



Is there a place for nutrition in palliative care?

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Abstract

Purpose Although nutritional interventions are becoming widely used in cancer patients, purposes and results of such treatment are not always well-defined. This is because nutrition is traditionally considered a palliative treatment to be confined to the area of palliative cares, whereas the modern approach includes nutrition as an early supplemental support to improve compliance of patients with the oncologic therapies and total parenteral nutrition may be recommended in patients who would be destined to succumb prior from starvation-malnutrition than from tumour progression. Purpose of this paper is to define the potential as well as the limitations of nutritional interventions on both the survival and the quality of life of the advanced cancer patients.

Recent findings Some RCT on the use of oral, enteral and supplemental parenteral nutrition in patients on oncologic therapy show some benefit on compliance with therapy and in some domains of quality of life. Some malnourished (hypo)aphagic incurable cancer patients may survive longer thanks to parenteral nutrition, while few data suggest that quality of life may be maintained for a limited period of time.

Summary With a few exceptions, oncology and nutrition have till recently travelled on parallel tracks without talking each other. The oncologist who knows the natural history of the patients should understand which risk of complication and of poor tolerance to the treatment can malnourished patients carry and which is the potential of parenteral nutrition in hypophagic incurable patients.

Keywords Oral nutritional supplements · Enteral feeding · Supplemental parenteral nutrition · Total parenteral nutrition · Home nutrition · Cancer cachexia

Introduction

The title of this paper conceals two ambiguities: on one side, the classic statement of the WHO defines palliative care “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness,

Key points • Malnourished patients poorly tolerate the oncologic therapies

- Nutritional status and compliance with chemo/radiation therapy can improve thanks to nutritional interventions
- Nutritional interventions can be “supplemental” that is adjunctive to a reduced oral intake of nutrients or exclusive (i.e. total parenteral nutrition)
- Nutrition may be supplemental and is indicated in malnourished (or at risk of malnutrition) patients on oncologic therapy or total (i.e. parenteral nutrition) in incurable hypophagic patients.
- Aim of the supplemental nutrition is to potentiate the effects of the oncologic therapy while that of total parenteral nutrition is prolonging survival of incurable patients

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through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”.

Frankly, we are not so sure that nutritional interventions improve quality of life (QoL) of the advanced cancer patients receiving palliative care, a scenario which usually encompasses a large area of severely ill subjects, mainly with an advanced tumour which is often incurable.

On the other hand, according to the recent ASCO recommendations [1] endorsed by the National Comprehensive Cancer Network [2], the time to start palliative care is as soon as a patient’s cancer becomes advanced and in newly diagnosed patients with advanced cancer, early palliative care involvement should occur within 8 weeks after diagnosis. Favourable experiences of early palliative care (including nutritional support) have been already published or are in progress both in the USA [3, 4] and in Europe [5]. In this perspective, nutritional interventions seem to play a role which can be defined more “supportive” than “palliative”.

Finally, the overwhelming majority of nutritional interventions published in the literature have targeted at improving the

nutritional status of weight-losing or hypophagic patients and, in more extreme cases, to prolong survival. If such attempts then can translate in a palliative effect and in an improved QoL, this may happen as a by-product more than as the main end-point of the treatment.

From a clinical perspective, cancer patients requiring a nutritional intervention belong to two broad areas: those who are on oncologic therapy and those no more amenable to any oncologic treatment, the so-called incurable cancer patients. Reasons for distinguishing these two categories are essential from the standpoint of the indication of nutritional interventions and the expected outcome. If patients receive an oncologic therapy, the role of the nutritional intervention is “permissive”, that is maintaining the general status of the patients in condition to better tolerate a therapy which may be toxic for the GI function. In these patients, the indication for a nutritional intervention strictly parallels the indication for the oncologic treatment and its aim is to allow the course of oncologic therapy to proceed normally. However, since palliative chemotherapy too can benefit the patient [6], if there is an improvement of the QoL, both the oncologic and nutritional interventions may credit the therapeutic success. Finally, patients on oncologic therapy are in better general and nutritional conditions than the incurable ones: they are often able to eat and nutritional intervention is usually supplemental, that means that it is possible to perform randomized studies where the control group only receives the standard treatment without a specific nutritional intervention. On the contrary, the main aim of feeding the incurable patients is the attempt to delay an early demise due to starvation and progressive malnutrition. Hence, the indication for a nutritional support follows a comprehensive evaluation of different issues pertinent to oncology, nutritional status, habits, QoL and patients and family expectations. In this situation, the improvement of QoL is often a secondary end-point. These very advanced patients are usually severely hypophagic and randomized studies with a control non-fed group are ethically unacceptable.

