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Randomized Control Trials

Home parenteral nutrition increases fat free mass in patients with incurable gastrointestinal cancer. Results of a randomized controlled trial

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SUMMARY

Objective: Preventing loss of muscle mass and function is an enduring challenge in malnourished patients with incurable cancer. The benefit of supplemental home parenteral nutrition has not been firmly established. Our aim was to evaluate the effects of supplemental home parenteral nutrition, the primary endpoint being fat free mass (FFM) and secondary: muscle function, quality of life and overall survival.
Design and methods: In a single centre open-label randomised controlled trial, patients with incurable gastrointestinal cancer, nutritionally at risk, were randomly assigned to either; a) best practice nutritional care and dietetic counselling (non-sHPN) or b) dietetic counselling and supplemental home parenteral nutrition (sHPN group). Treatment duration was 24 weeks with visits every six weeks for five scheduled visits.
Main outcome was gain in bioelectrical impedance analyses (BIA) estimated FFM. Secondary outcomes were muscle strength, quality of life and survival.
Results: Eligible for inclusion were 234 patients, 47 of these accepted enrolment; 25 were randomized to non-sHPN and 22 to sHPN according to performance status, age and diagnoses. Median age was 66.9 (41.5–88.2), BMI 21.3 (14.8–35.7) and (91%) were receiving palliative chemotherapy. Median FFM and fat free mass index increased in the sHPN group. At 12 weeks a significant difference ($p < 0.01$) was found between the groups; in the sHPN group 69% of the patients (versus 40%) increased their FFM. Handgrip strength increased in both groups but without significance between the two. Quality of life at 12 weeks was significantly better ($p < 0.05$) in the sHPN group. No difference was noticed in survival, median 169 (CI 88–295) days versus 168 (CI 80–268) days. Study completion was accomplished by 36%; 60% died before end of study.
Conclusions: Providing supplemental home parenteral nutrition may prevent loss of FFM, and it is even possible to increase FFM in patients with incurable gastrointestinal cancer. Supplementation with parenteral nutrition might have a temporarily positive impact on quality of life.
Trial registration: (NCT02066363) www.clinicaltrials.gov.

1. Introduction

Muscle depletion and weightloss are correlated with a worse outcome in cancer patients [1,2]. Malnourished patients with cancer have a lower response rate to - and shorter duration of -chemotherapy [3], higher rates of hospital admissions and prolonged hospital stays [4]. Supplementation with home parenteral nutrition (HPN) in aphagic patients with advanced cancer has shown improved quality of life [5,6] and energy balance, stabilised body composition, and prolonged survival [7,8]. Malnutrition and weight loss are cardinal symptoms of cancer cachexia. Cachexia is a complex metabolic syndrome associated with underlying illness and defined by weight loss of at least 5%, loss of muscle mass and loss of appetite [9]. Patients suffering from cachexia are in a

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catabolic state due to metabolic changes including alterations in carbohydrate, lipid, and protein metabolism, leading to loss of fat and muscle mass [10,11]. Cachexia correlates with poor performance status, poor quality of life, and a high mortality rate in advanced cancer patients [12]. Cachexia as a continuum, can be classified into three phases; precachexia, cachexia and refractory cachexia [13]. The best approach to the treatment of cancer cachexia is probably early multimodal intervention with nutrition, exercise, rehabilitation programs, and multi-target drug therapies [14]. Loss of muscle mass accelerates with age [15] this decline is augmented in undernourished patients, and especially if there is an insufficient protein supply. Sarcopenia, decrease in muscle mass and function, is a prominent symptom of the cachexia syndrome and the loss of muscle mass occurs particularly due to impaired food intake, malabsorption of nutrients, and lack of physical activity. Exercise helps to maintain muscle mass and strength, but probably does not affect the biological process, which ultimately leads to sarcopenia [16].

Although, it has been suggested that cancer patients may benefit from an improved nutritional state, few clinical prospective studies have addressed this – and in particular whether parenteral nutrition adds value in preventing loss of muscle mass. Our aim was to evaluate whether supplemental HPN given to patients with incurable cancer would benefit the patient by preventing the functional decline accompanying cachexia.

