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Review article: anorexia and cachexia in gastrointestinal cancer

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SUMMARY

In patients with gastrointestinal malignancies, i.e. cancers of the stomach, colon, liver, biliary tract or pancreas, progressive undernutrition can be regularly observed during the course of illness. Undernutrition significantly affects the patients' quality of life, morbidity and survival.

Pathogenetically, two different causes are relevant in the development of undernutrition in patients with gastrointestinal cancer. One cause is reduced nutritional intake. This condition is referred to as anorexia and can be worsened by the side effects of cancer therapy. The other cause is the release of endogenous transmitters and/or other products of the tumour leading to the cachexia syndrome, which is characterized by loss of body weight, negative nitrogen balance and fatigue. Cancer anorexia and cancer cachexia may have synergistic negative effects in affecting the patients' status.

In this review, current nutritional support strategies with respect to different clinically relevant situations are described. An algorithm of the treatment strategies, including dietetic counselling, oral supplements, enteral and parenteral nutritional support is given. One focus is the approach of nutrition-focused patient care, which shows promising results. In addition, the possibilities of pharmacological intervention are discussed.

INTRODUCTION

Signs of undernutrition can be regularly observed during their course of illness in patients with gastrointestinal (GI) malignancies, i.e. cancers of the stomach, colon, liver, biliary tract or pancreas. According to the World Health Organization the term undernutrition includes undernourished patient presenting with a body mass index (BMI) <18.5 kg/m^2. This neglects those patients with an higher BMI but with a recent significant weight-loss, which are at risk to become undernourished. Therefore, in the following text the term undernutrition includes both patient groups. Undernutrition significantly affects patients' quality of life (QOL), morbidity and survival.

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Undernutrition mainly affects patients with oesophageal-, gastric or pancreatic cancer, whereas undernutrition in patients with cholangiocellular, hepatocellular- and colon cancer are less likely to be of concern.[1] In those patients with oesophageal and gastric cancer a reduced caloric intake is often because of on-site problems. But often parallel to loss of body weight further symptoms like anorexia, taste abnormalities, early satiety and fatique occur – especially in patients with pancreatic cancer. Although concrete definition is lacking, these symptoms are summarized as cachexia. Cachexia is associated with reduced QOL and prognosis.[2, 3] The symptoms associated with cachexia become most disturbing for the patient and represent a challenge to the physician in charge. In cancer patients nutritional therapy is often a supportive measure. Especially in palliative care nutritional therapy is part of a global patient management with the main aim to maintain or improve QOL.

CAUSES OF CANCER-ASSOCIATED UNDERNUTRITION

In essence two different explanatory models exist for the development of undernutrition in malign diseases: one is that disease can lead to a reduction in nutritional intake, for instance because of stenosis of the GI tract, malaise, taste alterations and/or loss of appetite. This condition is termed anorexia and may be worsened by the side effects of treatment. Anorexia is frequently seen in head and neck, oesophageal – and gastric malignancies, because of primary dysphagia. In addition, in patients with peritoneal malignant disease or a abdominal tumour mass disturbance of the motility or repeated (sub)ileus may contribute to nausea and vomiting and therefore to reduced nutrient intake. However, often energy intake is low in relation to usual body weight but may be adequate in relation to actual body weight.[1]

In addition, previous surgery may affect the digestive capacity. Pancreatic as well as gastric resections can result in pancreatic exocrine and endocrine insufficiency, creating major nutrition problems such as steatorrhoea and hyperglycaemia. Extensive resection of the small bowel can lead to malabsorption, whereas small resections of the bowel usually do not lead to major nutrition problems.[4]

The second model is characterized by the release of endogenous transmitter substances or products of tumours leading to cancer cachexia. Regulation of appetite is altered in cancer patients because of central effects of cytokines or tumour peptides (Figure 1). Energy intake is controlled by the hypothalamus, where peripheral signals on energy intake (e.g. ghrelin, CCK) and adiposity status (e.g. insulin, leptin) are signalled. In the hypothalamus, particularly in the arcuate nucleus, this information are transduced into behavioural responses.[5]

Because of their central role in energy homeostasis a number of studies investigated the role of the prophagic (orexigenic) signal Neuropeptide Y (NPY) in the pathogenesis of cancer anorexia. In weight-loss conditions NPY is important in stimulating hunger and hyperphagia. Leptin and insulin are capable of blocking NPY production and, vice versa increased NPY decreases leptin and insulin production. Next to orexigenic also anorexigenic signals are involved in energy homeostasis. The hypothalamic anorexigenic neuropeptides melanocortin, CFR and α-MSH, which is a product of pro-opiomelanocortin have a role in normal control of food intake. α-MSH induces anorexia by activating the receptors MC3R and MC4R, which are both expressed in the hypothalamus and other brain regions. In experimental cancer model cachexia was ameliorated by central MC4R blockade.[6] The inability of the hypothalamus to respond appropriately to consistent peripheral signals in cancer anorexia seems to be related to the central effect of cytokines.[7] However, increasing food consumption alone is not always capable of reversing the cachectic process (see below), but this is still an active area of research.