Such distinction may be not shared in literature and some oncologists include in the group of patients defined incurable also those who undergo antineoplastic treatment aimed at prolonging life and/or alleviate symptoms [7], without considering that the role of the so-called palliative chemotherapy is still controversial among the same oncologists. Some of them agree [6] with the true palliative role of chemotherapy in the last months of life while others strongly argue against it [8].

Patients on oncologic therapy

From the analysis of two recent reviews examining nutritional support interventions in patients on oncologic therapy [7, 9] and the personal data-base including the more recent literature, we found 12 RCTs [10–21] where nutritional

intervention was a special diet [11, 16] or was just delivered via a tube [15] or was an oral supplementation containing omega-3 fatty acid [14, 17, 20, 21] or enriched in proteins [12, 13] or mixed (protein plus omega-3 fatty acid) [18]. These studies reported some statistically significant benefit in some domains of QoL, with the exception of Paulsen’s study [18] and of Baldwin’s study [10] which reported no effect on QoL using dietary advice, non-enriched or non-fortified nutritional supplements or dietary advice plus supplements. Notably, the RCT of Cereda et al. [13] was also able to show a reduced chemotherapy toxicity and a benefit in QoL. On the contrary, two studies by Gavazzi et al. and by Laviano et al. [15, 17] did not show any benefit in the fed group as regards the primary end-points. The RCT by Ravasco et al. [19], who also showed a benefit in QoL in head-neck cancer patients through dietary counselling with regular foods, is difficult to interpret because some of the patients were receiving an adjuvant oncologic therapy that means that some of them were cancer-free or with a minimal neoplastic burden.

The potential role of home parenteral nutrition (HPN) on QoL has been explored in two RCT [22, 23]. The old study by Lundholm et al. [22] randomized 309 to HPN or no-HPN when oral intake dropped to 21–24 kcal/kg/day and although it did not directly address to QoL, however, it showed an increase of the maximal exercise capacity in patients able to be treated with parenteral nutrition (PN). The recent study by Obling et al. [23] showed that patients on HPN had a benefit in QoL evaluated through the EORTC QLQ-C30 versus no-HPN patients.

In conclusion, there is evidence from RCTs that an appropriate oral nutritional supplementation is able to improve some indexes of QoL in cancer patients maintaining some capability of oral food intake and undergoing oncologic therapy (mainly chemotherapy) while the evidence of benefit with PN relies more on prospective single-arm studies which used validated scores of evaluation of QoL [24–29] than on RCTs.

Patients without oncologic therapy (incurable)

These patients are frankly malnourished and hypophagic for a variety of reasons (severe anorexia, early satiation, chronic intestinal (sub)obstruction etc.) and are usually unfit for an oral nutritional intervention. The tube feeding could be an alternative for some of these patients, provided their gut is normally working, but this approach is considered too invasive and psychologically detrimental and hence is only confined to some patients with head-neck cancer. Consequently, most clinical investigations on nutritional support of incurable cancer patients have the following four main characteristics:

- PN, more frequently HPN, represents the only available way for supporting some incurable patients. Most of these

patients receive total HPN even if initially the PN can be supplemental and swifts to total along with the progression of the disease. An exception was the paper by Uster et al. [30] who used dietary counselling and food fortification and oral nutritional supplements (if required) and did not get any clinical benefit.