2. Patients and methods

2.1. Study design

This prospective clinical trial was designed as a single centre, open label randomised trial comparing best practice nutritional care and dietetic counselling (Non-sHPN group) to supplemental home parenteral nutrition (sHPN group) and dietetic counselling. Patients with incurable gastrointestinal (GI) cancer were included from May 2014 until November 2016 at Odense University Hospital Denmark.

2.2. Ethics

Ethical approval was obtained from the local Ethics Committee (S-20120094). Written informed consent was given by all participants. Permission for handling and storage of the data was obtained from the Danish Data Protection Agency (14/6784). The study was registered at Clinical Trials.gov (NCT02066363). Permission for handling and storage of data from patients not included was obtained from the Danish Data Protection Agency (16/24969). The clinical trial complied with the Helsinki Declaration from 2008, the principles of Good Clinical Practice (GCP) guidelines and the Federal Data Protection Act.

2.3. Patients

Patients attending the outpatient clinic of Oncology for evaluation or chemotherapy were screened and had their nutritional status assessed. Patients were approached by the primary investigator or a project nurse during chemotherapy. *Inclusion criteria* were histologically confirmed incurable gastrointestinal cancer (locally advanced or metastatic), age > 18 years, performance status (PS) 0–2 [17], nutritionally at risk according to NRS 2002 score ≥2 [18]. Chemotherapy was not an exclusion criterion. *Exclusion criteria* were functional or actual short bowel syndrome. Patients were seen by a dietician and the primary investigator every six weeks, for five scheduled visits. Treatment duration was 24 weeks.

2.4. Randomization

Patients were randomized according to performance status, diagnosis, and age to either; (a) best practice nutritional care and dietetic counselling (non-sHPN group) or (b) best practice nutritional care, dietetic counselling and sHPN (sHPN group). Because of the sample size and the total number of strata decided upon, a minimization procedure was planned. Patients were enrolled in the study and allocated to one of two treatment groups using the restricted randomisation method minimization [19,20]. Using the minimization method with a random component the patient factors for diagnosis (oesophagus, gastric, duodenal, pancreatic, bile ducts or colorectal cancer), age (<70 or ≥70) and PS (0, 1 or 2) were balanced to make the treatment groups similar. The web-based open source program MinimPy [21] was used for the minimization process by a specialist nurse who was not otherwise involved in the project.

In both intervention groups, nutrition impact symptoms were addressed by diet modification recommendations and patients were encouraged to take the medications prescribed at department of oncology, particularly pancreatic enzyme replacement, analgesics, and laxatives. All medications, including glucocorticoids were handled entirely by staff at the department of oncology.

2.5. Intervention (a) best practice nutritional care and dietetic counselling (non-sHPN group)

Patients randomized to the non-sHPN group received dietetic counselling at every visit in the study the aim was to ensure an intake of at least 75% of the estimated energy and protein requirements. To assess the individual nutritional intake the structured interview “24 h recall” was used to obtain information about the macronutrient and fluid consumption, including quantities and preparation methods during the previous day. Advice was offered to address eating difficulties and to stimulate nutritional intake. Nutritional requirements were estimated using the Harris Benedict equation. There were no restrictions on nutrients and the patients were offered various methods to help overcome the eating difficulties. Supplemental oral nutrition formulas were recommended on patient request, and/or when protein and calorie requirements were unmet by ordinary food. If the estimated need of nutrient intake (75%) was not attained patients were offered a feeding tube.

