D6.2: ESPEN Guideline 2014: Nutrition in Cancer. Nutritional and metabolic problems in cancer patients, effects on clinical outcome and aims of nutritional therapies

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GL Nutrition in Cancer

The aim of this document is to translate current evidence and expert opinion into recommendations for the multi-disciplinary team responsible for identification and treatment of reversible elements of malnutrition in cancer patients.

CHAPTER A

NUTRITIONAL AND METABOLIC PROBLEMS IN CANCER PATIENTS, EFFECTS ON CLINICAL OUTCOME AND AIMS OF NUTRITIONAL THERAPIES

Basic statements and definitions

A patient with cancer is a patient with a cancer diagnosis who is either waiting for or on cancer directed treatment, on symptomatic treatment and/or receiving palliative care. Patients cured from their cancer are termed cancer survivors.

A. Major alterations in cancer patients

1: Inadequate nutritional intake is observed frequently in patients with cancer and is associated with weight loss, which may be severe. The causes for impaired intake are complex and multifactorial.

2: Physical activity and performance state are impaired in many patients with cancer and this is often accompanied by a loss of muscle mass.

3: A syndrome of systemic inflammation frequently is activated in patients with cancer, varying in degree but impacting on all relevant metabolic pathways including
   - Protein metabolism: systemic inflammation is associated with altered protein turnover, a loss of fat and muscle mass and an increase in the production of acute phase proteins
   - Carbohydrate metabolism: systemic inflammation is frequently associated with insulin resistance and impaired glucose tolerance
   - Lipid metabolism: The capacity for lipid oxidation is maintained or even increased in cancer patients especially so in the presence of weight loss

B. Effects on clinical outcome

4: Systemic inflammation is associated with the development of fatigue, impaired physical activity, anorexia and weight loss. This inflammatory syndrome also impairs or prevents a regain in body cell mass even if energy intake is normalized

5: Weight loss, impaired physical performance, and systemic inflammation, in patients with cancer, are each associated with an unfavorable prognosis, toxicity of anticancer treatment resulting in reductions or interruptions of scheduled treatment and a reduced quality of life

6: Weight loss, impaired physical performance and systemic inflammation are interacting and maintain a vicious cycle.
C. Aims of nutritional interventions

9: Nutrition and metabolic interventions are aiming to maintain or improve nutritional and metabolic status, physical performance, reduce the risk of reductions or interruptions of scheduled anticancer treatments and improve quality of life.

10: Given the high incidence of nutritional and metabolic risks, it is suggested to monitor relevant parameters regularly in all cancer patients and to initiate interventions early and against all relevant impairments to prevent excessive deficits.

11: Nutritional interventions include the following:

“Nutrition counseling” in distinction from possibly brief and possibly non-professional “advice” is a dedicated and usually repeated and evolving professional communication process aiming for thorough understanding and lasting changes in eating habits, including caloric enrichment of foods.

“Oral nutritional supplements” are commercially available homogeneous nutrient mixtures for oral consumption.

“Artificial nutrition” is the application of nutrients via enteral tubes (“enteral nutrition”) or parenteral infusions (“parenteral nutrition”).

“Muscle support” encompasses physical activities of daily life, exercise training and techniques to increase muscle mass and/or muscle strength, like electromyostimulation and other techniques.

In malnourished or advanced cancer patients, pharmacologic agents are mainly used a) to stimulate appetite and/or gut motility, b) to decrease systemic inflammation and/or hypercatabolism, or c) to increase muscle mass and/or improve hypoanabolism.

12: Comparable to the situation in non-cancer patients, nutritional interventions should be initiated only if their expected advantages outweigh their risks and burden and if and as long as the patient consents.

13: To organize and perform screening for nutritional risk, assessment of nutritional and metabolic parameters, nutritional interventions and monitoring of the outcome we recommend that each institution involved in treating cancer patients defines standard operating procedures, responsibilities and a quality control process.