- Since incurable patients are hypophagic, it is ethically impossible to perform RCTs which would include a non-fed arm.
- The primary end-point of HPN in incurable cancer patients is to delay an early death due to starvation
- HPN usually starts with the presumption that if the burden of symptoms is acceptable for the patient, QoL at home is likely better than in hospital.

HPN is often the only way to support incurable patients

An overview of the use of PN in cancer patients has been recently published [31]. A large review on thousands patients has shown that anorexia syndrome (including early satiety, nausea and taste alterations) has a prevalence exceeding 50% of patients when tumour is incurable [32] and peritoneal involvement causing a chronic picture of recurrent bowel obstruction is a frequent event in GI and ovarian cancer. Since symptoms in patients with chronic malignant intestinal (sub)obstruction are frequently related to the intake of food and total parenteral nutrition allows a bowel rest, HPN may be successful in maintaining alive the patient without symptoms because the gut does not work. This topic has been recently analysed in two systematic reviews [33, 34] and in a comprehensive appraisal of the literature [35].

RCT are ethically impossible in aphagic patients

We are not sure that nutrition is always able to prolong life in (hypo)aphagic incurable cancer patients; however, it is reasonable to believe that if progression of tumour is slow, vital organs are not severely compromised and patients are severely malnourished and do not eat enough, their demise may arrive earlier in absence of a nutritional intervention. Literature is full of scattered reports [31] which show that survival without intake of macronutrients does not exceed 2 months in normal people undergoing hunger strike and less than 1 month in patients with malignant obstruction after a simple explorative laparotomy or discharged home without any intravenous nutritional support. The more considerable experience on this issue is from patients undergoing a voluntarily stopping eating and drinking for advanced diseases [36]: median survival of 86 patients was 7 days with similar data also reported in the

Oregon experience with patients with an estimated life expectancy longer than 1 month [37]. The only RCT comparing PN versus no-PN in patients with malignant bowel obstruction was performed in Seoul, Korea, in 2014. Oh et al. [38] enrolled 31 consecutive incurable cancer patients with an estimated life expectancy of 4 months (or less): 16 patients were randomized to the PN and 15 to simple hydration (about 370 kcal/day). Median survival was 8 days in the fluid group and 13 days in the PN group, the difference being not statistically significant. The study, which should originally include 116 patients, ended early because many patients and families were extremely concerned about the lack of a proper nutritional support. This study is mentioned to show how many problems arise when a clinical investigator blindly follows the rules of the scientific research without respecting the more elemental ethical principles. The study was finally unsuccessful for several reasons:

- a if survival of arm on PN was only 13 days, this means that patients were likely to die because of the too advanced stage of the tumour and not because of starvation. Only if the patients are expected to die prior from progressive starvation (which usually takes some weeks or 2–3 months) and not from uncontrolled tumour growth, it is reasonable attempting to use PN. The authors grossly overestimated the life expectancy of their patients' population and the enrolment of metastatic patients with a low performance status (ECOG 3 or 4), anaemia, lymphopenia and low serum albumin, finally resulted in selecting a series of almost imminently dying patients with no indication for a nutritional support.
- b The study was prematurely closed because many patients and relatives were repulsed by the idea of taking part to the study due to their concerns about starving to death if the patient was allocated to the control arm. It is clear that there was, on one side, a very poor comprehension of the study by the patients (or their relatives) when they signed the consent and, on the other side, ethical problems were grossly underestimated by the researchers.
- c Finally, the major risk of this paper is that a hasty reader reaches the conclusion that there is no role for intravenous nutritional support in advanced patients with malignant bowel obstruction, without a clear awareness of the serious flaws of the study.

