Impact on Health-Related Quality of Life of Parenteral Nutrition for Patients with Advanced Cancer Cachexia: Results from a Randomized Controlled Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Malnutrition worsens health-related quality of life (HRQoL) and the prognosis of patients with advanced cancer. This study aimed to assess the clinical benefits of parenteral nutrition (PN) over oral feeding (OF) for patients with advanced cancer cachexia and without intestinal impairment.

Material and Methods. In this prospective multicentric randomized controlled study, patients with advanced cancer and malnutrition were randomly assigned to optimized nutritional care with or without supplemental PN. Zelen's method was used for randomization to facilitate inclusions. Nutritional and performance status and HRQoL using the European Organization for Research and Treatment of Cancer QLQ-C15-PAL questionnaire were evaluated at baseline and monthly until death. Primary endpoint was HRQoL deterioration-free survival (DFS) defined as a definitive deterioration of ≥10 points compared with baseline, or death.

Results. Among the 148 randomized patients, 48 patients were in the experimental arm with PN, 63 patients were in the control arm with OF only, and 37 patients were not included because of early withdrawal or refused consent. In an intent to treat analysis, there was no difference in HRQoL DFS between the PN arm or OF arm for the three targeted dimensions: global health (hazard ratio [HR], 1.31; 95% confidence interval [CI], 0.88–1.94; $p = .18$), physical functioning (HR, 1.58; 95% CI, 1.06–2.35; $p = .024$), and fatigue (HR, 1.19; 95% CI, 0.80–1.77; $p = .40$); there was a negative trend for overall survival among patients in the PN arm. In as treated analysis, serious adverse events (mainly infectious) were more frequent in the PN arm than in the OF arm ($p = .01$).

Conclusion. PN improved neither HRQoL nor survival and induced more serious adverse events than OF among patients with advanced cancer and malnutrition. *Clinical trial identification number.* NCT02151214 *The Oncologist* 2020;25:e843–e851

Implications for Practice: This clinical trial showed that parenteral nutrition improved neither quality of life nor survival and generated more serious adverse events than oral feeding only among patients with advanced cancer cachexia and no intestinal impairment. Parenteral nutrition should not be prescribed for patients with advanced cancer, cachexia, and

no intestinal failure when life expectancy is shorter than 3 months. Further studies are needed to assess the useful period with a potential benefit of artificial nutrition for patients with advanced cancer.

INTRODUCTION

Malnutrition occurs in 50%–80% of patients with advanced cancer, according to the type of cancer and the stage. It can severely impair clinical outcomes among patients with cancer, increasing morbidity and mortality and reducing treatment efficacy [1, 2]. Cachexia in advanced cancer is a multifactoriel syndrom that associates weight loss, sarcopenia and loss of fat tissue. Its pathophysiology is driven by various combinations of inadequate food intake and systemic inflammation response syndrome (SIRS), which in turn promotes metabolic disorders and catabolism, especially protein breakdown in skeletal muscle [3, 4]. In a vicious circle, systemic inflammation-induced fatigue contributes to decreased physical activity and thus reduces anabolic signals, promoting further muscle loss. Anticancer treatments can cause side effects that further compromise nutritional status, and muscle loss strongly predicts the development of chemotherapy toxicity [5, 6]. Patients with cachexia and sarcopenia report worse quality of life (QoL) and more depression symptoms [7, 8]. Furthermore, higher muscle strength at the start of palliative chemotherapy is associated with significantly better survival in older patients with advanced cancer [9, 10]. Indeed, the management of malnutrition is a very important target of patient-centered approach, as well as a necessity to increase anticancer treatment efficacy, which involves close collaboration between the oncologist and an integrated palliative care team [11, 12].

Nutritional guidelines for patients with advanced cancer recommend a multimodal management, including increasing food intake, promoting physical activity, and fighting against SIRS, alongside anticancer treatment [13, 14]. Nutritional interventions should aim at improving clinical outcomes such as changes in physical function and QoL. In patients undergoing anticancer treatments, if oral food intake is inadequate despite counselling and oral nutritional support, supplemental enteral nutrition or parenteral nutrition (PN) may be implemented. Careful consideration of the prognosis is required to avoid overtreatment with artificial nutrition at the end of life [15–18]. Enteral nutrition should be first considered for patients with a normally functioning gastrointestinal tract, but adverse effects of enteral nutrition are frequent (e.g., early satiety, nausea and vomiting, pulmonary aspiration, and metabolic complications) [19, 20]. It has been reported that most patients with advanced cancer do not wish to receive nasogastric tube feeding because of the psychological and social impact [21]. PN may be more effective for more rapidly increasing calorie intake, with fewer adverse events except for infectious complications [18–20].

