ESPEN Guidelines on Parenteral Nutrition: Non-surgical oncology

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SUMMARY

Parenteral nutrition offers the possibility of increasing or ensuring nutrient intake in patients in whom normal food intake is inadequate and enteral nutrition is not feasible, is contraindicated or is not accepted by the patient.

These guidelines are intended to provide evidence-based recommendations for the use of parenteral nutrition in cancer patients. They were developed by an interdisciplinary expert group in accordance with accepted standards, are based on the most relevant publications of the last 30 years and share many of the conclusions of the ESPEN guidelines on enteral nutrition in oncology.

Under-nutrition and cachexia occur frequently in cancer patients and are indicators of poor prognosis and, *per se*, responsible for excess morbidity and mortality. Many indications for parenteral nutrition parallel those for enteral nutrition (weight loss or reduction in food intake for more than 7–10 days), but only those who, for whatever reason cannot be fed orally or enterally, are candidates to receive parenteral nutrition. A standard nutritional regimen may be recommended for short-term parenteral nutrition, while in cachectic patients receiving intravenous feeding for several weeks a high fat-to-glucose ratio may be advised because these patients maintain a high capacity to metabolize fats. The limited nutritional response to the parenteral nutrition reflects more the presence of metabolic derangements which are characteristic of the cachexia syndrome (or merely the short duration of the nutritional support) rather than the inadequacy of the nutritional regimen. Perioperative parenteral nutrition is only recommended in malnourished patients if enteral nutrition is not feasible. In non-surgical well-nourished oncologic patients routine parenteral nutrition is not recommended because it has proved to offer no advantage and is associated with increased morbidity. A benefit, however, is reported in patients undergoing hematopoietic stem cell transplantation. Short-term parenteral nutrition is however commonly accepted in patients with acute gastrointestinal complications from chemotherapy and radiotherapy, and long-term (home) parenteral nutrition will sometimes be a life-saving maneuver in patients with sub acute/chronic radiation enteropathy. In incurable cancer patients home parenteral nutrition may be recommended in hypophagic/(sub)obstructed patients (if there is an acceptable performance status) if they are expected to die from starvation/under nutrition prior to tumor spread.

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Preliminary remarks

The opportunity has been taken to address what is often considered a controversial area, given the considerable differences in the use of parenteral nutrition (PN) in non-surgical oncology practice around the world. The authors have aimed to present the data in a format that addresses common clinical problems, and to identify clearly where evidence-based recommendations can be made. In many cases the evidence base is not strong and some recommendations have necessarily been the result of expert consensus.

1. Tumors and nutritional status

1.1. What is cancer cachexia?

From the clinical point of view cancer cachexia is a complex syndrome characterized by a chronic, progressive, involuntary weight loss which is poorly or only partially responsive to standard nutritional support and it is often associated with anorexia,

Summary of statements: Non-surgical Oncology

Subject	Recommendations	Grade	Number
Nutritional status	Nutritional assessment of all cancer patients should begin with tumor diagnosis and be repeated at every visit in order to initiate nutritional intervention early, before the general status is severely compromised and chances to restore a normal condition are few	C	1.1
	Total daily energy expenditure in cancer patients may be assumed to be similar to healthy subjects, or 20–25 kcal/kg/day for bedridden and 25–30 kcal/kg/day for ambulatory patients	C	1.4
	The majority of cancer patients requiring PN for only a short period of time do not need a special formulation. Using a higher than usual percentage of lipid (e.g. 50% of non-protein energy), may be beneficial for those with frank cachexia needing prolonged PN (Grade C)	C	1.5
Indications	Therapeutic goals for PN in cancer patients are the improvement of function and outcome by: • preventing and treating under-nutrition/cachexia, • enhancing compliance with anti-tumor treatments, • controlling some adverse effects of anti-tumor therapies, • improving quality of life	C	2.1
	PN is ineffective and probably harmful in non-aphagic oncological patients in whom there is no gastrointestinal reason for intestinal failure	A	2.1
	PN is recommended in patients with severe mucositis or severe radiation enteritis	C	2.1
Nutritional provision	Supplemental PN is recommended in patients if inadequate food and enteral intake (<60% of estimated energy expenditure) is anticipated for more than 10 days	C	2.2
	PN is not recommended if oral/enteral nutrient intake is adequate	A	2.2
	In the presence of systemic inflammation it appears to be extremely difficult to achieve whole body protein anabolism in cancer patients. In this situation, in addition to nutritional interventions, pharmacological efforts are recommended to modulate the inflammatory response	C	2.3
	Preliminary data suggest a potential positive role of insulin (Grade C). There are no data on n-3 fatty acids	C	2.4
Peri-operative care	Peri-operative PN is recommended in malnourished candidates for artificial nutrition, when EN is not possible	A	3.1
	Peri-operative PN should not be used in the well-nourished	A	3.1
During non-surgical therapy	The routine use of PN during chemotherapy, radiotherapy or combined therapy is not recommended	A	3.2
	If patients are malnourished or facing a period longer than one week of starvation and enteral nutritional support is not feasible, PN is recommended	C	3.2
Incurable patients	In intestinal failure, long-term PN should be offered, if (1) enteral nutrition is insufficient, (2) expected survival due to tumor progression is longer than 2–3 months),(3) it is expected that PN can stabilize or improve performance status and quality of life, and (4) the patient desires this mode of nutritional support	C	3.3
	There is probable benefit in supporting incurable cancer patients with weight loss and reduced nutrient intake with "supplemental" PN	B	3.4
Hematopoietic stem cell transplantation (HSCT)	In HSCT patients PN should be reserved for those with severe mucositis, ileus, or intractable vomiting	B	3.5
	No clear recommendation can be made as to the time of introduction of PN in HSCT patients. Its withdrawal should be considered when patients are able to tolerate approximately 50% of their requirements enterally	C	3.6
	HSCT patients may benefit from glutamine-supplemented PN	B	3.7
Tumor growth	Although PN supplies nutrients to the tumor, there is no evidence that this has deleterious effects on the outcome. This consideration should therefore have no influence on the decision to feed a cancer patient when PN is clinically indicated	C	4.1