Pancreatic cancer patients seem to be especially vulnerable to cachexia, about 80% of them presenting signs of cachexia already at the time of diagnosis. Often

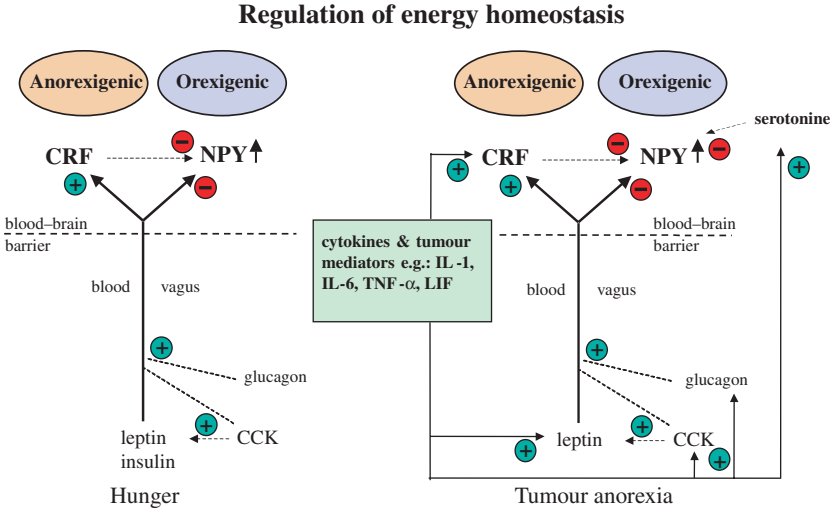

Figure 1. Simplified model of central regulation of energy homeostasis during starvation and in patients with tumour-associated anorexia. A negative energy balance (hunger) normally results in stimulation of orexigenic neuropeptides like neuropeptide Y (NPY). NPY mediate increased nutritional intake and compensatory reduction of energy expenditure. The process is disturbed in tumour patients because of central effects of cytokines and tumour peptides (for further explanation see text) (adapted from Ref. 19; CCK, cholecystokinin; CRF, corticotropin releasing factor; NPY, neuropeptide Y; IL, interleukin; LIF, leucemia inhibitory factor).

the discrepancy of poor prognosis and quite small tumour mass is striking. In these patients reduced nutritional status or death can often not be explained by the burden of tumour mass or multiplicity of metastases, but rather by metabolic effects of the pancreatic carcinoma.

Metabolic and hormonal alterations as well as changes in body composition are different in 'normal' starvation compared with cancer cachexia. Metabolically, cancer cachexia is mainly characterized by degradation of muscle protein with simultaneous increase in synthesis of visceral proteins. There are three metabolic pathways responsible for the catabolism of skeletal muscle protein: (i) the lysosomal system is concerned mainly with the proteolysis of extracellular proteins and cell surface receptors; (ii) the cytosolic calcium-activated system is involved mainly in tissue injury, necrosis, and autolysis; and (iii) the ATP-ubiquitin-dependent pathway is believed to be responsible for the accelerated proteolysis in a variety of wasting conditions such as fasting, sepsis, metabolic acidosis, acute diabetes, and cancer cachexia.[8–10] In this process, ubiquitin is bound covalently to the protein substrate, which acts as a signal for degradation by the multisubunit proteasome (Figure 2). This process requires ATP and might contribute to the elevated daily energy expenditure observed in cancer cachexia.[8,11] The first two pathways are responsible for about 20% of protein degradation, leaving the major effect to the ubiquitin-proteasome mechanism mainly targeting at muscle fibrils.

