy. Only 50% of patients remained on study for the planned treatment period of 12 weeks. Patients treated with oxandrolone still lost weight but experienced an increase in lean body mass, a reduction in fat mass and fewer self-reported anorexic symptoms (11).

Selective androgen receptor modulators (SARM) have been developed for treatment of muscle wasting and osteoporosis. The oral SARM enobosarm (Ostarine) was tested in phase II clinical trials in elderly women and men in comparison with placebo; it resulted in improved lean body mass and muscle function; the safety profile was favourable and no serious adverse events were reported (89).
Dobs et al. published a double-blind randomized study in 100 weight losing cancer patients comparing two doses of enobosarm vs placebo given for 113 days. Both enobosarm doses (1 and 3 mg/d) improved lean body mass, while placebo treatment did not; in addition, enobosarm improved muscle function as measured by stair climbing power (90).
Two large randomized phase 3 trials designed to study the effects of enobosarm on muscle wasting in patients with non-small cell lung cancer undergoing combination chemotherapy treatment failed to reach the prespecified combination endpoints (91). Though enobosarm resulted in better maintance of LBM and in better muscle function (measured as stair climb power) than placebo, responder analysis did not reach the required level of statistical significance.
SARM are promising agents for future treatment of cancer cachexia; they might also be good candidates for combination with other anticachexic agents.

ß-Adrenergic receptor modulators
ß-Adrenergic receptors are involved in anabolic signaling with effects on skeletal muscle (92) which may increase body cell mass, and they affect resting energy expenditure which may promote weight loss.
Hyltander et al. (93) studied resting energy expenditure (REE) in 10 weight losing cancer patients. Treatment with a selective ß1-antagonist (atenolol) as well as with a non-specific ß1,ß2-adrenoreceptor (propranolol) antagonist reduced REE; part of this reduction was explained by a decline in heart rate. Propranolol dosing to decrease the resting heart rate by 20% improved muscle protein balance in 25 children with acute and severe burns (94).

Administration of the ß2-agonist formoterol to both rats and mice bearing highly cachectic tumours resulted in a reversal of the muscle wasting process (95). Recently, in a small group of frail, comorbid patients with advanced cancer and involuntary weight loss, intake of formoterol in combination with the progestin megestrolacetate for 8 weeks resulted in an increase in quadriceps and hand grip strength (96). Further investigation of this concept appears warranted.
Because both ß-receptor agonists and antagonists have been proposed to improve weight and muscle mass, further studies are required to elucidate the balance between wanted and unwanted effects.

Metabolic agents

Proteasome inhibitors (bortezomib)

Bortezomib is an inhibitor of NFkB and ubiquitin-proteasome. In cancer cachectic mice, pharmacological inhibition of NF-κB and MAPK, but not of the proteasome system, induced a substantial restoration of muscle mass and force (97).
Although potentially promising, preliminary results showed negligible effects from this compound on cancer-related weight loss in patients with metastatic pancreatic cancer. The authors concluded that further study of bortezomib in this setting and for this indication were not warranted (98).

Hydrazine sulfate

Hydrazine is a non-competitive inhibitor of phosphoenolpyruvate carboxykinase, one of the enzymes needed for gluconeogenesis. Gold proposed that inhibiting gluconeogenesis would stop host energy-loss and thus the development of cachexia (99). In a randomized placebo-controlled study in 38 weight losing cancer patients hydrazine sulfate (180 mg/d) for 30 days resulted in a decrease in glucose production and improved glucose tolerance (100).
Five randomized placebo-controlled studies were published from 1987 to 1994 reporting on the effects of hydrazine sulfalte (180 mg/d) on appetite and body weight in advanced cancer patients. One 30-day study in 101 patients showed an improvement in appetite and body weight with hydrazine (101). Of the longer-term studies, another trial by Chlebowski et al. in 65 patients reported higher caloric intake in the hydrazine group, but no other benefit (101), while none of the other trials found any benefit from hydrazine treatment on appetite or weight. In fact, 2 studies (a total of 370 patients) reported a trend to poorer survival in the hydrazine group (102, 103) and 1 study (266 patients) reported significantly poorer quality of life in the hydrazine group.
Hydrazine is toxic and carcinogenic; short-term effects are usually mild and include minor nausea, vomiting, dizziness, excitement, polyneuritis; however, in rare cases fatal liver and kidney failure and severe neurotoxicity have been reported.
Hydrazine is not recommended for treatment of cancer anorexia or cachexia.

Adenosine 5'-triphosphate (ATP)

Adenosine 5'-triphosphate is a naturally occurring nucleoside triphosphate that plays a central role as an energy source in every cell of the human body. Extracellular ATP is involved in the regulation of a variety of biological processes. In non-randomized studies involving patients with different tumour types, ATP infusions appeared to inhibit loss of weight and deterioration of quality of life and performance status.