early satiety and asthenia. It is usually attributable to two main components: a decreased nutrient intake (which may be due to critical involvement of the gastrointestinal tract by the tumor, or to cytokines and similar anorexia-inducing mediators); and metabolic alterations due to the activation of systemic proinflammatory processes.

Resulting metabolic derangements include insulin resistance, increased lipolysis and 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 an inflammatory state is therefore referred to as cancer cachexia or cancer anorexia-cachexia syndrome. These cytokine-induced metabolic alterations appear to prevent cachectic patients from regaining body cell mass during nutritional support, and are associated with a reduced life expectancy, and are not relieved by exogenous nutrients alone.

Attempts to modulate these metabolic changes by other means should be integrated into the management of cancer patients. Nutritional assessment of all cancer patients should begin with tumor diagnosis and be repeated at every visit in order to initiate nutritional intervention early, before the general status is severely compromised and chances to restore a normal condition are few (Grade C).

Comments: While weight loss and under-nutrition, both moderate and severe, are frequent features in patients with malignant disease, many tumor-bearing patients display elevated inflammatory markers.[1–4] The observed release of cytokines, catabolic hormones and further regulatory peptides appears to be a primary reaction of the cancer patient's host tissues.[1–3] In addition, substances produced by tumor cells, such as tumor lipid mobilizing factor (LMF) and proteolysis inducing factor (PIF), have been reported to 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 tumor progression.[12,13] Cytokine-induced metabolic alterations also appear to prevent cachectic patients from regaining body cell mass 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 is 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 proteosome proteolytic system is activated at an early stage.[27,28]

Since the metabolic and molecular mechanisms ultimately leading to the phenotypic pattern of the anorexia-cachexia syndrome seem to be already operating early in the natural history of the tumor growth and development, oncologists should pay attention to this phenomenon as an event which perhaps could be prevented or at least delayed by means of early pharmacological and nutritional intervention.[29]

Cachexia cannot be easily differentiated from under-nutrition due to simple starvation: both cachectic and undernourished patients have lost their body weight and may be anorectic, however, simply undernourished patients show a tendency to save their protein mass, they decrease their resting energy expenditure and they respond quite well to the nutritional support if their general status is not compromised in an irreversible way. On the contrary, cachectic patients have depletion of both the fat and the muscular mass (with preservation of their central protein mass), they fail to adapt their energy requirements to a condition of nutrient deprivation, and they show an inflammatory response that prevents them from getting substantial benefit from nutritional support. Nonetheless a proactive approach can pay dividends, as in one study of patients with impending cachexia (weight loss 9–10% but nutrient intake >1600 kcal/day). Supplementary home PN administered for 7–8 weeks, when nutrient intake started to decrease to approximately 70–80% of the expected level, was associated with a significant expansion of whole body fat, improvement of energy balance and greater exercise capacity if analyzed on the basis of treatment given.[30]

1.2. Does cancer influence nutritional status?

Yes. Weight loss is frequently the first symptom occurring in cancer patients. Depending on the type of primary tumor and stage of disease, weight loss is reported in 30% to more than 80% of patients and is severe (loss >10% of the usual body weight) in some 15%.