In this context, in order to increase the level of evidence, we performed the first multicentric randomized study to assess the clinical impact of PN among malnourished patients with advanced cancer without gastrointestinal dysfunction.

MATERIALS AND METHODS

Study Design and Patients

The study is a prospective, national, multicenter, open-label randomized, parallel-group, controlled trial designed to compare PN with oral feeding (OF) for malnourished patients with advanced cancer and functional gastrointestinal tract. The detailed protocol has already been published [22], and we present here the outline.

Inclusion criteria were patients with malnutrition defined as a body mass index (BMI) <18.5 for patients aged less than 70 years and BMI <21 for those aged more than 70 years or as weight loss of 2% in 1 week, 5% in 1 month, or 10% in 6 months; life expectancy less than 12 months and more than 2 months; functional gastrointestinal tract without symptomatic peritoneal carcinomatosis or intestinal obstruction; and patients with a central venous catheter. Main exclusion criteria were patients with head and neck and esophageal-gastric cancer and any contraindication for PN (such as poorly controlled diabetes, severe heart failure, or severe ascites and edema). To assess life expectancy clinicians could use the previously published "surprise" question ("Would I be surprised if this patient died in the next 12 months?") for predicting death in seriously ill patients [23, 24].

All patients were systematically referred for a consultation with a dietician for assessment of symptoms limiting food intake; advice on hypercaloric, hyperproteic, and fractionated feeding; and prescription of oral nutritional complement if needed. Patients simultaneously received medical information and counselling about adapted physical activity. Patients were all already being followed by the palliative care team.

Patients were randomized following Zelen's single-consent design, which allows physicians to randomize patients before consent and then obtain informed consent on the intervention only from those patients randomized to the experimental arm [25, 26]. Patients in both arms gave their consent for the monthly follow-up with quality of life questionnaires. This choice of randomization method was guided by the difficulty of randomly assigning patients between two treatments of unequal appearance. Implementing parenteral nutrition or continuing with oral feeding are such different treatments that relatives and patients themselves may have a strong preference for one or the other. It can be influenced by their willingness to take action or "give up" or their preconceived ideas of which type of nutrition may be more effective, more toxic, or both. The use of Zelen's method was approved by patient associations gathered within the "Collectif Interassociatif Sur la Santé" and the clinical ethics committee of the Besançon University Hospital. Letters of support have been produced by these committees, highlighting the sensitivity of informing and having a random assignment for the mode of feeding for this particularly fragile and vulnerable study population. Some experts initially considered the Zelen method to be a violation of the ethos; then the method was found to be attractive for research in situations of great
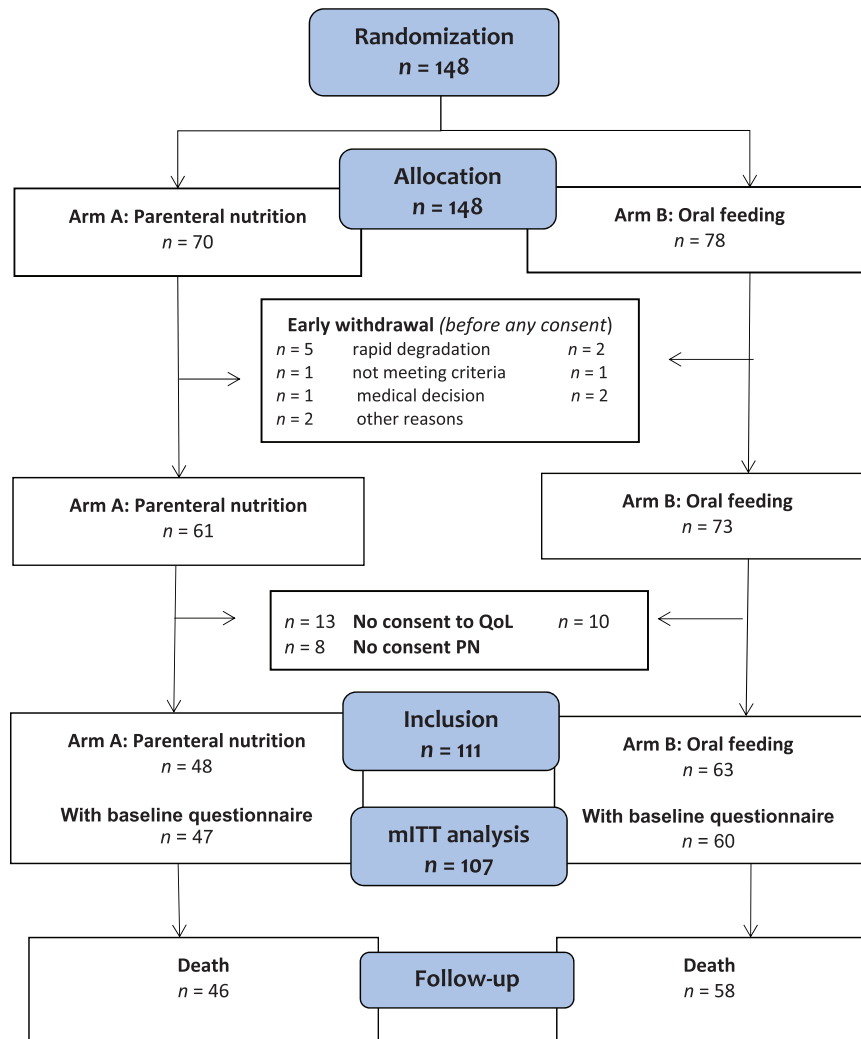
Figure 1. Flowchart of the study population.
Abbreviations: mITT, modified intent to treat; PN, parenteral nutrition; QoL, quality of life questionnaire.