14: Toxicity and risks of nutrition, “feeding the tumor”: There is no evidence that an adequate nutritional support increases tumour growth in humans (Bozzetti and Mori 2009).
CHAPTER B:

GENERAL CONCEPTS OF TREATMENT RELEVANT TO ALL CANCER PATIENTS

Section B1: Screening and Assessment

1. Screening

To detect nutritional disturbances at an early stage, nutritional intake, weight loss and BMI should be evaluated regularly, beginning with cancer diagnosis and repeated depending on the stability of the situation.

- Evidence level: very low
- Recommendation: strong
- Questions for research: effects of screening on assessment results, on initiated interventions and on clinical outcome
- Evidence tables: --

2. Assessment

In patients with abnormal screening we recommend objective and quantitative assessment of nutritional intake, physical performance and the degree of systemic inflammation.

- Level of evidence: very low
- Recommendation: strong
- Questions for research: Linking outcomes from current and future intervention trials with appropriate screening and assessment tools.
- Evidence tables: --
Section B2  Energy and substrate requirements

1. Energy requirements

We recommend, for practical purposes, that total energy expenditure of cancer patients, if not measured individually, may be assumed to be rather similar to healthy subjects and ranging between 25 to 35 kcal/kg/day.

Evidence level: low
Recommendation: strong
Questions for research: better prediction would be nice: activity, inflammation
Evidence tables: to be supplied ➔ EVIDENCE Table

2. Protein intake

We suggest that protein intake should be >1 g/kg and if possible up to 1.5g/kg/day

Evidence level: low
Recommendation: weak
Questions for research: effect on outcome of increased supply and composition of protein/amino acids
Evidence tables: ➔ evidence table ??

3. Choice of the energy substrates

In most patients general recommendations are applicable. In weight-losing patients with advanced cancer we recommend a fat intake of 35-50% of total energy requirement.

Evidence: low
Recommendation: strong
Questions for research: effect of high fat on outcome in specific patient group
Evidence tables: ➔ evidence table

4. Vitamins and trace elements

We recommend that vitamins and minerals be supplied in amounts approximately equal to the RDA and discourage the use of high-dose micronutrients in the absence of specific deficiencies.

Evidence: low
Recommendation: strong
Questions for research: --
Evidence tables: --
Section B3: Nutrition Interventions

1. Efficacy of nutritional intervention
We recommend nutritional interventions to increase oral intake in cancer patients who are able to eat but are malnourished or at risk of malnutrition. This includes dietary advice, the treatment of symptoms and derangements impairing food intake and offering oral nutritional supplements.
Evidence level: low quality
Recommendation: strong
Questions from research: effect of advice and ONS on outcome
Evidence Table: --

2. Special diets
We recommend against dietary provisions like anticancer diets which restrict food intake in patients with (impending) malnutrition.
Evidence level: low quality
Recommendation: strong
Questions from research: 
Evidence Table: 

3. Modes of nutrition
We recommend enteral nutrition if oral nutrition remains inadequate despite nutritional interventions and parenteral nutrition if EN is not sufficient or impossible.
Evidence level: moderate quality
Recommendation: strong
Questions from research: 
Evidence Table: 

4. Refeeding syndrome
If oral food intake has been decreased severely for a prolonged period of time, we recommend to increase enteral or parenteral nutrition only slowly over several days and to take additional precautions to avoid a refeeding syndrome.
Evidence level: low quality
Recommendation: strong
Questions from research: 
Evidence Table: 

5. Home artificial nutrition
In patients with chronic defects of dietary intake or absorption we recommend long-term artificial nutrition as home enteral or parenteral nutrition in suitable patients
Evidence level: low quality
Recommendation: strong
Questions from research: 
Evidence Table:
Section B4: Physical activity / Exercise

1. Exercise in combination with nutrition

We recommend to maintain or increase physical activity in cancer patients to support muscle mass, physical function and metabolic pattern.