The primary end-point of HPN is to delay an early death

If primary end-point of HPN in incurable patients is preventing an early premature death due to severe malnutrition, it is crucial to identify the right patients' population which could benefit from nutritional support. The higher

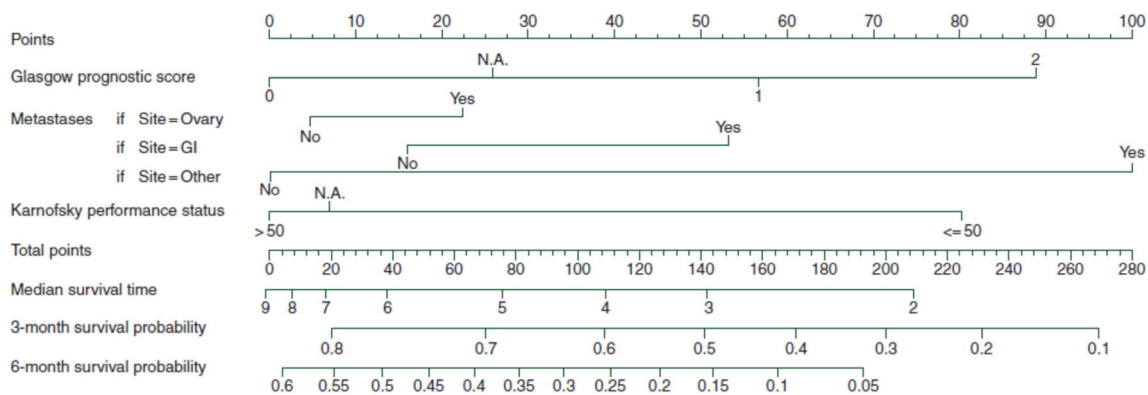


Fig. 1 Cox modelling-based nomogram for predicting 3-month, 6-month and median overall survival. Survival estimates are built by summing the points of Glasgow Prognostic Score, Sites of metastases and Karnofsky

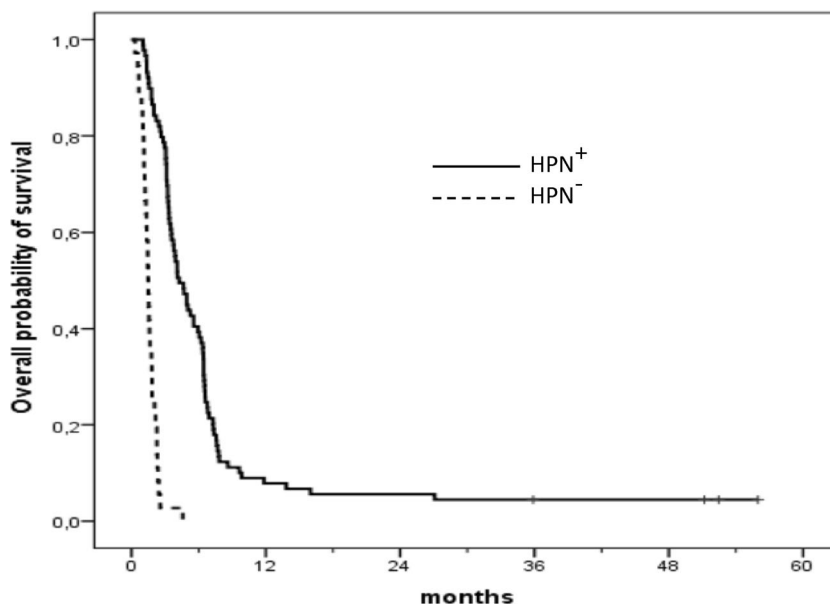
Performance Status. *GI* gastrointestinal, *N/A* not applicable. The final sum gives the estimate of median and 3- and 6-month survival

risk is to enrol in a HPN programme patients with such an advanced disease that progression of the tumour and not malnutrition is the main determinant of the early outcome. The opposite error for a caregiver is to consider that all advanced cancer patients will die *because* of the tumour (thus disqualifying them for a nutritional support), while some of them can die *with* the tumour but because of malnutrition. Unfortunately prediction of the prognosis is rather easy when patient is imminently dying, but is quite inaccurate when prognosis is of some weeks or a few months. According to a recent review on prognostication of survival [39], the temporal clinician prediction of survival often results in systematical overestimation and has a 20% to 30% rate of accuracy, defined as a predicted survival rate of within ± 33% of actual survival. Also, the palliative prognostic index which includes items on oral food intake has a similar poor accuracy [40, 41].