Comments: Weight loss preceding tumor diagnosis has been widely reported to occur in 31–87% of patients, depending on the site of the primary tumor.[31–34] A severe involuntary weight loss of more than 10% of usual body weight over the previous 6 months has already occurred in 15% of all patients at the time of diagnosis.[31] Eighty-five per cent of patients with pancreatic or stomach cancer have lost weight at the time of diagnosis, and in 30% this body weight loss was severe.[31] Both frequency and severity of weight loss are correlated with tumor stage.[35] Cancer therapies are associated with anorexia and/or decreased food intake and further weight loss if toxicity of treatment outweighs tumor response,.[36,37]

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

Yes. Impaired nutritional status is associated with reduced quality of life, lower activity levels, increased treatment-related adverse reactions, reduced tumor response to treatment and reduced survival. Although a cause and effect relationship appears probable this has not yet been firmly established.

Comments: Longitudinal studies have demonstrated that the prognosis for cancer patients with weight loss is worse than that for weight-stable patients. Even though tumor stage and unresponsiveness to the oncologic therapy are major prognostic factors for survival, a large body of literature has shown that weight loss is a significant and often independent predictor of decreased survival in medical oncologic patients.[38–46] Depletion of body proteins is also associated with poorer survival.[47] Malnourished cancer patients have a poorer response to chemotherapy in respect of both the rate of response and its duration.[34,48–50] Furthermore, malnourished cancer patients have higher rates of hospital readmissions, longer hospital stay,[51] increased symptom distress[52] and reduced quality of life.[34,53] In a recent trial total body nitrogen was found to be the most powerful predictor of neutropenia after chemotherapy in breast cancer patients.[54] Under-nutrition, therefore, appears to be a marker of disease severity and of poor prognosis. A percentage ranging from 4 to 23% of terminal cancer patients ultimately die because of cachexia.[55–58]

1.4. Does cancer influence resting energy expenditure?

Frequently yes. Cancer itself does not have a consistent effect on resting energy expenditure. Oncological treatment, however, may modulate energy expenditure. For practical purposes, and if not measured individually, total daily energy expenditure in cancer patients may be assumed to be similar to healthy subjects, or 20–25 kcal/kg /day for bedridden and 25–30 kcal/kg/day for ambulatory patients (Grade C).

Comments: 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.[59,60] In the large experience from the University of Gothenburg, approximately 50% of all weight-losing cancer patients were hypermetabolic when compared to appropriate controls with similar physical activity, body composition and age,[61] and weight loss and hypermetabolism were not compensated by an increase in spontaneous food intake. There is some variability depending on the different types of tumor: some authors report normal REE in patients with gastric and colorectal cancers[62,63] and higher than expected REE in subjects with pancreatic and lung cancers.[63–65] This increase in REE in lung cancer patients is related to the presence of a systemic inflammatory response.[66]

However, if we consider the total energy expenditure (TEE) which includes the resting energy expenditure plus the physical activity energy expenditure, this value is usually decreased in advanced cancer patients when compared to predicted values for healthy individuals,[64,65] mainly because of a reduction in physical activity. Recent data[67,68] from the use of a wearable device, the Sense-Wear armband indicate that TEE of weight-stable leukemic patients and of weight-losing patients with gastrointestinal tumors is about 24 and 28 kcal/kg/day, respectively.

There are few and inconsistent data regarding effects of cancer treatments on energy expenditure. Hansell et al.[62] studied 15 patients with colorectal cancer and did not observe any effects of curative surgery or of hepatic metastases on REE. Fredrix et al.[63] 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 tumor recurrence. Chemotherapy treatment in twelve patients with newly diagnosed small cell lung cancer reduced both circulating inflammatory mediators and REE.[66]

1.5. Do cancer patients require a distinct nutrient profile?

Probably yes.

The majority of ambulatory or hospitalized cancer patients requiring PN for only a short period of time (surgical patients, patients requiring bowel rest for severe gastrointestinal adverse effects from chemotherapy or radiation, etc.) do not need any specific formulation. However, special attention should be paid to patients with frank cachexia requiring PN for several weeks, because there are abnormalities in energy substrate metabolism in this condition. Pathophysiological and clinical considerations suggest that using a higher than usual percentage of lipid in the admixture (e.g. **50% of non-protein energy), is beneficial (Grade C).**

Comments: Since 1971[69] it has been known that fat is efficiently mobilized and utilized as a fuel source in cancer patients. The rationale for the use of fat emulsions in cancer patients stems from several sophisticated studies reported in the international literature[70,71,73–75] and relies on the following premises.

Several authors[70,71,73,75] have reported very efficient mobilization and oxidation of endogenous fat in the post-absorptive state, ranging from 0.7 to 1.9 g/kg/day, which corresponds to 6.3 to 17 kcal/kg/day (about 60 to 78% of the resting metabolic expenditure) both in weight-stable and weight-losing cancer patients.