Evidence level: low quality
Recommendation: strong
Questions for research: effect of activity on outcome
Evidence table: → Evidence Table

2. Type of exercise recommended

We recommend to perform individualized resistance exercise to maintain muscle strength and muscle mass.

Evidence level: low quality
Recommendation: strong
Questions for research: effect of activity on outcome
Evidence table: → Evidence Table
Section B5: Pharmacological Agents and Pharmaconutrients

In malnourished or advanced cancer patients, pharmacologic agents are mainly used
a) to stimulate appetite and/or gut motility,
b) to decrease systemic inflammation and/or hypercatabolism, or
c) to increase muscle mass and/or improve hypoanabolism.

Cancer-related weight loss, malnutrition and cachexia result from the variable combination of anorexia and reduced food intake, increased systemic inflammation, altered substrate metabolism, increased protein catabolism and reduced anabolism. Therefore, this approach is aimed at pharmacologically targeting the main pathogenic mechanisms of cancer cachexia. However, pharmacological treatment of the metabolic and nutritional sequelae of cancer cannot substitute conventional or specialized nutritional support, nor can modify nutritional needs of cancer patients, which should be adequately met, independent of pharmacological treatment. Several classes of drugs exist that may specifically target the pathogenic mechanisms of cancer-related weight loss and cachexia, but for only some of them sufficient data are available to recommend their use in clinical practice.

We selected to include in the guidelines only those drugs for which three or more phase II trials or two or more phase III trials have been published and for which efficacy has been proven on at least one of the three domains of intervention.

Molecules of unproven benefit, or for which evidence is still lacking, will be only mentioned. For those drugs of yet unproven benefit, two categories were identified: 1) drugs which have negative or unproven results mainly due to a) lack of definition of population, mixing pre-cachexia, cachexia and refractory cachexia, and b) due to lack of multi-dimensional management, mainly that simple starvation and also basic physical activity have not been improved; among these cannabinoids, prokinetics, eicosapentaenoic acid, anabolic steroids; 2) drugs which are under development. Currently there are many drugs in development targeting one or more main mechanisms of cancer-related weight loss or cachexia, typically with more specified populations, cachexia phase and multi-modal management. Currently, at least three Phase III trials are underway with one or two trials per drug. Results are expected at the end of 2014 or the beginning of 2015. These drugs include SRM, Anamorelin, anti-IL1; other Phase III trials are in planning, too. There are approximately forty running Phase II trials and several drugs have already one or two published Phase II trials. These molecules include ghrelins, anamorelin (an orally activated ghrelin receptor agonist) and muscle targeting agents.

1. Corticosteroids, progestins and cannabinoids

We suggest to use corticosteroids and progestins in selected patients with advanced cancer to stimulate the appetite, but potential unwanted effects have to be considered. Cannabinoids are not recommended due to their side effects.

Evidence level: high quality
Recommendation: weak
Questions for research: Evidence tables:

2. Androgenic steroids

Androgenic steroids cannot be recommended to increase muscle mass.

Evidence level: high quality
Recommendation: strong
Questions for research: Evidence tables:
3. Amino acids

In weight losing advanced cancer patients not responding to standard nutrition therapy we suggest to consider the supplementation with branched-chain amino acids to improve fat free mass.

Evidence level: low quality
Recommendation: weak
Questions for research:
Evidence tables:

4. Antiinflammatory agents

There is not enough data to recommend non-steroidal antiinflammatory drugs to improve body weight in weight losing cancer patients.

Evidence level: low quality
Recommendation: weak
Questions for research:
Evidence tables:

5. Long-chain fatty acids

In weight losing advanced cancer patients not responding to standard nutrition therapy we suggest to consider the supplementation with long-chain n-3 fatty acids and fish oil to decrease systemic inflammation and improve appetite, food intake and body weight.