precariousness and has been used in a variety of different contexts, including cancer treatment [26–31]. The Zelen procedure protects patients in the control arm who receive routine care from anxious questioning related to a randomization and offers a true informed choice and consent for parenteral nutrition for patients in the intervention arm. More formally, in accordance with the regulations applicable in France, the study protocol subsequently received a favorable opinion from the "Comité de Protection des Personnes" and the institutional review boards of the participating centers and an authorization from the national health authority ("Agence nationale de sécurité du médicament et des produits de santé").

The study was performed in accordance with Good Clinical Practice guidelines and with the Declaration of Helsinki.

Intervention: Parenteral Nutrition
Parenteral nutrition was administered by central venous route using industrial ternary preparations and systematic daily addition of polyvitamins, trace elements, and electrolytes (sodium, potassium, vitamin K, magnesium, phosphorus), adapted as required. The dosage depended on the patient's food intake to achieve 30–35 kcal/kg/day with 1.2–1.5 g/kg/day

of protein, without exceeding 1.25 times the resting state energy expenditure calculated according to the Harris-Benedict equation. For patients who maintained an oral diet, a minimum intake of 1,000 kcal/day and 6 g of nitrogen was prescribed 5 days a week.

Objectives and Assessments
The primary objective was to assess the impact of PN on QoL for malnourished advancer cancer patients with no intestinal failure. Health-related QoL (HRQoL) was assessed in each treatment arm at least once per month until death using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL. This questionnaire is a validated tool in the French language to assess HRQoL in palliative cancer care patients [32].

The primary endpoint was HRQoL deterioration-free survival defined as time from inclusion in the study to the first deterioration of ≥10 points in the HRQoL scale scores with no further improvement of at least 10 points as compared with the baseline score, or death [33]. We targeted three dimensions of the EORTC QLQ-C15-PAL: overall quality of life, physical functioning, and fatigue.

Table 1. Baseline characteristics of the patients included (*n* = 111)

Characteristics	Parenteral nutrition arm (*n* = 48), n (%)	Oral feeding arm (*n* = 63), n (%)	All patients (*n* = 111), n (%)
Age			
Mean ± SD	66.6 ± 9.7	66.2 ± 9.2	66.3 ± 9.4
Median (IQR)	66.5 (61–75)	67 (59–72)	67 (60–72)
Gender			
Male	22 (45.8)	28 (44.4)	50 (45.05)
Female	26 (54.2)	35 (55.6)	61 (54.95)
Cancer site			
Digestive	14 (29.17)	18 (28.57)	32 (28.83)
Pelvis	8 (16.67)	11 (17.46)	19 (17.12)
Lung	9 (18.75)	12 (19.05)	21 (18.92)
Prostate	5 (10.42)	7 (11.11)	12 (10.81)
Sarcoma	0 (0)	4 (6.35)	4 (3.60)
Breast	11 (22.92)	5 (7.94)	16 (14.41)
Melanoma	0 (0)	1 (1.59)	1 (0.90)
Other	1 (2.08)	5 (7.94)	6 (5.41)
Number of metastases			
Mean ± SD	2.25 ± 1.03	2.24 ± 1.41	2.25 ± 1.26
Median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
ECOG performance status			
1	4 (8.33)	3 (4.92)	7 (6.42)
2	22 (45.83)	26 (42.62)	48 (44.04)
3	18 (37.50)	28 (45.90)	46 (42.20)
4	4 (8.33)	4 (6.56)	8 (7.34)
Chemotherapy			
Ongoing	21 (43.75)	29 (46.03)	50 (45.05)
Prior treatment	25 (52.08)	30 (47.62)	55 (49.55)
Hormone therapy			
Ongoing	2 (4.17)	1 (1.59)	3 (2.7)
Prior treatment	12 (25)	9 (14.29)	21 (18.92)
Targeted therapy			
Ongoing	0 (0)	1 (1.59)	1 (0.9)
Prior treatment	5 (10.42)	6 (9.52)	11 (9.9)
Body mass index			
Mean ± SD	20.45 ± 4.39	20.68 ± 3.73	20.58 ± 4.01
Median (IQR)	19.03 (14.72–32.93)	20.23 (12.29–31.88)	19.87 (12.3–32.93)
Weight variation since last month			
Weight gain	5 (11.90)	9 (15)	14 (13.73)
0%–5% loss	20 (47.62)	23 (38.33)	43 (42.16)
5%–10% loss	8 (19.05)	12 (20)	20 (19.61)
>10% loss	9 (21.3)	16 (26.67)	25 (24.51)
Albumin, g/L			
Mean ± SD	30 ± 7	29 ± 7	29 ± 7
Median (IQR)	30 (13–42)	28 (17–43)	29 (13–43)
CRP, mg/L			
Mean ± SD	72 ± 76	85 ± 72.51	79 ± 74
Median (IQR)	54 (1–363)	71 (1–275)	63 (1–363)
LDH, UI/L			
Mean ± SD	513 ± 579	508 ± 580	510 ± 577
Median (IQR)	306 (4–2,997)	289 (107–3,809)	289 (4–3,809)

Abbreviations: CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range (quartile 1 to quartile 3); LDH, lactate dehydrogenase.
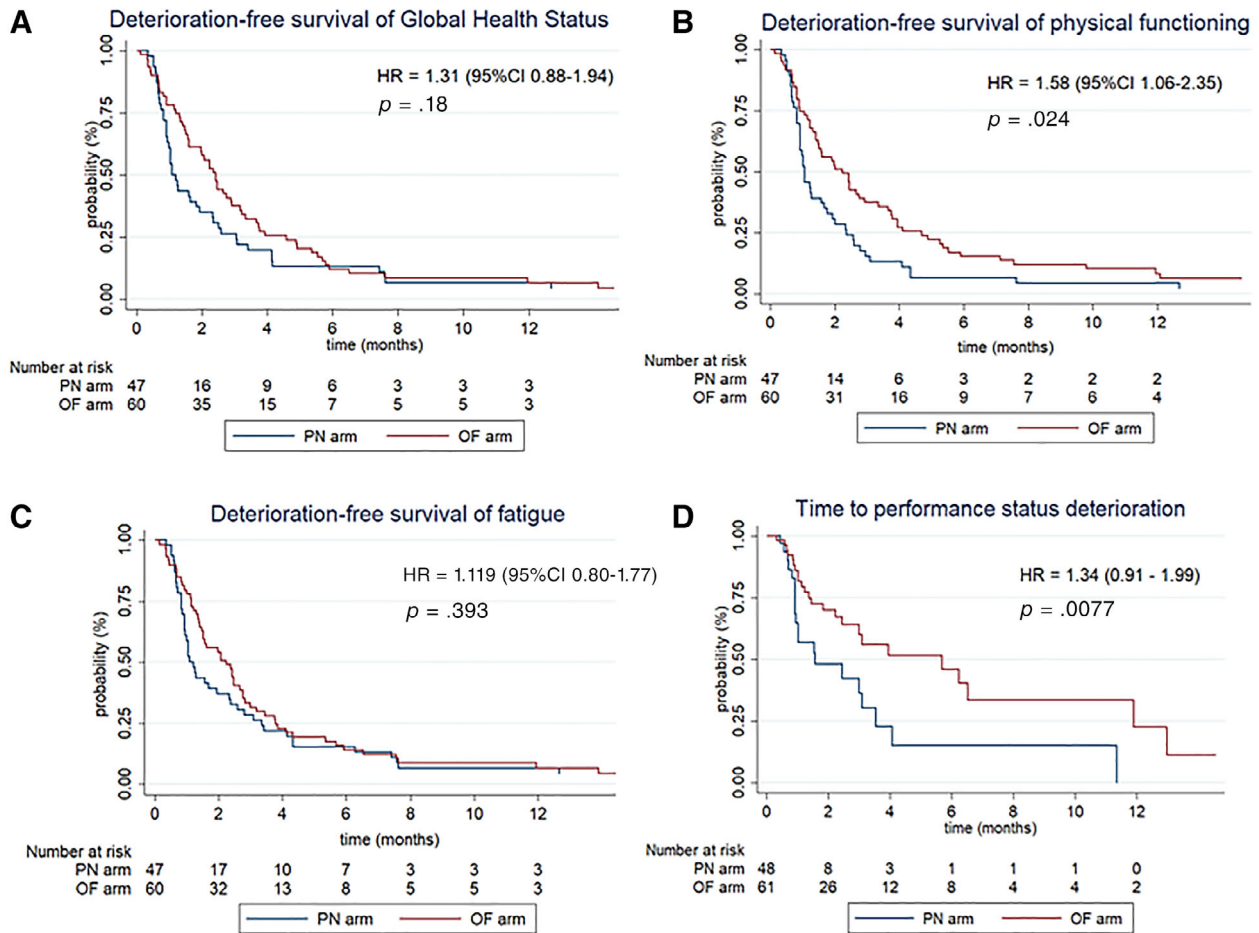
A

Deterioration-free survival of Global Health Status

HR = 1.31 (95%CI 0.88-1.94)
p = .18

time (months)

Number at risk

	0	2	4	6	8	10	12
PN arm	47	16	9	6	3	3	3
OF arm	60	35	15	7	5	5	3

— PN arm   — OF arm

B

Deterioration-free survival of physical functioning

HR = 1.58 (95%CI 1.06-2.35)
p = .024

time (months)

Number at risk

	0	2	4	6	8	10	12
PN arm	47	14	6	3	2	2	2
OF arm	60	31	16	9	7	6	4

— PN arm   — OF arm

C

Deterioration-free survival of fatigue

HR = 1.119 (95%CI 0.80-1.77)
p = .393

time (months)

Number at risk

	0	2	4	6	8	10	12
PN arm	47	17	10	7	3	3	3
OF arm	60	32	13	8	5	5	3

— PN arm   — OF arm

D

Time to performance status deterioration

HR = 1.34 (0.91 - 1.99)
p = .0077

time (months)

Number at risk

	0	2	4	6	8	10	12
PN arm	48	8	3	1	1	1	0
OF arm	61	26	12	8	4	4	2

— PN arm   — OF arm

Figure 2. Kaplan-Meier curves of health-related quality of life deterioration-free survival for the three target dimensions and time to performance status deterioration.
Abbreviations: CI, confidence interval; HR, hazard ratio; OF, oral feeding; PN, parenteral nutrition.

Secondary endpoints were secondary HRQoL dimensions, nutritional parameter (food intake, digestive symptoms, weight, oral nutritional complement intake), adverse events, and survival.

Statistical Analysis
Sample size calculation was based on a median deterioration-free survival of 1 month versus 2 months, with a hazard ratio (HR) of 0.50, a bilateral type I error of .0166 (three targeted dimensions), and a statistical power of 80%. This corresponded to a total enrolment of 96 patients followed and 89 events to be observed, that is, patients who had a significant deterioration in HRQoL or died, whichever occurred first. Considering a 10% rate of switching between treatment arms as a result of the use of Zelen's randomization, a total of 106 patients with available data were required.

The intent to treat (ITT) population was defined as all randomized patients score available, regardless of whether eligibility criteria were met and regardless of treatment received. The primary endpoint was analyzed in a modified intention-to-treat (mITT) population, that is, considering all ITT patients with at least a baseline HRQoL score available. A post hoc analysis for the primary endpoint was conducted

for the first 6 months of follow-up only in order to reduce the bias caused by long survivors. Deterioration-free survival was estimated using the Kaplan-Meier method. Adverse events were analyzed in the as treated population and were considered for patients receiving at least 1 day of treatment in the PN arm and only patients without artificial nutrition in the OF arm. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). All analyses were two sided, and the statistical significance value was fixed at .0166 to take account of the number of comparisons performed.

RESULTS

Patient Characteristics
Between June 2012 and March 2017, 148 patients with cancer were randomized in the 13 participating centers. As some patients did not consent to the completion of the quality of life questionnaires (13 in PN arm and 10 in control arm) and early withdrawal was observed, a total of 111 patients were included: 48 (42.3%) in PN arm and 60 (54.1%) in the OF arm. Eight patients in the PN arm only consented to QoL questionnaire completion. Because

Table 2. Quality of life deterioration-free survival for each dimension in the modified intention-to-treat population

Dimensions	n (events)	Patients event free at 1 month, % (95% CI)	Median (95% CI)	HR (95% CI)	p value
Targeted dimensions					
Global health status					
Oral feeding arm	60 (57)	78 (65.1–86.6)	2.43 (1.61–3.22)	1	.18
Parenteral nutrition arm	47 (46)	60.9 (45.3–73.3)	1.15 (0.99–2.33)	1.31 (0.88–1.94)	
Physical functioning					
Oral feeding arm	60 (57)	74.6 (61.4–83.8)	2.23 (1.48–3.65)	1	.024
Parenteral nutrition arm	47 (45)	56.5 (41.1–69.4)	1.05 (0.92–1.77)	1.58 (1.06–2.35)	
Fatigue					
Oral feeding arm	60 (56)	78 (65.1–86.6)	2.23 (1.51–2.76)	1	.393
Parenteral nutrition arm	47 (45)	58.7 (43.2–71.3)	1.15 (0.95–2.37)	1.19 (0.80–1.77)	
Secondary dimensions					
Emotional functioning					
Oral feeding arm	60 (58)	72.9 (59.6–82.4)	2.07 (1.48–2.89)	1	.753
Parenteral nutrition arm	47 (45)	54.3 (39–67.4)	1.05 (0.92–2.37)	1.07 (0.72–1.58)	
Nausea					
Oral feeding arm	60 (57)	79.7 (67–87.9)	2.66 (1.58–3.78)	1	.0283
Parenteral nutrition arm	47 (46)	60.9 (45.3–73.3)	1.23 (0.99–2.37)	1.56 (1.05–2.31)	
Pain					
Oral feeding arm	60 (57)	78 (65.1–86.6)	2.23 (1.58–2.99)	1	.004[a]
Parenteral nutrition arm	47 (46)	50 (34.9–63.3)	1.00 (0.92–1.25)	1.79 (1.20–2.66)	
Dyspnea					
Oral feeding arm	59 (56)	67.2 (53.6–77.7)	1.69 (1.22–2.66)	1	.389
Parenteral nutrition arm	47 (46)	58.7 (43.2–71.3)	1.05 (0.95–2.53)	1.19 (0.80–1.76)	
Insomnia					
Oral feeding arm	60 (56)	78 (65.1–86.6)	2.43 (1.61–2.96)	1	.0442
Parenteral nutrition arm	47 (46)	60.9 (45.3–73.3)	1.10 (0.99–2.33)	1.50 (1.01–2.23)	
Appetite loss					
Oral feeding arm	60 (56)	79.7 (67–87.9)	2.46 (1.91–3.65)	1	.233
Parenteral nutrition arm	47 (46)	69.6 (54.1–80.7)	1.45 (1.05–2.79)	1.27 (0.86–1.88)	
Constipation					
Oral feeding arm	57 (53)	80.4 (67.3–88.6)	2.07 (1.51–2.99)	1	.166
Parenteral nutrition arm	47 (46)	63 (47.5–75.2)	1.23 (1.05–2.53)	1.33 (0.89–1.98)	

[a]Statistically significant at the level of .016.

Abbreviations: CI, confidence interval; HR, hazard ratio.

of edema, five patients in each arm did not adhere to the inclusion criteria regarding weight loss and/or BMI. The flowchart for the study population is shown in Figure 1.