After the administration of LCT or LCT/MCT emulsions the lipid clearance (g/kg/day) was reported to be 1.4 vs. 2.3 vs. 3.5 or 1.2 vs. 1.6 vs. 2.1 in healthy controls vs. weight-stable vs. weight-losing cancer patients, respectively.

The oxidation rate (g/kg) after infusion of LCT or LCT/MCT emulsions in malnourished cancer patients was reported to be 1.3–1.6 or 0.62 respectively.[74]

Some investigators are however concerned about the potential toxicity of long-term administration of lipids and suggest limiting administration to no more than 1 g/kg/day. It is important to point out that these recommendations mainly refer to the experience with soybean oil emulsions, and data with LCT/MCT are more promising. Carpentier et al[77] reported 20 patients on HPN receiving mixed emulsions for 3–6 months and showed good liver tolerance. Simoens et al.[78] compared plasma triacylglycerol clearance of a lipid emulsion (5:4:1) made of 50% MCT, 40% LCT, and 10% fish oil (wt:wt:wt) to a control (5:5) preparation with 50% MCT and 50% LCT. Inclusion of 10% fish oil in mixed emulsion particles enhanced plasma clearance of infused triacylglycerols (18%, $p < 0.0001$). The faster elimination of 5:4:1 emulsion appeared related to an enhanced uptake of remnant particles rather than to faster intravascular lipolysis. Moreover, each infusion of 5:4:1 emulsion raised EPA concentration in blood cell phospholipids to reach a 7-fold enrichment in platelets and greater than 2-fold enrichment in leukocytes after 4 infusions.

As regards the effects of fat infusion in cancer patients data from literature are scanty. Shaw and Holdaway[79] reported that the infusion of Intralipid ($\sim$29 kcal/kg/day) was able to significantly decrease net protein catabolism in patients with lower GI tumors but not upper GI tumors.

A glucose-based PN may cause positive balance of water and sodium in cancer patients.[80–82] Insulin, a potent antinaturetic and antidiuretic hormone[83] is the most probable mediator for this effect. The majority of cancer patients requiring long-term PN are cachectic and hypophagic because of (sub-acute) intestinal obstruction due to peritoneal carcinomatosis. This condition is often associated with expansion of the extracellular water volume and an overzealous administration of glucose might easily precipitate a peritoneal effusion which then forces withdrawal of the intravenous nutrition. In addition, the concurrent presence of nausea or the administration of morphine, is associated with an excessive production of antidiuretic hormone.

A clinical study in patients undergoing allogeneic bone marrow transplantation for hematologic malignancies showed reduced rates of lethal acute graft-versus-host diseases when receiving high-LCT parenteral nutrition regimens.[84]

In conclusion, a one-to-one fat-to-glucose energy ratio might be a sensible standard approach in cancer patients, and higher ratios might be tried when pleural or peritoneal effusions are limiting this approach.

Adverse effects reported with LCT emulsions mostly occur when lipid infusion rate are greater than 2.6 g/day (that is about 20–24 kcal/kg/day),[85] considerably in excess of the quantities recommended here.

The optimal nitrogen supply for cancer patients cannot be determined at present.[86] Recommendations range between a minimum amino acid supply of 1 g/kg/d[86] and a target of 1.2–2 g/kg/day.[87,88]

2. Indications for and goals of PN

2.1. What are the specific nutritional goals of PN in cancer patients?

Therapeutic goals for PN in cancer patients are the improvement of function and outcome by:

- **preventing and treating under-nutrition/cachexia,**
- **enhancing compliance with anti-tumor treatments,**
- **controlling some adverse effects of anti-tumor therapies,**
- **improving quality of life (Grade C).**

PN is ineffective and probably harmful in non-aphagic oncological patients in whom there is no gastrointestinal reason for intestinal failure (Grade A).

PN is recommended in patients with severe mucositis or severe radiation enteritis (Grade C).

Comments: There are good reasons for considering PN in cancer care, but its use is justifiable only when there is evidence to demonstrate that it is effective. In general, this evidence is lacking. In the majority of the studies with PN, which failed to achieve nutritional benefit, PN was administered in conventional nutritional regimens, and was unable to overcome the metabolic alterations characteristic of overt cachexia. PN was generally used for such limited periods of time (usually in hospitalized patients) that it proved impossible to reverse a state of malnutrition which had been present for many months. In the longer-term studies involving aphagic patients with a non-working gut, it would have been ethically unacceptable to have a non-PN control arm, so any prospectively controlled evidence of potential benefit is denied. Therefore it is important to separate the studies investigating the effects of a short-term PN from those, which are generally more favorable, involving long-term PN.