Evidence level: low quality
Recommendation: weak
Questions for research:
Evidence tables:
CHAPTER C

INTERVENTIONS RELEVANT TO SPECIFIC PATIENT CATEGORIES

Section C1: Surgery

1. Traditional peri-operative care
   In upper GI cancer patients undergoing surgical resection in the context of traditional perioperative care we recommend oral/enteral immunonutrition.
   Evidence level: high quality
   Recommendation: strong
   Questions for research:
   Evidence tables:

2. Enhanced recovery after surgery care
   In all cancer patients undergoing palliative or resectional surgery we recommend management within an enhanced recovery after surgery program.
   Evidence level: high quality
   Recommendation: strong
   Questions for research:
   Evidence tables:

3. Multimodal oncology care
   For each surgical episode in patients undergoing multimodal oncological therapy we recommend management within the context of an ERAS program.
   Evidence level: low quality
   Recommendation: strong
   Questions for research:
   Evidence tables:

4. Care after hospital discharge
   In surgical cancer patients at moderate or severe nutritional risk we recommend appropriate ONS/enteral nutritional support both before and following discharge from hospital.
   Evidence level: moderate quality
   Recommendation: strong
   Questions for research: The role of immunonutrition when upper GI cancer patients are managed within an ERAS pathway.
   The optimal post-operative regimen in terms of type, preparation and access to normal food +/- oral nutritional supplements for patients managed within an ERAS pathway.
   The role of n-3 enriched oral supplements/enteral nutrition in upper GI cancer patients for preservation of lean body mass and optimisation of organ function.
   Evidence tables:
Section C2: Radiotherapy

1. Adequate nutrition
We recommend that during RT to the head-neck, upper and lower GI tract and thorax, an adequate nutritional intake should be ensured primarily by individualized nutritional counseling and/or with use of ONS.
Evidence level: moderate quality
Recommendation: strong
Questions for research:
Evidence tables:

2. Tube feeding
We recommend tube feeding in radiation-induced severe mucositis or in head-neck/thoracic cancers with obstructive tumor masses.
Evidence level: low and moderate quality
Recommendation: strong
Questions for research:
Evidence tables:

3. Swallowing
We recommend that patients should be encouraged and educated on how to maintain their swallowing function during enteral nutrition.
Evidence level: low quality
Recommendation: strong
Questions for research:
Evidence tables:

4. Glutamine
We recommend not to use glutamine during pelvic radiotherapy to prevent radiation-induced enteritis/diarrhoea.
Evidence level: low quality
Recommendation: strong
Questions for research:
Evidence tables:

5. Probiotics
There is not enough data to recommend Lactobacillus-containing probiotics; some studies suggest that they may reduce the incidence/severity of RT-induced diarrhea, yet more studies are needed.
Evidence level: low quality
Recommendation: strong
Questions for research:
Evidence tables:
Section C3: Curative chemotherapy and targeted therapy

1. Adequate nutrition
During anticancer drug treatment we recommend to ensure an adequate nutritional intake and to maintain physical activity.
Evidence level: very low quality
Recommendation: strong
Questions for research:
Evidence-Table:

2. Artificial nutrition
If oral food intake is inadequate despite counseling and ONS we recommend to initiate enteral, or if this is not sufficient or possible parenteral nutrition.
Evidence level: low quality
Recommendation: strong
Questions for research:
Evidence-Table:

3. Glutamine
There is insufficient evidence to recommend glutamine supplementation during conventional cytotoxic or targeted therapy.
Evidence level: low quality
Recommendation: none
Questions for research:
Evidence-Table:

4. Fish oil
There is insufficient evidence to recommend for or against fish oil supplementation during chemotherapy.
Evidence level: low quality
Recommendation: none
Questions for research:
Evidence-Table:
Section C4: High-dose chemotherapy and hematopoietic stem cell transplantation (HSCT)

1. Adequate nutrition and physical activity

During high-dose anticancer drug treatment and stem cell transplantation we recommend to maintain physical activity and to ensure an adequate nutritional intake. This may often require artificial nutrition.