Agteresch et al. (104) randomly assigned 58 patients with non-small cell lung cancer to receive intravenous 30-hour infusions of ATP every 2 to 4 weeks or no ATP. After 28 weeks, patients who received ATP retained their original weight, while the control group lost 1 kg per month (104). In addition, muscle strength and quality of life scores were more favourable in the ATP-treated group. In weight losing patients overall survival was significant longer in patients receiving ATP (101).
Beijer et al. randomly allocated 99 preterminal cancer patients to receive either intravenous ATP weekly for 8 weeks or no ATP. Triceps skinfold thickness and 8-week survival was significantly better in the ATP treated patients (105), while there was no improvement in quality of life, functional status or fatigue (106).
Side effects of ATP infusions are tolerable and include dyspnoea, chest discomfort and the urge to take a deep breath. All studies on ATP were performed by one study group. ATP is a promising agent but is not recommended outside clinical trials.

Experimental agents

Anti-myostatin antibodies

Myostatin is a member of the transforming growth factor-ß superfamily and downregulates skeletal muscle mass by binding to the activin A receptor IIB (Act RIIB). Myostatin levels are increased in tumour-bearing rats and thus might be a therapeutic target in cancer cachexia (107). In a mouse model injection of the myostatin binding soluble Act RIIB after tumour cell implantation resulted in reversal of tumour-induced weight loss and improved survival.
Several companies have initiated clinical trials with different anti-myostatin antibodies. LY2495655 was tested in patients with advanced pancreatic cancer receiving gemcitabine chemotherapy; LY2495655 resulted in an increase in death rate and treatment was terminated (108). Other companies withdrew this group of agents after observing insufficient effects in clinical trials.
At this time anti-myostatin agents do not appear to offer clinical benefit.

Selumetinib

Induction of muscle anabolism by physical activity occurs by pathways involving RAF, MEK and MAPK/ERK kinases (90). The anti-cancer agent selumetinib is a MEK inhibitor, has tumour suppressive activity and has been shown to inhibit IL-6 production. In a phase II trial, retrospective analysis of skeletal muscle mass demonstrated that patients with cholangiocellular carcinoma were markedly catabolic and lost muscle mass when undergoing standard treatment, but gained muscle mass when treated with selumetinib (90). It is not known whether interaction with IL-6 synthesis or other processes are responsible for the anabolic effect. Further investigation of these beneficial effects is required.

Interleukin 15

The cytokine IL-15 shares biological activities with IL-2 but is not produced by activated T cells but by skeletal muscle, kidney, lung and heart. IL-15 favours muscle fibre hypertrophy and partly inhibits muscle wasting in tumour-bearing rats (109). Overexpression of IL-15 induces skeletal muscle hypertrophy accompanied by increased levels of sarcomeric myosin heavy chain and alpha-actin in cultures of differentiated myotubes. IL-15 stimulates protein synthesis as well as inhibiting protein degradation (110). No clinical trials using IL-15 have been reported.

4. Supportive and Palliative Care

4.1 Nutrition Impact Symptoms

Many debilitating cancer- and treatment-associated symptoms may impair appetite and interfere with maintaining nutritional status. These symptoms are referred to as nutrition impact symptoms (NIS) (111–113). All cancer patients at risk of or diagnosed with malnutrition should be assessed regularly for the presence and severity of these symptoms, preferentially by using a checklist (113).
Typical NIS to be assessed are anorexia, nausea, taste and smell alterations, mucositis, constipation, dysphagia, chronic and abdominal pain, diarrhoea, as well as aspects of gastrointestinal function potentially responsible for these symptoms; in addition, attention should be given to fatigue, physical activity, shortness of breath and psycho-social distress. It has been shown in patients with advanced cancer, that those with cachexia have more severe nutrition impact symptoms and report more nutrition-related distress (114).

4.2 Gastrointestinal (GI) Support

GI functions are essential for uptake and assimilation of energy and nutrients. This includes chewing, swallowing, propulsion, digestion and absorption. The anatomical and functional integrity of the GI tract should be checked regularly in all cancer patients at risk of malnutrition. Dysfunctions and defects may diminish or prevent food uptake. Defects in dental status should be corrected, xerostomia supported, and nausea and stomatitis treated effectively. A blocked GI passage requires endoscopic or surgical opening or an intervention to circumvent the stoppage by an anastomosis or by placing a distal feeding tube. Disturbed GI motility may result in regurgitation, nausea, vomiting, abdominal bloating or pain, diarrhoea, constipation or ileus. Depending on the cause appropriate treatments will differ and may include among others: anti-emetics, prokinetic agents or inhibitors of GI motility, anti-infective or anti-inflammatory agents, removal of drugs with GI toxicity, proton pump inhibitors, and mucosal protective agents.

Prokinetic agents
Metoclopramide (80 mg/d) has been investigated in 2 studies with a total of 55 patients (6). Both studies found an improvement in nausea but no increase in caloric intake or appetite. Erythromycin improves delayed gastric emptying by binding to motilin receptors and inducing activity of the interdigestive migratory motor complex (115). Both these prokinetics are frequently used to improve the success of enteral feeding in critical ill patients (116).

