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ORIGINAL ARTICLE

Early 7-day supplemental parenteral nutrition improves body composition and muscle strength in hypophagic cancer patients at nutritional risk

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Abstract

Purpose The international guidelines recommend the use of supplemental parenteral nutrition (SPN) in cancer patients when they are malnourished and hypophagic and where enteral nutrition is not feasible. However, there are limited data on the short-term effects of SPN in this patient population.

Methods The aim of this bicentric single-arm clinical trial (NCT02828150) was to evaluate the effects of early 7-day SPN on bioimpedance vectorial analysis (BIVA)–derived body composition, handgrip strength (HG), and serum prealbumin (PAB) in 131 hypophagic, hospitalized cancer patients at nutritional risk, with contraindications for enteral nutrition.

Results One hundred eighteen patients (90.1%) completed the 7-day SPN support regimen and 102 of them (86.4%) were in advanced disease stage.

SPN induced a significant improvement of phase angle (PhA, + 0.25 [95% CI 0.11, 0.39]; $p = 0.001$), standardized phase angle (SPA, + 0.33 [95% CI 0.13, 0.53]; $p = 0.002$), HG (+ 2.1 kg -95% CI 1.30, 2.81]; $p < 0.001$), and PAB (+ 3.8 mg/dL [95% CI 2.1, 5.6]; $p < 0.001$).

In multivariable analysis, the effects on BIVA parameters were more pronounced in patients ($N = 90$, 76.3%) in whom estimated protein and calorie requirements were both satisfied (adjusted difference: PhA, + 0.39 [95% CI 0.04, 0.73]; $p = 0.030$; SPA, + 0.62 [95% CI 0.16, 1.09]; $p = 0.009$).

No significant changes in hydration status were detected and no severe metabolic or other complications occurred.

Conclusions Early 7-day SPN resulted in improved body composition, HG and PAB levels in hypophagic, and hospitalized cancer patients at nutritional risk in the absence of any relevant clinical complications. Further trials, aimed at verifying the efficacy of this early nutritional intervention on mid- and long-term primary clinical endpoints in specific cancer types, are warranted.

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Keywords Supplemental parenteral nutrition · Cancer · Malnutrition · Bioelectrical impedance vectorial analysis · Body composition · Handgrip strength

Introduction

Malnutrition is common in cancer patients and negatively affects treatment tolerance, survival, functional status, and quality of life [1–4]. It is known that nutritional status tends to worsen during hospitalization [5, 6] and that inadequate nutritional support may negatively affect not only nutrition and function but also prognosis in cancer patients [2, 7]. In recent years, there is growing evidence that increased treatment toxicity and poorer prognosis are associated with lean body mass loss [8], which leads to sarcopenia in the most common cancer types [9–11] and, consequently, to impaired functional status and quality of life [12–14]. Therefore, more proactive or even intensive nutritional support should be considered in this patient population [15].

The most recently available guidelines recommend the use of supplemental parenteral nutrition (SPN) during non-surgical therapy (grade C), if cancer patients are malnourished, hypophagic, or affected by iatrogenic gastrointestinal complications, and if enteral nutrition is not feasible [3, 4]. However, a recent task force of the American Society for Parenteral and Enteral Nutrition (ASPEN) has recommended artificial nutrition, including PN, at the earliest opportunity in malnourished patients [16]. Unfortunately, by following standard guideline-based nutritional intervention algorithms, SPN is neglected as a useful short-term strategy, in the hospital setting [15]. The limited available evidence on the efficacy of SPN in cancer patients is positive, in particular with regard to quality of life [17], but mostly refers to mid-term interventions (> 3 months) and it is not sufficient to recommend its use routinely [18–21]. Furthermore, there is no data on the short-term effects of SPN on this patient population, for example, during acute or elective hospitalization.

Indeed, another major problem is the lack of reliable parameters with which to monitor the efficacy of SPN in the short term. In a recent study, we have demonstrated that phase angle (PhA) and handgrip strength (HG) variations are early markers of anabolic/catabolic impairment [22]. Furthermore, several studies have proven that PhA and standardized PhA (SPA) predict prognosis (mortality, disease progression, incidence of postoperative complications, length of hospital stay) in different cancer populations [23] and that PhA is a reliable marker for the detection of sarcopenia in cancer patients [24, 25]. Useful prognostic information in cancer patients is also provided by the measurement of HG [26] and serum prealbumin (PAB) [27], which are both influenced by nutritional support [22, 28].

The aim of this bicentric single-arm clinical trial (NCT02828150) was to evaluate the effects of early 7-day SPN on bioimpedance vectorial analysis (BIVA)–derived body composition, HG, and PAB in hypophagic, hospitalized cancer patients at nutritional risk.

Methods

Subjects

The subjects were hypophagic, hospitalized non-surgical patients with different cancer types (Table 1), at nutritional risk, assessed during nutritional consultations carried out within 24 h of admission by the staff of the Clinical Nutrition and Dietetics Unit in the Medical Oncology Unit of the Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) and by the Clinical Nutrition Service in the Medical Oncology Unit 1 of the Veneto Institute of Oncology-IRCCS (Padova, Italy).

Inclusion criteria

- Oncologic disease included in the following diagnostic groups: head and neck, lung, upper gastrointestinal tract, pancreas and biliary tract, colon and rectum, non-myeloid hematological disorders;
- Nutritional Risk Screening 2002 [29] score ≥ 3;
- presence of hypophagia (estimated oral intake < 60% of estimated caloric requirements);
- contraindication for enteral nutrition by tube in the view of the clinical nutritionists (i.e., presence of diarrhea, vomiting, nausea, mood disorders, tube dislocation risk) or patient's refusal;

Table 1 Study population by cancer site and stage

Cancer site	Overall		Assessed at 1 week	
	All (*N*)	Stage 4 (*N*)	All (*N*)	Stage 4 (*N*)
Head and neck	19	15	18	15
Gastroesophageal	22	22	20	18
Pancreas, liver, and intrahepatic bile ducts	13	13	11	11
Colorectal	15	15	14	14
Genitourinary	20	13	20	13
Respiratory	19	18	15	15
Hematologic	18	12	16	12
Others	5	5	4	4
Total	131	113	118	102

- clinical and logistical practicality of SPN for at least seven consecutive days;
- a priori feasibility of instrumental measurements; and
- written informed consent.

