

# Enteral versus parenteral nutrition in cancer patients: evidences and controversies

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**Abstract:** The debate over the use of enteral nutrition (EN) and parenteral nutrition (PN) is an old but evergreen and hot topic. Since many years, studies comparing EN and PN have been a pivotal ‘leitmotif’ in the published literature on artificial nutrition (AN). Actually, there is a background misunderstanding in this debate; specifically, that EN and PN are competitors in the choice of the route for delivering nutrition support in cancer patients. Conversely, EN and PN have specific indications and contraindications. This review has the purpose to discuss the indications and complications as well as pros and cons of EN and PN in cancer patients, the crucial role of nutrition support in oncology patients during anticancer treatments and throughout the course of disease, and, finally, the role of AN in advanced cancer patients. In summary, we have no evidence-based data able to definitively indicate the optimal method for delivering AN in cancer patients. EN and PN have to be considered equally effective in maintaining or improving nutritional status in cancer patients. Besides, this review strongly supports the recommendation that a baseline nutritional assessment should be carried out by a healthcare professional expert in AN for all cancer patients at the time of diagnosis or anticancer treatment plan, taking the nutritional status, estimated duration of AN, AN-related potential benefits and possible complications into consideration on an individual basis. Moreover, the patient symptoms, performance status, estimated life expectancy, and mainly, will or preferences have to be evaluated and incorporated into the nutrition support plan before the definitive choice of the route for delivering nutrients is decided. Finally, the application of a decision-making process tailored to patient needs—regardless of whether receiving or not anticancer treatment—allows to choose reasonably the optimal nutritional support strategy.

**Keywords:** Artificial nutrition (AN); cachexia; nutrition support; oncology; palliative care

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## Introduction

The debate over the use of enteral nutrition (EN) and parenteral nutrition (PN) is an old but evergreen and hot topic. Since many years, studies comparing EN and PN have been a pivotal ‘leitmotif’ in the published literature on artificial nutrition (AN). Moreover, during the last 15 years conflicting results have been coming out from randomized controlled trials (RCT) and meta-analysis regarding the benefits of EN versus PN in intensive care unit (ICU), surgical or cancer populations. Specifically, the

issue of the route for delivering AN in cancer patients is important and attractive. Thus, I read the paper of Chow *et al.* (1) with interest, and I compliment with the authors for facing such a controversial topic. As in many other papers of this type, any conclusion is hardly generalizable to the overall cancer population. Actually, there is a background misunderstanding in this debate; specifically, that EN and PN are competitors in the choice of the route for delivering nutrition support in cancer patients. Conversely, EN and PN have specific indications and contraindications.

This review has the purpose to discuss the indications and complications as well as pros and cons of EN and PN in cancer patients, the crucial role of nutrition support in oncology patients during anticancer treatments and throughout the course of disease, and, finally, the role of AN in advanced cancer patients.

### Parenteral nutrition (PN)

In cancer patients undergoing chemotherapy, the guidelines (2-4) recommend to initiate EN if oral food intake remains insufficient despite dietary counseling and oral nutritional supplementation, and PN if EN is not sufficient or feasible. Moreover, in patients with chronic insufficient oral food intake and/or uncontrollable malabsorption due to partial obstruction of the gastrointestinal (GI) tract, home AN (HAN) is recommended. Incurable cancer patients may enter a home PN (HPN) program if they are unable to meet their nutritional requirements by oral or enteral route and there is a risk of death due to malnutrition (5).

Prescribing, compounding, and dispensing PN in cancer patients is a multidisciplinary process involving many healthcare professionals: physicians, dietitians, nurses, and pharmacists, usually as members of a Nutrition Support Team (6). The prescriber of PN should be well versed in the appropriate indication for PN, basic in sterility and infection control, vascular access devices (peripheral and central) and their associated complications. An appropriate use of PN can maximize its clinical benefits while minimizing the potential risks for adverse effects. For this reason, the American Society of Parenteral and Enteral Nutrition (ASPEN) keeps on providing us of guidelines and recommendations about PN safety (7). One of the changes that surely improved HPN safety has been the introduction in the clinical practice of multichambered bags (the so-called 'all-in-one bags'). The ASPEN guidelines suggest their use as an available option to best meet patient needs (7).

### PN complications

The first rule to avoid PN complications is to prevent them. Complications from PN can be divided into four categories: (I) metabolic; (II) infectious; (III) mechanical; and (IV) psychological. Usually, the metabolic complications can occur acutely, such as hyperglycemia, electrolyte disturbances, and altered hydration status. These complications are rare and easy to manage. Differently, metabolic complications such as metabolic bone disease

and liver dysfunctions [the so called PN associated liver dysfunction (PNALD)] may be associated with long-term PN use (i.e., years). However, this is not the case for cancer patients on HPN that usually have a median survival ranging between 6 and 12 months (8,9).

Refeeding syndrome (RS) describes the biochemical changes (electrolyte abnormalities), clinical manifestations (fluid retention), and potential complications (cardiorespiratory dysfunction) that can occur as a consequence of feeding a severe malnourished person. Indeed, this complication may occur only in extreme cases, such as in cancer patients with a body mass index less of 14 or a starvation longer than 15 days. In these patients, RS can be prevented by a stepwise and tailored refeeding protocol as well as providing optimal management and monitoring. A prophylactic supplement of phosphate should be always prescribed as well as serum phosphate levels should be closely monitored in patients at risk of the RS. Also, a restricted policy regarding sodium and IV fluids should be adopted in order to maintain zero balance. Finally, consider thiamine supplements (to the level of 100–300 mg/day) during the first 3 days in order to prevent neurological side effects associated with glucose delivery from PN (10).

In the past, the use of high doses of glucose resulted in hyperglycemia, hypertriglyceridemia, and hepatic steatosis. Nowadays, glucose-related abnormalities can be prevented to a large extent by choosing parenteral mixtures with a reduced glucose content. For the few cancer patients on HPN that need to continue insulin therapy (e.g., patients with diabetes, steroid therapy or pancreatic cancer), it is important they to be educated about glycemic control and be provided with a glucometer. Lipid-related abnormalities occur very rarely in cancer patients on HPN, usually related to liver dysfunctions (i.e., cholestasis) due to the progression of cancer disease in the liver. When a triglyceride level greater than 5 mmol/dL (or >400 mg/dL) is reached, the fat content may be reduced (i.e., opening the bag lipid compartment from 1 to 4 times per week) according to the triglyceride level.

An interesting question is: which is the most feared and relevant complication of PN in cancer patient? The answer is catheter-related bloodstream infection (CRBSI), but this is just catheter-related and not PN-induced complication. Also, mechanical complications (i.e., catheter dislocation, lumen occlusion, rupture of external tract, and venous thrombosis), as infectious complications, are catheter-related complications (CRCs) and not PN-induced complications. In cancer patients is particularly important the prevention of

catheter-related central venous thrombosis due to a higher risk of deep vein thrombosis in these patients. Thrombosis is avoided by the use of appropriate insertion techniques including: (I) the ultrasound guidance at insertion; (II) the choice of a catheter with the smallest caliber possible; and (III) the position of the catheter tip at or near the atriocaval junction (11).

In recent years, several technological novelties have considerably improved the safety of central venous access devices (VADs) in cancer patients (i.e., peripheral insertion of VAD, ultrasound-guided venipuncture, novel materials, and sutureless devices for catheter securement), whereas new policies have successfully decreased the overall risk of complications (well-defined ‘bundles’ of evidence-based interventions, strict policies on hand washing, proper skin antisepsis, training of healthcare professionals, etc.) (12).

Finally, which is the psychological impact of HPN on patient’s quality of life (QoL)? According to the literature, HPN improves QoL in advanced cancer patients (13-15). An important factor that markedly reduces psychological impact of HPN is the infusion delivery during the nighttime. Like this, HPN has minimal impact on a patient’s daily activities.

The second rule to avoid PN complications is monitoring cancer patients on HPN. Every healthcare provider involved in the care of cancer patient should be prepared to recognize signs of CRCs and early intervene for treating them. In our management process, the occurrence of CRCs is closely monitored by the physician responsible for HPN through regularly scheduled and structured telephone interviews (at least every 15 days), in-hospital medical examinations (at least every month), and home visits by specifically trained nurses (initially every day for 2–3 weeks and at least every 7 days thereafter). If accurately managed, HPN can be safely provided for most cancer patients, even in an advanced stage, without expecting a relevant incidence of CRCs (16).