Cytokines, like tumour necrosis factor (TNF)-α, interleukin (IL)-6 or interferon-γ have already been discussed as mediators of protein catabolism for a long period of time. However, some of the reports are conflicting, making interpretation of data difficult. Although both TNF-α and IL-6 increase the production of ubiquitin, sole addition to muscle cells *in vitro* do not lead to increased proteolysis. Guttrigde *et al.*[12] have shown recently, that combination of TNF-α and IFN-γ leads to post-transcriptional suppression of myoD and myosin expression through activation of NF-κB in myocytes. NF-κB is a major cellular transcription factor, whereas myoD is essential for repairing and regenerating muscle fibrils. These results may lead to the assumption that cytokine-mediated sarcopenia is mediated by the activation of NF-κB through hampering regeneration of muscles (Figure 2). In addition, TNF-α and IL-6 are major proinflammatory cytokines, which

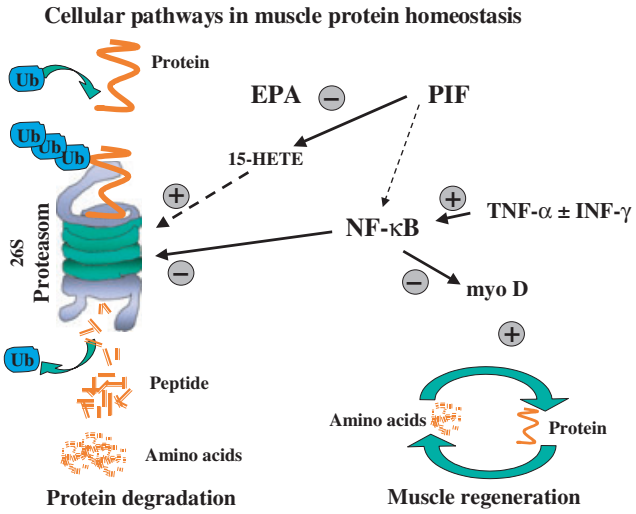

Figure 2. Tumour necrosis factor-α in combination with interferon-γ lead to an activation of NF-κB, which inhibits expression of myoD. MyoD is a transcriptional factor needed for restoration of muscle proteins, and therefore, its inhibition results in disturbed muscle regeneration. After proteins have been marked with ubiquitin (Ub) they are broken down by the ubiquitin-proteasome-system. Activation of NF-κB results in reduced protein degradation by inhibiting a subunit of the proteasome. However, tumour products like proteolysis-inducing factor (PIF) increase protein degradation through increased production of proteasomes. This effect is mediated e.g. by 15-HETE (15-hydroxyeicosatetraenoic acid). There might be some additional direct effects (dashed line). Eicosapentaenoic acid (EPA) blocks 15-HETE production and thereby averts loss of muscle mass in tumour patients. adapted from (Beck & Tisdale 1989 19/id): Ub, ubiquitin; EPA, eicosapentaenoic acid; PIF, proteolysis-inducing factor; 15-HETE, 15-hydroxyeicosatetraenoic acid.

are up regulated in chronic inflammation or infection, which also leads to loss of muscle and fat mass. This demonstrate the similarities of cancer cachexia and wasting related to chronic infection like the human immunodeficiency virus or *Mycobacterium tuberculosis*.[13] Recently, myostatin, a new regulating peptide in muscle catabolism and regeneration has been discovered, but its role in muscle catabolism observed in cancer has to be defined.[14]

All the above mechanisms contribute to the characteristic clinical feature of cachectic underweight patients with very low subcutaneous fat mass and reduced muscle mass but with about normal serum proteins.[2] Whereas in pure anorexia metabolism is almost normal and undernutrition can be improved by supply of adequate nutrition (tube-feeding, parenteral nutrition), therapeutic success in cancer cachexia is often limited

when central and metabolic alterations are present (Table 1).

THERAPEUTIC GOALS

Therapeutic goals of nutritional support in patients with GI cancer are:

1. Improvement of nutritional status.
2. Improvement of subjective QOL.
3. Increase in therapy efficacy and reduction of side effects.
4. Improvement of prognosis.

Therapeutic goals of nutritional support in the individual patient may have different focuses during the course of disease. Whereas at the beginning maintenance of nutritional status and reduction of treatment-associated morbidity are central aspects, they often lose in importance at the expense of palliative aspects and especially QOL.

It should be mentioned here that the effects of nutritional management can hardly be compared with other medical (pharmacological or interventional) treatment. The major difference is that withholding a certain therapeutic measure (e.g. medication) in an otherwise healthy human is not disadvantageous, whereas the adequate provision of nutrients and energy is essential for both the healthy and diseased organism.[15, 16]

A special therapeutic goal is the prevention of recurrence in patients after curative cancer treatment. Here the main patient group are colon cancer patients after R0 resections (see below).

