Clinical practice guidelines on cancer cachexia in advanced cancer patients

with a focus on refractory cachexia

EUROPEAN CLINICAL GUIDELINES

Developed on behalf of the European Palliative Care Research Collaborative

DISCLAIMER

This guideline was produced after carefully considering the available evidence and evaluating the opinion of experts with specialist knowledge and experience.The evidence-base used for the guideline was closed about 2 years ago and there may well be new evidence which the reader should take into consideration before making a clinical decision. Every effort has been made to ensure the accuracy of this text. Nevertheless, the recommendations contained in the guideline reflect the judgment of the Guideline Development Group and have been curtailled by the methodology that was used. The guideline should be taken into account when making clinical decisions, but it does not override the individual responsibility of healthcare professionals to make decisions appropriate to their local context and the circumstances of individual patients. The authors do not assume any legal liability or responsibility for the accuracy or completeness of any information herein disclosed. It is intended to update the present guideline in the near future

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Guideline Development Process

Scope and Purpose

Overall objective

- To produce a consensus- and evidence-based clinical practice guideline for the management of cancer cachexia in advanced cancer patients with a focus on refractory cachexia, on behalf of the European Palliative Care Research Collaborative (EPCRC http://www.epcrc.org). The EPCRC is a project funded by the European Commission's Sixth Framework Programme, with the overall aim of improving the management of pain, depression and cachexia through translational research.

The patient group covered

- Patients with advanced cancer.

Target audience

- All health professionals involved in the provision of palliative care and in the care of patients with advanced cancer.

Rigour of development

- The method for guideline development was based on the NICE recommendations.
- A Guideline Development Group was constituted, comprising clinicians and researchers based at the Department of Palliative Medicine of the RWTH Aachen. This group was responsible for coordinating guideline development and writing the guideline.
- An Expert Group was constituted to help identify clinical priorities and offer opinion on uncertain or contentious areas of clinical practice. The Expert Group was multi-national and multi-disciplinary, including patient representatives and professionals from palliative care, oncology and nutritional therapy.
- Key clinical questions considered important to patients and clinicians were identified by the Expert Group to define the scope of the guideline.
- After formulating the key questions scoping literature reviews led to draft recommendations. These draft recommendations covered the fields Nutritional Treatment, Non-Drug-Treatment, Drug-Treatment, Multimodal Therapy and Prophylaxis of cancer cachexia. They addressed the net-benefit of the intervention for a palliative patient, not only its efficacy. In total the document included 18 recommendations. In May 2008 the draft recommendations were placed on the EPCRC website into the public area as a first, preliminary version of the guidelines.
- The recommendations were formulated using the levels of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) group (strong positive / strong negative, weak positive / weak negative) (Atkins 2005).
- In the next step consensus for the draft recommendations was sought from the expert group using the Delphi Method. The first Delphi round was conducted in September 2008, the second round in March 2009. Using a mean score of 7 on an 11-step agreement scale (0= total disagreement, 10= total agreement) as a cut off level, there was adequate consensus for 16 out of 18 recommendations in the external expert group. Consensus levels as mean scores on the 0 to 10 scale are provided with each recommendation. The level of consensus was inadequate for 2 recommendations (on omega-3-fatty acids and supplements, vitamins and minerals). Systematic reviews were performed for these two recommendations. The results of the systematic reviews confirmed both recommendations.
- The EPCRC work group on assessment and classification of cachexia contributed to the guidelines with their latest research results on the definition, diagnosis and classification of

cachexia. The guidelines have been developed for patients with advanced cancer, likely to suffer from refractory cachexia in the new classification system.

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Competing interests

No competing interests were declared by the members of the expert group.

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Contents

1	**Definition**	**7**
2	**Classification and assessment**	**8**
2.1	Stages of cachexia	8
2.2	Severity	9
2.3	Signs and symptoms	10
2.4	Prognosis	10
2.5	Assessment	10
3	**Patient management**	**11**
3.1	Communication and information	13
3.2	Coordinating care	13
3.3	Palliative care and support	14
3.4	Refer to specialist team	14
4	**Treatments**	**14**
4.1	Nutritional treatment	15
4.1.1	Enteral nutrition therapy	15
4.1.2	Parenteral nutrition therapy	16
4.1.3	Supplements, vitamins and minerals	17
4.2	Non-drug treatment	18
4.2.1	Net benefit of non-drug treatment	18
4.2.2	Nutritional counselling or education	18
4.2.3	Psychotherapeutic interventions	19
4.2.4	Physical training and other physical interventions	19
4.3	Drug treatment	20
4.3.1	Thalidomide and cytokine antagonists	20
4.3.2	Cannabinoids	21
4.3.3	Omega-3-fatty acids, including eicosapentaenoic acid (EPA)	21
4.3.4	Megestrol and progestins	22
4.3.5	Steroids	23
4.3.6	Non-steroidal anti-inflammatory drugs	24
4.3.7	Prokinetics	24
4.3.8	Anticancer treatment	25
4.4	Multimodal therapy	25
4.5	Prophylaxis	26
5	**Conclusions**	**26**
6	**References**	**28**
7	**Appendix**	**36**

CACHEXIA IN ADVANCED CANCER

Cachexia has been recognized as a frequent problem in cancer patients. Cachexia refers to the synergistic combination of a variable decrease in appetite and weight and an increase in the catabolism of fat and lean body mass. In addition to the metabolic disorder that is primary para-neoplastic, secondary causes such as impaired integrity and function of the gastrointestinal tract from mouth to anus and poorly controlled physical and psychosocial symptoms including pain, shortness of breath, depression, or severe fatigue will contribute to cachexia.

Patients suffer from weight loss and appetite loss, as well as from the reduction in phyisical function (Moses 2004), tolerance to anti-cancer therapy (Bachmann 2008) and survival (Dewys 1980; Fearon K.C. 2006; Spiro 2006) that are related to cachexia in advanced cancer. Weight loss and problems with nutrition may also be a significant emotional burden, as nutrition and nutritional status have a central position in the concept of health and wellbeing for many patients and care givers, and weight loss and inadequate nutritional intake can lead to anxiety and hopelessness.

In contrast to these needs, cachexia often is overlooked or not assessed or treated adequately, as it is considered to be unavoidably linked with disease progression (Pacelli 2008; Spiro 2006). Cachexia represents a significant unmet need.

The European Palliative Care Research Collaboration (EPCRC) has developed evidence based recommendations on classification and treatment of cachexia in advanced cancer patients as part of its clinical guideline work. The present treatment guidelines focus on patients with advanced cancer likely to suffer from refractory cachexia. Many of these patients are receiving palliative care, and life expectancy often is short. Only little cachexia research has been done on this patient group, and the treatment guidelines had to consider whether research results from other disease stages are applicable for these patients with advanced and incurable disease and for refractory cachexia.

1 Definition

Although understanding of cachexia has progressed over the last decade (Argiles 2010; Argiles 2007), lack of consensus on a definition, diagnostic criteria and classification has impeded advancement in both in clinical trials and clinical practice (Argiles 2010; Fox 2009; Jatoi 2008; Senior 2007).

Whereas the definition of cachexia has focussed on weight loss and appetite loss initially, newer definitions try to integrate the concept of cachexia as a complex metabolic disorder, which is distinctly different to malnutrition. For cancer-related cachexia, the differentiation between cachexia and other causes of weight or muscle loss such as malnutrition related to anorexia or malabsorption related to impaired gastrointestinal function can be difficult. In some definitions cancer-related cachexia has been combined with anorexia as a cachexia-anorexia syndrome (Strasser 2004).