Inhibitors of gastrointestinal motility
Diarrhoea induced by chemotherapy agents will lead to weight loss and exsikkosis. Inhibition of intestinal transit time may diminish diarrhoea by increasing the time for reabsorption of secreted intestinal fluids. Typical agents used are opioids, calcium channel blockers, and clonidine. Topical steroids like budesonide may antagonize diarrhoea induced by toxic effects on the small intestinal mucosa as for example from the active irinotecan metabolite SN-38.

Proton pump inhibitors
Drugs frequently used in cancer patients, e.g. corticosteroids, NSAIDs, chemotherapy treatments and other stressors, increase the occurrence of GI ulceration, which may lead to abdominal pain, nausea, vomiting, anorexia and weight loss. Inhibition of gastric acid secretion is an effective way to allow healing of ulceration. Proton pump inhibitors are the most powerful drugs available to achieve this end.

Parasympathomimetics
Many drugs as well as radiotherapy to the head and neck region may cause dry mouth (xerostomia). Pilocarpine is a parasympathomimetic plant alkaloid; it is a non-selective muscarinic receptor agonist and stimulates the secretion of large amounts of saliva and sweat. This may help to increase appetite and achieve improved conditions for chewing and swallowing.

4.3 Pain Treatment

Psychotropic drugs and analgesics may diminish the burden of anxiety, restlessness and depression, and chronic pain in cancer patients. Since these symptoms will invariably diminish or abolish appetite and food intake, it is of considerable importance for the nutritionist to be aware of their presence. Any instance of psychological distress or chronic pain should be recognized and every effort should be undertaken to relieve these barriers to normal appetite and adequate food intake.

4.4 Psychological Support

Anorexia and fatigue are among the top symptoms in the last 6 months before death (117). Patients and families experience stressful changes in eating and the threat to human existence from loss of weight and function. Cancer cachexia alters appearance with adverse consequences on the patient's self-image, self-esteem and socialization (118). Additionally, cachexia impacts on family functioning with respect to the role and the meaning of food during their assistance. Addressing the psychosocial impact of cachexia as early as possible can improve the QoL for both patients and their families even during curative treatments. It is, therefore, advisable to screen all cancer patients for psychological distress and offer appropriate psychological support.

4.5 Social Support

In many seetings, social support today is weaker than 50 or even 20 years ago. Living alone or without adequate social support may impair the effect of other interventions to prevent or treat cancer cachexia. To realistically plan and organize a complex anti-cachexia strategy it is important to routinely assess the social environment of cancer patients at risk of or diagnosed with malnutrition. Including the expertise of a social worker is essential to support the patient at home and to maintain an environment conducive to an effective therapeutic approach.

4.6 Physiotherapy, Exercise Training

Maintaining or improving body resources will require regular activity of all involved organs. With respect to skeletal muscle mass as the largest component of body cell mass, only

regular muscle training will enable other interventions to effectively stimulate and maintain muscle mass and function. See **Module 26.3**.

5. Multi-modal Therapy: Clinical Trials

Multimodal therapy as an answer to complex debilitating derangements was first proposed by Fearon (119). Following this lead, Maddocks et al. assembled some practical examples of approaching such multimodal care (120). However, few clinical trials combining several treatment modalities have yet been reported. Ongoing investigations appear to be focussed primarily on simultaneously targeting nutritional support, muscle training and anti-inflammatory concepts. Studies published to date report improvements in multiple domains, most notably physical endurance and depression scores (121).

It has been shown in healthy subjects that bouts of physical exercise significantly prolong the increase in muscle protein synthesis induced by feeding (122). A 6-week intervention combining the NSAID celecoxib, nutritional advice, oral supplements enriched in EPA and physical exercise was compared to standard treatment in 46 patients commencing chemotherapy in a randomized trial (123). This feasibility study showed promising effects on body weight and muscle mass and is being followed now by a phase III study recruiting patients with lung and pancreatic cancer (MENAC trial). Other similar projects are being launched (124).

In a randomized trial of 58 patients with advanced cancer Uster et al. provided the intervention group with a 12-week exercise training programme combined with repeated nutritional counselling. Compared to standard clinical care, the combined programme resulted in a significant increase in protein intake and a decrease in nausea and vomiting, while overall quality of life did not change (125).

Given the proposed major importance of combining different anti-cachexia concepts, further well-designed trials are anxiously awaited.

6. Summary

In cancer patients, body resources may be threatened by a large number of tumour- and treatment-induced factors as well as by concomitant medications and psycho-social distress. To best support the patient, the complex network of derangements needs to be assessed carefully, and all deficits diagnosed should be addressed and alleviated as best as possible. This requires a multi-targeted multi-modal and multi-professional approach of closely interacting experts. To treat the frequently prevalent systemic inflammation, of the factors studied so far, the following agents have been shown to be effective in certain circumstances: corticosteroids, progestins, insulin, NSAIDs and N-3 fatty acids. Other promising agents are under investigation. Multi-modal treatment concepts including pharmacological agents, nutritional interventions and muscle training are being studied within clinical trials.

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