Table 1. Comparison of anthropometric and metabolic features in human starvation and in patients suffering from tumour cachexia; ↓ decreased; ↑ increased; ← → not changed; ↑↓ inconclusive data[2]

	Hunger	Cachexia
Body weight	↓	← → /↓
Body cell mass (muscle mass)	↓	↓↓↓
Body fat mass	↓↓↓	↓↓
Energy intake	↓↓↓	↓
Total energy expenditure	↓↓	↓↑
Resting energy expenditure	↓↓↓	↑↑
Protein synthesis	↓↓↓	↓↑
Protein degradation	↓↓↓	↑↑↑
Serum insulin	↓↓↓	↑↑↑
Serum cortisol	← →	↑↑

IMPLEMENTATION OF NUTRITIONAL SUPPORT

Nutritional assessment

In all cancer patients primary assessment of nutritional status and energy intake should done already at the beginning of the disease. It is important to measure weight at regular intervals. Undernutrition is likely when a patient has lost more than 10% of his/her actual weight over the last 6 months or more than 5% over the last 3 months or when BMI is lower than 18.5 kg/m^2.[17]

Several clinical and laboratory scores have been developed to identify malnourished patients and/or patients at risk of undernutrition. One of the best evaluated scores is the 'Subjective Global Assessment' (SGA), which is based exclusively on anamnestic criteria like weight change, GI symptoms, performance status, nutrient requirement and a simple physical examination (oedemas, ascites, muscle mass, fat mass).[18, 19] Thereby, nutritional status is subjectively classified as A = well-nourished, B = moderately malnourished/at risk of undernutrition, C = severely malnourished.

ESPEN, the European Society of Clinical Nutrition and Metabolism, only recently recommended two simple but validated screening questionnaires, the Nutritional Risk Screening 2002 (NRS2002) and the Malnutrition Universal Screening Tool (MUST).[17]

The NRS2002 consists of a four-question prescreening and a final screening that is divided in items dealing with nutritional status and severity of disease. MUST, a five-step screening tool, was originally developed for out-patients but its high practicability and reliability renders it valuable for hospital patients as well (questionnaire and more information: http://www.bapen.org.uk) The main advantages of the SGA, NRS2002 (http://www.espen.org/education/) and MUST are that attention for nutritional problems can be drawn to even nutritionally inexperienced clinicians within a couple of minutes without technical devices.[17] The Joint Commission on Accreditation of Healthcare Organizations has already a nutritional assessment integrated in their quality standards for hospital patients at admission (http://www.jcaho.org).

Indication and timing of nutritional therapy

The German Guidelines on enteral nutrition propose a simple algorithm for the indication for a nutritional intervention (Figure 3).[20] One major indication is low

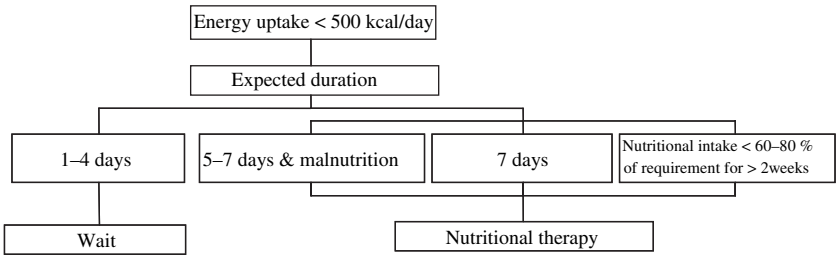

Figure 3. Algorithm of time and indication of nutritional intervention in cancer patients.[20]

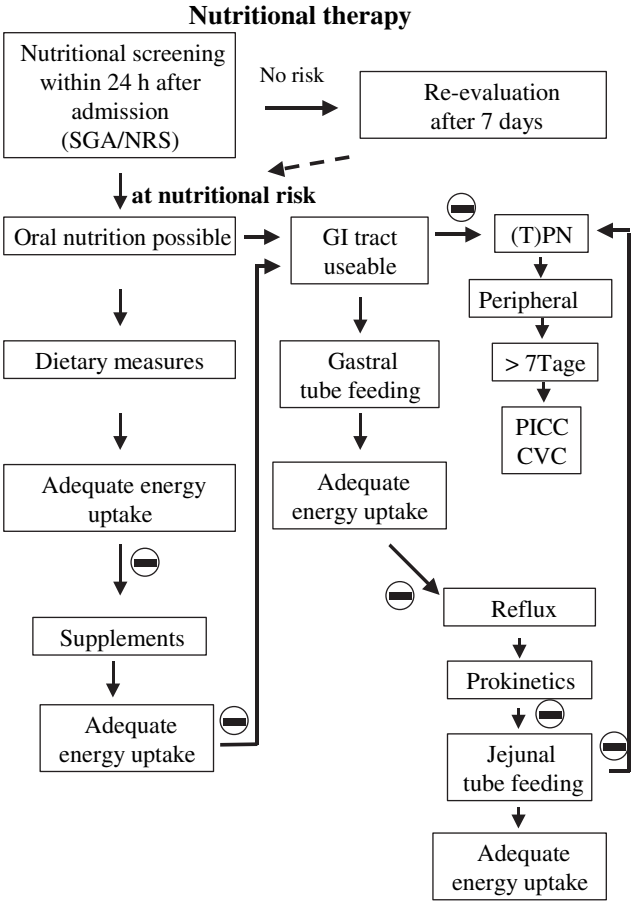

Figure 4. Algorithm for nutritional intervention in cancer in-patients. A denotes impedimental factors leading to unsatisfying results in the previous step. (T)PN, (total) parenteral nutrition; PICC, peripherally inserted central catheter; CVC, central venous catheter; SGA, subjective global assessment; NRS, nutritional risk score.