Exclusion criteria

- Age < 18 years;
- Eastern Cooperative Oncology Group performance status > 2 [30];
- preadmission home artificial nutrition;
- fasting glycemia ≥ 200 mg/dL and/or serum triglycerides ≥300 mg/dL at admission; and
- hemodynamic instability or signs of cardio-respiratory insufficiency at admission.

Assessments

- Demographic and clinical data: age, sex, diagnosis, oncologic stage, and reasons for hospital admission.
- Anthropometry: body weight [at the nearest 0.1 kg; Wunder mechanical weighing scales]; 6-month and 1-month previous unintentional body weight loss; height [at the nearest 0.5 cm]; body mass index (BMI).
- Nutritional requirements: energy needs were estimated multiplying the resting energy expenditure calculated by the Harris-Benedict equation by a correction factor of 1.5 (in obese patients [BMI > 30 kg/m^2], ideal body weight [i.e., with BMI = 23 kg/m^2] was used in the equation), while protein requirements were set to 1.5 g/kg actual body weight (in obese patients [BMI > 30 kg/m^2] = 1.5 g/kg ideal body weight [i.e., with BMI = 23 kg/m^2]).
- Calorie and protein oral intakes at the initial baseline visit were estimated by 24-h dietary recall, while total energy and protein intakes throughout the treatment period were calculated as the mean of three evaluations [at first visit, day 3, and day 7] and included 24-h dietary recalls and SPN prescriptions; intakes were considered satisfied when total energy and protein requirements were ≥ 90% and ≥ 1.5 g/kg/day, respectively.
- Blood tests: glycemia (plus fingersticks three times on days 1 and 2, then if indicated thereafter), Na, K, Cl, Ca, Mg, P [at first visit, day 1, day 3, and day 7]; triglycerides, serum creatinine, urea [at first visit, day 3, and day 7]; total cholesterol, HDL cholesterol, GGT, ALT, AST, total bilirubin, PAB, C-reactive protein (CRP) [at first visit and day 7].
- BIVA: the Nutrilab bioimpedance vector analyzer (Akern s.r.l.) was used. The method involved a tetrapolar technique to deliver a single-frequency electrical current of 50 kHz (± 5%). The external calibration of the analyzer was checked daily using an impedance calibration circuit (R = 470 Ω, Xc = 90 Ω). The testing procedure was conducted in line with methods described by Lukaski [31, 32] and other recommendations [33, 34]. Then, the impedance vector (*Z*) was plotted as a bivariate vector from its components, R (*X* axis) and Xc (*Y* axis), after being standardized by height; this forms two correlated normal random variables (i.e., a bivariate Gaussian vector) [35]. Elliptical probability regions of the mean vector are plotted on the RXc plane forming elliptical probability regions on the RXc plane, which are tolerance ellipses for individual vectors and confidence ellipses for mean vectors [36, 37]. Tolerance ellipses are the bivariate reference intervals of a normal population for an observation. The RXc graph features three tolerance ellipses: the median, the third quartile, and the 95th percentile (i.e., 50%, 75%, and 95% of individual points). Participant data were plotted on the RXc point graph using the 50%, 75%, and 95% tolerance ellipses from a non-cancer reference population (BIVA point graph analysis) [36]. Hydration status was determined by the individual's baseline bioimpedance vector position on the BIVA RXc nomogram and the calculation of the new Hydragram® scale, which allows the immediate, bedside classification of hydration.
- Muscle strength: HG was measured by a digital hand dynamometer; (DynEx™, Akern/MD Systems).

Treatment

Treatment consisted of 7-day SPN using multi-chamber bags containing glucose, amino acids, with or without olive oil—based lipids, and electrolytes (Olimel®/Clinimix®, Baxter, Chicago, IL, USA), and supplemented with multivitamin (Cernevit™ Baxter, Chicago, IL, USA) and multimineral trace elements (Addamel N®, Fresenius Kabi, Bad Homburg, Germany). SPN was infused via either central or peripheral infusion lines (as available at admission) for 12–24 h per day according to the clinical status of the patient and the availability of hospital facilities. Patients were encouraged to continue eating with individual tolerance in mind, and dietary modifications were made according to patients' preferences. SPN was firstly prescribed in accordance with clinical conditions (hydration status) and biochemical data (baseline serum electrolytes, glucose, and lipids), in order to satisfy the estimated energy and protein requirements at admission. In particular, PN bags without lipids were prescribed in the presence of basal triglycerides levels > 200 mg/dL. Oral intake was reassessed on day 3 and SPN prescription was adapted accordingly, when possible. Home PN (HPN) was prescribed to patients who had insufficient oral intake before discharge [3, 4].

Endpoints

The primary endpoint was the change in PhA after 7 days of SPN. Secondary endpoints were the change in SPA (key secondary), body weight, BMI, HG, and the prevalence of treatment-related clinical (infections; cardiac, renal, and respiratory dysfunctions; hypertension; clinically evident fluid retention [presence of Hydragram® scale variation > 5% with a vectorial shift above the 75% tolerance ellipse]; and peripheral phlebitis) and metabolic complications occurring during the treatment period (definitions are provided in Supplementary Table 1). An exploratory evaluation of the effect of support on PAB was also considered.

Statistics

A sample size of 109 patients was calculated, based on our previous data [31], as necessary to detect a difference in means of 0.5° (between a baseline mean PhA of 5.0° and a 7-day PhA mean of 5.5°; 10% increase), assuming a standard deviation of differences of 1.5° and 80% power and using a paired *t* test with a 0.010 two-sided significance level (the conservative alpha level being chosen to allow for multivariable analyses).

Continuous variables were presented as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Categorical variables, including clinical complications (infections, cardiac, renal, and respiratory dysfunctions; hypertension; fluid retention; peripheral phlebitis), were described as counts and percentages. Pre-SPN characteristics were compared between patients achieving and those not achieving estimated energy requirements, by using either the unpaired Student's *t* test or the Mann-Whitney *U* test (as appropriate) and the Fisher exact test for continuous and categorical variables, respectively.

Patients undergoing the primary endpoint evaluation were included in efficacy analysis. Values of PhA, SPA, anthropometry, HG, and PAB at the end of SPN were compared to baseline by means of generalized linear models for repeated measures, with calculation of robust Huber-White standard errors to account for intra-patient correlation. We also fitted a multivariable generalized regression model on the computed change for PhA and SPA to assess the influence of whether the energy intake was satisfied, while adjusting for a series of potential confounders; these were identified a priori based upon their clinical value and included age, gender, TNM class (0–2/3–4), weight loss in the previous 6 months, baseline CRP levels, type of venous access (central/peripheral), change in calorie and in protein intake, and change in the Hydragram® scale.

Patients receiving at least one SPN infusion were included in safety analysis.

All statistical analyses were performed using STATA 15.1 statistical software (Stata Corporation, College Station, TX, USA). A two-sided p level of < 0.05 was adopted as significant.

Results

Of the 149 screened patients, 131 were eligible for enrollment. Thirteen patients (10%) were not evaluable at 7 days (dropouts) and were not included in the final analyses. Their baseline characteristics were not different from those of patients completing the study (Tables 1 and 2). Reasons for dropout were as follows: unplanned anticipated discharge ($n = 8$), worsening of clinical conditions ($n = 4$), unplanned surgical intervention ($n = 1$), refusal to complete the intervention ($n = 1$). HPN was prescribed to 42 patients (35.6% of the analyzed sample).

Efficacy analyses

Of the 118 patients included in the final efficacy analyses, 102 were in advanced disease stage (86.4%), 101 (85.6%) received chemotherapy ($N = 16$, adjuvant; $N = 27$, first line; $N = 14$, second line; $N = 21$, third line; $N = 23$, maintenance), and 8 (6.8%) received radiotherapy during hospitalization, while the other 9 (7.6%) were admitted exclusively for supportive care; 18 patients (15.2%) were contemporarily followed by our Palliative Care Unit. After the day 3 checks, SPN prescription was modified in 10 patients (8.5%), while we were unable to increase the intake of calories and/or amino acids in 33 patients (27.9%), due to difficulties with peripheral access and/or the risk of fluid overload or metabolic derangements. Overall, among patients completing the 7-day intervention, 90 (76.3%) attained the estimated energy and protein requirements.

Patients satisfying the estimated protein-calorie requirements were those presenting at a younger age, and/or who had a lower weight and BMI, lower CRP levels, greater protein and calorie intake, and a marginally significant greater HG at baseline. Changes in energy and protein intakes in the study population at day 7 are reported in Table 3.

SPN resulted in a significant improvement in PhA (+ 0.25° [95% CI 0.11, 0.39]; $p = 0.001$) and in all the other secondary efficacy endpoints (Table 4). The changes in mean impedance vectors and confidence ellipses on the BIVA nomogram by gender for the overall population are reported in Fig. 1, while treatment effects according to gender, together with the achievement of estimated protein-calorie requirements, are presented in Fig. 2.

In multivariable analysis, the effects on BIVA parameters were more pronounced in patients ($N = 90$, 76.3%) in whom estimated protein and calorie requirements were both satisfied: adjusted difference in PhA (+ 0.39 [95% CI 0.04,

Table 2 Clinical features of the study population according to 7-day reassessment and the satisfaction of estimated energy requirements

Variable	Assessed at 1 week ($N = 118$)	Satisfied ($N = 90$)	Not Satisfied ($N = 28$)	p value[a]	Dropout ($N = 13$)	p value[b]
Gender (male), N (%)	76 (64.4)	59 (65.6)	17 (60.7)	0.66	10 (76.9)	0.54
Age (years), mean (SD)	59.9 (14.7)	58.1 (14.3)	66.0 (14.5)	0.012	62.1 (13.7)	0.62
Cancer stage = 4, N (%)	102 (86.4)	79 (87.8)	23 (82.1)	0.53	11 (84.6)	1.00
Baseline body weight (kg), mean (SD)	57.1 (11.2)	55.1 (10.3)	63.4 (12.2)	0.001	56.5 (14.1)	0.85
Baseline body mass index (kg m^{-2}), mean (SD)	20.3 (3.6)	19.6 (3.3)	22.5 (4.0)	< 0.001	19.7 (3.0)	0.58
6-month weight loss (%), mean (SD)	14.0 (7.7)	14.7 (6.9)	12.0 (9.7)	0.29	14.0 (7.8)	0.41
NRS-2002 score, median [IQR]	3.7 (0.9)	3.7 (0.9)	3.8 (0.8)	0.86	4.1 (0.9)	0.20
Phase angle (°), mean (SD)	4.12 (1.23)	4.23 (1.25)	3.78 (1.11)	0.51[c]	4.15 (0.90)	0.91[c]
Standardized phase angle, mean (SD)	− 1.58 (1.55)	− 1.55 (1.44)	− 1.66 (1.88)	0.75	− 1.73 (1.42)	0.75
Body cell mass (kg), mean (SD)	18.7 (6.5)	19.0 (6.5)	17.7 (6.5)	0.96[c]	19.2 (6.1)	0.97[c]
Total body water (L), mean (SD)	34.4 (6.3)	34.3 (6.5)	34.7 (5.9)	0.48[c]	34.1 (6.3)	0.49[c]
Hydragram (%), mean (SD)	76.3 (5.5)	76.0 (5.4)	77.2 (5.6)	0.30	76.2 (3.3)	0.97
Handgrip strength (kg), mean (SD)	18.8 (9.3)	19.7 (9.1)	15.8 (9.3)	0.30[c]	15.7 (6.9)	0.18[c]
Prealbumin (mg/dL), mean (SD)	16.4 (7.5)	16.7 (7.4)	15.5 (7.6)	0.81[c]	19.3 (4.0)	0.20[c]
C-reactive protein (mg/dL), mean (SD)	5.7 (7.3)	4.9 (6.2)	8.3 (9.5)	0.032	4.9 (3.9)	0.77
Administration of PN (central infusion line), N (%)	67 (56.8)	56 (62.2)	20 (71.4)	0.50	7 (53.8)	1.00
Estimated energy requirements (kcal/day), mean (SD)	1913 (297)	1896 (294)	1971 (303)	0.24	1871 (384)	0.67
Estimated energy requirements (kcal/kg/day), mean (SD)	34.0 (4.2)	34.7 (3.6)	31.7 (5.2)	0.001	33.7 (4.4)	0.85
Estimated protein requirements (g/day), mean (SD)	85.6 (16.7)	82.7 (15.4)	95.1 (18.5)	0.001	84.1 (22.7)	0.78
Estimated protein requirements (g/kg/day), mean (SD)	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)	1.00	1.5 (0.1)	1.00
Baseline energy intake (kcal/day), mean (SD)	584 (258)	627 (272)	446 (136)	0.001	600 (257)	0.85
Baseline energy intake (kcal/kg/day), mean (SD)	10.6 (5.0)	11.6 (5.1)	7.4 (3.1)	< 0.001	11.2 (4.9)	0.74
Percentage of requirements (%), mean (SD)	30 (15)	33 (16)	22 (11)	< 0.001	33 (13)	0.60
Baseline protein intake (g/day), mean (SD)	22.4 (12.2)	25.0 (12.3)	14.0 (6.8)	0.001	26.3 (16.8)	0.35
Baseline protein intake (g/kg/day), mean (SD)	0.40 (0.24)	0.45 (0.24)	0.22 (0.14)	< 0.001	0.47 (0.27)	0.41
Percentage of requirements (%), mean (SD)	27 (16)	30 (16)	15 (10)	< 0.001	31 (18)	0.41

[a] For comparison between patients satisfying and those not satisfying protein-calorie requirements by unpaired Student's t test or Fisher's exact test or linear regression

[b] For comparison between patients assessed at 1 week and dropout by unpaired Student's t test or Fisher's exact test or linear regression analysis

[c] Adjusted for age and gender

0.73]; $p = 0.030$ (crude change in the satisfied group, + 0.36 [95% CI 0.21, 0.52]; crude change in the unsatisfied group, − 0.11 [95% CI − 0.40, 0.17])); adjusted difference in SPA (+ 0.62 [95% CI 0.16, 1.09]; $p = 0.009$ (crude change in the satisfied group, + 0.51 [95% CI 0.29, 0.74]; crude change in the unsatisfied group, − 0.26 [95% CI − 0.65, 0.14])).

Safety analyses

At the end of the study period, we registered fluid retention in 11 patients (9.3%), hyperglycemia in 4 patients (3.1%), hypertriglyceridemia in 8 patients (6.1%), and hypokalemia (K = 2.88 mEq/L) in 1 patient (0.8%). Among the subjects with basal normal liver function (99, 75.6%), at day 7, we found ALT, AST, and GGT levels two times above the upper normal ranges in 8 (8.1%), 4 (4.1%), and 0 patients, respectively. Eight out of these 12 patients (66.7%) were concomitantly receiving CT during the hospital stay.

Hyperglycemia was corrected by adding insulin to the PN bags, hypertriglyceridemia by reducing or avoiding the infusion of lipids, and hypokalemia by adding potassium chloride to the PN bags. All the other blood tests improved or did not substantially change. Interestingly, 7 out of the 11 patients with fluid retention (63.6%) did not meet protein requirements.

No infectious complications occurred.

Discussion

This study provides the evidence that strictly monitored early short-term SPN results in the improvement of BIVA-derived body composition, functional status (HG), and PAB in hypophagic hospitalized cancer patients at nutritional risk, in the absence of any relevant clinical complication. It also underlines the relevance of fully satisfying both calorie and protein requirements for the initial improvement of nutritional status in this patient population.

Preliminary data from small samples of malnourished pancreatic cancer patients showed that SPN may be effective in improving nutritional status as assessed by BIVA [18, 19].

However, in these studies, treatment initiation and/or duration was heterogeneous and the improvements lasted only a few weeks.

A recent randomized study [37] found a beneficial effect on body weight (+ 1.7 kg) of routine in-hospital peripheral PN on fasting days (1000 mL/24 h, 700 kcal) in 100 patients

Table 3 Change in energy intake in the study population after one-week personalized nutritional support according to the satisfaction of stimated energy requirements

Variable	Overall ($N = 118$)	Satisfied ($N = 90$)	Not satisfied ($N = 28$)	p value[a]
Final energy intake, mean (SD)				
Total (kcal/day)	2016 (340)	1986 (334)	2111 (346)	0.090
Total (kcal/kg/day)	36.4 (8.5)	39.1 (7.7)	27.8 (4.6)	< 0.001
Percentage of requirements	106 (18)	112 (16)	88 (11)	< 0.001
Oral food	14.1 (6.3)	16.1 (5.8)	7.6 (2.7)	< 0.001
Supplemental PN	22.3 (5.6)	23.0 (6.0)	20.2 (3.6)	0.020
Final protein intake, mean (SD)				
Total (g/day)	88.6 (15.6)	88.2 (15.1)	90.0 (17.2)	0.60
Total (g/kg/day)	1.59 (0.31)	1.71 (0.22)	1.19 (0.15)	< 0.001
Percentage of requirements	106 (20)	114 (15)	79 (10)	< 0.001
Oral food	0.64 (0.25)	0.73 (0.19)	0.32 (0.15)	< 0.001
Supplemental PN	0.95 (0.20)	0.98 (0.20)	0.87 (0.18)	0.008

[a] For comparison between patients satisfying and not satisfying protein-calorie requirements by unpaired Student's *t* test or Fisher's exact test or linear regression

undergoing in-hospital work-up for biliopancreatic mass lesions, irrespective of their nutritional status. After a median 7-day duration, PN was even more effective in patients with malignant lesions (+ 2.7 kg), but was accompanied by the decrease in PhA and the increase in extracellular mass/water. These results are not surprising, considering that SPN was provided on fasting days and that even patients receiving PN were substantially underfed. In line with this evidence, the results of our trial highlight the importance of avoiding not only fasting but also underfeeding. PhA did not improve in patients not achieving the estimated requirements and most patients with fluid retention did not satisfy protein requirements.