A generic definition for all types of cachexia in both adults and children has been proposed recently: *"Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders)."* The definition also states that anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia, but that cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism (Evans 2008). However, the proposed diagnostic criteria were not cancer–specific and have not been validated (Strasser 2008). Two other definitions of cancer cachexia have been proposed

(Bozzetti 2009b; Fearon K.C. 2006), but both were based on single-centre experience and did not follow any formal consensus process.
The EPCRC expert group on classification of cancer pain has suggested the following definition of cancer cachexia (Fearon K (in press)):

> Cancer cachexia is a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.

The metabolic conditions observed in cancer cachexia include increased resting energy expenditure, loss of adipose tissue due to an increased lipolysis by tumor or host products, and loss of skeletal muscle resulting from a depression in protein synthesis combined with an increase in protein degradation. The increase in protein degradation may include both increased activity of the ubiquitin-proteasome pathway and lysosomes. Tumor factors such as proteolysis-inducing factor and host factors such as pro-inflammatory cytokines, angiotensin II, and glucocorticoids all contribute to the catabolic state of metabolism (Argiles 2007; Tisdale; 2009). Cachexia has been described as an inflammatory reaction, mediated via cytokines and involving hypothalamic mechanisms, which interact with neurotransmitters that influence both appetite and metabolism (Grossberg 2010).

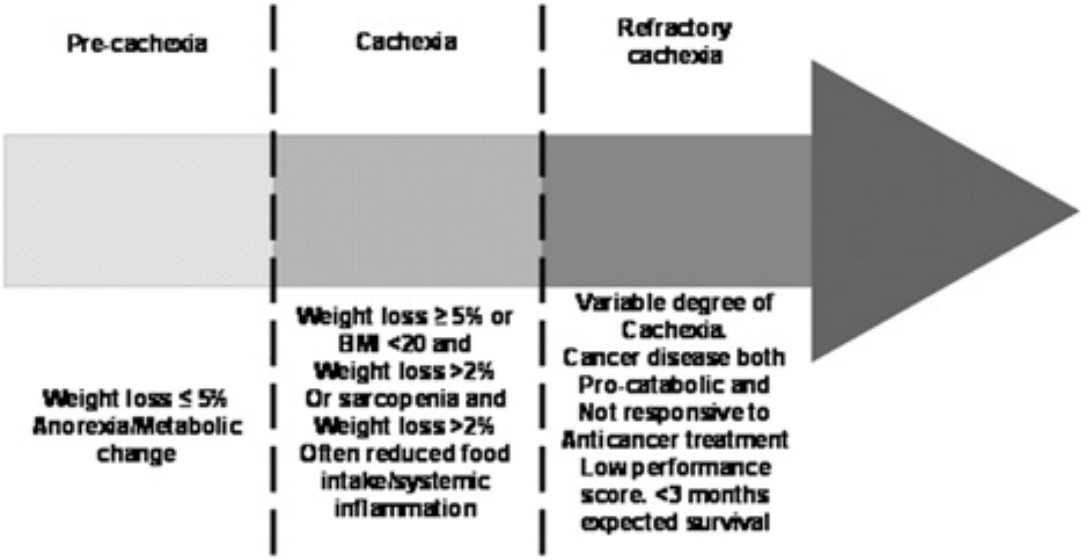
2 Classification and assessment of cachexia

2.1 Stages of cachexia

Cancer cachexia represents a continuum with three stages of clinical relevance: pre-cachexia, cachexia and refractory cachexia. Not all patients traverse the entire spectrum. At present there are no robust biomarkers to identify those pre-cachectic patients who are likely to progress further down the trajectory or the rate at which they will do so (Fearon K (submitted)).

The cachexia stages are defined essentially on the basis of the patient's clinical characteristics and circumstances.

Refractory cachexia represents a stage where reversal of weight loss seems no longer possible due to very advanced or rapidly progressive cancer unresponsive to anti-cancer therapy. In this stage the burden and risks of artificial nutritional support likely outweigh any potential benefit, and therapeutic interventions focus typically on alleviating the suffering associated with cachexia, such as symptom control with appetite stimulation and treatment of nausea or eating-related distress of patients and families.
Refractory cachexia is characterised by a low performance status (WHO 3 or 4) and life expectancy less than 3 months. Identification of patients with refractory cachexia may be aided by early and repeated consultation with end of life care teams. It is important to appreciate that often it may be the overall medical condition of the patient rather than the severity of cachexia that may render them refractory.



Current diagnostic criteria for refractory cachexia include:[1]

Fulfil critera for cachexia definition
Prognosis < 3 months
Performance status WHO 3 or 4
Unresponsive to anti-cancer therapy
Ongoing catabolism at increasing rate
Unsuitable for artificial nutritional support

2.2 Severity of cachexia

In addition to the stage of cachexia an assessment of severity of depletion is suggested. Severity is related to the rate of ongoing loss of weight and to the degree of depletion of energy stores and body protein mass. Thus a fall of 5 kg body weight in 4 weeks would be more severe than a fall of the same amount in 8 weeks, and a fall of 5% from an initial BMI of 22 would be more severe than the same loss from an initial value of 30.

[1] An overview on classification systems has been published recently (Blum 2010). Similar stages of cachexia have been put forward by the Special Interest Groups (SIG) “Cachexia-Anorexia in Chronic Wasting Diseases” and “Nutrition in Geriatrics” of the ESPEN. The SIGs suggested only two stages with pre-cachexia and cachexia. They did not identify refractory cachexia as a third stage, though they stated in their consensus paper that late-stage cachexia is substantially untreatable with currently available tools (Muscaritoli).
The Patient-Generated Subjective General Assessment (PG-SGA) also suggests three stages based on weight loss, though the criteria do not correspond well to the stages describe in these guidelines, and the stages are more targeted on an action plan rather than the definition of different stages.

2.3 Signs & symptoms

Assessment of signs and symptoms has to cover different dimensions of cachexia. A model with 4 dimensions has been proposed, including Storage, Intake, Potential and Perfomance (SIPP).

Storage: assess gap of usual to current weight, speed of weight loss, weight loss corrected for fluid retention or obesity, deficits for specific nutrients
Intake assess anorexia, early satiety, nausea, vomiting, disturbances of taste or smelling, other gastrointestinal symptoms, percentage of normal intake, dietary diary for 1-2 days
Potential assess tumor [catabolic] activity, C-reactive protein
Performance assess performance status, cachexia-related suffering, prognosis

2.4 Prognosis

It is most probable that the majority of patients in palliative care with cancer cachexia have progressed to the stage of refractory cachexia, and this has to be considered in the therapeutic approach towards cancer cachexia in palliative care. Management of symptoms is required, for example patient education about the trajectory of cachexia and the course of the disease, in order to decrease the physical and emotional burden or the patient.

2.5 Assessment

Assessment of cachexia and anorexia should cover the signs and symptoms in the dimensions described above. Parameters that should be considered for assessment are listed below. Screening should include at least appetite and gastrointestinal symptoms, history of weight change and BMI, CRP and performance status.

Subjective symptoms: Appetite, early satiety, nausea, vomiting, disturbances of taste or smelling, other gastrointestinal symptoms, weakness, disease-related burden, well-being
History Weight change, speed of weight loss, percentage of normal intake
Clinical examination Inspection of mouth, abdomen, hydration status, oedema, body weight, perceived physical strength
Laboratory examination CRP, blood sugar profile, testosterone
Activity monitoring Performance status (ECOG or Karnofsky), upper limb hand-grip dynamometry, body-worn activity meters
Body Composition Cross-sectional imaging (CT or MRI), dual energy x-ray imaging (DEXA), anthropometry (mid-arm muscle area), bioelectrical impedance analysis (BIA)

All secondary causes for decreased oral nutritional intake should be actively assessed and reversed if possible. Evaluation by an experienced oncologist is required to evaluate whether the cancer disease is refractory to anti-cancer treatment and how severe the catabolic drive of the cancer disease is expected to be.