### Enteral nutrition (EN)

EN is the preferred method of nutritional support when the GI tract is functional and the cancer patient is unable to have an adequate oral intake of nutrients to meet his/her nutritional requirements. The guidelines (3,4,17) recommend that EN may be done using nasogastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG) in radiotherapy—induced severe mucositis or in head-neck/thoracic cancers with obstructive tumor masses. Long-term home EN may be provided, usually through a PEG. About

10% of head and neck cancer patients require permanent EN (8). The enteral route is efficient and cost-effective, however it is not always as easy as it looks.

### EN complications

Also EN may cause complications that can be divided into three categories: (I) GI; (II) mechanical; and (III) metabolic. Early satiety, nausea, and vomiting occur in approximately 20% of patients receiving EN due to several causes—usually, the pathogenesis is multifactorial in cancer patient—but delayed gastric emptying is the most common cause. If delayed gastric emptying is suspected, consider the following strategies: (I) reducing the rate of infusion; (II) reducing opioid medications—if it is possible; (III) switching to a low-fat enteral formula; (IV) administering the enteral formula at room temperature; and (V) finally, administering prokinetic and/or antiemetic medications. If the patient present abdominal distension, check gastric residuals before the next bolus feeding or every 4 hours for continuous feeding. During EN administration, diarrhea is common, occurring in 2–63% of patients; obviously, the incidence is depending on how diarrhea it is defined (i.e., as having 3 or more loose or liquid stools per day, or as having more stools than is normal for that person). Constipation is less common and usually is more probably due to the disease (i.e., peritoneal carcinomatosis and/or intra-abdominal recurrences) than the EN formula.

Pulmonary aspiration is the most feared and relevant complication of EN and can be life-threatening. The incidence of clinically significant aspiration pneumonia is rare. However, aspiration of small amounts of EN formula may not cause immediate symptoms, but the appearance of fever in a cancer patient in EN requests to exclude a aspiration pneumonia. As for PN, mechanical complications are tube-related and may arise during the placement of the EN access device into the GI tract or later from its presence. The more common complications are tube malposition and clogging. Several studies compared the rate of tube-related complications in case of NGT or PEG. There was not sufficient evidence to determine between NGT and PEG the optimal method of enteral feeding for patients with head and neck cancer receiving radiotherapy and/or chemoradiotherapy (18). However, head and neck cancer patients with NGT feeding were more likely to experience tube dislodgement, while NGT caused less incidence of dysphagia than PEG (19). Also, cancer is identified as a significant risk factor of PEG-related infection (20).

Metabolic complications of EN are similar to those that occur during PN. RS may occur also with EN. As for PN, careful monitoring can minimize or prevent these complications.

### Enteral versus parenteral nutrition

Initially, PN was considered to be the standard of care when a patient needs AN. Without any doubt the introduction of PN in the clinical practice in the late 1960s significantly helped many surgical and critically ill patients to recover from previously life-threatening clinical conditions. However, the widespread use of this treatment, in the form of ‘hyperalimentation’ (i.e., hypercaloric PN)—also called overfeeding—in all patients even with uncertain indications generated doubts and mistrust and consequently increased the role of EN (21).

This is so true that, at the beginning of this millennium, Heyland wrote in an editorial there are limited data demonstrating that PN positively impacts clinically-relevant end points in critically ill patients. Moreover, Heyland asserted that studies comparing EN with PN suggest that EN is associated with reduced infectious complications while PN is associated with increased morbidity and mortality in some subgroups of critically ill patients (22). In contrast, Jeejeebhoy, another master of nutrition, in the same years had a completely opposing opinion regarding PN and wrote that the dangers of PN-induced complications have been exaggerated. Further, Jeejeebhoy clearly and concisely defined in his editorial the role of PN writing that ‘PN is an equally effective alternative to EN when a risk of malnutrition is present and EN is not tolerated or when gut failure is present’ (23).

In 2014, it was published a RCT comparing early NE with early PN in 2,400 critically ill patients. The results were: (I) there were no significant differences between the parenteral and the enteral group in the mean number of treated infectious complications, in rates of 14 other secondary outcomes, or in rates of adverse events; (II) caloric intake was similar in the two groups, with the target intake not achieved in most patients. The conclusions of the authors were: (I) no significant difference in 30-day mortality associated with the route of delivery of early nutritional support in critically ill adults; (II) early nutritional support through the parenteral route, as it is typically administered, is neither more harmful nor more beneficial than such support through the enteral route (24).

In the late 1980s emerging evidence from animal studies

supported the concept that EN promotes gut function and prevents the translocation of intestinal bacteria. Therefore, total PN was considered to be a ‘dangerous’ form of therapy (e.g., ‘more harm than good’ or ‘a poison’) and this belief resulted in EN becoming the new standard of care in AN. These studies influenced the choice of ICU physicians of route for delivering nutrients. Moreover, these conclusions were translated in the clinical practice for the nutrition support of all other patients requiring AN. However, the cancer patient is different from the ICU patient in total PN. Usually, cancer patients are not aphagic; particularly patients on anticancer treatment. Aphagic patients receiving total HPN are less than 10% in our experience while the others cancer patients in HPN have residual—but insufficient—oral food intake (usually, a median of 500 Kcal per day) (16). These non-aphagic cancer patients underwent supplemental PN (SPN). Specifically, SPN provides additional amino acids and energy to offset the protein and weight loss experienced from declining food intake. SPN at home provides a median amount of 1,000–1,250 kcal per day, from 3 to 6 times per week. Moreover, there are some advantages of SPN in comparison with total PN: low risk of overfeeding—and therefore of hyperglycemia—overhydration, and liver dysfunction. Finally, the QoL is improved by a non-daily infusion of HPN.

In cancer patients, only a few old studies that were randomized (25–27) or prospective and controlled (27), compared short-term EN with PN. These studies reported that PN was more effective than EN in achieving weight gain (27), even though this gain may be due to an increase of fat mass or water. Moreover, these studies showed that PN was able to preserve a better nitrogen balance and plasma amino acid level (25–27).

Actually, the choice between EN and PN depends on the disease site. A recent study in 1903 French cancer patients showed that the percentage of patients receiving EN (13.8) was not so far from that of patients receiving PN (9.6) (28); particularly, patients with pancreatic, colorectal, gynecological, and hematologic tumors receiving PN were 2–4-fold more than those receiving EN.

The most common reason because a cancer patient may need nutrition support is that he/she very often experiences food intake problems due to negative side effects of the anticancer treatments (surgery, chemotherapy, and radiation therapy). If patients develop GI toxicity from neoadjuvant therapy (i.e., radiation enteritis or chemotherapy/radiation-induced diarrhea), short-term PN is usually better tolerated and more efficient than EN to restore the intestinal

**Table 1** Criteria for withholding artificial nutrition in cancer patients

Short estimated life-expectancy (less than 2–3 months)
Karnofsky performance status scale <50 (ECOG 3–4)
Severe organ dysfunction
Symptoms that are not controlled
Patient will

ECOG, Eastern Cooperative Oncology Group.

function and prevent nutritional deterioration (2). Actually, in cancer patients the GI tract is not always able to tolerate the infusion of the amount of EN formula to meet patients' nutritional requirements due to peritoneal carcinomatosis and/or intra-abdominal recurrences. Moreover, many patients do not tolerate NGT or refuse the placement of PEG and/or jejunostomy. Besides, Orrevall *et al.* showed that nausea, vomiting, and GI obstructions were the most common indications for PN in palliative patients (29). Also, PN should be initiated if adequate EN is not possible in patients with severe radiotherapy-induced mucositis or enteritis and head-neck/esophageal obstructive cancer masses (4).

In the past, many physicians were concerned to start HPN because of the risks potentially associated with the placement and management of central VADs. Currently, this consideration should not still have influence on the decision to feed a cancer patient when PN is clinically indicated. Besides, nowadays almost all cancer patients have a central VAD for a safe administration of chemotherapy.

A criticism directed at PN is to be over twice the cost of EN. Indeed, evidence clearly demonstrated that both EN and PN are relatively cheap adjuvant therapies—helpful to enhance effectiveness of anticancer therapies—especially if compared to other treatments (30). On the contrary, a prolonged in-hospital length of stay is dramatically more expensive than HPN.

Finally, the patient perception of the comfort of the feeding method should be the most important determinant in the choice of the route for delivering AN. Scolapio *et al.* (31) reported that when given a choice between PN and EN, 91% cancer patients preferred IV feeding.