Therefore, two critical issues need to be discussed more extensively: the timing of PN initiation and the amount of protein and calories to be provided. A very recent critical review of the guidelines by the European Society on Clinical Nutrition and Metabolism (ESPEN), of the ASPEN consensus statements and the available literature, has suggested that SPN should begin at hospital admission in non-intensive care malnourished patients [15, 16]. The ESPEN guidelines recommend with a low level of evidence the use of PN if oral/enteral food tolerance is insufficient to supply the required amounts of energy and nutrients [3]. However, by following standard nutritional treatment algorithms, in the context of full evaluation of oral and enteral nutrition feasibility and efficacy, PN is not likely to be implemented as a short-term strategy, or in acute conditions. Nonetheless, the efficacy of enteral vs parenteral nutrition in patients with inadequate nutritional intake undergoing curative anticancer treatment remains an open issue for research [3], bearing in mind that SPN is apparently the most frequent modality of administration of PN support in cancer patients [38].

With respect to energy and protein intakes, guidelines recommend providing 25–30 kcal/kg/day and up to 1.5 g/kg/day, respectively [3, 4]. Interestingly, the mean total energy and protein intakes given to our patients were 36 kcal/kg/day and 1.6 g/kg/day, which increased up to 39 kcal/kg/day and 1.7 g/kg/day in those patients who fully attained estimated requirements, while patients not attaining them received 28 kcal/kg/day and 1.2 g/kg/

Table 4 Analysis of the primary, secondary and exploratory endpoints in patients completing the one-week personalized nutritional support

Endpoints	Baseline Mean (SD)	Day 7 Mean (SD)	Mean change (95% CI)	p value
Phase angle (°)	4.12 (1.23)	4.37 (1.30)	0.25 (0.11–0.39)	0.001
Standardized phase angle	− 1.58 (1.55)	− 1.25 (1.75)	0.33 (0.13–0.53)	0.002
Body weight (kg)	57.1 (11.2)	57.8 (11.4)	0.7 (0.4–1.1)	< 0.001
Body mass index (kg m^{-2})	20.3 (3.6)	20.6 (3.6)	0.3 (0.1–0.4)	< 0.001
Handgrip strength (kg)	18.8 (9.3)	20.9 (9.3)	2.1 (1.3–2.8)	< 0.001
Prealbumin (mg/dL)	16.4 (7.5)	20.2 (10.2)	3.8 (2.1–5.6)	< 0.001

SD, standard deviation

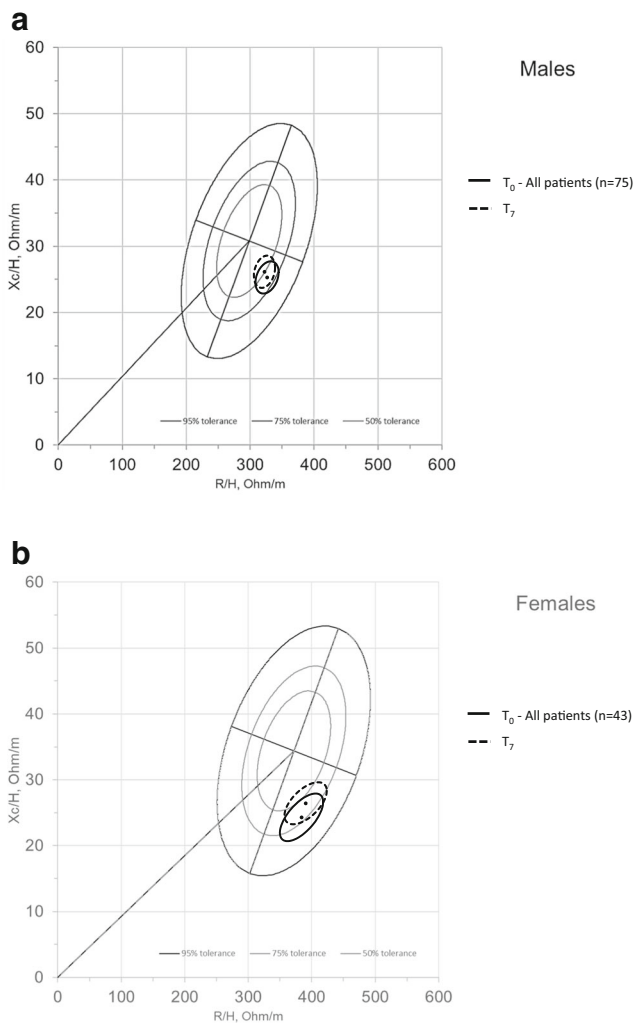

Fig. 1 Changes in mean impedance vectors and confidence ellipses on the BIVA nomogram by sex for the overall study population