A widely quoted systematic review and meta-analysis of randomized clinical trials (RCTs) of adjuvant PN versus no PN, performed on behalf of the American Gastroenterological Association,[89] showed that PN had higher rates of complications and infections and no benefits in oncological outcomes (Level Ia). These conclusions however were criticized because all the studies dated back to the

past century, the nutritional regimens were far from what is now considered optimal and, mainly, because malnutrition and/or aphagia were not absolute criteria for entering the patients in the trials. So the conclusion that PN in cancer patients is useless and probably harmful is valid only if PN is used as an adjunct to patients who are not malnourished or hypophagic (Level Ia) (Grade A).

No study reported a benefit of PN in preventing side-effects of chemotherapy or radiation therapy, but when severe mucositis or severe acute radiation enteritis have occurred the efficacy of PN is internationally accepted[90] (Level II) (Grade C). The value of long-term PN in patients with sub-acute and chronic radiation enteropathy is well-recognized[91,92] (Level II) (Grade C) (see also the ESPEN Guidelines on HPN).

2.2. When should PN be started?

Nutritional support should be started if patient is undernourished or if it is anticipated that the patient will be unable to eat for more than seven days. It should also be started if an inadequate food intake (<60% of estimated energy expenditure) is anticipated for more than 10 days (Grade C). In such cases if nutritional support for any reason cannot be given through the enteral route, it has to be delivered by vein. A "supplemental" PN should substitute the difference between the actual oral/enteral intake and the estimated requirements (Grade C).

There is no rationale for giving PN if the nutrients intake by oral or enteral route is adequate, and for these reasons PN should not be administered in such conditions (Grade A).

Comments: To demonstrate a reduced intake of normal food, a simple 24 hour recall is usually sufficient. 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. The use of a visual nutritional atlas is recommended to help the patient quantify his/her daily nutritional intake.

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

Yes, but only if the nutritional depletion is not extreme.

In patients who are losing weight mainly because of an insufficient nutritional intake, artificial nutritional support should be provided to maintain nutritional status or at least prevent further nutritional deterioration. This may also contribute to the maintenance of quality of life. Any such improvement in the nutritional status is usually modest and is most expected when weight loss is mainly due to hypophagia. In the presence of systemic inflammation, however, it appears to be extremely difficult to achieve whole body protein anabolism in cancer patients. In this situation, in addition to nutritional interventions, pharmacological efforts are recommended to modulate the inflammatory response (Grade C).

Comments: Short-term experimental studies[93–97] have shown both the limited efficacy of PN in balancing the metabolism of the cancer patients and the equivalence between PN and EN. Long-term clinical studies are very few, but the experience with HPN[98–103] shows that this form of nutritional support is able to maintain the nutritional status of the patients for longer than expected in aphagia. Recent studies by Lundholm et al.[30] have quantitatively defined some nutritional benefits of long-term PN. Patients who received the planned amounts of energy and nitrogen (given by vein when necessary) had improved energy balance, increased body fat and greater maximum exercise capacity, in addition to

prolonged survival when compared to patients randomized to support without PN.

2.4. Is supplementation with special substrates or modulators beneficial in cancer patients?

Preliminary data suggest a potential positive role of insulin (Grade C). There are no data on n-3 fatty acids.

Comments: Lundholm et al.[104] reported prolonged survival in weight-losing cancer patients who were treated with subcutaneous insulin in addition to optimal nutritional support including PN.

With reference to supplementation with n-3 fatty acids, a recent Cochrane systematic review[105] of the published studies on EPA in cancer patients concluded that there was no benefit from the oral administration of EPA in patients with consolidated cachexia. A careful analysis of these studies shows that in at least two of them there were important flaws (including less EPA administered than prescribed) that could have biased the conclusions according to intention-to-treat. In addition, in another three RCTs the short duration of the study or the inclusion of patients with a primary tumor located in the gastrointestinal tract (and presumably unable to comply with an adequate nutrient intake) could have precluded the demonstration of efficacy of the EPA. It is interesting to speculate that these major restrictions of the oral administration of EPA would be easily overcome if an adequate energy and protein supply combined with n-3 fatty acid administration was provided intravenously. Moreover, this review underscores the need for further RCTs addressing the prevention, rather than the treatment of cachexia, with specialized nutritional/pharmacological interventions.

Experience with parenteral EPA is limited to perioperative patients where its short-term administration proved to be safe in respect of hemostasis,[106] and where it reproduced the expected modulations of the eicosanoids,[107,108] improved liver and pancreatic function,[109] and reduced immunosuppression induced by postoperative chemoradiation therapy.[110] Furthermore a recent RCT[111] comparing a fish oil-containing lipid emulsion with a standard soya-bean oil emulsion reported a significantly shorter length of hospital stay with the enriched PN.