The assessment of a patient with refractory cachexia should necessarily focus on cachexia related symptoms that are amenable to active management rather than on the specifics of nutritional status.

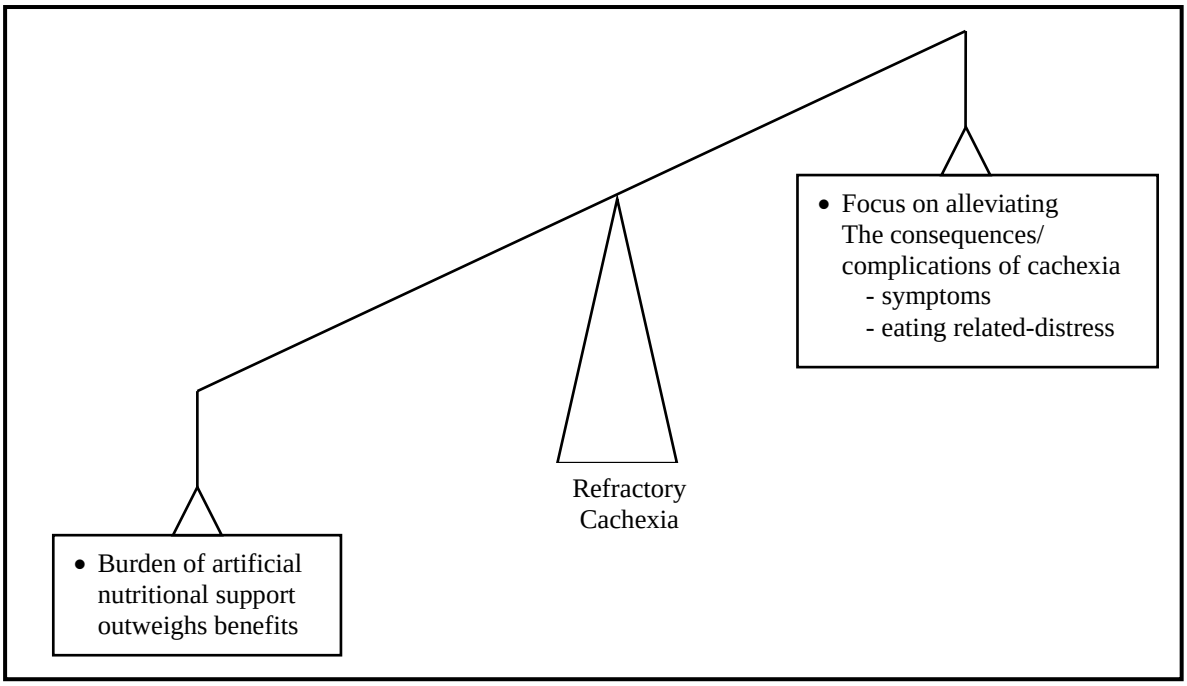
Comprehensive questionnaires have been developed for the subjective assessment by patients. The Functional Assessment of Anorexia / Cachexia Treatment (FAACT) is a combination of the general core questions of the Functional Assessment of Chronic Illness Treatment (FACIT) and an additional module with questions on nutritional issues including appetite (Chang 2005; Ribaudo 2000). Similarly, the North Central Cancer Treatment Group (NCCTG) (Grothey 2008) includes 15 items, 10 of which directly related to nutritional issues, including appetite.
Subjective self-assessment by the patient is also the main focus of the Patient-Generated Subjective Global Assessment of nutritional status (PG-SGA), which covers the domains of weight, food intake, symptoms as well as activities and function. In the PG-SGA these patient-generated assessments are combined with some information from the therapists on disease and metabolic demand (Detsky 1987). The Mini-nutritional Assessment (MNA) (Guigoz 1996) is used frequently in geriatric care, and is also available as a short form that has been recently revised (Kaiser 2009).
The use of multidimensional and standardized instruments is recommended. The SIPP model described above can be used as an assessment instrument with a brief, but comprehensive score card (see appendix).

3 Patient management

These guidelines focus on refractory cachexia in patients with advanced cancer. In advanced cancer and more specifically in palliative care, time is usually short. Management of cachexia must take into account the patient's prognosis. As stated previously, refractory cachexia represents a stage where reversal of weight loss seems no longer possible due to very advanced or rapidly progressive cancer unresponsive to anti-cancer therapy. In this stage the burden and risks of artificial nutritional support are likely outweigh any potential benefit, and therapeutic interventions focus typically on alleviating the consequences and complications of cachexia, such as symptom control with appetite stimulation and treatment of nausea or eating-related distress of patients and families.

At any stage of cachexia a state of the art assessment of secondary causes for decreased nutritional intake or simple starvation is mandatory. Patient assessment must determine whether there is a functional or anatomic barrier from the mouth to the anus or other interfering symptoms such as dyspnoea or incident pain which may decrease the ability of the patient to eat.

Health professionals should discuss all treatment options with the patient and ensure that they are well informed. Patients should have equal access to appropriate assessment and management of cachexia whether they are homecare, day care or inpatients.



Good palliative care is of itself a key strategy for alleviating relevant symptoms of cachexia at the end of life. All patients should be able to benefit from the palliative care approach which integrates physical and psychological care and symptom control. This approach can be applied by all health professionals; general practitioners, oncologists, psycho-oncologists, physiotherapists, pain management specialists or nutritional specialists can all apply these holistic principles. However, many patients who have complex or multiple needs will require referral to a specialist team in palliative care with additional knowledge and expertise. Care planning with good coordination of care is crucial - including different services, different health professionals, as well as patients and their families. Actively listening, empathizing and asking open-ended questions encourage patients to express their problems and preferences, in turn enabling health professionals to provide appropriate information and support. Palliative care aims to diminish distress by addressing symptoms, and control of pain and other troublesome physical symptoms are likely to be effective preventive strategies.

Management approach for cachexia

- The treatment goal for full cachexia should be the reversal of the loss of body weight and muscle mass. As a minimal goal body weight should be maintained and further loss prevented.

- The treatment approach should be multimodal and similar to pre-cachexia. This includes detailed assessment and repeated monitoring, vigorous nutritional support, anti-inflammatory treatment, treatment of secondary gastrointestinal symptoms and other causes for decreased oral nutritional intake as well as evaluation of anti-neoplastic options to reduce the catabolic drive of the cancer.

Management approach for refractory cachexia

- For refractory cachexia the primary treatment goal should not be reversal of weight loss, but rather alleviation of cachexia-related symptoms and overall increase of well-being.

- These guidelines focus on cachexia in patients with advanced cancer likely to suffer from refractory cachexia. In these patients and more specifically in palliative care, time is usually short. Management of cachexia must take into account the patient's prognosis. It may take several weeks for patients to respond to anti-cachectic treatment. For patients with a short life expectancy, these treatment options may add to the burden without offering adequate efficacy in the balance and thus may not be appropriate for this setting. Health professionals should discuss all treatment options with the patient and ensure that they are well informed. Patients should have equal access to appropriate assessment and management of cachexia whether they are homecare, day care or inpatients.