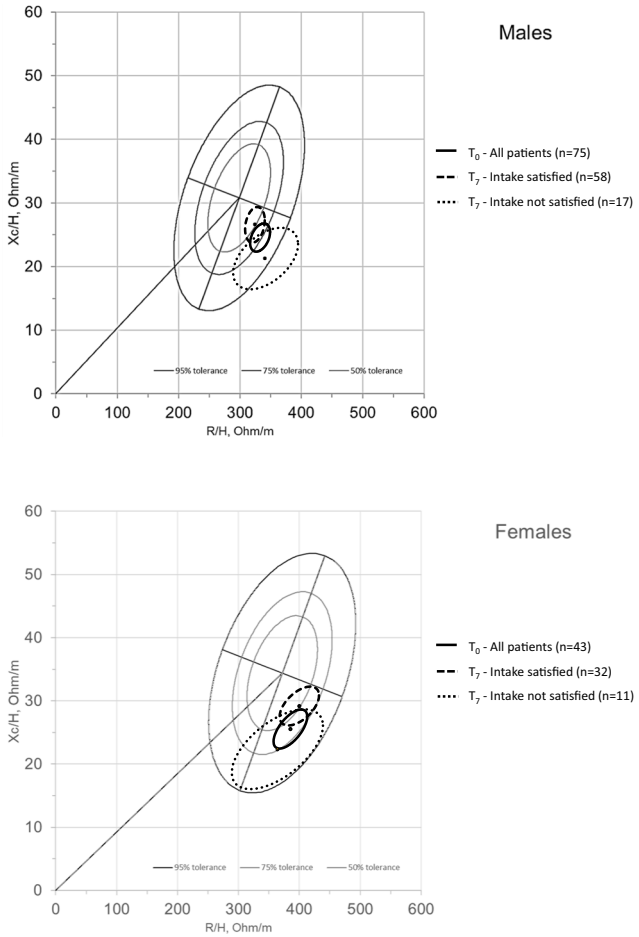

Fig. 2 Changes in mean impedance vectors and confidence ellipses on the BIVA nomogram according to gender and the satisfaction of estimated energy and protein requirements

day. Hence, protein-calorie targets need to be reconsidered, at least in severely hypophagic, malnourished advanced cancer patients. A recent trial on enteral nutrition in head and neck cancer patients showed that the average caloric intake sufficient to maintain body weight during CT-RT was 35 kcal/kg/day [39], and in the same patient population, it has already been proposed that requirements should be tailored on usual body weight before diagnosis [40]. An interesting aspect is that the difference in total calorie and protein intakes between those patients who meet the estimated requirements, and those who do not, was due to oral intake, which can be difficult to increase in poor responders due to their clinical condition. Besides, protein intake appeared to be the major determinant of fluid retention, supporting the critical role of protein supply in the anabolic pathways of cancer patients [3]. Although we could have hypothetically risked overfeeding patients, the strict monitoring meant we observed only a few and easily remedied metabolic complications. At the same time, the prescription of SPN according to the clinical conditions, which included the evaluation of basal hydration status by BIVA, allowed us to minimize the proportion of patients with fluid retention occurring.

All these considerations are consistent with the tight caloric control (TiCaCo) approach proposed in oncology by De Waele and colleagues [41]. Unlike the TiCaCo pilot study, we did not use indirect calorimetry to assess energy requirements. This could have impaired the accuracy of our intervention, but, on the other hand, indirect calorimetry is still expensive, time-consuming, and hardly feasible in the everyday clinical activity of most oncologic centers. However, indirect calorimetry remains a tool of paramount importance, whose recent technical developments will allow a broader use in patients with different diseases and clinical conditions and may contribute to optimize the efficacy and safety of nutritional therapy in the future [42].

We recognize the following limitations. A possible critical aspect may be single-arm study design. A concomitant comparative arm would have enabled the detection of a proper cause-effect relationship between SPN and the selected endpoints. However, the use of placebo (hydration) would have been unethical, while a comparison with the guidelines-based

nutritional support algorithm would have probably resulted in inadequate protein-calorie intake in several patients due to the delay in satisfying the estimated requirements. Nonetheless, the significant differences detected between patients satisfying and those not satisfying the estimated nutritional requirements support for the effectiveness of the intervention.

We are aware that the 7-day treatment duration may limit the relevance of the results; however, it corresponds to the median time of hospitalization in our Institution and it is consistent with the study of Krüger and colleagues [37]. We are also conscious that our endpoints were based on secondary nutritional and functional parameters, although they are associated with primary clinical outcomes. Moreover, our population consisted of a very fragile class of oncologic patients, i.e., requiring admission for active treatments or supportive care, for different cancer types of varying prognoses. This reflects the reality of hospital everyday life, but limits the specificity of our findings. Therefore, we acknowledge that this study is propaedeutic to future trials aimed at verifying the clinical efficacy of this early nutritional approach in the mid and long term in specific cancer types. Indeed, one such trial is currently being designed by our group for newly diagnosed metastatic gastric cancer patients.

We should point out that our study has several strengths and interesting aspects, which make it innovative and useful for the development of new therapeutic approaches. First, it indicates that early SPN can safely bring to the improvement of relevant nutritional parameters in one of the most fragile hospital populations, such as hypophagic, advanced cancer patients at nutritional risk with contraindications for enteral support, in a time frame which may correspond to the median hospital stay. This implies that an early approach, followed by strict monitoring of SPN adequacy and safety, could be adopted during hospitalization in a large clinical population, in whom other nutritional support strategies may not be tolerated or practicable, thereby satisfying an unmet need and avoiding detrimental weight loss [43]. In this scenario, our data suggest that the systematic use of BIVA in the monitoring of SPN is feasible and may assist in improving the accuracy of the clinical assessment and the quality and efficacy of nutritional interventions.

With respect to this last issue, also, PAB has gained the interest of clinicians because of its short half-life (2 days), which permits not only the detection of short-term impairment in energy balance but also the monitoring of the effectiveness of nutritional support [27, 28]. An association between reduced PAB and adverse outcomes has been detected in several chronic diseases [28]. Similarly, HG is a simple and inexpensive prognostic marker in cancer patients [26, 44]. A recent study showed that HG was compromised (− 2.3 kg) within the first 7 days of hematological treatment [45]; our results indicate that SPN contributed to improve this parameter in the same time frame.