energy intake for a longer period of time. In case of persisting undernutrition early onset of nutritional therapy is indicated. Figure 4 shows a more detailed pathway for the indication and timing of nutritional therapy in oncological patients. The beneficial effect on physical activity and survival of such an algorithm has been shown in a randomized trial, recently.[21]

Energy and nutrient requirement

Depending on the clinical situation energy intake should be 1.2 –1.5 times the resting energy expenditure, i.e. about 30–35 kcal/kg bw/day. To supply more energy would result in overnutrition which is considered detrimental. Generally, oral nutrition and tube-feeding should be preferred over parenteral nutrition. The principles of 'healthy' and/or fat-reduced diets have their actual role in prevention but not in the treatment of cancer related undernutrition. To prevent further energy losses and/or to counteract cachexia the lipid proportion of nutrition should exceed the recommended 30% for healthy individuals. Energy goals can hardly be reached otherwise in cancer patients. Protein requirements are slightly higher than in healthy people but not different to general recommendations in clinical nutrition, i.e. 1.0–1.5 g/kg bw/day. Compositions of commercially available enteral formulations are shown in Table 2.

Dietary supplements, vitamins and trace elements

No recommendation for increased intakes of e.g. anti-oxidants, glutamine or vitamins can be given in cancer patients because of insufficient data.[16,22] Table 3 lists the recommendations for dietary supplements according to the American Institute of Cancer Research.[22]

Documentation of nutritional intake and counselling

To identify reduced energy or nutrient intakes it is necessary to assess actual intake.

Energy intake is determined preferably by an interview technique or by food diaries being filled out by the patient over several days (3–7 days). Both techniques and following nutritional care should be implemented and evaluated by well-trained nutrition experts, e.g. dieticians.

Nutritional counselling in order to achieve adequate energy intake is the first step in nutritional care. There

Table 2. Composition of sip feeds and tube formulations (standard vs. special formulations)

Formulation	Energy (kcal/mL)	Carbohydrates (%)	Lipids (%)	Proteins (%)	Fibres	Connotations
Standard	1	50–55	30–35	15–18	+	Polymeric nutrients
High-energy	1.5–2.0	50–55	30–35	15–18	+/−	Liquid content reduced
High-lipid special	1.3	30–32	50–55	30–32	+	4–6 g n3-fatty acids/1.5 L
Low-protein, low-electrolyte	1.5–2.0	80–84	10–12	5–7	−	Potassium and phosphate reduced
Enriched with BCAA	1.3	55	33	12	+	Hepatic encephalopathy
Immuno-modulating	1.0	50–55	25–30	18–22	+	Enriched with glutamine, arginine, n3-fatty acids and nucleotides
Low molecular weight	1.0	50–60	20–25	18–22	−	Use in malabsorption, short bowel syndrome, jejunal feeding

Table 3. Dietary supplements during cancer treatment: specific recommendations from the American Institute for Cancer Research[22]

- Supplementation of the diets of cancer patients undergoing active treatments with individual or combined antioxidants above their recommended dietary allowances (RDA) or adequate intakes (AI) cannot be recommended as safe or effective
- Use of high levels of antioxidants as the sole treatment protocol is not advisable because they might be deleterious to normal cells via a prooxidant effect or may possibly confer an advantage to cancer cells
- Evidence is not sufficiently strong to warrant routine use of vitamin E supplementation in patients receiving chemotherapy or radiation therapy. Oversupplementation is not recommended during traditional therapies
- Cancer patients should follow a reasonable diet that provides vitamin C at the RDA or no more than double that amount
- Patients should not take large amounts of β-carotene
- Evidence is not sufficient at this time for either broad or precise recommendations about selenium
- The lack of information on antioxidant interactions raises concern about making recommendations for the indiscriminate use of combinations of antioxidants
- Information is not sufficient to make a recommendation about soya foods or soya products. Supplements containing soya isoflavones are not recommended because the levels of the isoflavones contained are in most cases much higher than can be obtained from the diet
- Cancer patients and healthy people can consume the recommended AI for polyunsaturated fatty acids
- Recommendations for vitamin D_3 cannot be made for cancer patients
- A daily multivitamin containing supplements at levels of the DRI can be used safely as part of a programme of healthy nutrition including five to ten servings of fruits and vegetables daily

is no specific 'cancer diet'. In fact, the diet should be composed individually aiming at adequate provision and intake of energy, macro- and micronutrients.