3.1 Communication and information

- Communication with patients and their relevant others as well as information and shared decision-making on treatment planning should follow acknowledged basic principles for the care of severely ill patients (Block 2001; Boyle 1970; Department of Health 2008; Elkin 2007; National Institute for Health and Clinical Excellence 2006; Radbruch 2009)

- Listen to the patient's problems, preferences, questions and concerns, and determine their desired level of information and involvement in treatment decisions

- Inform patients about the range of treatment options as well as the range of local support available to them, and involve them in treatment decisions.

- Include relevant others in the information and decision making, if the patient agrees to this. However for adequate information and involvement family roles, conflicts, and how these have changed as a result of the illness have to be considered.

- Repeat the assessment of needs and preferences at key points in the disease trajectory, for example with impending change of the care setting, as priorities may change over time. This assessment should also include preferred place of care, and may include preferred place of death.

3.2 Coordinating care

- There should be close collaboration between oncology and palliative care services where appropriate (Cherny 2010; Ferris 2009).

- Coordination of care should include also nutritional, physiotherapy and mental health care services, as well as the general practitioner and the nursing service caring for the patient.

- Case management should be available for coordination of services across all settings and services to ensure adequate quality and continuity of cachexia management and treatment.

- Patients and their care givers should be aware of ongoing communication and collaboration within the multidisciplinary team, and their needs and priorities should be considered in the planning and coordination of care.

3.3 Palliative care and support

- Ensure that patients' physical symptoms (e.g. pain, fatigue, breathlessness) are being assessed and managed effectively, as this may improve appetite, ability to take up food and general wellbeing (Doyle D 2004).
- Take account of psychosocial needs as well as physical ones to reduce emotional distress.
- Consider referral to specialist palliative care for symptom control, physical, emotional, social and spiritual support (Hearn 1998).
- Health professionals should be aware that some patients may have financial, social or spiritual needs, and arrange support from appropriate advisers (e.g. social workers, chaplains) when necessary.
- Caring for a person with advanced disease can be physically and emotionally stressful. Be aware of the needs and concerns of family members and caregivers, and where possible provide psychological and practical support.

3.4 Refer to specialist team (palliative care, nutritional specialist):

- If there is uncertainty about the stage and severity of cachexia.
- If there is no clear differentiation between the contribution of malnutrition and metabolic change to cachexia.
- If treatment goals of patient or family are vastly inappropriate.
- If cachexia-related burden is disproportionate to symptom load and prognosis.

4 Treatments

The treatment guidelines provided here are based on a formal consensus procedure with a group of experts from oncology and palliative care, supported by scoping reviews of the literature and by systematic reviews where consensus was not high enough. The consensus process has focussed on advanced cancer, most likely to be related to later stages of cachexia. The consensus process of the treatment guidelines had been completed before the classification system of EPCRC had been finalized, and subsequent discussions clarified that experts understood the guidelines presented here to be most valuable for patients with refractory cachexia.
The expert group identified key questions from on nutritional treatment, non-drug treatment, drug treatment, multi-dimensional therapy and prophylaxis as major domains.
Evidence from randomized trials on treatment of cachexia in advanced cancer is scarce, and in many publications only little information is available on stages or dimensions of cachexia. If more detailed information on classification is included in future studies and reports, more detailed evaluation and graded recommendations may become possible in subsequent updates of this guideline.

4.1 Nutritional Treatment

4.1.1 Enteral nutrition therapy

- Enteral nutrition is understood as the use of dietary foods for special medical purposes, and this includes tube feeding via nasogastric, nasoenteral or percutaneous tubes as well as oral nutritional supplements (ONS) (Lochs 2006).

- The guideline on enteral nutrition of the European Society of Clinical Nutrition and Metabolism (ESPEN) (Arends 2006) states that patients losing weight due to insufficient nutritional intake should be provided with enteral nutrition to improve or maintain nutritional status. Enteral nutrition should also be provided if it is anticipated that the patient will not be able to eat for more than 7 days, or will not be able to maintain an adequate oral intake (at least 60% of estimated energy expenditure) for more than 10 days.

- The ESPEN guideline explains that in the presence of systemic inflammation it appears to be extremely difficult to regain lost body cell mass with enteral nutrition alone (Arends 2006).

- For incurable patients, the ESPEN guideline states that they should be provided with enteral nutrition in order to minimise weight loss as long as the patient consents and the dying phase has not started (Arends 2006).

- The guideline on artificial nutrition versus hydration in terminal cancer patients from the European Association for Palliative Care (EAPC) (Bozzetti 1996) states that no rigid treatment guidelines can be formulated, but three steps are recommended for the decision-making process for or against enteral nutrition therapy. In the first step the key elements necessary to reach the decision should be assessed (clinical and oncological situation, symptoms, expected length of survival, hydration and nutritional status, voluntary nutrient intake, psychological attitude, gut function and route of administration, need for special services based on nutritional support prescribed). In the second step the decision is made, and in the third step patient and treatment are re-evaluated in specified intervals. The guidelines provide examples where artificial nutrition is recommended, but do not differentiate between enteral and parenteral nutritional therapy.

- Strasser (2003) reported from a workshop on eating-related disorders in patients with advanced cancer. Workshop participants stressed the ethical questions that have to be applied in the decision-making process for or against nutritional therapy, including questions of autonomy (do patients have a right to receive medically futile treatments?), beneficience (does the treatment result in a net benefit for the patient?) and justice (can the benefit justify the resources required?). The enteral route should be preferred for nutritional therapy if the gastro-intestinal tract is functioning, but potential side effects of enteral nutrition are listed: aspiration, pneumonia, fistulae, diarrhoea, constipation, short bowel obstruction, occlusion or displacement of the feeding tube, vomiting, mal-absorption, electrolyte abnormalities, hyperglycaemia and infections.

- Skipworth and Fearon (Skipworth 2007) state that nutritional support is of paramount importance in the management of patients with cancer-related cachexia to arrest or reverse weight loss. However, the complex mix of different mediators involved in the pathophysiology of cancer-related cachexia renders uni-modal nutritional intervention a strategy that is unlikely to succeed completely.

- In the American Cancer Society guide for informed choices Doyle et al. state that many persons with advanced cancer need to adapt food choices and eating patterns to meet nutritional needs and to manage symptoms and adverse effects (Doyle C 2006). Additional

nutritional support such as nutrient-dense beverages can be provided for those that cannot eat enough solid food to maintain energy intake. For tube feeding and parenteral nutrition associated risks for complications should be acknowledged, and nutritional therapy has to be based on individual needs.

Recommendation

Enteral nutrition therapy may be partially effective for selected patient groups (level of recommendation: **strong positive**; **mean consensus 7.03** on a scale from 0=completely disagree to 10=completely agree). For refractory cachexia the provision of appetising food and enteral nutritional support in a context that does not add to eating-related distress is recommended.

4.1.2 Parenteral nutrition therapy

- The ESPEN guidelines on parenteral nutrition (Bozzetti 2009a) recommend that parenteral nutrition should not be given in cancer patients, when there is no decreased ability to eat; however in one recommendation it focuses on patients with intestinal failure and recommends that in patient who have a longer prognosis with more than 2 months survival from the cancer disease, but less expected survival due to malnutrition, then parenteral nutrition might be recommended. Recent data (Orrevall 2009; Shang 2006) suggest that there may be patients where simple starvation or secondary nutrition impact symptoms are not well diagnosed and who might profit even in advanced cancer stages from parenteral nutrition. However, this is a research question and should not be applied outside a clinical study.

- American College of Physicians (American College of Physicians 1989) stated in 1989 that parenteral nutritional support was associated with net harm, and that in cancer patients no conditions could be defined in which such treatment appeared to be of benefit.

- Bosaeus (Bosaeus 2008) elaborates that parenteral nutrition is difficult to supply over extended periods of time. It is associated with a number of complications, and a number of parenteral nutrition trials in the 1980s showed no benefit but an increase of infectious complications. Nutritional therapy alone does not appear to affect overall survival in advanced cancer, but in combination with anti-inflammatory treatment or therapies targeted against metabolic change, it may have a positive effect.

- Torelli et al. (Torelli 1999) reported the use of parenteral nutrition in 26 patients with limited life expectancy due to end-stage cancer either as adjunct to in-hospital aggressive anti-neoplastic treatment or for supportive care, and found that it did not improve the quality of life or ultimate outcome.

- Strasser (Strasser 2003) in a report from a workshop on eating-related disorders in patients with advanced cachexia described potential side effects of parenteral nutrition as infections, central venous access complications, volume/ electrolyte and glucose imbalance as well as increased costs. In selected patients parenteral nutrition can prevent hospital admissions and enable patients to stay at home. However, parenteral nutrition seems to be indicated only for a small subgroup of patients with predominant starvation, inability to take enteral nutrtion, good performance status, reasonable life expectancy >3 months, good understanding of effects and side-effects of this therapy and an accurate estimation of their own life expectancy.

- As described in the section on enteral nutrition, the guideline on artificial nutrition versus hydration in terminal cancer patients from the European Association for Palliative Care (EAPC)

(Bozzetti 1996) states that no rigid treatment guidelines can be formulated, but three steps are recommended for the decision-making process for or against parenteral nutrition therapy: assessment of key elements, making the decision and re-evaluation in specified intervals. The guidelines provide examples where artificial nutrition is recommended, but do not differentiate between enteral and parenteral nutritional therapy.

- The American Cancer Society guide for informed choices (Doyle C 2006) states that the use of tube feeding and total parenteral nutrition should be individualized with clear recognition of the associated risks for complications. The guide states that both the American Society for Parenteral and Enteral Nutrition (Mirtallo 2004) as well as the American Dietetic Association (Maillet 2002) recommend that total parenteral nutrition should be used selectively and with caution.

Recommendation

Although there may be occasional situations that require the initiation of parenteral nutrition, in advanced cancer these situations will be rare (level of recommendation: **strong negative**; **mean consensus 7.46**). In refractory cachexia the burden of parenteral nutrition will likely out-weigh any benefits.

4.1.3 Use of supplements such as vitamins or minerals

- The term supplement is not used uniformly in the literature on cachexia, and has been used to include minerals, vitamins, but also omega-3-fatty acids or protein-enriched nutrition. Supplementation with EPA, antioxidants and proteins may be able to reverse severe weight loss in cancer patients with high inflammatory stress (Grimble 2003). However, the author does not relate this statement to cancer stage.

- In an overview on three controlled studies, one of them in cancer patients, with a combination of ß-hydroxy-ß-methylbutyrate (HMB), arginine and glutamine Rathmacher et al (Rathmacher 2004) demonstrated an overall benefit with an increase in lean body mass, improved emotional profile, less weakness and improved haematological parameters compared with placebo. Supplementation was safe, though blood urea nitrogen was increased in the cancer patients receiving the supplement.

- Supplementation with Medium Chain Triglycerides lowers the production of TNF-alpha in cachectic patients and in combination with hydrolyzed casein protein led to better weight maintenance during radiotherapy than ad libitum diet ("Medium chain triglycerides. Monograph" 2002).

- However, the present recommendation on the use of supplements focuses on minerals and vitamins, as fatty acids and proteins will be covered in other sections of the guideline. The American Cancer Society guide for informed choices (Doyle C 2006) describes a probable benefit of taking a standard multiple vitamin and mineral supplement during and after cancer treatment, in order to provide the daily need of these micronutrients which may not be covered due to side effects from treatment on the gastrointestinal tract. In case of vomiting or hypophagia special preparations are recommended. However, the use of very large doses of vitamins, minerals or other dietary supplements is not recommended. High dose supplements may even be harmful, as beta-carotene supplements have been shown to increase the rate of recurrence of lung cancer.

- In the guideline development group consensus was below the predefined level, and a systematic review will be performed to provide additional information on the net-benefit of supplements.

Recommendation

There is not enough evidence for a general recommendation (**mean consensus 6.97**). However, patients who are not able to consume the recommended daily amount of vitamins and minerals may try to balance this with supplements.

4.2 Non-Drug-Treatment

4.2.1 Net benefit of Non-Drug-Treatment

In cachectic patients with advanced cancer and reduced life expectancy options for medical interventions are restricted. However, non-drug treatments should be considered in all patients, even if the reversal of the metabolic changes does not seem possible and reversal or interruption of weight loss is unrealistic. For these patients interventions such as counselling or mild physical exercise (adapted to performance status) may be beneficial. Discussing and consenting on realistic treatment goals with the patients and care givers as well as in the care team is of major importance.

Recommendation

There is evidence that non-drug treatment is effective in the treatment of cancer cachexia as shown in subsequent parts 4.2.1 and 4.2.2 (level of recommendation: **strong positive**; **mean consensus 8.17**). However, evidence for patients with refractory cachexia is insufficient.

4.2.2 Nutritional counselling or education

- Nutritional counselling has been reported to improve nutritional intake in patients undergoing chemotherapy (Strasser 2003). However, the influence of counselling on reducing expectations and psychological distress in patients with a palliative care setting remains to be established. Adequate education and counselling should include the concern of the family member that their relative is “starving to death”, and differences between starvation and cachexia should be addressed.

- Nutritional counselling has been shown to improve quality of life in patients with head and neck cancer undergoing radiotherapy (Ravasco 2007). Even more important, in comparison with an ad-libitum diet with high protein supplementation, only individualized nutritional counselling was capable of sustaining a significant impact on patients’ outcomes 3 months after its completion. However, this effect has not yet been reproduced in other trials.

- The appropriate provision of counselling, for example dietetic consultation or information sheet has not been established for patients with refractory cachexia. Even if there is no evidence that nutritional counselling improves overall quality of life or physical functioning in refractory cancer cachexia patients, there is a strong support by experts that nutritional counselling can aid cancer patients and family members to understand the changes, and to differentiate what they can improve and where the limitations of nutrition are. However this requires high psychological and nutritional skills of the counsellors.

Recommendation

There is some evidence that counselling has positive effects on nutritional status and quality of life in cancer patients undergoing anti-neoplastic therapy (level of recommendation: **strong positive**; **mean consensus 9.08**). There is no evidence to support or refute the value of counselling in advanced cancer/refractory cachexia.

4.2.3 Psychotherapeutic interventions

- Transient anorexia may occur in cancer patients secondary to psychological distress, though cachexia is related to other pathophysiological changes. Behavioural techniques such as those used in anorexia nervosa do not seem to be beneficial in cancer cachexia. However, creation of a pleasant environment for meals, encouraging patients to eat with adequate attention to the food preferences of the patient are promising areas of psychological interventions (Holland 1977).

- Relaxation training with deep abdominal breathing, autosuggestion, controlled tension and relaxation of body parts and voluntary image control has been tested as a nursing intervention for cancer patients with risk of cachexia. Relaxation had positive effects on weight in cachectic cancer patients and improved performance status (Dixon 1984). However, this study included patients at risk, but not patients with major weight loss, and the results have not been collaborated in more recent research.

- Recent work (Hopkinson online first) supports the view that psychosocial interventions focussed on eating related distress and weight loss related distress and including interactions between family members and patient can improve overall wellbeing and distress of cancer patients as well as of family members. However, this data is not supported by large quantitative outcomes. The concept of eating related distress, weight loss-related distress and family-related distress can support effective counselling. However, the evidence based and the definitions are still weak.