In conclusion, early 7-day SPN resulted in improved body composition and HG and PAB levels in hypophagic, hospitalized cancer patients at nutritional risk, the majority of whom were in advanced disease stage, in the absence of any relevant clinical complications. Full attainment of both calorie and protein requirements may be a key issue in the initial improvement of nutritional status in this patient population. Further trials, aimed at verifying the efficacy of this early nutritional intervention on mid- and long-term primary clinical outcomes in specific cancer types, are warranted.

Authorship RC, EC, CK, and PP participated in the study concept and design. RC, EC, PP, MN, MC, SC, VB, AT, II, AL, JS, LC, MB, and VZ participated in the clinical evaluation and management of the patients and in the data collection and interpretation. RC, EC, CK, and PP participated in writing the manuscript. CK performed the statistical analysis.

All authors approved the final version of the manuscript.

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Compliance with ethical standards

The study was approved by the Institutional Ethics Committee of the Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) and by the Ethics Committee of the Veneto Institute of Oncology-IRCCS (Padova, Italy). It was conducted according to the Declaration of Helsinki. Written informed consent was obtained from each patient.

Conflict of interest RC has received research funding from Baxter Healthcare Corporation. RC and PP have served as consultants and/or on advisory panels for Baxter Healthcare Corporation. RC and PP have participated in speakers' bureaus for Baxter Healthcare Corporation. RC and EC have participated in speakers' bureaus for Akern s.r.l.

References

1. Hébuterne X, Lemarié E, Michallet et al (2014) Prevalence of malnutrition and current use of nutrition support in patients with cancer. JPEN 38:196–204
2. Van Cutsem E, Arends J (2005) The causes and consequences of cancer-associated malnutrition. Eur J Oncol Nurs 9:S51–S63
3. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC (2017) ESPEN guidelines on nutrition in cancer patients. Clin Nutr 36:11–48
4. Caccialanza R, Pedrazzoli P, Cereda E, Gavazzi C, Pinto C, Paccagnella A, Beretta GD, Nardi M, Laviano A, Zagonel V (2016) Nutritional support in cancer patients: a position paper from the Italian Society of Medical Oncology (AIOM) and the Italian Society of Artificial Nutrition and Metabolism (SINPE). J Cancer 7:131–135
5. Caccialanza R, Klersy C, Cereda E, Cameletti B, Bonoldi A, Bonardi C, Marinelli M, Dionigi P (2010) Nutritional parameters

