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Review article

Parenteral nutrition

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Although about 50 y have elapsed since the introduction of parenteral nutrition (PN) in oncologic clinical practice [1–3], it is only in recent years that its use has been included in international guidelines [4–6].

It is useful to distinguish the two types of PN, total (TPN) and supplemental PN (SPN), because they differ in aims, nutritional regimen, and user friendliness.

Total parenteral nutrition

PN is defined as "total" when the intravenous (IV) administration of nutrients represents the exclusive (or the near-exclusive) technique for feeding the patient and is used when patients cannot eat by mouth, and tube feeding is not possible or not accepted by the patient [7]. This treatment is quite demanding, requiring a specific technique to avoid excessive or deficient administration of nutrients and to prevent metabolic complications and catheter mechanical and infection problems. Long-term TPN, and especially home TPN (HPN), usually require the presence of a dedicated service or a nutrition support team [8].

TPN meets the original need to use an artificial gut to replace one that is either absent or not working [9]. TPN is not the primary treatment of cachexia—which is characterized both by starvation and alteration of the metabolic pathways—because it can control only the "nutritional" component of this syndrome. From this perspective, the clinical benefit of TPN can be expected only in patients with cancer for whom nutrient deprivation plays a major role in the outcome. However, it should be considered that no anticachectic treatment should be expected to be beneficial if the patient is not adequately fed. Furthermore, recent research on the different uses of nutritional substrates in healthy individuals and patients with cancer shows that it is possible to optimize the IV diet with a regimen that is specific for the malnourished patient with cancer, in which case the aim is to feed the patient rather than the tumor.

Given these premises, it appears rational that TPN be proposed generally for hypo-aphagic outpatients (HPN), whose life expectancy owing to the tumoral spread is reasonably long and can be adversely affected by a progressive nutritional deterioration owing to unrelenting starvation. In clinical practice, this happens when the oral intake is almost totally precluded by the presence of a malignant obstruction of the bowel, often owing to a peritoneal carcinomatosis. In such cases, the obstruction may also be intermittent—immediately worsening when the patient attempts to eat something—and is associated with early satiation, nausea, vomiting, abdominal distension, and pain. Sometimes there is a severe anorexia; however, a few patients may refrain from eating just to avoid the onset of gastrointestinal symptoms and they can experience some feeling of hunger. Almost all these patients are incurable even if few are still receiving some type of so-called palliative chemotherapy.

Rationale for HPN in incurable cancer patients

Worldwide experience shows that HPN is used in patients with cancer in very advanced stages of disease, when death from

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progressive starvation is expected to occur before the evolution of the cancer toward the final outcome. The quality of life (QoL) of the patients at their entry in a program of HPN should be acceptable and concurrent symptoms rather mild or well controlled, otherwise the indication for a program of HPN would immediately decay.

Cachexia is the main cause of death of patients with cancer, ranging from 5% to 23% [10–14]. Even if cancer cachexia cannot be equated with simple starvation, a wide body of literature has shown that weight loss in patients with cancer is proportional to the severity of anorexia or to the reduction of nutrient intake or to persistence of negative energy balance [15–19]. On the other hand, there is now increasing evidence showing that specific nutritional support is able to maintain or improve body weight and lean soft tissue.

It is well known that the life expectancy of patients undergoing total starvation is quite limited. The survival of healthy people undergoing an extreme hunger strike is about 2 mo [20–22] and mean survival of patients with cancer undergoing total or almost total macronutrient deprivation (usually for malignant bowel obstruction) is reported to be 62 d in those undergoing surgical exploration only [23–28] and 52 d in hospitalized patients [29–36] without nutritional support. If we consider patients with cancer discharged at home without HPN, the literature reports a mean survival of 19, 27, and 15 d [37–39], respectively. These were the basic reasons why an International Consensus [40] more than 20 y ago suggested that HPN in advanced hypo-aphagic patients with cancer should be considered only if the expected survival owing to the malignancy was ≥2 mo.