Intermittent small bowel obstruction can be managed with a low residue or liquid diet.[23]

Sip feeding

Is adequate energy intake not feasible despite individualized nutritional counselling, use of oral sip feedings high in energy and protein are recommended. Pilot studies have shown that sip feedings that contain omega-3-fatty acids and antioxidants seemed to be promising.[24] The intention-to-treat analysis of a recent prospective, randomized trial in 200 patients with pancreatic cancer showed that intake of high-energy, high protein sip feeding (600 kcal/day, 32 g protein) irrespective of supplementation with omega-3-fatty acids and antioxidants resulted in stable weights in both study groups [25]. But retrospective sub-analysis revealed that intake of omega-3-fatty acids was associated with a higher gain of fat-free mass. Best results were seen in patients drinking more than two and more supplements a day.

Tube-feeding

Tube-feeding is indicated when energy and nutrient goal cannot be met by oral strategies over a longer period of time (Figure 4). As tube-feeding is considered an invasive therapeutic measure, the indication should be settled together with the patient, considering the clinical situation (see also 'Palliative situation'). Although pathophysiological reasons and experimental data indicate that a high-lipid tube formulations might be beneficial, it is not confirmed in adequate clinical

trials and therefore, cannot be generally recommended. A low-volume tube formulation resulting in higher energy density has been proven to be beneficial in patients with early satiety, reduced volume tolerance and reduced GI motility.

Patients undergoing high-dose chemotherapy have traditionally been given parenteral nutrition. However, there is increasing evidence that tube-feeding may suffice if nausea and vomiting can be controlled. Jejunal feeding may be given via a nasojejunal tube or an percutaneous endoscopic gastrostomy (PEG) with a jejunal tube placed through it.[23]

Parenteral nutrition

In brief, parenteral nutrition is indicated when enteral nutrition is contraindicated (e.g. intestinal obstruction). In patients with advanced cancer parenteral nutrition can lead to the stabilization of body weight. However, often detailed analysis of body composition shows increases in fat – and extracellular mass (body fluid), but not in body cell mass (muscle mass).[26] Furthermore, parenteral nutrition is cost intensive and not free of complications.

Results of successful nutritional intervention in cancer patients often demonstrate that negative energy balance is not the only cause of cachexia.[3,27] This is true even when adequate energy and nutrient intake has been achieved and independent of the way of nutritional support (nutritional counselling and/or enteral or parenteral nutrition).

However, the results must not lead to therapeutical nihilism. In cancer patients nutritional therapy, at least for a limited period of time, can help to attenuate deterioration of nutritional status and improve QOL.[26] Specialized, nutrition focused patient care has shown significant beneficial effects in recent randomized and prospective trials,[21,28] (see next paragraph). However, the more invasive the way of providing nutrition, the more serious indication for it should be thought over. Patients who cannot tolerate oral or tube feedings are normally patients with well-advanced cancer (see section 'Palliative situation').

Specialized, nutrition focused patient care

The term 'specialized, nutrition focused patient care' was coined by Lundholm *et al.*[21] and describes a concrete stepwise pathway to evaluate the nutritional situation of a patient allowing the best possible individual approach at standardized conditions (Figure 2). This pathway asks for good communication, coordination and expertise within multiprofessional team. It could be shown that specialized, nutrition focused patient care was able to improve exercise capacity and survival significantly in patients with progressive cachexia secondary to malignant disease.[28] The individual multimodal approach seems to be the major advantage, which may explain why nutritional therapy apparently worked in the new studies in contrast to the older studies. In addition, further improvement of QOL may be achieved by energy conservation and activity management for fatique reduction and maintenance of functional performance in cancer patients undergoing treatment.[29]

Pharmacological intervention

Pharmacological intervention in the treatment and prevention of tumour cachexia has been mainly aimed at the use of appetite enhancers to increase oral nutritional intake so far. Best examined are synthetic progesterone derivates, in which stimulation of NPY led to increased appetite. In most studies megestrolacetate or medroxyprogesterone have been used for appetite enhancement.[30] Use of megestrolacetate (160–800 mg/day) in patients with previous weight loss led to increases in weight, but this was because of increased fat mass not muscle mass.[31] Karnofski-index could not be improved either. Dosage recommendation is 480 mg/day.[32] Also steroids have been shown to improve appetite.[32] It should be emphasized that these agents stimulate appetite but also induce muscle breakdown. They may be tried in those patients with a short life expectancy.