- Evidence level: very low quality
- Recommendation: strong
- Questions for research: Evidence-Table:

2. Artificial nutrition

If artificial nutrition is required we suggest to prefer enteral tube feeding over parenteral nutrition, unless there is severe mucositis or symptomatic gastrointestinal GvHD.

- Evidence level: low quality
- Recommendation: weak
- Questions for research: Evidence-Table:

3. Germ-free food

There is not enough evidence to recommend germ-free food for patients more than 30 days after allogeneic transplantation.

- Evidence level: low quality
- Recommendation: none
- Questions for research: Evidence-Table:

4. Glutamine

There is not enough evidence to recommend for or against glutamine to reduce anticancer therapy side effects especially in high dose protocols.

- Evidence level: low quality
- Recommendation: none
- Questions for research: Evidence-Table:
Section C5: Cancer survivors

1. Physical activity
   Cancer survivors should continue to engage in regular physical activity and avoid physical inactivity.
   Evidence level: low quality
   Recommendation:
   Questions for research:
   Evidence-Table:

2. Healthy lifestyle
   In cancer survivors we recommend a healthy weight and a healthy plant based diet, high in fruits, vegetables and whole grains, and low in fat, low in red meat and low in alcohol.
   Evidence level: low quality
   Recommendation:
   Questions for research:
   Evidence-Table:
Section C6: Advanced, incurable cancer patients

In settings with advanced and often progressing cancer, patients are threatened not only by the presence and progression of the tumor but also by inadequate food intake (due to a multitude of causes), physical inactivity as well as metabolic derangements promoting anorexia, fatigue and catabolism.

The clinical challenge in advanced, incurable cancer patients is to identify both the deficit in energy and substrate intake (leading to starvation) and the tumor-associated metabolic components altering all major substrate pathways (leading to cachexia). Starvation occurs with secondary-nutrition impact symptoms including functional and structural barriers of the gastrointestinal tract and insufficient dietary habits. Cachexia is promoted by cancer-mediated inflammatory reactions and catabolic as well as hypo-anabolic mechanisms resulting in impaired appetite, early satiety and loss of muscle mass and function. Currently cancer cachexia conceptual frameworks are defined, but in clinical practice the presence, severity and reversibility of cachexia has to be estimated based on muscle and weight loss, decreased appetite and nutritional intake, inflammatory markers like CRP and Albumin, and cancer progression and impaired physical function. Since patients often present with combined starvation and cachexia, patients with cachexia should always be evaluated for nutritional support. The combination of % weight loss and BMI has a strong prognostic value for survival, but does not distinguish starvation and cachexia.

Optimal palliative cancer care has been outlined by ESMO (policy statements Ann Onc), EAPC (white paper), ASCO (JCO), and the WHO definition as the early integration of palliative care interventions by oncologists, palliative care specialists and other disciplines of multi-professional teams and should include palliative care interventions (diagnostic, therapeutic, coordinative) provided together with anti-cancer treatment from early in the course of disease (Temel, NEJM 2011) and then until death and beyond.

1. Screening and assessment

We recommend that all advanced, incurable cancer patients receiving or not receiving anti-cancer treatment be routinely screened for impaired appetite, decreased nutritional intake, weight loss and physical fatigue and if found at risk, be assessed further.

Evidence level: moderate quality
Recommendation: strong
Questions for research:

Evidence-Table:

2. Nutrition intervention in patients with incurable cancer and insufficient intake

We recommend to use nutritional interventions in patients with advanced incurable cancer if the expected benefit of the intervention outweighs the potential harm and if the patient wants it.

Evidence level: low quality
Recommendation: strong
Questions for research:

Evidence-Table:

3. Nutrition and hydration during the last weeks of life (terminal care)

In patients who are imminently dying we recommend treatment based on comfort. Artificial hydration and nutrition are unlikely to provide any benefit for most patients.

Evidence level: low quality
Recommendation: strong
Questions for research:

Evidence-Table: