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ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology ☆

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Summary Enteral nutrition (EN) by means of oral nutritional supplements (ONS) and tube feeding (TF) offers the possibility of increasing or ensuring nutrient intake in cases where normal food intake is inadequate.

These guidelines are intended to give evidence-based recommendations for the use of ONS and TF in cancer patients. They were developed by an interdisciplinary expert group in accordance with officially accepted standards, are based on all relevant publications since 1985 and were discussed and accepted in a consensus conference.

Undernutrition and cachexia occur frequently in cancer patients and are indicators of poor prognosis. EN should be started if undernutrition already exists

Abbreviations: TF, tube feeding; ONS, oral nutritional supplements; EN, enteral nutrition. This is used as a general term to include both ONS and tube feeding. When either of these modalities is being discussed separately this is specified in the text; Normal food/normal nutrition, normal diet as offered by the catering system of a hospital including special diets; PEG, percutaneous endoscopic gastrostomy; RCT, randomised controlled trial

☆For further information on methodology see Schütz et al.[144] For further information on definition of terms see Lochs et al.[145] For cancer patients receiving surgery see guidelines ''Surgery incl. Organ Transplantation'' Weimann et al.[146]

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or if food intake is markedly reduced for more than 7–10 days. Standard formulae are recommended for EN. Nutritional needs generally are comparable to non-cancer subjects. In cachectic patients metabolic modulators such as progestins, steroids and possibly eicosapentaenoic acid may help to improve nutritional status. EN is indicated preoperatively for 5–7 days in cancer patients undergoing major abdominal surgery. During radiotherapy of head/neck and gastrointestinal regions dietary counselling and ONS prevent weight loss and interruption of radiotherapy. Routine EN is not indicated during (high-dose) chemotherapy.

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Summary of statements: Non-surgical oncology

Subject	Recommendations	Grade[144]	Number
General	Nutritional assessment of cancer patients should be performed frequently, and nutritional intervention initiated early when deficits are detected.	C	1.1
	There are no reliable data that show any effect of enteral nutrition on tumour growth. Such theoretical considerations should, therefore, have no influence on the decision to feed a cancer patient.	C	4.1
Indication			
General	Start nutritional therapy if undernutrition already exists or if it is anticipated that the patient will be unable to eat for >7 days.	C	2.2
	Start enteral nutrition if an inadequate food intake ($<60\%$ of estimated energy expenditure for >10 days) is anticipated. It should substitute the difference between actual intake and calculated requirements.	C	2.2
	In weight losing patients due to insufficient nutritional intake enteral nutrition should be provided to improve or maintain nutritional status.	B	2.3
Perioperative	Patients with severe nutritional risk benefit from nutritional support 10–14 d prior to major surgery even if surgery has to be delayed.	A	3.1
During radio- or radio-chemotherapy	Use intensive dietary advice and oral nutritional supplements to increase dietary intake and to prevent therapy-associated weight loss and interruption of radiation therapy.	A	3.2
	Routine enteral nutrition is not indicated during radiation therapy.	C	3.2
During chemotherapy	Routine enteral nutrition during chemotherapy has no effect on tumour response to chemotherapy or on chemotherapy-associated unwanted effects and, therefore, is not considered useful.	C	3.3
During stem cell transplantation	The routine use of enteral nutrition is not recommended.	C	3.4
	If oral intake is decreased parenteral nutrition may be preferred to tube feeding in certain situations (i.e. increased risk of haemorrhage and infections associated with enteral tube placement in immuno-compromised and thrombocytopenic patients).	C	3.4

In incurable patients	Provide enteral nutrition in order to minimise weight loss as long as the patient consents and the dying phase has not started.	C	3.6
	When the end of life is very close most patients only require minimal amounts of food and little water to reduce thirst and hunger.	B	3.6
	Small amounts of fluid may also help to avoid states of confusion induced by dehydratation.	B	3.6
	Subcutaneously infused fluids in hospital or at home may be helpful and also provide a vehicle for the administration of drugs.	C	3.6
Application	Prefer the enteral route whenever feasible.	A	3.1
	Administer preoperative enteral nutrition preferably before admission to the hospital.	C	3.1
Route	Use tube feeding if an obstructing head or neck or esophageal cancer interferes with swallowing or if severe local mucositis is expected.	C	3.2
During radio- or radio-chemotherapy	Tube feeding can either be delivered via transnasal or percutaneous routes.		3.2
	Because of the radiation induced oral and esophageal mucositis a percutaneous gastrostomy (PEG) may be preferred.	C	3.2
Type of formula			
General	Use standard formulae.	C	1.5
	Regarding ω-3 fatty acids, randomised clinical trial evidence is contradictory/controversial and at present it is not possible to reach any firm conclusion with regard to improved nutritional status/physical function.	C	2.5
	It is unlikely that ω-3 fatty acids prolong survival in advanced cancer.		2.5
Perioperative	Use preoperative enteral nutrition preferably with immune modulating substrates (arginine, ω-3 fatty acids, nucleotides) for 5–7 d in all patients undergoing major abdominal surgery independent of their nutritional status.	A	3.1
During stem cell transplantation	Enteral administration of glutamine or eicosapentanoic acid is not recommended due to inconclusive data.	C	3.5
Drug treatment	In the presence of systemic inflammation pharmacological efforts are recommended in addition to nutritional interventions to modulate the inflammatory response.	C	2.3
	In cachectic patients steroids or progestins are recommended in order to enhance appetite, modulate metabolic derangements, and prevent impairment of quality of life.	A	2.4
	Administer steroids for short-term periods only weighing their benefits against their adverse side-effects.	C	2.4
	Consider the risk of thrombosis during progestin therapy.	C	2.4

Grade: Grade of recommendation; Number: refers to statement number within the text.

1. Tumour and nutritional status

1.1. What is cancer cachexia?

In the majority of tumour-bearing patients systemic proinflammatory processes are activated. Resulting metabolic derangements include insulin resistance, increased lipolysis and high normal or increased lipid oxidation with loss of body fat, increased protein turnover with loss of muscle mass and an increase in production of acute phase proteins.

The systemic inflammatory reaction that develops with many cancers is an important cause of loss of appetite (anorexia) and weight. The syndrome of decreased appetite, weight loss, metabolic alterations and inflammatory state is referred to as cachexia, cancer cachexia or cancer anorexia–cachexia syndrome (CACS).

These cytokine-induced metabolic alterations appear to prevent cachectic patients from regaining body cell mass (BCM) during nutritional support, are associated with a reduced life expectancy (III), and are not relieved by exogenous nutrients alone. Attempts to modulate these changes by other means should be integrated into the management of cancer patients (C). Nutritional assessment of cancer patients should be performed frequently, and nutritional intervention initiated early when deficits are detected (C).

Comment: While undernutrition, both moderate and severe, is frequent in patients with malignant disease, many tumour-bearing patients display elevated inflammatory markers.[1–4] The observed release of cytokines, catabolic hormones and further regulatory peptides appears to be the primary reaction of the cancer patient's host tissues.[1–3] In addition, substances produced by tumour cells, such as tumour lipid mobilising factor (LMF) and proteolysis inducing factor (PIF), may add catabolic signals and further stimulate cytokine production and the acute phase response.[5,6] The systemic inflammatory reaction is assumed to be involved in causing loss of appetite[7] and body weight[8–11] and may facilitate tumour progression.[12,13] Cytokine-induced metabolic alterations also appear to prevent cachectic patients from regaining BCM during nutritional support[14] and are associated with a reduced life expectancy.[4,6,8,15–17]

Impaired glucose tolerance due to insulin resistance was an early finding in cancer patients.[18] The relation of insulin to catabolic hormones is altered and an increased cortisol secretion as well as a reduced insulin:cortisol ratio are common.[2,19] As a result glucose turnover and gluconeogenesis are increased.[3]

Weight loss in cancer patients is accompanied by a loss of fat as well as by enhanced plasma levels of triglycerides. Lipid oxidation can be normal or increased. What causes the alterations in lipid metabolism remains unclear.[2] However, increased lipolysis is frequently observed.[20,21] Simultaneously, lipid oxidation is increased[21–23] or in the high normal range,[24] while glucose oxidation is impaired. These observations may be taken to support recommendations to increase the fat/carbohydrate ratio in feeding cancer patients.

The pro-inflammatory milieu[5,25] induces skeletal muscle proteolysis[3,26] resulting in a loss of muscle mass and simultaneously leads to an increased production of acute phase proteins. The ATP- and ubiquitin-dependent proteasome proteolytic system is activated at an early stage.[27,28] Thus, cachexia should be no longer considered a *late* stage phenomenon. Rather, since the metabolic and molecular mechanisms ultimately leading to the phenotypic pattern of the anorexia–cachexia syndrome are already operating early during tumour growth and development, cachexia should be seen as a partially preventable phenomenon, the onset of which could be at least delayed by means of early pharmacological and nutritional intervention.

1.2. Does cancer influence nutritional status?

Yes. Weight loss is frequently the first symptom occurring in cancer patients. Depending on tumour entity, weight loss is reported in 30 to more than 80% of patients and is severe (>10% of initial weight) in some 15% (IIb).

Comment: Weight loss preceding tumour diagnosis has been reported by many groups to occur in 31–87% of the patients, depending on the tumour entity[30–33] (III). A severe involuntary weight loss of more than 10% of initial weight over the previous 6 months has already occurred in 15% of all patients at the time of diagnosis.[30] Eighty-five per cent of patients with pancreatic or stomach cancer have lost weight at the time of diagnosis, and in 30% the loss was severe.[30] Both frequency and severity of weight loss are correlated with tumour stage[34] (III).

Quite often, when toxicity of treatment outweighs tumour response, cancer therapies are associated with anorexia and further weight loss[35,36] (IV).

1.3. Does nutritional status influence the clinical course and the prognosis?

An impaired nutritional status is associated with reduced quality of life, lower activity level,

increased treatment-related adverse reactions, reduced tumour response to treatment and reduced survival (IIb). However, a cause–effect relationship has not yet been established.

Comment: Longitudinal studies have demonstrated that the prognosis for cancer patients with weight loss is worse than that for weight-stable patients. There are more pronounced treatment-related adverse reactions,[33] the response to cancer treatment is impaired,[30,33,37] and there is reduced activity level,[30,33] subjective quality of life[33,38] and survival[30,33,37–43] (IIb; III). Next to sepsis, cachexia is one of the commonest causes of death in cancer, ranging from 5% to 25%[44–47] (III).

In a recent trial total body nitrogen was found to be the most powerful predictor of neutropenia after chemotherapy in breast cancer patients[48] (III).

Undernutrition, therefore, appears to be a marker of disease severity and poor prognosis, although it has not been established, whether undernutrition per se has a direct influence on prognosis, independently of the underlying disease.

1.4. Does cancer influence energy expenditure?

Cancer itself does not have a consistent effect on resting energy expenditure. Oncological treatment, however, may modulate energy expenditure (III).

Comment: Resting energy expenditure (REE) can be unchanged, increased or decreased in relation to the predicted energy expenditure. The energy requirements of cancer patients should therefore be assumed to be normal unless there are specific data showing otherwise. In about 25% of patients with active cancer, REE measured by the gold standard method, indirect calorimetry, is more than 10% higher, and in another 25% it is more than 10% lower than predicted energy expenditure. The extent or direction of the error cannot be predicted for individual cases[49,50] (III). The mean value in a group of cancer patients did not differ from the mean value of healthy subjects[50,51] (III). Studies in subjects with different types of tumour reported normal REE in patients with gastric or colorectal cancers[52,53] (III) and higher than expected REE in subjects with pancreatic or lung cancers[53–55] (III). The increase in REE in lung cancer patients is related to the presence of a systemic inflammatory response[56] (III) More detailed investigations in patients with advanced small cell lung or pancreatic cancer demonstrated a relative increase in REE, while physical activity level and total energy expenditure (TEE) were decreased when compared to predicted values for healthy individuals[54,55] (III). Thus, if REE cannot be measured in individual cases then assumption of TEE calculated from equations is acceptable.

As a rule-of-thumb the following assumptions for TEE can be made for non-obese patients using the actual body weight:

Ambulant patients : 30−35 kcal/kgBW/d,
Bedridden patients : 20−25 kcal/kgBW/d.

These assumptions are less accurate for severely underweight (actual TEE per kg is higher in this group) and for severely overweight subjects (actual TEE per kg is lower). More accurate estimates of REE may be obtained from published reference calculations derived from healthy subjects[57–59] (III).

There are few and inconsistent data regarding effects of cancer treatments on energy expenditure. Hansel et al. studied 15 patients with colorectal cancer and did not observe any effects of curative surgery or of hepatic metastases on REE[52] (III). Fredrix et al. compared REE in healthy controls and 104 patients with gastric or colorectal cancer and 40 patients with non-small cell lung cancer before and 1 year after surgery. Subjects with gastrointestinal cancer had normal REE, which rose slightly after surgery, while lung cancer patients had elevated REE which fell after curative resection, although not if there was tumour recurrence[53] (III). Chemotherapy treatment in twelve patients with newly diagnosed small cell lung cancer reduced both circulating inflammatory mediators and REE[60] (III).

1.5. Do cancer patients require a distinct nutrient composition?

Standard formulae are recommended for enteral nutrition (EN) of cancer patients (C).

Comment: There are no data from controlled studies to suggest a cancer-specific enteral formula. Since glucose tolerance may be impaired[18] (III) while lipid oxidation is normal or increased,[21–24] lipids might be the preferred substrate for cancer patients. However, only a few studies have compared lipid-free and lipid-containing nutrition and have found no clear difference in effectiveness[61]: in these studies the parenteral and not the enteral route of feeding was used. Therefore, standard formulae can be safely and effectively employed (IV).

The optimal nitrogen supply for cancer patients cannot be determined at present.[61] Recommendations range between a minimum protein supply of 1 g/kgBW/d[62] and a target supply of 1.2–2 g/kgBW/d[61] (IV). The special case of metabolic modulation

by ω-3 fatty acids is considered in statement 2.5 of this chapter.

There are no data—other than in perioperative nutrition—available on the effects of formulae enriched with glutamine or other immune modulating substances on the nutritional status of cancer patients.

If patients experience a feeling of early satiety and refuse the full volume of the prescribed EN, then high-energy and high-protein formulae may be preferable (IV).

Nutrition must be supplemented with electrolytes, trace elements and vitamins.[63] For EN, recommendations are based on the RDA/AI levels.[64] Because markers of oxidative stress are elevated and levels of antioxidants are decreased in cancer patients[65] [III], inclusion of increased doses of antioxidant vitamins might be suggested; however, there are no data to demonstrate a clinical benefit from this.

2. Indications and goals of EN

2.1. What are specific nutritional goals in cancer patients?

Therapeutic goal for cancer patients is the improvement of function and outcome by:

- ***preventing and treating undernutrition,***
- ***enhancing anti-tumour treatment effects,***
- ***reducing adverse effects of anti-tumour therapies,***
- ***improving quality of life.***

Comment: An improvement in survival due to nutritional interventions has not yet been demonstrated convincingly. However, it should be considered that the main reason for the lack of evidence of benefit in terms of survival is that all randomised controlled trials (RCTs) have included, for ethical reasons, only those cancer patients with undisturbed oral intake, normal body weight, and without significant weight loss. Cancer patients who are unable to swallow will starve but may survive several months with tube feeding (TF).

In a small randomised trial ($n = 60$) oral supplementation with fish oil resulted in a significant prolongation of survival in patients with advanced cancers[66] (Ib). However, the trial population was small and heterogeneous and no other RCT has yet shown a similar survival advantage.

A recent study in colorectal cancer patients undergoing radiotherapy indicates that nutritional counselling improves patient outcomes (nutritional status, Subjective Global Assessment and European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire). Nutritional counselling was shown to be as effective as high energy and high protein ONS during radiotherapy, whereas after three months of radiotherapy "*it was the only method to sustain a significant impact on patient outcomes*".[67]

EN may allow completion of radiation therapy without interruption[68,69] and perioperative EN may reduce complications of major abdominal cancer surgery (see also statement 3.2).

2.2. When should EN be started?

Nutritional therapy should be started if undernutrition already exists or if it is anticipated that the patient will be unable to eat for more than seven days. EN should also be started if an inadequate food intake (<60% of estimated energy expenditure) is anticipated for more than 10 days (C).

It should substitute the difference between actual intake and calculated requirements (C).

Comment: Despite inconsistent data the consensus group has agreed upon the above recommendations. Several groups and nutritional societies have published guidelines concerning when to initiate EN in patients with decreased oral intake.[70–75] These recommendations are generally based on clinical experience or expert committee reports.

If nutritional intake is chronically reduced, then a corresponding weight loss and a concomitant worsening of prognosis are anticipated (see also statement "Does cancer influence nutritional status?"). To demonstrate a reduced intake of normal food, a simple 24 h recall is usually adequate. If this proves difficult in individual cases, it may be appropriate to ask the patient whether his/her nutritional intake is less than 50% (low intake) or less than 25% (minimal intake) of their usual intake before the onset of the disease.

2.3. Can EN maintain or improve nutritional status in cancer patients?

Yes. In patients who are losing weight due to insufficient nutritional intake, EN should be provided to improve or maintain nutritional status (B). This may also contribute to the maintenance of quality of life (Ib).

In the presence of systemic inflammation, however, it appears to be extremely difficult to achieve whole body protein anabolism in cancer patients. In these situations in addition to nutritional interventions pharmacological efforts

are recommended to modulate the inflammatory response (C).

Comment: In a recent systematic review Baldwin and Parsons evaluated 24 randomised trials comparing nutritional counselling alone, ONS alone, or nutritional counselling plus ONS in people with illness-related undernutrition. In this review ten studies involving cancer patients were included[76] (Ib). There were no significant differences in mortality or morbidity between the treatment groups. However, those receiving ONS gained significantly more or lost significantly less weight than those who received nutritional counselling alone. Unfortunately, only two studies involving cancer patients were evaluable for this comparison[76] (Ib).

Nutritional intervention can prevent or at least ameliorate any deterioration in nutritional status when normal eating is still possible but inadequate to meet nutritional needs. Bozzetti evaluated studies on the role of EN in cancer cachexia and found a stabilising effect of this treatment in situations where a deterioration of nutritional status was anticipated[77] (III). Lindh et al. were able to halt weight loss by administering 30–40 kcal/kgBW/d by TF to patients with advanced gastrointestinal cancer who were losing weight[78] (III). Ongoing weight loss could also be stopped in 93 patients with oropharyngeal and oesophageal cancer using EN given via a PEG[79] (III). Similar results were found in 20 patients with lung, breast or ovarian cancer using ONS[80] (III) and in 200 patients with unresected pancreatic cancer using ONS enriched with fish oil in half of the patients[81] (IIa). Other studies also observed reductions in weight loss with EN in patients with head and neck or oesophageal cancers[82–84] [III].

Recently, Isenring et al. demonstrated, in comparison to standard care, smaller reductions in weight and quality of life when intensive nutritional counselling and ONS were offered to oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck areas[85] (Ib).

Ravasco et al. randomised 111 colorectal cancer outpatients, referred for radiotherapy, to nutritional counselling, high protein ONS or neither of these. While they observed no difference in weight changes between the three groups, nutritional counselling or ONS resulted in significantly better energy intake, protein intake and improvement in quality of life function scores[67] (Ib).

In the presence of systemic inflammation it appears to be extremely difficult to regain lost body cell mass by supplying energy and substrates alone.[2,8,10,14,86,87] Since, without effective antitumour therapy, it is impossible to reverse this process, the Ethics Committee of Baylor College in Houston (*"if no physiological benefit anticipated"*) decided to declare the use of PEG unethical in patients with malignant anorexia–cachexia syndrome and to reject it.[88] This extreme view was questioned in a detailed German comment, since there is evidence to show that maintaining weight or minimising weight loss through nutritional intervention can result in the maintenance of mobility and quality of life.[89] Furthermore, it should be considered that total macronutrient deprivation in ill subjects is associated with substantial mortality within a few weeks. Hence cancer patients who are unable to eat and who are going to die early from pure starvation rather than from tumour progression, can benefit from nutritional support.

2.4. Can metabolic modulators increase nutritional intake?

Steroids or progestins are recommended in order to enhance appetite (prevention of weight loss), modulate metabolic derangements, and prevent impairment of quality of life in cachectic patients (A).

Steroids should preferably be administered for short-term periods only and their benefits weighed against their adverse side-effects (C). The risk of thrombosis during progestin therapy has to be considered (C).

Comment: RCTs[90,91] (Ib) have demonstrated that steroids can improve appetite, nausea, pain intensity and/or parameters of subjective quality of life (five studies) and that progestins improved appetite, nutritional intake, body weight and mood (nine studies). Stabilisation or improvement in body fat mass can be achieved, whereas no impact on fat free or muscle mass has been reported.[92–95] One RCT observed no effect of progestin (38 cancer patients, 480 mg megestrol acetate for 12 weeks)[93] (Ib). Two systematic reviews of randomised studies on the effect of progestins in cancer anorexia or cachexia found a significant benefit of progestins on appetite, on weight gain and on quality of life[96,97] (Ia). A decrease in cytokine levels may be involved in the anti-anorectic mechanism of progestins[98,99] (III).

Androgens may induce an increase in body weight, but they are less efficient than steroids or progestins in stimulating appetite and oral intake; however, unwanted effects during androgen therapy are less frequent than during treatment with steroids and are comparable to those of progestins[100] (Ib).

ω-3 fatty acids are competitive antagonists of the ω-6 eicosanoid precursor arachidonic acid and

are converted to less active pro-inflammatory mediators.[101] ω-3 fatty acids have been studied in cancer patients to improve appetite and body weight (see 2.5).

2.5. Does supplementation with ω-3 fatty acids have a beneficial effect in cancer patients?

Randomised clinical trial (RCT) evidence is contradictory/controversial and at present it is not possible to reach any firm conclusion with regard to improved nutritional status/physical function (C). It is unlikely that ω-3 fatty acids prolong survival in advanced cancer.

Comment: Eicosapentaenoic acid (EPA) can be administered in capsules as mixed marine triglycerides (fish oil) or as a semi-purified ethyl ester. EPA has also been administered (as fish oil) in combination with a high protein, high energy ONS or in combination with other anti-cachectic agents such as megestrol acetate.

There are only two *placebo* controlled, randomised trials of sufficient duration (>4 weeks) to assess weight, function or survival as end-points. Gogos et al. ($n = 60$) did not address effects of EPA on nutritional status but showed a significant prolongation of survival[66] (Ib). However, the trial population was small and heterogeneous and no other RCT has shown a survival advantage for an EPA-containing arm.

The Scotia Trial (ESPEN 2005, $n = 518$) has demonstrated a non-significant but potentially clinically relevant treatment effect on weight ($P = 0.06$) and physical function ($P = 0.04$) with a dose of 2 g but not 4 g EPA diethyl ester (Ib). Compliance with the capsule regimen has not yet been reported but may have been different in the two treatment arms.

In a randomised but uncontrolled small trial Takatsuka et al. reported on 16 consecutive patients, 7 of whom received 1.8 g/d EPA orally from 30 days before until some 180 days after allogeneic HSCT[102] (IIa). EPA lowered levels of prostanoids and cytokines and complications of HSCT were less and the survival rate was significantly higher in the group treated with EPA.

There are two other RCTs (>4 weeks duration) where EPA (as fish oil) in combination with an ONS has been tested against an alternative regimen. In the trial reported by Fearon et al. ($n = 200$) EPA/ONS was compared with the ONS alone[81] (Ib). On an intention to treat analysis there was no advantage from addition of EPA to the ONS. However, compliance was suboptimal (only 70% of intended dose) and measurement of plasma EPA levels revealed that a substantial proportion of the patients in the ONS arm had been taking fish oil capsules. In the trial reported by Jatoi et al. ($n = 410$) EPA/ONS was compared with megestrol acetate alone or megestrol acetate plus EPA/ONS[103] (Ib). The authors concluded that EPA/ONS either alone or in combination with megestrol acetate did not improve weight or appetite more than megestrol acetate alone. This study is difficult to interpret as the primary end-point was weight gain of more than 10%. Body composition was not measured and it is therefore difficult to exclude the possibility that fluid retention (a known side-effect of megestrol acetate) confounded the trial result. Moreover, compliance was not measured.

Further evidence is contradictory. In a short-term (two weeks duration) placebo-controlled trial Bruera et al. studied 60 weight losing cancer patients and found no effect of 1.8 g EPA/day on appetite, tiredness, nausea, well-being, caloric intake, nutritional status or function[104] (Ib). Ingested EPA will accumulate in tissues over time and two weeks may be too short to induce clinically measurable effects.[105]

Recent findings obtained in an uncontrolled phase II study suggest that ω-3 fatty acids may induce weight stabilisation or weight gain in a small subset of patients with cancer-related cachexia, when administered in doses of 4.7 g EPA/day, that were more than twice those used in the previously published phase III trials[105] (IIb). Similarly, in a very small randomised study Persson et al. supplied 4.9 g of EPA and 3.2 g of docosahexaenoic acid to cachectic cancer patients and observed more frequent weight stabilisation compared to the control group[106] (Ib).

The efficacy of treatment with EPA/ONS appears to be critically dependent on the patients' compliance. In addition to anorexia, patients' compliance with prescribed high-energy and high-protein EPA/ONS is limited by the frequently complained unpleasant aftertaste. Therefore, it will be necessary to improve the palatability of EPA/ONS in order to improve patients' compliance with treatment and hopefully its effectiveness.

The results of further trials are awaited.

3. EN in special situations

3.1. What is the indication for perioperative EN in cancer patients?

General indications for perioperative EN also apply for cancer patients. The strongest recommendations relevant to cancer patients refer to severe nutritional risk states and to preoperative

nutrition. Refer to guidelines ''Surgery incl. Organ Transplantation'' for further details and comments.

Patients with severe nutritional risk benefit from nutritional support for 10–14 days prior to major surgery even if surgery has to be delayed (A). Whenever feasible, the enteral route should be preferred (A).

In all cancer patients undergoing major abdominal surgery preoperative EN preferably with immune modulating substrates (arginine, ω-3 fatty acids and nucleotides) is recommended for 5–7 days independent of their nutritional status (A).

3.2. Is there an indication for EN during radiotherapy or combined radio-chemotherapy?

Yes. Use intensive dietary counselling and ONS to increase dietary intake (A) and to prevent therapy-associated weight loss and interruption of radiation therapy in patients undergoing radiotherapy of gastrointestinal or head and neck areas (A). If an obstructing head and neck or oesophageal cancer interferes with swallowing, EN should be delivered by tube (C). TF is also suggested if severe local mucositis is expected, which might interfere with swallowing, e.g. in intensive radiotherapy or in combined modality radio-chemotherapy regimens including radiation of throat or esophagus (C).

TF can either be delivered via the transnasal or percutaneous routes. Because of radiation induced oral and esophageal mucositis a PEG may be preferred (C).

Routine EN is not indicated during radiation therapy of other body regions (C).

Comment: It is generally accepted that the concomitant mucositis during radio/chemotherapy results in weight loss in head and neck or esophageal cancer patients[68,84,107] (IIb): this loss cannot be completely prevented by nutritional counselling.[108] In a small randomised pilot study in 17 patients mouth swishes with a glutamine solution reduced objective signs but not subjective symptoms of radiation-induced mucositis; there was no effect on body weight[109] (IIa). However, a randomised study performed in 60 oncology outpatients receiving radiotherapy to the gastrointestinal (12%) or head and neck areas (78%) documented statistically smaller deteriorations in weight, nutritional status and global quality of life when intensive, individualised nutritional counselling and ONS were used instead of standard nutritional care which included general advice and a nutrition booklet[85] (Ib). A recent meta-analysis of three randomised controlled studies concluded, that in patients undergoing radiotherapy ONS significantly increase energy intake by 381 kcal/d[110] (Ia).

A prospective trial in 50 head and neck cancer patients treated with definitive ambulatory radiation therapy showed that ONS increased total protein and total energy intake but could not reduce weight loss[69] (IIa). Nayel et al. studied 32 head and neck cancer patients during radiation therapy of whom eleven were randomised to receive ONS. All patients in the study group gained weight and underwent radiation therapy without interruption, whereas 7 of the 12 remaining patients lost weight and in 5 the radiation therapy had to be interrupted[111] (Ib). Bozzetti et al.[83] have demonstrated that home EN is able to prevent a deterioration in nutritional status among dysphagic undernourished patients with esophageal cancer receiving CT and RT, while non-dysphagic patients who did not receive EN actually lost weight.

In one prospective[83] and several retrospective[82,84,112,113] (III) trials ONS or TF were shown to significantly reduce weight loss compared to normal food. As a consequence, quality of life could be maintained[107] (IIb), interruptions of treatment could be prevented[68] (IIb),[91] (III) and the frequency of hospital admissions could be reduced[68,83] (IIb),[82] (III).

There are no RCTs comparing PEG with nasogastric TF in this setting. Radiotherapy of throat and/or hypopharynx, however, regularly results in a dose-dependent mucositis, which is still present 4 weeks after completion of radiotherapy.[114] In one retrospective study the authors reported that their patients preferred PEG over nasogastric TF.[115] Lees compared prospectively the outcome of 100 head and neck cancer patients with either PEG or nasogastric TF. Both methods were found to be equally effective at maintaining body weight, but PEG was found to be superior since it was associated with greater mobility, better cosmetic appearance and improved subjective quality of life.[116] Roberge evaluated the impact of three weeks of home EN via nasogastric TF in 39 consecutive patients treated for head and neck or oesophageal cancer, and reported that some 60% of the patients experienced psychological problems and 25% experienced social strain[117] (III).

There are no clinical studies reporting relevant data on the administration of glutamine or other substrates in radiotherapy patients.

3.3. Is there an indication for routine EN during chemotherapy?

No. Routine EN during chemotherapy has no effect on tumour response to chemotherapy nor on chemotherapy-associated unwanted effects. Therefore, based on the available knowledge it is considered not useful (B).

Comment: In 1994 Klein and Koretz analysed seven RCTs investigating EN in combination with chemotherapy[118] (Ib). Evaluation proved difficult since all the studies differed in important details, the patient groups were heterogeneous and underwent different anti-cancer therapies, different nutritional formulae were administered, the studies differed in length and timing of the nutritional regimens and the sample sizes were small. Importantly, the studies were carried out mainly in patients with normal or only moderately impaired nutritional status. No obvious advantage of EN could be observed with regard to survival, response to treatment or toxicity of chemotherapy.

A recent meta-analysis of four RCTs concluded, that in patients undergoing chemotherapy/radiotherapy ONS or TF had no effect on mortality when compared to routine care.[110] It has to be assumed, however, that if response to anti-tumour treatment is lacking, stabilisation of weight cannot be anticipated, since additive catabolic effects result from both the inflammatory response and the chemotherapy.

3.4. Is there an indication for routine EN during autologous or allogeneic hematopoietic stem cell transplantations (HSCT)?

No. There are no proven effects on tumour response, therapy-associated side effects, graft survival, graft-versus-host disease or overall survival. The routine use of EN, therefore, is not recommended (C). In addition, if oral intake is decreased, the increased risk of haemorrhage and infections associated with enteral tube placement in immuno-compromised and thrombocytopenic patients has to be considered; in certain situations, therefore (e.g. allogeneic HSCT) parenteral nutrition (PN) may be preferred to TF (C).

Comment: After autologous transplantations nutritional intake is restricted for only a short time, whereas after allogeneic transplantations more intensive and long-term problems occur. Autologous patients are generally not in need of nutritional support. Patients undergoing allogeneic transplantation receive PN early after intervention in most transplantation centres since EN is usually not well tolerated.[119–121]

There are very few studies investigating EN during HSCT. Two small trials in adult patients did not distinguish between autologous and allogeneic transplantation.[122,123] Szeluga et al. conducted a prospective RCT comparing an individualised EN program (counselling, high protein snacks and/or TF) in 57 patients (Ib). EN was more cost effective but otherwise there were no differences in outcome between the two regimens.[122] Roberts et al. reported retrospectively on their experiences with 16 patients, who received EN via PEG[123] (III). Similarly, in pediatric patients undergoing bone marrow transplantation, a comparative study showed, that TF is possible and equal in efficacy to PN, but only rarely patients could be fed exclusively by EN.[124]

3.5. Is enteral delivery of glutamine or EPA useful in hematopoietic stem cell transplantation?

Current study findings are inconclusive and therefore the expert group reached a consensus not to recommend the enteral administration of glutamine or EPA in patients undergoing haematopoietic stem cell transplantation (C).