associated with prolonged hospital stay among ambulatory adult patients. CMAJ 182:1843–1849
6. Kyle UG, Schneider SM, Pirlich M, Lochs H, Hebuterne X, Pichard C (2005) Does nutritional risk, as assessed by Nutritional Risk Index, increase during hospital stay? A multinational population-based study. Clin Nutr 24:516–524
7. Norman K, Pichard C, Lochs H, Pirlich M (2008) Prognostic impact of disease-related malnutrition. Clin Nutr 27:5–15
8. Prado CM, Antoun S, Sawyer MB, Baracos VE (2011) Two faces of drug therapy in cancer: drug-related lean tissue loss and its adverse consequences to survival and toxicity. Curr Opin Clin Nutr Metab Care 14:250–254
9. Aoyama T, Kawabe T, Fujikawa H, Hayashi T, Yamada T, Tsuchida K, Yukawa N, Oshima T, Rino Y, Masuda M, Ogata T, Cho H, Yoshikawa T (2015) Loss of lean body mass as an independent risk factor for continuation of S-1 adjuvant chemotherapy for gastric cancer. Ann Surg Oncol 22:2560–2566
10. Jung HW, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, Lee KW, Kim DW, Kang SB, Kim KI, Kim CH, Kim JH (2015) Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. Support Care Cancer 23:687–694
11. Strulov Shachar S, Deal AM, Weinberg M, Nyrop KA, Williams GR, Nishijima TF, Benbow JM, Muss HB (2017) Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane based chemotherapy. Clin Cancer Res 23:658–665
12. Nipp RD, Fuchs G, El-Jawahri A, Mario J, Troschel FM, Greer JA, Gallagher ER, Jackson VA, Kambadakone A, Hong TS, Temel JS, Fintelmann FJ (2018) Sarcopenia is associated with quality of life and depression in patients with advanced cancer. Oncologist 23:97–104
13. Batsis JA, Mackenzie TA, Lopez-Jimenez F, Bartels SJ (2015) Sarcopenia, sarcopenic obesity, and functional impairments in older adults: National Health and Nutrition Examination Surveys 1999-2004. Nutr Res 35:1031–1039
14. Guinan EM, Doyle SL, Bennett AE, O'Neill L, Gannon J, Elliott JA, O'Sullivan J, Reynolds JV, Hussey J Sarcopenia during neoadjuvant therapy for oesophageal cancer: characterising the impact on muscle strength and physical performance. Support Care Cancer 2017. https://doi.org/10.1007/s00520-017-3993-0
15. Russell MK, Wischmeyer P (2018) Supplemental parenteral nutrition: review of the literature and current nutrition guidelines. Nutr Clin Pract 33:359–369
16. Worthington P, Balint J, Bechtold M, Bingham A, Chan LN, Durfee S, Jevenn AK, Malone A, Mascarenhas M, Robinson DT, Holcombe B (2017) When is parenteral nutrition appropriate? JPEN J Parenter Enteral Nutr 41:324–377
17. Cotogni P, De Carli L, Passera R, Amerio ML, Agnello E, Fadda M, Ossola M, Monge T, De Francesco A, Bozzetti F (2017) Longitudinal study of quality of life in advanced cancer patients on home parenteral nutrition. Cancer Med 6:1799–1806
18. Pelzer U, Arnold D, Gövercin M, Stieler J, Doerken B, Riess H, Oettle H (2010) Parenteral nutrition support for patients with pancreatic cancer. Results of a phase II study. BMC Cancer 10:86
19. Richter E, Denecke A, Klapdor S, Klapdor R (2012) Parenteral nutrition support for patients with pancreatic cancer–improvement of the nutritional status and the therapeutic outcome. Anticancer Res 32:2111–2118
20. Wu W, Zhong M, Zhu DM, Song JQ, Huang JF, Wang Q, Tan LJ (2017) Effect of early full-calorie nutrition support following esophagectomy: a randomized controlled trial. JPEN 41:1146–1154
21. Obling SR, Wilson BV, Pfeiffer P, Kjeldsen J (2017) Home parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomized controlled trial. Clin Nutr. https://doi.org/10.1016/j.clnu.2017.12.011
22. Caccialanza R, Cereda E, Klersy C, Bonardi C, Cappello S, Quarleri L, Turri A, Montagna E, Iacona I, Valentino F, Pedrazzoli P (2015) Phase angle and handgrip strength are sensitive early markers of energy intake in hypophagic, non-surgical patients at nutritional risk, with contraindications to enteral nutrition. Nutrients 7:1828–1840
23. Pereira MME, Queiroz MDSC, de Albuquerque NMC, Rodrigues J, Wiegert EVM, Calixto-Lima L, de Oliveira LC (2018; in press) The prognostic role of phase angle in advanced cancer patients: a systematic review. Nutr Clin Pract. https://doi.org/10.1002/ncp.10100.
24. Pérez Camargo DA, Allende Pérez SR, Verastegui Avilés E, Rivera Franco MM, Meneses García A, Herrera Gómez Á, Urbalejo Ceniceros VI (2017) Assessment and impact of phase angle and sarcopenia in palliative cancer patients. Nutr Cancer 69:1227–1233
25. Souza BU, Souza NCS, Martucci RB, Rodrigues VD, Pinho NB, Gonzalez MC, Avesani CM (2018) Factors associated with sarcopenia in patients with colorectal cancer. Nutr Cancer 70:176–183
26. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA (2013) Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. Support Care Cancer 21:3261–3270
27. Caccialanza R, Palladini G, Klersy C, Cereda E, Bonardi C, Quarleri L, Vadacca G, Albertini R, Merlini G (2013) Serum prealbumin: an independent marker of short-term energy intake in the presence of multiple-organ disease involvement. Nutrition 29:580–582
28. Dellière S, Cynober L (2017) Is transthyretin a good marker of nutritional status? Clin Nutr 36:364–370
29. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group (2003) Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr 22:321–336
30. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649–655
31. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA (1986) Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol 60:1327–1332
32. Nwosu AC, Mayland CR, Mason S, Cox TF, Varro A, Ellershaw J (2016) The association of hydration status with physical signs, symptoms and survival in advanced cancer-the use of bioelectrical impedance vector analysis (BIVA) technology to evaluate fluid volume in palliative care: an observational study. PLoS One 11(9):e0163114
33. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, Schols AM, Pichard C (2004) Composition of the ESPEN Working Group. Bioelectrical impedance analysis- part I: review of principles and methods. Clin Nutr 23:1226–1243
34. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, Lilienthal Heitmann B, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, Schols A MWJ, Pichard C, ESPEN (2004) Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 23:1430–1453
35. Piccoli A, Rossi B, Pillon L, Bucciante G (1994) A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. Kidney Int 46:534–539
36. Piccoli A, Nigrelli S, Caberlotto A, Bottazzo S, Rossi B, Pillon L, Maggiore Q (1995) Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. Am J Clin Nutr 61:269–270
37. Krüger J, Meffert PJ, Vogt LJ, Gärtner S, Steveling A, Kraft M, Mayerle J, Lerch MM, Aghdassi AA (2016) Early parenteral

nutrition in patients with biliopancreatic mass lesions, a prospective, randomized intervention trial. PLoS One 11(11):e0166513
38. Drissi M, Cwieluch O, Lechner P, Radziwill R, Vehling-Kaiser U, Hengst K, Masin M (2015) Nutrition care in patients with cancer: a retrospective multicenter analysis of current practice - indications for further studies? Clin Nutr 34:207–211
39. Della Valle S, Colatruglio S, La Vela V, Tagliabue E, Mariani L, Gavazzi C (2018) Nutritional intervention in head and neck cancer patients during chemo-radiotherapy. Nutrition 51–52:95–97
40. Giles KH, Kubrak C, Baracos VE, Olson K, Mazurak VC (2016) Recommended European Society of Parenteral and Enteral Nutrition protein and energy intakes and weight loss in patients with head and neck cancer. Head Neck 38:1248–1257
41. De Waele E, Mattens S, Honoré PM, Spapen H, De Grève J, Pen JJ (2015) Nutrition therapy in cachectic cancer patients. The Tight Caloric Control (TiCaCo) pilot trial. Appetite 91:298–301
42. Oshima T, Berger MM, De Waele E, Guttormsen AB, Heidegger CP, Hiesmayr M, Singer P, Wernerman J, Pichard C (2017) Indirect calorimetry in nutritional therapy. A position paper by the ICALIC study group. Clin Nutr 36:651–662
43. Bally MR, Blaser Yildirim PZ, Bounoure L, Gloy VL, Mueller B, Briel M, Schuetz P (2016) Nutritional support and outcomes in malnourished medical inpatients: a systematic review and meta-analysis. JAMA Intern Med 176:43–53
44. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, Seron P, Ahmed SH, Rosengren A, Kelishadi R, Rahman O, Swaminathan S, Iqbal R, Gupta R, Lear SA, Oguz A, Yusoff K, Zatonska K, Chifamba J, Igumbor E, Mohan V, Anjana RM, Gu H, Li W, Yusuf S (2015) Prospective Urban Rural Epidemiology (PURE) Study investigators. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet 386:266–273
45. Teodozio CGC, Chaves GV, Arcuri IP, Frajacomo FT (2018) Does grip strength decrease in the very early stages of hematological treatment? Support Care Cancer 26:333–335