Recommendation

There some evidence that psychotherapeutic interventions (relaxation therapy) have positive effects on quality of life (level of recommendation: **strong positive**; **mean consensus 7.14**). There is no evidence that psychotherapeutic interventions have an effect on nutritional status. Moreover, for refractory cachexia, reduced performance status and short prognosis may preclude this intervention.

4.2.4 Physical training and other physical treatment options

- Physical exercise may be beneficial in the treatment of cancer-related cachexia as it increases insulin sensitivity, protein synthesis rate as well as activity of anti-oxidative enzymes. It also may lead to a suppression of the inflammatory response and to an enhancement of immune function (Ardies 2002). All these mechanisms can contribute to curb the pathophysiological changes underlying cachexia.

- There is significant evidence that endurance exercise (high number of repetitions performed over extended time periods against relatively low resistance) ameliorates cancer-related fatigue (al-Majid 2001). However, it is not clear how this influences muscle mass in cachectic cancer patients. In contrast, resistance exercise (lower number of repetitions against higher resistance) attenuates muscle wasting in different catabolic conditions. However, only a few

  studies have investigated the effects of resistance exercise on muscle mass of cancer patients.

- Physical therapy is also advised during periods of bed rest that may be caused by disease or therapy, as reduced fitness and strength as well as loss of lean body mass are to be expected (Doyle C 2006).Physical therapy will help to counteract fatigue and depression and will maintain strength and range of motion. However, there is only limited research on exercise in patients with advanced cancer.

- a recent systematic review (Lowe 2009) on physical activity as a supportive care intervention in palliative cancer patients found no conclusive evidence in the six trials that were included. It is still under discussion which patients with refractory cachexia might profit from mild physical activity interventions. Counselling patients on cancer-related fatigue can aid patients to maintain a minimal form of activity and to slow down the decrease in physical function and quality of life.

Recommendation

In cancer patients, physical training and other physical treatment options are beneficial as a preventive procedure to maintain functional status. The activities and training interventions have to be individualized (overall level of recommendation: **strong positive**; **mean consensus 7.92**). However, most research has been done in patients treated with curative intent, and it is not clear to what extent physical training is appropriate in patients with advanced cancer/refractory cachexia.

4.3 Drug Treatment

Most drug trials have targeted patients with cachexia rather than refractory cachexia. However, it is evident from the rapidity and level of trial drop-out that a significant proportion of patients included in these trials were already in a refractory state of cachexia'. Thus it may be inferred that the evidence of these trials pertains to some degree also to patients with refractory cachexia.

4.3.1 Thalidomide and cytokine antagonists

- Thalidomide is an inhibitor of tumour necrosis factor alpha (TNF-a) synthesis. As TNF-a as well as other pro-inflammatory cytokines play a prominent role in the inflammatory reaction that underlies cancer cachexia, thalidomide may represent a novel and rational treatment approach (Gordon 2005). In patients with advanced pancreatic cancer thalidomide was well tolerated and effective at attenuating loss of weight, arm muscle mass and physical function.

- Similarly, thalidomide treatment resulted in weight gain and increase of lean body mass over a 2-week trial period in patients with oesophageal cancer (Khan 2003)l However, this study included only 11 patients and was of a short duration.

- Bruera et al. (Bruera 1999) tested thalidomide in patients with metastatic cancer and found increased appetite and sensation of well-being comparable with megesterol. No information on weight or weight change was given. The study plan allowed inclusion of patients with a short life expectancy, and only half of the patients were able to complete the 10-day study period.

Recommendation

There is not enough evidence on the net benefit of thalidomide or cytokine antagonists (level of recommendation: **weak negative**; **mean consensus 7.57**). The use of thalidomide is not recommended in patients with refractory cachexia.

4.3.2 Cannabinoids

- Tetrahydrocannabinol (THC) was an effective, well tolerated appetite stimulant in 19 patients with advanced cancer (Nelson 1994). However, one fourth of the patients suffered from side effects.

- The Cannabis-In-Cachexia-Study-Group compared cannabis extract (with standardized content of THC and cannabidiol) with THC alone and with placebo (Strasser 2006) in a large group of patients with advanced incurable cancer. Cannabis extract was well tolerated by the patients with cancer-anorexia and cachexia syndrome but there were no differences in appetite or quality of life between the groups. Weight loss was similar in all three groups. However, lack of efficacy may have been related to the dose of THC.

- In an even larger study with 469 patients with advanced cancer in a study of the North Central Cancer Treatment Group (NCCTG) THC was compared with megesterol and with placebo (Jatoi 2002): Megestrol proved to be more effective than Dronabinol in terms of appetite improvement and weight gain, with only 3% of weight gain for THC treatment. Combination of megesterol and THC was not superior to megestrol alone.

- These studies have used a fix-dose regimen. Individual titration may be more efficient but has not been investigated in clinical trials yet.

Recommendation

Cannabinoids may increase appetite in selected patients but overall there is not enough evidence to support their use (level of recommendation: **weak negative**; **mean consensus 7.78**). The use of cannabinoids is not recommended in patients with refractory cachexia.

4.3.3 Omega-3-fatty acids, including eicosapentaenoic acid (EPA)

- A Cochrane review on eicosapentaenoic acid (EPA) for treatment of cancer cachexia identified 5 studies with a total of 587 patients until February 2005 (Dewey 2007): Trials compared different dosages of EPA with placebo or with active matched control. Only data from two trials could be compared directly. The authors concluded that the use of EPA cannot be recommended, as there is not enough evidence to demonstrate a net-benefit compared with placebo. There was a wide range of dosages of EPA and docosahexanenoic acid (DHA). High doses of EPA and DHA led to more frequent reports of vomiting.

- Mozzotta and Jeney (Mazzotta 2009) performed a systematic literature review of the role of polyunsaturated fatty acids in the management of symptoms, survival and quality of life in advanced cancer. The review identified 7 randomized controlled trials in the review period until October 2006. Only one study showed a positive effect on weight, but not on lean body mass, the other trials found no clinically or statistically significant effect in the outcome parameters surveyed. The range of doses varied widely between studies, and studies comparing different dose levels did not find dose-response relationships.

- In the systematic review of Colomer et al. (Colomer 2007) on n-3 fatty acids for cachexia in cancer patients, 17 controlled or observational studies were included, covering the time period until 2006. Eight of these studies were described as high quality. Four of the studies with higher quality and 7 with lower quality reported change of weight or lean body mass as outcome. The authors concluded that n-3-fatty acids have a positive effect on weight, appetite and QoL in advanced cancer patients, though it has been studied only in patients with pancreatic or upper gastrointestinal cancer. They recommend doses of 1500 mg EPA and DHA per day or more, and treatment periods of at least 8 weeks may be required to show an effect. EPA was tolerated better when it was administered as part of a low-fat nutritional formula instead of concentrated capsules.

- Fearon et al. evaluated 200 patients with pancreatic cancer (Fearon K. C. 2006). There was no sigificant difference between EPA and an identical oral isocaloric supplement without EPA, with weight loss and lean body mass stabilized in both groups. However, net food intake was increased in the EPA group.

- The review of Jatoi (Jatoi 2005) found a large body of literature for the use of omega-3 fatty acids for the treatment of cancer-related weight loss. However, three large clinical trials demonstrated only minimal clinical benefit.

- Similarly, in a study with 91 cancer patients with weight loss and anorexia EPA and DHC were not different to treatment with olive oil (Bruera 2003) for weight change, appetite and caloric intake. However, there was a high number of drop-outs in both groups and the treatment duration was only two weeks.