Comment: None of the four trials investigating oral glutamine could prove any major advantages[125–128] (Ib). Anderson et al. studied 193 patients and observed that 4 g/day oral glutamine decreased the severity and duration of oropharyngeal mucositis in autologous but not in allogeneic transplantation patients.[125] Neither Schloerb and Skikne[126] ($n = 66$ patients) nor Coghlin Dickson et al.[127] (Ib) ($n = 58$ patients) found positive effects of 30 g/d of glutamine in patients after allogeneic or autologous transplantation. In addition, in a small RCT in 24 patients after autologous HSCT oral glutamine (16 g/d) had no effect on the incidence of oral mucositis, the frequency of diarrhoea nor on the recovery of haemoglobin, white blood cells or platelets.[128] Thus, consensus exists that further well designed clinical studies are needed to definitely assess the benefits of supplementation of GLN as a single oral supplement or as part of an enteral formula on outcome of HSCT patients.[129]

Takatsuka et al. reported on 16 consecutive patients, 7 of whom received 1.8 g/d EPA orally from 30 days before until some 180 days after allogeneic HSCT[102] [IIa]. Complications of HSCT were less and the survival rate was significantly higher in the group treated with EPA.

3.6. Is there an indication for EN in advanced stages of incurable cancer patients?

EN should be provided in order to minimise weight loss, as long as the patient consents and

the dying phase has not started (C). When the end of life is very close, most patients require only minimal amounts of food and little water to reduce thirst and hunger (B). Small amounts of fluid may also help to avoid states of confusion induced by dehydration (B). Subcutaneously infused fluids in hospital or at home may be helpful and also provide a vehicle for the administration of drugs (C).

See also chapter ''Ethical and legal aspects of enteral nutrition''.

Comment: Patients with incurable disease may have, despite the lack of further available anticancer therapies, a life expectancy of several weeks or months. If the expected survival due to spread of the cancer exceeds 2–3 months, which is the survival time of a completely starving subject, it can be reasonably expected that EN will prolong the survival of an incurable cancer patient, who is unable to eat[130] (IV).

Close to the end of life, guidelines for preserving nutritional state are no longer relevant and intensive nutritional therapy may worsen the condition of dying cancer patients[131] (IV). McCann et al. treated 32 terminally ill mentally aware patients for a median of 40 days and documented the amount of food and fluids necessary to relieve hunger and thirst; 20 patients experienced no hunger and either no thirst or thirst only initially; in all patients, symptoms of hunger and thirst could be alleviated with small amounts of foods and fluids[132] (III). In a palliative care unit Bruera et al. demonstrated that most terminal cancer patients could be adequately treated by subcutaneous hydration at a daily volume of some 1000 ml[133] (III). Subcutaneous infusions can be administered at home safely and effectively.[134] The symptom of dry mouth is very frequent but does not correlate with the state of hydration or the amount of fluid given;[135] however, it may be alleviated by the use of ice chips and lubrication to the lips[132] (III).

Since it may be difficult to judge the expected survival time of a cancer patient and thus the potential benefit of EN, these patients should be seen and discussed together by the oncologist, the nutritionist and the palliative care specialist, and the treatment designed on a personalised basis.

4. Risks of EN

4.1. Does EN ''feed'' the tumour?

There are no reliable data that show any effect of EN on tumour growth. Such theoretical considerations should, therefore, have no influence on the decision to feed a cancer patient (C).

Comment: There are no well-controlled clinical studies by which this issue may be judged. There are, however, a number of observations in cancer patients treated with parenteral nutrition (PN) or EN. All of these studies where performed in patients with gastrointestinal or head and neck cancers.

Comparing tumour and normal tissues, Cao et al. showed an increase in S+G2+M-phases in gastric cancer tissue but not in normal mucosa during PN, while at the same time a positive nitrogen balance was reached[136] (III). Two other groups, however, taking biopsies from head and neck[137] (III) or gastrointestinal cancer patients[138] (III) could not demonstrate any effect of PN on tumour cell kinetics.

McNurlan et al. reported increased rates of protein synthesis in both muscle and tumour tissue removed at surgery after preceding intravenous nutrition infusions[139] (III). Comparing preoperative PN in patients with colorectal cancer and non-cancerous diseases, Ota et al. observed an increase in red blood cell putrescine levels in cancer patients but not in the other group[140] (III).

Baron et al.[141] (III) and Bozzetti et al.[142] (III) compared total PN to normal food in undernourished patients with head and neck or gastric cancers, respectively. Both groups reported an increase in tumour cell proliferation by PN. Recently, Bozzetti et al. by using positron emission scanning demonstrated that, in the fasting state, glucose uptake by liver metastases from colorectal cancer is remarkably elevated compared to normal liver, but that there is no additional effect of glucose- or lipid-based parenteral nutrition[143] (III).

Finally, only one group compared the effects of EN versus normal food on cell cycle distribution in head and neck cancer patients (Edstrom et al., 1989) and reported a larger increase in cell proliferation after EN.

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