### Artificial nutrition in advanced cancer patients

The role of AN in advanced incurable cancer patients is without doubt the most controversial topic in debate today.

There are pros and cons regarding the use of AN in this oncology population. First of all, we have to distinguish advanced cancer patients between incurable and end-of-life patients, because it is crucial to be sure that the debate refers to the same kind of patients. Worldwide accepted guidelines (2–4) recommend to feed malnourished incurable cancer patients who are still in active treatment with adequate nutrition support in order to enhance compliance with anticancer treatments and control some adverse effects of anticancer therapies (32). Actually, muscle loss strongly predicts the development of chemotherapy-related dose-limiting toxicity (33).

Is there an evidence according to the results of a RCT? Unfortunately no RCT was carried out, because any prospectively controlled evidence of potential benefit is denied due to the unethical nature of longer-term studies having a non-AN control arm including aphagic patients or with markedly insufficient oral food intake (2).

Nowadays, there is an increasing number of cancer patients who survive in a chronic condition of reduced oral food intake. But, the key question is: is there the indication for HAN in patients with no further treatments? (34). The European guidelines state that stopping anticancer treatments is not a contraindication for HAN (2). The rationale is that some advanced cancer patients, especially those with GI tract tumors may die from progressive starvation but not because the tumor (8). Incurable cancer patients should receive nutritional interventions if their expected benefit outweighs the potential harm and, obviously, the patient wants this therapy (4). However, HAN should not be prescribed to all patients with incurable cancers. The major challenge is how to identify patients with a performance status and tumor stage/spread which allow them to survive more than 3 months (9). In these patients, is really important to discuss the role of nutrition support in this phase of their disease. In the *Table 1* are shown our criteria for withholding AN in cancer patients. Finally, in patients who are imminently dying artificial hydration and nutrition are unlikely to provide any benefit. However, providing AN or artificial hydration to cancer patients who are in the last week of life is a frequent practice (35). In the *Table 2* are shown our criteria for withdrawing AN in cancer patients.

In the past, it was a common experience that the vast majority of cancer patients referred to the nutrition team for nutritional evaluation had an evident cachexia. According with the classification of cancer cachexia (36), refractory cachexia is characterized by a low performance status



**Table 2** Criteria for withdrawing artificial nutrition in cancer patients

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Short estimated life-expectancy (days)
Uncontrolled or refractory symptoms:
Pain
Vomiting
Dyspnea
Delirium
Progression of major organ failure as reflected by:
Increase of liver tests
Increase of creatinine
Need of oxygen supply
Refractory hypotension
Decrease of performance status scale
Patient will

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[Eastern Cooperative Oncology Group (ECOG) 3 or 4] and an estimated life expectancy of less than 3 months. In this phase of disease trajectory, the cancer patient is not responsive to anticancer treatment as well to AN aiming to reverse cachexia. In fact, an opportunity for nutritional interventions to stop or reverse cachexia exists when the expected survival is more than 3 months (37). Therefore, therapeutic interventions should focus on alleviating the consequences and complications of cachexia, i.e., symptom palliation (appetite stimulation, management of nausea or eating-related distress of patients and caregivers).

## Conclusions

AN is essential to meet the nutritional needs of cancer patients at risk of undernutrition as the latter can lead to a poorer prognosis for these patients. There is debate over which method of AN provides the most benefit to the cancer patient for outcomes such as nutritional benefit and QoL, as well as avoiding delays in anticancer treatments. However, due to the small number of comparative studies available, we have no evidence-based data able to definitively indicate the optimal method for delivering AN in cancer patients.

In summary, EN and PN have to be considered equally effective in maintaining or improving nutritional status in cancer patients (8). Besides, this review strongly supports the recommendation that a baseline nutritional assessment should be carried out by a healthcare professional expert

in AN for all cancer patients at the time of diagnosis or anticancer treatment plan, taking the nutritional status, estimated duration of AN, AN-related potential benefits and possible complications into consideration on an individual basis. Moreover, the patient symptoms, performance status, estimated life expectancy, and mainly, will or preferences have to be evaluated and incorporated into the nutrition support plan before the definitive choice of the route for delivering nutrients is decided. Finally, the application of a decision-making process tailored to patient needs—regardless of whether receiving or not anticancer treatment—allows to choose reasonably the optimal nutritional support strategy.

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## Footnote

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