Prospective studies on survival of patients with incurable cancer on HPN

Because most of the studies on HPN in hypo-aphagic advanced cancer patients are retrospective and most of the wider series are collected from HPN registries, it appears quite difficult to draw conclusions on the precise indication for such treatment (and consequently on the results) because of the heterogeneity of the patient population. Few studies are prospective [37,41–44] and hence more reliable as concerns the outcome data. The largest prospective series [42] on 414 patients reported a 4.7- and a 3-mo mean and median survival, respectively.

A meta-analysis by Naghibi et al. [45] reviewed this topic focusing on patients with inoperable malignant bowel obstruction and reported, from the analysis of 12 papers meeting the criteria of eligibility, a median survival of 83 d (95% confidence interval, 67–100 d) and a mean of 116 d. Survival was 86%, 64%, 45%, 31%, 26%, and 22% at 1, 2, 3, 4, 5, and 6 mo, respectively. These data show that if we accept a threshold of 2 mo as the longest potential length of survival tolerated by patients undergoing total starvation, the treatment with HPN might prolong survival in about half of them.

More recently, a Cochrane review on the same topic [46] concluded that because the very low certainty of evidence, it is difficult to assess whether HPN improves length of survival in patients with malignant bowel obstruction and emphasized the limitations of the existing literature. Such conclusion is not surprising because the quality assessment according to the methodology of Cochrane analysis relies on parameters (random sequence generation, allocation concealment, criteria for assigning treatments, comparability of treatment groups, blinding of participants and personnel, etc.), which are adequate for evaluating the effectiveness of drugs (which can be—or not be—administered) but do not fit as well for nutrients that are deemed essential for health. This intrinsic discrepancy between a pharmacologic therapy and a nutritional treatment had been already emphasized in the introduction to the ESPEN Guidelines on Parenteral Nutrition [47]. On the other hand, if we consider success to be survival of aphagic patients with cancer on total starvation as >2 mo and we recalculate the survival of the five prospective series [37,41–44], which are more reliable as regards the outcome data, we get a mean survival of exceeding 4 mo on a total of 593 patients.

We followed a different approach: In a large international prospective study on patients with incurable cancer on HPN, when we identified three prognostic factors for survival at the multivariable analysis, namely, the Glasgow Prognostic Score, the Karnofsky Performance Status, and tumour spread [42], the prognostic value of these variables, coupled with type of primary tumor, was subsequently validated on another series of patients [48] and led to the construction of a prognostic nomogram reported in Figure 1.

This nomogram, especially when considering its extreme values, may represent a guide for assessing the potential benefit of HPN and give the caregiver the possibility of negotiating with the patient the option of a program of HPN on the basis of the expected survival.

It is noteworthy that a subanalysis of patients with so-called "refractory" cachexia according to an International Consensus [17] (i.e., Karnofsky Performance Status index was ≤50 and life expectancy ≤3 mo), showed a 3- and 6 mo survival of 29.4% and 8.4%. These figures were 31.7% and 12.2% for patients without vital organ