The baseline clinical and sociodemographic characteristics of the patients were well balanced between treatment arms (Table 1). The median age was 67 years (interquartile range, 60–72), 61 patients were women (55%), and the most common cancer localization was digestive cancer (28.8%). Almost all patients (98%) were metastatic, with a life expectancy of less than 1 year (for 14% it was less than 3 months, for 54% less than 6 months), and 49% were still on systemic anticancer treatment. The patients were malnourished with a median weight loss of 8.20 kg (range, 10–26.5) in the previous 6 months, 73% had low albumin, and the mean food intake was 40%.

HRQoL Deterioration-Free Survival

In the mITT analysis, there was no difference on HRQoL deterioration-free survival in the oral nutrition group versus the PN arm for the three dimensions targeted: global QoL (HR, 1.31; 95% confidence interval [CI], 0.88–1.94; p = .18), physical functioning (HR, 1.58; 95% CI, 1.06–2.35; p = .024), and fatigue (HR, 1.19; 95% CI, 0.80–1.77; p = .393; Fig. 2). The post hoc analysis excluding data beyond 6 months of follow-up showed a statistically significant increase in deterioration-free survival for physical functioning, with a median of 2.23 months for the OF arm versus 1.05 months for the PN arm (HR, 2.03; 95% CI, 1.33–3.12; p = .0008).

For secondary HRQoL dimensions there was a statistically significant increase in deterioration-free survival for the pain dimension (HR, 1.79; 95% CI, 1.20–2.66; p = .004)
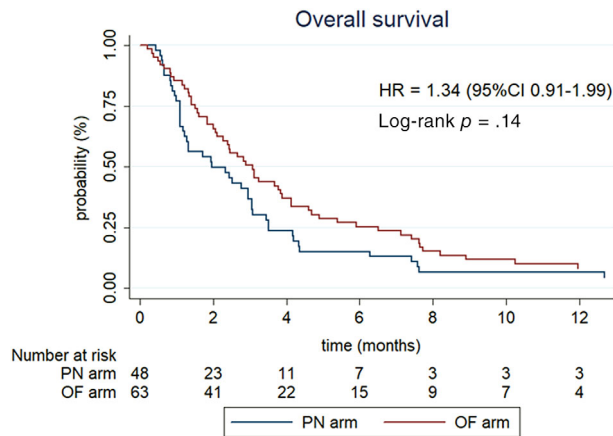
Overall survival

HR = 1.34 (95%CI 0.91-1.99)
Log-rank *p* = .14

Number at risk

PN arm	48	23	11	7	3	3	3
OF arm	63	41	22	15	9	7	4

Figure 3. Overall survival curve according to the Kaplan-Meier estimate per treatment arm (intention-to-treat population). Abbreviations: CI, confidence interval; HR, hazard ratio; OF, oral feeding; PN, parenteral nutrition.

in the OF arm versus the PN arm and a trend in favor of OF with an HR >1 for the other dimensions (Table 2).

Survival

The median follow-up was 33.8 months (95% CI, 14.6–not available). In total 104 patients died: 46 in the PN arm and 58 in the OF arm. For the whole population, the Kaplan-Meier median survival was 2.66 months (95% CI, 1.97–3.09), with 59.6% of patients alive at 2 months and 20.8% alive at 6 months (Fig. 3). There was no statistically significant difference in overall survival, with a median of 3 months (95% CI, 2.1–3.9) for the OF arm versus 2 months (95% CI, 1.2–3.0) for the PN arm (HR, 1.34; 95% CI, 0.91–1.99; *p* = .14). At each time point, overall survival for PN arm was below that of the OF arm.

Nutritional Parameters

For all patients in both arms, the mean ± SD change between baseline and last available measure in the first 2 months was a gain of 0.44 ± 2.13 for visual analog scale of ingesta and 0.33 kg ± 3.09 for weight, with no statistically significant difference observed between treatment arms. The time to performance status deterioration was significantly longer in the OF group, with a median of 1.6 months (95% CI, 0.92–3.5) in the PN arm versus 5.7 months (95% CI, 2.5–11.9) in the OF arm (HR, 2.24; 95% CI, 1.21–4.15; *p* = .008).

Toxicities

In as treated analyses, severe adverse effects were higher in the PN arm than in the OF arm, with seven patients within the PN arm versus only one patient in the OF arm (*p* = .0105). The main severe adverse events were catheter infection (*n* = 5), infection (*n* = 1), and acute pulmonary edema (*n* = 1).