We tried to overcome this problem in an empiric way analysing on a prospective series of some hundred of malnourished cancer patients on HPN which variables, at the entry into the HPN programme, were associated with survival [42]. After an external validation of the variables identified as prognostically valid at the multivariable analysis, it was possible to build a nomogram which reasonably predicts 3- and 6-month and median survival (Fig. 1) [43]. This nomogram does not mean that the old rule of thumb of an expected survival longer than 2 months is no more required to reasonably recommend HPN [44] but, simply, it may objectively support such decision. Furthermore, it may help the clinician to modulate the strength of the recommendation in favour or against a programme of HPN when the score is placed at the extremities.

Whereas a scientific evidence of efficacy of HPN cannot be obtained through RCT, the recent experience of the Molinette Hospital of Turin cannot be overlooked [unpublished data].

Fig. 2 Survival of 89 patients on HPN (—) versus 36 without HPN (- - -)



Briefly, 125 incurable patients were accepted in a programme of HPN because suitable according to the recommendations of ESPEN Guidelines [45]. However, before starting the treatment, 36 patients declined from the programme for a variety of reasons (difficulty to find an adequate caregiver, admission to hospice etc....) and the remaining 89 patients received the planned intervention. Notably, there were no statistically significant differences as regards many characteristics and prognostic variables (sex, gender, age, tumour site, tumour stage, ECOG, BMI, weight loss, mGPS, PG-SGA) between the no-HPN and HPN groups when the patients were accepted in the HPN programme. We found that survival, as shown in Fig. 2, was almost three times longer in HPN group of patients and, at a multivariate analysis, HPN was by far the strongest variable significantly associated with survival. This study well demonstrates in a quasi-RCT the potential of HPN in malnourished incurable cancer patients when selected according to the indications of ESPEN.

HPN and quality of life

Data on quality of life as summarized in the review by Naghibi et al. [33] are scanty and difficult to interpret. The attempt to correlate HPN with change of the QoL is problematic for a couple of reasons:

- (1) if a disease is incurable, it is natural that, as the final outcome is approaching, there is a progressive deterioration of the QoL. This was clearly shown in the only available study which sequentially analysed the variation of parameters of QoL during the trajectory of the disease towards the final outcome in incurable patients on HPN [46] where QoL parameters maintained somewhat unchanged till 2–3 months before death.
- (2) domains of QoL and factors impacting on it are so many and heterogeneous that it may appear naïve to speculate that a single intervention is effective on QoL. The only recent contribution to this topic [24] regards a heterogeneous group of patients where the incurable ones were a minority and is in keeping with previous observation of a limited benefit in some domains, followed by a decline. An old paper by August et al. [47] reported 17 patients: in 14, both patients and their families (82%) perceived their therapy as highly beneficial or beneficial. On the whole, the meagre available literature would suggest a limited transient benefit or maintenance of QoL indexes during HPN. Only one small study [48] investigated the burden superimposed to the family caregivers by a 2-week course of HPN in these patients and reported no increase of the basal level of strain but one could speculate that it was already extremely high when patients were discharged home.

Conclusion

Nutritional interventions in cancer patients on oncologic therapy are more supportive than palliative *sensu strictiori*, main aim being the improvement of the compliance with chemotherapy and radiation therapy. Regardless of the route of administration, these interventions are usually supplemental and most RCTs have shown a clinical benefit for the patients. Nutritional interventions in incurable cancer patients are more frequently confined to PN, which aims to prolong survival and appears successful in patients in which final outcome appears more related to malnutrition and starvation than to tumour spread progression. In such conditions, benefit in QoL appears little documented and rather transient.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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