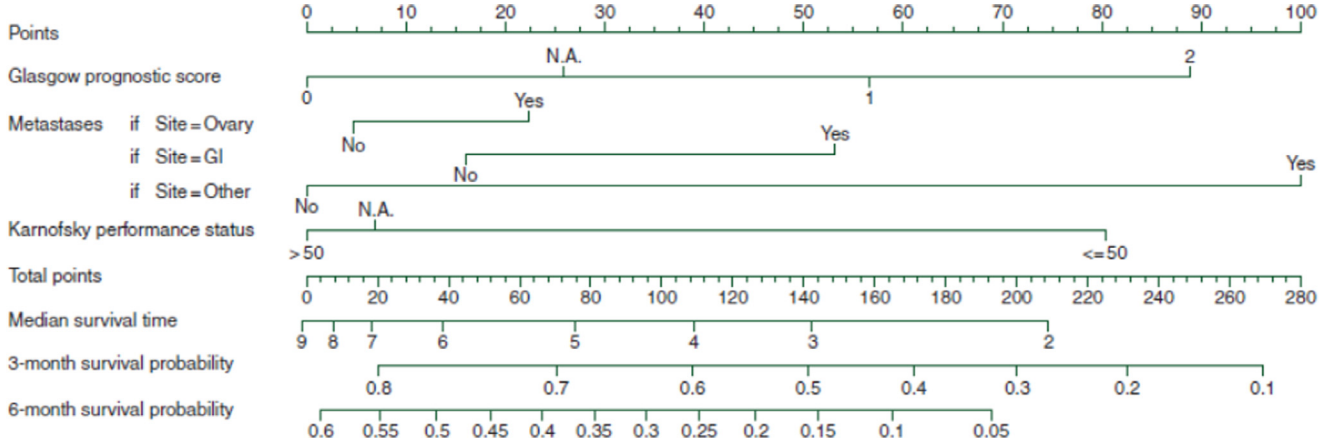

Fig. 1. Cox modeling-based nomogram for predicting 3-mo, 6-mo, and median overall survival. Instructions on how to use the nomogram for building survival estimates are provided at the end of the Results section. GI, gastrointestinal; NA, not applicable.

involvement and 27.1% and 5.9% for those with vital organ involvement. These figures argue against an "en principle" denial of PN in patients with so-called refractory cachexia as stated in the International Consensus [17].

In 33% of these incurable patients, HPN was withdrawn a few days before of death and reasons were tumor progression (73%), patient refusal (20%), onset of HPN/central venous catheter (CVC) complications (6%), and family refusal (0.7%). The cause of death was vital organ failure (46%), progressive wasting (33.8%), HPN or CVC complications (1.2%), and unknown in the remaining patients.

In clinical practice, the discrimination between good and poor candidates may not be easy and in these cases it is worthwhile to adopt a trial-and-error method. That is, one can initiate HPN and withdraw it if it is found to be inappropriate or not beneficial on a subsequent reassessment. This was also the final conclusion of the Consensus Meeting launched by the European Association for Palliative Care in 1996 [40].

Prospective studies on QoL in patients with incurable cancer on HPN

Data on QoL, as summarized in the review by Naghibi et al. [45], are scanty and difficult to interpret. There are only two prospective studies. August et al. [49] reported 17 patients, of which 14, both patients and their families (82%), perceived their therapy as highly beneficial or beneficial. The Nutritional Support Team agreed with this assessment in 11 patients but did not share this perception in 3. These 3 patients had a short duration of HPN (<25 d) or minimal rehabilitation.

Another study [41] investigated the QoL of 69 patients with incurable cancer through the Rotterdam Symptom Checklist questionnaire. These variables were collected at the start of HPN and then at monthly intervals. Median survival was 4 mo (range 1–14) and QoL parameters remained approximately stable until 2 to 3 mo before death. A study that is often quoted, albeit retrospective [50], used a validated instrument to measure QoL, and reported statistically significant improvement in gastrointestinal discomfort, nausea, vomiting, fatigue level, morale, and social interactions during HPN use compared with pre-HPN status. It should be noted, however, that 7 of 92 patients were on HPN because of surgical or radiation therapy late complications.

It is clear that evidence of a benefit from such studies is very limited; however, it should be considered that no randomized controlled trial (RCT) is possible in this clinical context and such matter of investigation is per se so subjective that it appears quite difficult to find appropriate parameters of evaluation. The potential benefit reported in some papers is in keeping with the experience of Orrevall et al. [51] in a similar patient population, where the authors found that QoL could be positively affected by the sense of relief and security in both patients and relatives because the nutritional needs were met through HPN. There is, to our knowledge, only one study [52] investigating the burden superimposed on the family caregivers by HPN in patients with incurable cancer. It reported on a small series of patients for whom the basal level of strain was already high among the relatives and caregivers and did not increase after 2 wk of home care.

Studies regarding the effect on nutritional status of HPN in patients with incurable cancer

Three studies [41,50,53] measured the nutritional status in 150 patients and found that it was maintained.

Complications from HPN

Only a few studies [37,42,44,46,54–56] reported sufficient data to allow calculation of CVC sepsis rates, which ranged from 0.40 to 2.89 per 1000 d. Thrombotic complications were reported by two studies [55,57] with a wide discrepancy between them: One reported a rate of 0.19 per 1000 d [57] and the other [55] 4.34 per 1000 d. Metabolic complications were reported by four studies [42–44,56] and ranged from 0.32 to 1.37 per 1000 d.

Controversial issues in patients with incurable cancer on HPN

Indications for HPN in patients with incurable cancer represent a continuous source of debate and controversy, not only among different specialists, but also among health professionals belonging to the same specialty.

There are a few issues to consider:

1. On the one hand, there is the clear awareness of clinicians involved in clinical nutrition that current medical care has evolved to such an extent—by transforming previously lethal diseases, like cancer, into chronic conditions—that malnutrition and inability to feed may finally represent in some patients the main determinant for length of survival. On the other hand, all caregivers involved in HPN practice are perfectly aware that patients with benign intestinal failure survive "thanks" to HPN, whereas patients with cancer finally die "despite" nutritional support. The consequence of this last evidence is an undervaluation of the role of HPN in cancer patients.
2. There is some confusion in the terminology regarding HPN in patients with advanced cancer since the word *terminal*, which often appears when referring to incurable patients, and PN are ambiguous and misleading. In common language the word *terminal* is often used with reference to patients almost imminently dying, whereas in oncologic jargon it may mean that anticancer therapy is no longer available. The survival of these oncologic patients may range from a few days to several months [58]. Hence, there should be an implicit awareness that some of these terminal patients with cancer are not "biologically" terminal, but simply incurable. To avoid any ambiguity in defining the severity of the state of the patients with special reference to their potential candidacy for HPN, it is wiser to use the term *incurable* for those patients who have exhausted all available oncologic therapies, with the awareness that a subset of them might sometimes require PN if they are aphagic and not imminently dying.
3. A further area of controversy relies on the different conception of PN as medical therapy or just a supportive care. Currently, a medical therapy needs to be validated through RCTs to be accepted as an evidence-based treatment and in such a trial one arm may receive no treatment or merely the standard treatment. However, in aphagic/obstructed patients with cancer, it would be impermissible to have a randomized no-treatment arm, which means progressive undernutrition until death because the standard treatment simply does not exist. Such discrepancy is not confined to the health professional [59–63] but more importantly, involves the relatives of the patients because the anorexia and hypophagia of a patient with advanced cancer represent a major concern for both the patient and their family members [64–66]. Miles [67], emphasizing the cultural and symbolic value of nourishment, which is traditionally viewed as an expression of love and care for both the living and the dying, made with extreme acuity the important distinction that although physicians tend to see "nourishment" as a medical

treatment aimed at achieving physiologic objectives, families see feeding "as an act of community." A specific study on the nutritional situation before the introduction of HPN, from the perspective of patients with advanced cancer and their family members to understand factors contributing to the decision to accept HPN was published in 2004 [66]. Patients reported wanting and trying to eat but being unable to do so; family members experienced powerlessness and frustration because they could not enable the patient to eat. This desperate and chaotic nutritional situation in the family influenced the patient's willingness to accept HPN. A further study of the same authors reported that the interviewed patients with advanced cancer and their family members experienced physical, social, and psychological benefits from HPN treatment [51].

How to approach HPN for the patient with incurable cancer

An approach that fits all possible situations of a patient with incurable aphagic cancer does not exist. The ideal condition of a patient who is perfectly aware of his or her prognosis, asks for the potential benefits and adverse effects of HPN, and then decides whether to enter a program of HPN, is really an exception. Certainly, awareness of the diagnosis and the prognosis are essential for an informed consent to HPN, but this matter may be extremely complicated and delicate. In fact, many patients arrive to the candidacy for HPN late, being already conditioned, regarding their prognosis, by the information provided by the several specialists who followed them in the previous phases of disease.

What really matters is an exhaustive predefinition of the goals of HPN and the chances of success. It cannot be just about avoiding overoptimistic expectations such as "my husband was condemned to die because he could not eat . . . now HPN will avoid it!" Furthermore, if HPN will not be able to attain the predefined endpoints, withdrawing it will be less traumatic for the family and ethically acceptable for the physician.

The main expectation of a clinician who recommends HPN is to maintain the patient with a QoL that is probably better because the patient receives the same treatments at home rather than in hospital.