- The North Central Cancer Treatment Group has included 421 patients in a study that compared EPA-enriched nutrition supplement with megesterol and with a combination of both (Jatoi 2004). Changes in weight and appetite were the same in the EPA and megestrol groups. The trial sample size was not designed to prove equivalence.

- In the guideline development group consensus was below the predefined level, and a systematic review was performed to provide additional information on the net-benefit of omega-3-fatty acids. In addition to the systematic reviews listed above 18 randomized controlled studies, 8 non-randomized controlled studies and 8 case series were retrieved. Meta-analysis was not possible as a variety of outcome parameters were used and study designs were not comparable. However, the bulk of the evidence indicates that EPA and DHC are of limited value in the treatment of cancer cachexia.

Recommendation

There is not enough evidence to reach consensus on the net benefit of omega-3-fatty acids in patients with advanced cancer/refractory cachexia (**mean consensus 6.54**). Omega-3-fatty acids may be effective in specific patients who achieve effective blood levels. More research is needed to optimise compliance and determine the potential role of omega-3-fatty acids in multimodal regimens

4.3.4 Megestrol and progestins

- A systematic literature review from Cochrane evaluated megestrol for treatment of anorexia-cachexia syndrome (Berenstein 2005). The review was not restricted to cancer cachexia, and retrieved 30 studies in the time period until 2002. Twenty-two studies with a total of 3445 patients had tested megestrol in cancer-related cachexia. The review described statistically significant benefit for appetite and weight gain, but not in quality of life, in cancer patients compared to placebo. Megestrol acetate did not show benefits compared with other drugs such as steroids, cannabinoids or prokinetics. The authors also compared high and low dosages with the daily dosage of 400 – 480 mg that most frequently used, and found no significant differences. There was a low incidence of adverse effects, and only oedema of the lower limbs was significantly more frequent than with placebo.

- The North Central Cancer Treatment Group has included 421 patients in a study that compared EPA-enriched nutrition supplement with megestrol and with a combination of both (Jatoi 2004). Body weight increased in the treatment arm with megesterol, but not with EPA. Combination of EPA with megesterol did not increase the efficacy of megestrol.

- In another study of the same group 469 patients with advanced cancer megestrol was compared to tetrahydrocannabinol (THC) and to a combination of both (Jatoi 2002). Megestrol was more effective than THC in terms of appetite improvement and weight gain. Combination

of megestrol with THC did not add to the efficacy. An increased incidence of impotence was documented for men receiving megestrol.

- Information on the net-benefit of megestrol can be interpolated from a large scale trial in cachectic nursing home residents comparing 709 patients treated with megestrol to 1418 matched controls with similar weight loss but without receiving megestrol (Bodenner 2007). Megestrol treatment resulted in a significant increase in mortality and reduction of survival time, without a significant increase of body-weight.

- A recent review summarised the results from placebo-controlled trials on the effect of methylprogesterone on cancer cachexia (Madeddu 2009). Studies have reported an improvement of body weight, anorexia and quality of life. However, weight gain was related to an increase in body fat, whereas lean body mass was not influenced significantly.

Recommendation

Megestrol or progestins seem to stimulate appetite and increase body weight, though not muscle mass (level of recommendation: **weak positive**; **mean consensus 7.73**). Progestins should be considered for patients with refractory cachexia and with anorexia as a major distressing symptom.

4.3.5 Steroids

- Several controlled trials of corticosteroids have demonstrated a limited benefit in appetite, nausea, caloric intake, pain control and the sensation of well being, but no increase in body weight. Effects were limited up to one month. Longer treatment duration may lead to the usual side effects of corticosteroids including weakness (Melstrom 2007).

- Methylprednisolone had improved appetite and activity in terminally ill cancer patients after 14 days of treatment (Bruera 1985).

- A similar trial with prednisolone also improved on appetite and the sense of well being, without significant effect on weight gain compared with placebo (Willox 1984).

- Similarly, dexamethasone improved appetite and sense of wellbeing in patients with far advanced cancer, but without any effect on weight (Moertel 1974).

- In a large 8-week study with 402 patients methylprednisolone was compared with placebo (Della Cuna 1989). Treatment with methylprednisolone was linked to increased appetite and well-being and less vomiting, but no significant effect on weight was observed. Mortality rates were similar to the placebo group for males, but higher for females.

- In a similar study design with 173 female terminal cancer patients methylprednisolone improved quality of life significantly in the eight week study period. The incidence of side effects and mortality rates were not higher compared to the group with placebo, though gastrointestinal and cardiovascular events were reported more frequently in the methylprednisolone group (Popiela 1989).

Recommendation

Steroids may be beneficial in patients with refractory cachexia for stimulation of appetite and improvement in quality of life (level of recommendation: **strong positive**; **mean consensus 8.50**). However, the use of steroids is recommended for short (maximal 2 weeks) periods as longer duration of treatment may increase the burden on the patient from side effects and may cause a deterioration in muscle strength.

4.3.6 Non-steroidal anti-inflammatory drugs

- As the etiology of cancer-related cachexia is linked to the systemic inflammation, the use of non-steroidal anti-inflammatory drugs aiming to reduce that inflammation seems a promising option. In a controlled trial both indomethacin and prednisolone prolonged mean survival time significantly compared to placebo (Lundholm 1994). Body weight and arm muscle circumference were significantly increased with prednisolone treatment, but not in the indomethacin group.

- Lundholm et al. (Lundholm 2004) performed a retrospective case control study comparing weight-losing cancer patients with undernourished non-cancer patients. Elevated resting energy expenditure in the cancer group was reduced with long-term indomethacin treatment. Total body fat was more preserved, though lean body mass was uninfluenced by indomethacin in the cancer group.

- In a controlled trial treatment with megestrol alone did not prevent weight loss, whereas the combination of megestrol and ibuprofen lead to an increase in body weight (McMillan 1999). This increase was also correlated to an increase in quality of life.

Recommendation

Non-steroidal anti-inflammatory drugs alone seem to offer little benefit (level of recommendation: **weak negative**; **mean consensus 7.36**). NSAIDs may be more effective as part of a multi-modal intervention. The indication is still under discussion for patients with high CRP-blood levels. The use of NSAIDs for treatment of refractory cachexia is not recommended.

4.3.7 Prokinetics

- In an older topical review (Vansteenkiste 1996) the authors concluded that metoclopramide can improve gastric function in patients with gastroparesis. However, though appetite was improved in small case series, no effect on weight was described.

- In the review of Strasser and Bruera (Strasser 2002) several studies with prokinetic drugs are described. Metoclopramide has been best studied, the role of other drugs such as domperidone or newer serotonine 5-HT4-agonits remains to be clarified. Metoclopramide was effective for treatment of nausea and early satiety in cachectic cancer patients. However, extrapyramidal side effects may put a limit to the dosage.

- In a large trial in 129 patients with head and neck cancer undergoing radiotherapy Chen et al. compared megestrol, the prokinetic drug cisapride and placebo (Chen 1997). The megestrol group had significantly less body weight loss and improved appetite. However, these effects were not seen for cisapride compared with placebo. However, cisapride has been withdrawn from the market due to the risk of arrythmic complications.

Recommendation

Prokinetics are recommended in patients with early satiety, chronic nausea, dyspeptic symptoms and gastroparesis (level of recommendation: **weak positive**; **mean consensus 8.53**). There is no evidence that prokinetics will improve the nutritional status of patients with advanced cancer/refractory cachexia.