3. PN in special situations

3.1. Is peri-operative PN indicated in cancer patients?

Yes. Perioperative PN is recommended in malnourished candidates for artificial nutrition, when EN is not possible, (Grade A).

Peri-operative PN should not be used in well-nourished cancer patients (Grade A).

Comments: In weight-losing cancer patients, at least two RCTs[112,113] have shown that peri-operative EN (with/without immune nutrients) is more effective than perioperative PN. However, if for any reason peri-operative EN is not feasible, peri-operative PN starting 7–10 days pre-operatively and continuing into the post-operative period, has been shown to be able to decrease complications and/or mortality in two RCTs[114,115] and in one post hoc analysis[116] in studies including malnourished cancer patients only. See also ESPEN Guidelines for PN in Surgery.

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

The routine use of PN during chemotherapy, radiotherapy or combined therapy is not recommended (Grade A).

However, if patients are malnourished or facing a period longer than one week of starvation and enteral nutritional support is not feasible, PN is recommended (Grade C).

If patients develop gastrointestinal toxicity from chemotherapy or radiation therapy, short-term PN is usually better tolerated (and more efficient) than EN to restore the intestinal function and prevent nutritional deterioration.

Comment: A systematic review of the RCTs on nutritional interventions accompanying chemo-radiotherapy published in 2001[89] showed no benefit but possible harm when PN was given as an adjunct to chemotherapy in patients who were neither uniformly malnourished nor hypophagic. However in patients who are malnourished, hypophagic, or affected by severe iatrogenic gastrointestinal complications, the recommendation of PN is supported by its frequent successful use in current clinical practice. Randomized clinical trials are not easily feasible in these situations because of the absence of equipoise.[118]

3.3. Is long-term (home) PN recommended in incurable cancer patients?

Sometimes yes. In aphagic incurable cancer patients survival may be limited more by under-nutrition than by tumor progression.

In intestinal failure, long-term PN should be offered, if[1] enteral nutrition is insufficient,[2] expected survival due to tumor progression is longer than 2–3 months),[3] it is expected that PN can stabilize or improve performance status and quality of life, and[4] the patient desires this mode of nutritional support (Grade C).

Comments: There are no recent RCTs evaluating the effectiveness of PN in incurable and aphagic/obstructed cancer patients[119,120] because randomization between PN and no PN is not normally ethically acceptable in such conditions. Furthermore, it is hard to consider PN as a palliative treatment if we accept the time-honored concept of palliation as a treatment aiming to relieve symptoms—without addressing the basic disease—because often these patients are anorectic and there is no evidence that parenteral nutrition improves this or associated asthenia.

The main rationale for giving HPN in cancer patients is the awareness that survival of healthy individuals submitted to total macronutrient starvation, hardly exceeds 2 months, and that in patients with malignant obstruction receiving palliative care but no nutritional support the mean survival is around 48 days.[121] In contrast 20–50% of advanced cancer patients selected for HPN are alive at 6 months.[101–103,122]

The duration of HPN for the majority of these patients is nonetheless short-lived. King et al.[123] record a median duration of 66.5 days for patients with gynecological cancers. Other studies demonstrate a median duration of around 4 months.[124] King et al.[123] reported an HPN-related complication rate of 9%, mostly catheter-related sepsis, with no HPN-related mortality. In the Cozzaglio study[124] there were many readmissions to hospital totaling about 4% of the entire HPN period, but only about one third of this time was for HPN-related complications. More recent data indicate a frequency of PN-associated infections of between 0.34 and 2.68 cases per 1000 catheter days.[126–129] This suggests that HPN is relatively safe, with an acceptable number of hospital readmissions, if performed by experienced centers.

The evidence of improved quality of life (QoL) on HPN in advanced cancer is poor and its use probably says more about a country's culture or attitudes to palliation than about medical judgment. The dilemma remains whether to burden the patient with complex technology with the risk of complications and re-admittances to hospital in order to buy extra time and possibly a small improvement in QoL, or let the patient die sooner but perhaps with more dignity.[130]

It is still not clear whether the impaired QoL which is reported in literature is related to the complex technology of administering HPN or to the underlying disease state that necessitates its use.[131,132] King et al.[123] showed an overall improvement in QoL compared to the pre-HPN state. Morale and social interactions improved, as did gastrointestinal discomfort, nausea, vomiting and fatigue. Sixteen percent of patients were again able to work outside the home and 6.6% undertook recreational travel. However, the results of this study must be questioned as the QoL assessment was based on the impressions of clinicians who undertook a retrospective review of patient case notes using an arbitrary scoring system. Cozzaglio et al.[124] who also reported improved QoL for patients who survived for more than 3 months, also based their conclusions on clinicians' judgments rather than from direct patient participation.