It can be assumed that success of nutritional therapy could be improved, if we succeed to influence the 'metabolic inefficiency' induced by the tumour itself or by the inflammatory reaction, respectively. Treatment with pentoxifylline or thalidomide, both reducing TNF-alpha production, unfortunately have no significant effects on anorexia and/or cachexia.[33, 34] Further substances have been studied, for instance metoclopramide, cannabinoide (dronabinol), hydrazine, cyproheptadine and non-steroidal anti-inflammatory agents (NSAIDS). Especially NSAIDS seem to be promising. In addition to the anti-inflammatory effect a antiprolifer-

ative effect on the tumour cells is being discussed. Combined therapy of megestrolacetate and a cyclooxygenase-inhibitor (ibuprofen) increased body weight significantly (+2.3 kg) in the treatment group in a randomized, placebo-controlled study in 35 and 38 patients, respectively.[35] Monotherapy of megestrolacetate, however, led to a median loss of weight of 2.8 kg.[35]

Data available at present do not allow routine recommendations for appetite enhancers. Mantovani *et al.*[30] provide a comprehensive and up-to-date review of drug therapy in tumour-associated anorexia.

SPECIAL CLINICAL SITUATIONS

Nutrition in chemotherapy

Chemotherapy can lead to reduced energy intake because of nausea, vomiting and loss of appetite and therefore, consequently to weight losses. Chemotherapy-associated anorexia has to be clearly distinguished from the symptom 'anorexia' in the tumour cachexia. Prospective trials have already demonstrated as early as in the 1980s that routine nutritional therapy (nutritional counselling, sip- or tube-feeding) is not beneficial during chemotherapy with regard to morbidity, toxicity and therapy response.[16, 36, 37] A recent meta-analysis examined the benefit of routine concomitant parenteral nutrition and came to the same conclusion.[38]

But it should be stressed here again, that individual decisions for nutritional support in patients with undernutrition and/or reduced food intake should not be influenced by the negative results of routine treatment. Special nutritional focused patient care should be the mean of choice (see paragraph above).

Cancer with dysphagia and/or radio-chemotherapy

Persisting difficulties in swallowing because of head and neck cancer or obstructive oesophageal carcinoma are indications for tube-feeding.[16] For long-term tube-feeding a gastrostomy, preferably a PEG, should be inserted. During radio-chemotherapy in oesophageal cancer significant losses of weight because of mucositis are often observed. Nutritional support with sip feeding and, in case of pronounced dysphagia, with tube-feeding improves QOL and decreases the number of forced cancer therapy breaks and hospitalizations.[16] Our own experience taught us that early insertion of PEG is to be recommended. Placement of PEG is no contraindication for a possibly forthcoming curative surgery (oesophageal resection with gastric replacement).[39] This has been strengthened by the data of a recent randomized, controlled trial by Ravasco *et al.*[40] In the literature the complication of the iatrogenic implantation of site metastases after PEG tube placement (pull technique) are described.[41] This problem may be overcome by a modified introducer technique in combination with endoscopically controlled gastropexy, which avoids the passage of the feeding tube at the tumour side. Modified PEG with gastropexy-early experience with a new introducer technique.[42]

Patients before elective tumour surgery

A special situation is given in patients with GI tumours who undergo elective surgery. Nutritional support in these patients has been evaluated in several prospective, randomized trials and meta-analyses. Post-operative parenteral nutrition compared with enteral nutrition resulted in both a reduction of infectious complications and length of hospital stay (LOS).[43] A recent study demonstrated that the preoperative intake of immuno-modulating substances (arginine, omega-3-fatty acids and ribonucleotides) as sip feeding (e.g. 3×250 mL/day) for 5–7 days contributes to lower post-operative morbidity and reduced LOS not only in patients with persisting undernutrition but also in well nourished patients.[44, 45] Gianotti *et al.*[46] have also shown in a prospective trial in 305 well-nourished patients with GI tumours that the pre- and perioperative supply of immuno-modulating sip feeding led to both reduced complications and LOS. The same working group has demonstrated that nutritional therapy is cost-effective because savings due to a lower number of complications exceed extra costs of nutritional therapy. Average total cost in the treatment group were EUR 1.115 vs. EUR 2.447 in controls.[45]

Cost-effectiveness of perioperative nutritional intervention was reconfirmed by Smedley *et al.*[28] in patients with lower GI tract surgery: Here sip feeding with a high-energy standard formulation not only reduced costs but also significantly diminished the degree of weight loss and incidence of minor complications.