4.3.8 Net benefit of anticancer treatment for treating cancer cachexia?

In consideration of the multi-facetted etiology of cancer-related cachexia it has to be stressed that in many patients reversible secondary causes may contribute to cachexia and anorexia. Treatment of these causes may alleviate cachexia, though it does not target the metabolic change (Strasser 2002). This includes systemic antineoplastic treatment, as reduction of the tumor mass will reverse or at least ameliorate cachexia. However, existing studies assessing chemotherapy in advanced cancer for symptom control suffer from major bias, for example the placebo group in controlled studies usually has been treated with best supportive care, which is not standardized and may have included effective symptom management interventions.

Recommendation

The best way to cure cachexia is to cure the cancer. However, for cachectic patients who have progressed through anticancer treatment, the use of further palliative anticancer treatment (where the chance of response is low and where side-effects may lead to further nutritional decline) should be considered very carefully, involving oncological and palliative care expertise (level of recommendation: **weak negative**; **mean consensus 7.97**). The use of anticancer treatment for alleviation of refractory cachexia is clearly not recommended.

4.4 Multimodal Therapy

4.4.1 Multimodal therapy for cancer cachexia

For the majority of patients with advanced cancer, metabolic change and reduced energy intake (either from cancer, from cancer-related symptoms or treatment-related) will contribute to cancer cachexia. A multimodal treatment approach would target more than one of the contributing factors, and thus should be offered.
However, there are only a few studies that have tested combination regimens in cancer cachexia and none of them in refractory cachexia. There is strong support from the experts that optimal palliative care should be initiated to manage the individual symptoms associated with refractory cachexia and that research in this domain should be promoted.

- Some studies investigated the combination of megestrol with other drugs. The combination with THC (Jatoi 2002) and EPA (Jatoi 2004) did not provide any benefits compared with megestrol alone. However, megestrol with ibuprofen was more effective than either alone (McMillan 1999).

- A recent study with 332 patients comparing medroxyprogesterone, megestrol acetate, oral supplementation with eicosapentaenoic acid, L-carritine and thalidomide found that the combination of all drugs was superior to any of the other treatment arms with single drug treatment (Mantovani 2010). The combination led to increased lean body mass, decreased resting energy expenditure and improved appetite.

- In the guideline development group high consensus was evident among the experts, that for most patients with cancer-related cachexia a multimodal treatment regimen is required, as has been suggested by Fearon et al. (Fearon K C 2008).

Recommendation

Multimodal therapy for cancer cachexia should be offered, as a combination of nutrition, medication and non-drug-treatment may be more effective than monotherapy (level of recommendation: **weak positive**; **mean consensus 8.32**). However, more research is needed to evaluate the concept also for refractory cachexia.

4.5 Prophylaxis

4.5.1 Therapy for prophylaxis of cancer cachexia

No literature is available on prophylaxis of cachexia in patients with advanced cancer. However, it is self evident that the burden of refractory cacheixa would be reduced if the number of patients entering this phase could be decreased. Even in advanced cancer patients in pre-cachectic stage and at risk of developing the full cachexia syndrome should be treated in a prophylactic manner, with nutrition, non-drug and drug interventions as indicated. This should include treatment of secondary causes of malnutrition as well as counselling, education and physical training. These management approaches have the potential to delay the onset of cancer cachexia.

Recommendation

Patients at risk of losing weight should be offered prophylactic interventions such as nutritional counselling and physical training, as these interventions are thought to be beneficial in delaying or preventing the development of the full anorexia-cachexia syndrome (level of recommendation: **weak positive**; **mean consensus 8.65**). Per definition, prophylaxis is not relevant for patients with refractory cachexia.

5. Conclusions

Management of cancer cachexia requires assessment and staging first. Depending on current cancer status anti-cancer treatment may be beneficial. For patients at risk with pre-cachexia prophylactic treatment will be needed to prevent deterioration. For cachexia and refractory cachexia different treatment strategies will be required. This paper provides guidance for patients with advanced cancer, most of them with short life expectancy. Refractory cachexia will be predominant in these patients and the guidelines have been drafted with a focus on these patients and this cachexia stage.

In the consensus process that was part of the development of these guidelines high consensus was evident among the experts, that for symptom management in refractory cachexia steroids or progestins can be used (especially for anorectic patients).More aggressive management with multimodal intervention should be reserved for patients before they reach the refractory phase.

For most areas of the recommendations more research is needed. Patients with refractory cachexia are less likely to be included in clinical trials. However, in order to be able to offer the best possible treatment to these patients and to avoid burdening them with ineffective interventions clinical trials are needed for treatment of cachexia in patients with advanced cancer, patients receiving palliative care and patients with refractory cachexia.

The EPCRC guidelines compiling assessment and classification with treatment recommendations ultimately will help to provide a differentiated therapeutic approach for many patients with cancer-related cachexia who until now are not treated adequately. Implementation of these guidelines in clinical practice is not self-fulfilling, and requires specific care and dedicated resources. For clinical practice, pathways may be useful, including screening steps for early identification of patients who are at high risk of developing cachexia

or are in early stages of weight loss, as well as classification and differential diagnosis, and from there to treatment algorithms and outcome control.

For patients with refractory cachexia consider the following interventions:

• *That patients with simple starvation/secondary nutrition impact symptoms have been identified. For example, it is important to diagnose constipation, incident pain and other factors that might lead to the false diagnosis of refractory cachexia.*
• *Appetising food or ONS within a context that does not exaggerate eating-related distress*
• *Educate patient/family to minimise eating related distress, counsel them about weight loss related distress and end of life issues and appraise rational factors of distress related to eating.*
• *Encourage physical activities related to comfort of patients as far as possible, but do not set false goals of muscle mass or strength related to overactivity.*
• *Progestational agents for short term use with the major goal of improving the objective symptom of anorexia.*
• *Corticosteroids for very short term use (1-2 weeks) for improvement of appetite, mood, for special life events.*

6. References

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7. Appendix

7.1 Functional Assessment of Anorexia / Cachexia Treatment (www.facit.org)

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C6	I have a good appetite	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight	0	1	2	3	4
ACT3	Most food tastes unpleasant to me	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
ACT13	My general health is improving	0	1	2	3	4

SAMPLE

7.2 SIPP Tool

S	► **BMI:** ► **Involuntary weight loss:** ► **Duration of weight loss:**	_____ **kg/m2** _____% _____ months
I	► **Estimation: % of normal Intake** ► **Anorexia** ► **Taste/smell problems:** ► **Early satiety:** ► **GI-dysmotility:** ► **secondary nutrition impact symptoms:** ----------	_____% VAS: ____ ☐ yes ☐ no ☐ yes ☐ no ☐ yes ☐ no ☐ no ☐ medium ☐ high
P	► **Tumor activity** ► **CRP**	☐ low ☐ high _____
P	► **Karnofsky PS:** ► **Cachexia related distress:**	_____% ☐ no ☐ medium ☐ high

7.3 Drug Treatment: drugs and dosages investigated in clinical trials in advanced cancer patients with cachexia

Drug class	**Drug**	**Daily dosage**
Cytokine antagonists	Thalidomide:	(100-) – 200 mg at night
Cannabinoids	Tetrahydrocannabinoid	5 – 7.5 mg
Omega-3-fatty acids	Eicosapentaic acid (EPA)	170 - 4900 mg
	Decosahexanoic acid (DHA)	115 – 3200 mg
Progrestins	Megestrol	100 – 1600 mg
Steroids	Methylprednisolone	32 - 125 mg
	Prednisolone	15 mg
	Dexamethasone	3 – 6 mg
Non-steroidal antiinflammatory drugs	Indomethacine	100 mg
	Ibuprofen	1200 mg
Prokinetics	Metoclopramide	40 - 90 mg