Bozzetti et al. studied QoL in 69 Italian patients using the Rotterdam Symptom Checklist, a validated cancer-specific tool, at the start of HPN and then at monthly intervals. Half of the patients complained of worries, tension and desperate feelings about the future. Anorexia, tiredness, lack of energy and decreased sexual interest were evident. Most were unable to do housework, climb stairs, do odd jobs, walk outside or go to work, or they needed help to do these activities. Yet, when asked "how are you today", 58% answered "well". After one month on HPN around half the patients deteriorated, 40% improved and the rest remained the same in terms of physical, psychological and activity assessments.

Both the Italian studies[124] demonstrated improved or stabilized QoL for patients surviving longer than 3 months, although QoL always deteriorated during the last two months of life. This indicates that for HPN to impact positively on QoL the patient needs to survive for at least 3 months. Those with the highest performance scores at the time of tumor diagnosis tend to have the best survival and QoL over the course of their illness, and patients starting HPN with a Karnowsky performance score of more than 50 survive longer than those with lower scores.

In conclusion, PN may be recommended in incurable cancer patients who cannot be fed orally or enterally: (a) if they are estimated to die sooner from starvation than from tumor progression (typically because of intestinal obstruction and/or aphagia; (b) if their performance status and quality of life are acceptable; and (c) if there is strong patient and family motivation for a demanding procedure the success of which has not yet been fully validated.[133,134]

3.4. Is there a benefit in supporting incurable cancer patients with weight loss and reduced nutrient intake with "supplemental" PN?

Probably yes. There is probable benefit in supporting incurable cancer patients with weight loss and reduced nutrient intake with "supplemental" PN (Grade B).

Comments: There are few studies on this specific topic.[30,104,135,136] The most significant is the experience from the University of Goteborg where the authors[30,104] tested a "supplemental" PN in weight-losing cancer patients undergoing multi-modal palliation which included the use of COX inhibitors (usually indomethacin, 50 mg twice daily), erythropoietin (15–40,000 units per week) and insulin (0.11 units/kg/day). This study on 309 weight-losing patients with solid tumors (primarily gastrointestinal lesions), with an expected survival of at least 6–12 months, showed that on an intention-to-treat basis patients randomized to

receive supplemental nocturnal HPN (20–25 kcal/kg/day; 0.10–0.15 g nitrogen per kg per day) had an improvement in energy balance ($p < 0.03$). The as-treated analysis demonstrated that these patients had prolonged survival ($p < 0.01$), improved energy balance ($p < 0.001$), increased body fat ($p < 0.05$) and a greater maximum exercise capacity ($p < 0.04$).

Much less convincing is the prospective clinical trial of Shang et al.[135] They considered 152 patients with at least 5% weight loss or BMI <20 with advanced, mainly gastrointestinal, cancer who intermittently received oncologic therapy and an intensified oral enteral nutrition, and randomized them to receive supplemental PN (680 kcal/day and 26 g protein /day) or not. The median follow-up was 11.1 months and at various intervals benefits in nutritional variables, quality of life, and survival were observed in patients on supplemental HPN. Since benefit was confined to PN patients though both groups received the same amount of calories (~2200 kcal/day), it was speculated that absorption of enteral nutrients was abnormal. What appears definitely unusual is that the control group, despite chemotherapy, radiotherapy or both, maintained an oral enteral intake of 33 kcal/kg/day even during the late phases of progression of the disease.

The recent paper by Finocchiaro et al.[136] is an uncontrolled study of PN in severely malnourished patients who were aphagic (36% of cases) or hypophagic (<500 kcal /day; 64%) and often in receipt of palliative chemotherapy. The median survival was less than 2 months.

In conclusion, the current results of HPN in incurable cancer patients who are fed intravenously because of intestinal obstruction and/or aphagia, and are estimated to die from starvation sooner than from tumor progression, are controversial because there is an intrinsic difficulty in predicting whether the final outcome is due to the tumor progression or to progressive nutritional deterioration.

On the contrary, early intravenous nutritional support in less-advanced cancer patients with mild hypophagia and mild malnutrition could protect integrated metabolism and metabolic function in these subjects. This would also support the concept that nutrition is a limiting factor influencing survival when the disease is advanced but death is not imminent.

3.5. Is there a role for PN in patients receiving hematopoietic stem cell transplantation (HSCT)?

Yes. However, in HSCT patients PN should be reserved for those with severe mucositis, ileus, or intractable vomiting (Grade B).