Tumour- or therapy-associated maldigestion

In addition to anorexia, undernutrition can be also caused by tumour- and therapy-associated maldigestion. Maldigestion also results in a progressive loss of weight. Tumour-associated malfunctions of the intestinal tract or therapy-associated dysfunctions (radio- or antineoplastic therapy) should be treated with the appropriate substitutions (e.g. pancreatic enzymes) and/or modified diets (e.g. medium chain triglycerides).

PALLIATIVE SITUATION

The decision for or against artificial nutrition (enteral or parenteral) is especially difficult in palliative care patients who have entered their final phase of life.

Quality of life is certainly the most important criteria in these patients and is mainly dependent on nutritional status.[47] In the past nutritional intervention focused only on one specific intervention like dietary counselling, sip feeding or artificial nutrition. This approach has not been shown conclusively to be beneficial. Lundholm *et al.*[21] tested different approaches by randomizing patients in the palliative situation for specialized, nutrition focused patient care versus standard care. It was found that the specialized approach meet the complex situation better than a specific 'single intervention' (see section 'Specialized, nutrition focused patient care'). Strains through the disease itself but also through therapeutic measures have an major impact on QOL. Therefore, the actual current situation of the patient should be newly evaluated regularly. Home enteral and parenteral nutrition not only allows the patients to be at home, but also is more cost-effective than in-patient care.

If life expectancy is <3 months and/or Karnofsky-Index <50%, the indication for parenteral nutrition should be thoroughly reviewed.[32,48,49] However, implementation of home parenteral nutrition should be always seen in context of the patients' wish, medical condition, family and therapeutic objectives.[50–52] In a recent study patients and family members who were interviewed described nutritionally related difficulties that not only resulted in physical problems, such as weight loss and weakness, but also altered their social lives and their family interactions. The nutritional issues raised by these patients and their family members could serve as a basis for designing questions for inclusion in quality-of-life instruments to be used in evaluations of treatments that might affect patients' food intake and nutritional status.[53]

During the very final phase of life, hydration with 1000–1500 mL (i.v. or s.c.) of isotonic saline is often sufficient. At the very final time of life, at least every decision on therapeutic interventions should base on the individual situation and needs of the patients.

Nutrition in curative tumour therapy

Totally different is the situation in patients in whom a potentially curative tumour therapy had been undertaken. These are mainly colon cancer surgery patients and here adequate data exist. Recommendations regarding nutrition behaviour and life style are based on the German Gastrointestinal Society[54] and the recently published recommendations of the American Cancer Society[55] and are listed in Table 4 with the according level of evidence. In essence data show that a diet rich in fruits and vegetables (five a day) and moderate physical activity seem to have protective effects on the recurrence of colon carcinoma, QOL and survival. Probably it is the combination of different food

Table 4. American Cancer Society (ACS) grading of evidence for benefit vs. harm of weight optimization, physical activity and nutritional behaviour in colon cancer patients after curative surgery[55]

	Cancer recurrence	Overall survival*	QOL
Striving for healthy weight			
During treatment	A3	B	B
After treatment	A3	A2	A2
Increasing physical activity			
During treatment	B	A3	A2
After treatment	A3	A2	A2
Limiting			
Total fat	B	B	B
Saturated fat	A3	A3	B
Increasing vegetables and fruits	A3	A3	B
Increasing			
Fibres	B	A3	B
Omega 3 fatty acids	B	B	B
Soya	B	B	B

A1, convincing evidence for a benefit; A2, probable benefit; A3, possible benefit; B, insufficient evidence to conclude benefit or risk; C, evidence of lack of benefit; D, evidence of harm.
* Includes not cancer-induced deaths.

components (ingredients) that show these effects. Whether dietary fibres are a marker of an increased intake of fruits and vegetables or have protective effects of their own is still being discussed.[56, 57]

CONCLUSION

Nutritional problems and undernutrition are often seen in patients with GI cancer and therefore, these patients are a therapeutic challenge for the attending physician. Nutritional problems and undernutrition are associated with reduced QOL and worsened prognosis of the patient. Adequate intake of energy and nutrients is the very base of every nutritional intervention, but this alone is not always sufficient to stop the development of cancer cachexia. Although anorexia is a common symptom in cachexia, it should not be used as a synonym. Cachexia is associated with characteristic metabolic alterations that are not present in anorexia. Individual nutritional therapy is a essential part of the multifaceted treatment modalities in patients with GI tumours, and the best possible approach to it is the so-called specialized, nutrition focused patient care. It has the potential to improve QOL and in part survival.

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