The phase of progressively withdrawing HPN is very delicate. It may appear that the general status of the patient progressively deteriorates, or liver or lung (or other vital organ) function is failing and requires continuous adjustments of the nutritional regimen, or symptoms are poorly controlled and QoL declines headlong. When this occurs it is important to gradually shift from a nutrition support to a palliative hydration with isotonic electrolyte-glucose mixed solutions.

Patients might have the impression of not being abandoned by their late caregiver but just accompanied in the progression of their disease.

Nutritional regimen

If PN is total, that is the nutrients' intake is negligible, it is important to meet all the nutritional requirements.

Energy requirement

Although several malnourished patients with cancer have resting energy expenditure (REE) higher than standard for sex, age, and weight, the total energy expenditure may be decreased in malnourished patients with cancer because of a reduction in physical activity. Total daily energy expenditure of weight-stable patients with leukemia [68] and of weight-losing bedridden patients with gastrointestinal tumors [69] is around 24 and 28 kcal/kg, respectively. ESPEN guidelines [6] recommend 30 kcal/kg; however, the daily intake of $\geq$30 kcal/kg and 1.2 g/kg protein were not able to attenuate weight loss in patients with head and neck cancer [70]. An adequate nutritional regimen should be likely combined with anabolic/anticatabolic agents to achieve a nutritional replenishment.

Calorie substrates

Fat-enriched regimens (50% of the non-protein calories) are recommended on the basis of the following pathophysiologic arguments:

- Literature [71–76] has shown an efficient mobilization and oxidation of endogenous fat in the postabsorptive state, which ranged from 0.7 to 1.9 g/kg daily (that is about 6.3 to 17 kcal/kg, ~60–78% of the REE), in weight-stable and weight-losing patients. A large study [77] has reported that patients with cancer consistently had a non-protein respiratory quotient <1.
- Subsequent investigations showed that, after administration of long-chain triacylglyceride (LCT) or mixed LCT and medium-chain triacylglyceride emulsions, the daily clearance of lipid was 1.4 versus 2.3 versus 3.5 or 1.2 versus 1.6 versus 2.1 g/kg in healthy individuals versus weight-stable versus weight-losing patients with cancer, respectively [76].
- After IV administration of LCT or mixed LCT and medium-chain triacylglyceride emulsions in weight-losing patients with cancer, the daily oxidation rate was reported to be 1.3 to 1.6 or 0.62 g/kg, respectively [76,78].

Amino acid requirement

Amino acid requirement relies on two orders of data:

1. The negative balance between whole body protein synthesis and breakdown measured in the postabsorptive state was 2.3 to 2.7 g protein/kg daily in patients with cancer versus 1.2 in healthy individuals [79].
2. A literature review [80] suggests that daily doses of amino acid closer to 2 g/kg may be required to control muscle and whole body catabolism and stimulate the synthesis.

Hence, the suggestion is to administer >1 g amino acid/kg daily and, if possible, $\geq$1.5 g/kg per day to support protein balance. Unfortunately, many of the commercial bags have high calorie-to-nitrogen ratio and hence supplying the suggested amount of amino acid carries the risk for overfeeding the patient. Regarding the quality of the amino acid, it should be considered that the accelerated rate of muscle protein breakdown that occurs in cachexia provides an abundant source of intracellular amino acid, which in turn stimulates muscle protein synthesis. However, some are oxidized and are not available for protein synthesis. Therefore, the rate of muscle protein synthesis will never keep pace with the accelerated rate of breakdown in the absence of intake of exogenous essential amino acid and branched-chain amino acid [79]. In the nutritive admixtures of HPN, essential amino acid should be present in large proportion and branched-chain amino acid should account for ~50% of total amino acid.

Supplemental parenteral nutrition

PN is supplemental when patients maintain a limited oral intake of nutrients. Such support may be used for some incurable patients, even if for a short time because of the progressive evolution of the disease toward a more severe hypophagia. Hence, most experiences with supplemental SPN or HPN are in patients undergoing an

Table 1
Prospective studies on the effects of supplementary HPN on QoL measured through validated scores in malnourished patients with advanced cancer on chemotherapy

Author	Patients (N)	Mode of HPN	Methods	Results	Comments
Finocchiaro, 2002	70	27 kcal + 1.1 g AA•kg•d^{-1}	TIQ at >2 mo	QoL 48%, ↑31.5%, ↓20.5	Evaluated 27 patients
Culine, 2013	437	26 kcal + 1.g AA•kg•d^{-1} usually overnight	FACT-G day 1–28	↑ physical, functional, emotional, familial/ social domains	Responsiveness to chemotherapy may affect QoL
Seys, 2014	221	Overnight	FACT-G day 1–28	↑body weight and global QoL in 68% and 59% of patients (and subscore physical, functional, emotional)	Regimen of HPN ill-defined, no statistical analysis, responsiveness to chemotherapy may affect QoL
Vashi, 2014	52	Total (oral + PN) 25–30 kcal + 25–30 g AA•kg•d^{-1}	EORTC QoL-C30	↑ Global QoL index at 1 to 3 mo	Small sample, loss of patients, responsiveness to chemotherapy may affect QoL, assessment of requirements unpractical
Girke, 2016	23	?	EORTC QLQ-C30 day 1–28	↑emotional/social domains, = muscle strength, physical activity, BMI, ↓phase angle	Nutritional regimen not assessed, large patient drop out
Cotogni, 2017	111	21 kcal + 0.8 g AA•kg•d^{-1}	EORTC QLQ-C30, monthly for 1–4 mo	↑ global QoL, physical-role emotional functioning, appetite and fatigue scores	High attrition rate to death in 49 of 111 completed at 4 mo

AA, amno acid; BMI, body mass index; FACT-G, Functional Assessment of Cancer Therapy: General; HPN, home parenteral nutrition; PN, parenteral nutrition; QoL, quality of life, TIQ, Therapy Impact Questionnaire

oncologic therapy when there is some worry that malnutrition or poor oral intake owing to cancer anorexia or to the adverse effects of the oncologic therapy may compromise the administration of the oncologic therapy. This approach represents something new when compared with the usual practice to reserve HPN for incurable patients who are expected to die mainly from starvation rather than from tumor progression. In addition, in this context, some RCTs are possible because the control arm includes patients receiving the standard supportive treatment and this appears ethically acceptable. Looking at the literature, we can focus on RCTs [81–83] or prospective studies that used validated methods of measure of QoL [84–89] (Table 1).

Even if prospective non-RCTs have clear limitations well pointed out in the recent reviews and meta-analyses [45,46], all these studies [83–87] reported some improvement in QoL evaluated through the recognized methodology (Therapy Impact Questionnaire, Functional Assessment of Cancer Therapy: General, EORTC-Quality of Life-C30), a finding also observed in the RCT by Obling et al. [82].

The nutritional status of the patients' data are relatively few and controversial because a benefit of fat-free mass was reported by Obling et al. [82] with a relatively low nutritional regimen and not by Hyltander et al. [88] with a full regimen, whereas the positive results by Lundholm et al. [81] also may be due to the concurrent anti-inflammatory treatment and the long duration of PN.

An important issue is that no study investigated the relationship between response to oncologic therapy and change of QoL, and obviously, the potential regression of the tumor could play an important role on patient QoL. However, the Cotogni study [87] reported that a benefit is also possible, even if lower, in patients with incurable cancer with no concurrent oncologic therapy.

Another point that warrants further investigation is the optimal nutritional regimen for patients on supplemental HPN. In some papers, the information was scant, but when available it ranged from a near-total nutrition [81,83,85,88,89] to a much lighter regimen [82].

Conclusion

Increased awareness of the relevance of good nutritional status and of nutritional support of the cancer patient by oncologists, coupled with availability of prepared all-in-one admixtures has simplified the nutritional approach in clinical practice.

We now are facing the transition from personalized TPN in the aphagic obstructed patient to the simpler IV support of the patient with poor oral feeding. In parallel, the oncologic experience is moving from total nutritional support provided at home to very advanced, cachectic, often incurable cancer patients by an experienced team of nutritionists, to a more simple partial support, which appears in the range of every clinician. After half a century from the naissance of TPN [90], this mode of nutritional support enters the clinical area, which is the most affected by the incidence and severity of malnutrition.

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