Comments: The gastrointestinal toxicity (mucositis, nausea, vomiting, and diarrhea) secondary to high-dose conditioning regimens in HSCT potentially impacts upon optimal nutrient intake and/or nutrient absorption. Despite the increasingly successful use of naso-gastric or naso-jejunal enteral nutrition during HSCT,[137,138] feeding tube placement and tolerance can be difficult or impossible once mucositis has developed, and enteral feeding may be poorly tolerated. However, it is possible to insert feeding tubes safely with up to Grade 2 mucositis, and this is a common practice in HSCT.[139] Nonetheless PN has been shown to be safe and feasible in patients undergoing HSCT[140] and is still widely used in such patients, allowing ease of modulation of fluid, electrolyte and macronutrient supplementation.[141] However, it should be reserved for use in patients with severe mucositis (Grade 3–4), ileus, and intractable vomiting.[139] There is an increased risk of line infections when compared with standard intravenous fluids.[142]

Although benefits of PN administration have been reported with respect to decrease in disease relapse rate, increase in disease-free survival and improved survival rate,[143] when the prevalence of malnutrition was considered as the only indication for PN

administration, up to 37% of autologous transplant recipients without whole body irradiation, up to 50% of autologous transplant recipients undergoing full intensity conditioning, 58% of allogeneic transplant recipients undergoing full intensity conditioning, and up to 92% of allogeneic transplants recipients with irradiation and HLA-non compatible donors, may have indications for PN.[144]

3.6. When should PN be initiated in HSCT patients?

No clear recommendation can be made as to the time of introduction of PN in HSCT patients. Its withdrawal should be considered when patients are able to tolerate approximately 50% of their requirements enterally (Grade C).

Comments: Timing of PN initiation is still a matter of controversy, especially since many patients are not malnourished at presentation. In some units, it is routine to commence PN on the first day after grafting[145] and to maintain it for 15–20 days; in others PN is started once oral feeding falls below 60–70% of requirements for three days. Withdrawal of PN is usually considered when patients are able to tolerate approximately 50% of their requirements enterally, but there are no data specific to this context.

3.7. Can HSCT patients benefit from specialized PN support?

Yes. HSCT patients may benefit from glutamine-supplemented PN (Grade B).

Comments: Some nutritional substrates such as glutamine (GLN) may influence physiological mechanisms, or protect the intestinal mucosa from the aggressive impact of chemotherapy and radiotherapy. In HSCT patients, GLN administration has been reported to minimize the intestinal mucosal atrophy associated with exclusive PN, as well as to reduce liver damage caused by chemotherapy or radiotherapy.[147,148] Some evidence exists that glutamine supplementation may also ameliorate a number of other clinical and biological parameters, such as nitrogen balance and immune system function, infection risk, length of hospital stay and financial costs, and survival.[142,149,150] A recent study by Gama Torres et al.[151] showed a positive effect on short-term mortality in allogeneic HSCT with GLN-supplemented PN, but other studies have failed to demonstrate such positive outcomes.[152] Although the optimal dose of GLN to be used in HSCT is not established, studies have suggested that a dose of around 0.6 g/kg/day of GLN may be appropriate.[153,154]

4. Risks of PN

4.1. Does PN "feed" the tumor?

Probably yes. Although PN supplies nutrients to the tumor, there is no evidence that this has deleterious effects on the outcome. This consideration should therefore have no influence on the decision to feed a cancer patient when PN is clinically indicated (Grade C).

Comments: The majority of the studies investigating the relationship between PN and tumor growth have been performed in tumor-bearing animals. However, the effects of PN on experimental tumors cannot be translated in the human field for a variety of reasons. Tumor weight/carcass weight ratio was about 10–20% in experimental tumors but rarely does it exceed 1% in humans. Tumor-bearing animals were typically fed for 1–2 weeks, meaning that the period of artificial nutrition covered about two thirds of the natural history of their disease. The cytokinetics of experimental

tumors are generally quite different (and faster) than in human tumors.

A review of the literature using PubMed and EMBASE identified 12 suitable papers[155–166] representing a total of 140 patients receiving nutritional support versus 84 controls. The studies were classified as randomized clinical trials,[5] comparative non-randomized clinical trials[3] and trials with patients who were controls for themselves.[4] Different indicators of increased tumor cells turnover used in the studies included the DNA index, ornithine decarboxylase activity, flow cytometric DNA distribution, and the labeling index with tritiated thymidine or bromodeoxyuridine. Increased tumor cells turnover was not observed in control patients receiving their usual diet, but it was reported in 7 out of 12 studies in patients receiving nutritional support.

However, there is no evidence in the literature to indicate whether this promotion of tumor metabolism was disproportionately high compared with stimulation of the body cells, and no clinically deleterious effect of PN on tumor growth has been reported when nutritional support was administered to patients who were aphagic and malnourished.

In conclusion, fear for a disproportionate and excessive tumor growth[167] should not lead to appropriate nutritional support being denied to cancer patients if this is indicated on clinical grounds.

Conflict of interest

Conflict of interest on file at ESPEN (espenjournals@espen.org).

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