DISCUSSION

In this study, PN failed to improve QoL for patients with cancer-related cachexia as well as survival. Moreover, PN caused more serious adverse events. This is the first study to assess PN for patients with advanced cancer with estimated life expectancy under 1 year, so comparison with data in the literature is difficult. In the only previous study

(in Sweden), 339 patients were randomized if they had cancer-related cachexia and functional gastrointestinal tract to receive nutritional support (including possibility of home PN) or not [34]. Unfortunately, HRQoL was not assessed, and the median overall survival did not differ in the ITT analysis. The authors mentioned the complexity of their current model, as additional interventions (i.e., cyclooxygenase inhibitors and erythropoietin) were offered to the best possible extent for patients in both the study and control arms. The authors concluded by not excluding the possibility that an interaction could have been overlooked by their relatively straightforward two-group analysis of a single intervention (i.e., nutritional support). On the other hand, numerous studies have shown clinical benefit of PN among malnourished patients with cancer and gastrointestinal dysfunction, improving HRQoL, performance and nutritional status, and sometimes survival [35–41].

Several reasons could explain this lack of efficacy of PN for patients with advanced cancer and cancer-related cachexia in our study. Trends in reduced survival and tumor response, as well as increased incidence of infectious complications in patients receiving PN, were reported in a meta-analysis performed years ago [42]. The short survival time of study population is certainly the major cause of the failure of PN, as a crucial issue is the timing of nutritional interventions. A window of anabolic potential seems to exist when survival is greater than 90 days, creating a chance for nutritional intervention to stop or reverse cachexia [43]. Artificial nutrition can maintain or improve nutritional status in patients with cancer, but only if depletion of muscular mass is not extreme, and can be more successful if started earlier. A recent study has assessed PN for 47 patients with incurable gastrointestinal cancer who were not malnourished but nutritionally at risk [44]. The results of this study show that HRQoL was better at 12 weeks, fat-free mass increased significantly, and the median overall survival was around 5 months. Indeed, implementing earlier PN in the course of the disease has some big promise in the management of malnutrition.

Several limitations in this study should be kept in mind. First, anthropometric criteria (weight loss and body mass index reduction) are insufficient to define malnutrition for patients with advanced cancer, who frequently suffer complications such as edema, ascites, or pleural effusion. Better selection of malnourished patients would have possible using bioelectrical impedance or skeletal muscle measures on computed tomography scans, which would have permitted more precise measures for malnutrition screening and assessment [45, 46]. Second, the slow accrual of patients in this study confirms the difficulty of performing clinical trials in this setting. Many patients did not complete the planned follow-up, mainly because of deterioration of their condition or death, a common difficulty in the field of palliative care clinical research. Finally, we observed a shorter median overall survival in the study population than expected, given that one of the inclusion criteria was a life expectancy of less than 1 year according to the "surprise" question. Prediction of the life expectancy is one of the most difficult tasks in oncology, relying on either clinical estimation or prognostics factors that can be added to build different scores. Today the optimal prognostic factors in patients with advanced cancer are not

known. Prognostic models such as the Glasgow Prognostic Score, Palliative Performance Scale, Palliative Prognostic Score, Palliative Prognostic Index, or Prognosis in Palliative Care Study predictor model may augment the clinician prediction of survival [47]. However, care must be taken to select the appropriate tool because prognostic accuracy varies by patient population, setting, and time frame of prediction. Results of a recent study on 478 patients with a median survival of 4.2 months showed that the modified Glasgow Prognostic Score was one of the most effective tools [48]. But even if prognostication is still a challenge, this might not be the only reason why clinicians have mainly included patients with life expectancy under 3 months. Bad representation of PN could have prevented physicians from including patients with good prognosis [49]. It seems like a bad general condition was unconsciously a necessary condition to consider prescription of PN.

Conclusion

PN improved neither HrQoL nor survival for patients with advanced cancer and cancer-related cachexia and caused more serious side effects. This study increases the level of evidence and supports the recommendation not to prescribe PN for patients with advanced cancer with life expectancy under 3 months and functional intestinal tract. Zelen's method can be useful in an ethical point of view allowing randomized study in an advanced care setting. On the other hand, a more accurate prognostic assessment is a key point to obtain a homogeneous study population. Further studies are needed to assess the best ways to use artificial nutrition for patients with advanced cancer with life expectancy of more than 3 months and how to overcome reluctance from clinicians to prescribe artificial nutrition in this situation.

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