2.6. Intervention (b) best practice nutritional care, dietetic counselling and sHPN (sHPN group)

Patients randomized to the sHPN group also received dietetic counselling and a 24 h recall was performed at each visit. Furthermore, patients in the sHPN group were admitted to the department of Medical Gastroenterology at Odense University Hospital, for information and training in catheter and HPN handling. An ultrasound guided tunnelled central venous access (tCVC) was placed by a radiologist, unless the patient already had a suitable central venous catheter, i.e. a totally implantable venous access device (Port à Cath) or a peripherally inserted central catheter (PICC). Two dedicated specialist nurses informed, educated, and trained the patients at the hospital. The PN used was all-in-one industrially prepared three chamber bags (Olimel N9E, Baxter International Corporation) containing 56.9 g protein, 1070 kcal/4477 kJ energy and 40 g fat per thousand ml. Nutritional needs was estimated to be: energy 125 kJ/kg, protein 1.5 g/kg/day and fluid 35 ml/kg/day. Patients received PN at 25–35% percent of the daily nutritional need, the dose being adjusted for practicality of administration. The patients were prescribed sHPN two to four days per week and preferably, the PN was administered during the night-time, to avoid interference with daytime activities. The PN

was delivered to and prepared at the patients' home. The sHPN was administered by the patient, a relative, or by the community nurse depending on patient preference, and in all cases preceded by careful training of all procedures.

Number of non-administrative admissions and catheter related infections were registered.

3. Definitions

To address hypercatabolism and reflect changes in inflammation modified Glasgow Prognostic Score (mGPS) was used. Weightloss and sarcopenia was combined with mGPS, in an attempt to express refractory cachexia.

All outcomes were measured at every completed visit.

3.1. Primary outcome

Fat free mass (FFM) was estimated using bioelectrical impedance analyses (BIA; Maltron Bioscan 920). FFM was normalized for height in (m^2) and reported as fat free mass index (FFMI). Cut offs for BIA measured sarcopenia was FFMI <14.6 kg/m^2 for men and <11.4 kg/m^2 for women. To reduce inaccuracy due to water imbalance, patients were encouraged to refrain from eating, drinking and exercising 8 h before the measurement.

3.2. Secondary outcomes

Handgrip strength was used to assess muscle function, and measured with a hand dynamometer; three measurements were made with the patient seated, elbow flexed at 90°, and the highest score was noted. The dominant side of the body was used for measurement except in patients with amputations, prosthetics or any other cause leading to declined function or severe oedema. Cut off for sarcopenia, was <20 kg for women and <30 kg for men [22].

Six minutes walking test (6MWT); to assess muscle performance the 6MWT was applied. The validated test 6MWT was measured on a marked 30 m walking distance [23]. A change in walking distance of 14.0- to 30.5 m was considered clinically relevant [24].

Skinfold; A three point skinfold measurement was performed using a Harpender skinfold Caliper at three predefined sites; subscapular, triceps, and the suprailiac crest [25], and the FFM estimated using the three-site skinfold formula [26,27].

Quality of life was estimated with the validated questionnaire EORTC QLQ-C15-PAL [28] and presented to the patient at every visit. The EORTC QLQ-C15-PAL contains one overall QoL and 14 questions reflecting physical and emotional functioning. The overall QoL was analysed, scaled from 1: very poor to 7: excellent overall QoL, each score being converted to a score ranging from 0 to 100.

*Overall survival w*as defined as the time from the date of inclusion in the study until the date of death from any cause or the last date known to be alive. Patients alive at the time of the analysis were considered censored.

3.3. Statistical analysis

Baseline comparisons between the two groups were made using Wilcoxon Rank Sum (Mann Whitney U test) for continued variables and Fishers exact test for ordinal scale data as appropriate. To evaluate the adjusted changes in group mean and the general variability in outcomes we used a linear mixed model to account for the equality of repeated measures on the same individual being more equivalent than responses from different individuals. “Patient” included as the random effect and “visit” as the fixed effect including covariance for sex and age and the baseline value of the outcome [29]. Post estimation tests were conducted to examine the model, with estimates of the random effects and residual diagnostics. Normal distribution of the residuals is required and was thus tested, before accepting the mixed model.

Univariate and multivariate logistic regression was applied to test for predictors of gain in FFM including variables for baseline BMI, age, mGPS and sex.

Overall survival was evaluated using Kaplan–Meier and Cox regression, respecting the assumption of proportional hazards. In the Cox proportional hazards regression covariates for, baseline handgrip strength, mGPS and BMI, age and sex were included. P-values of <0.05 in the two sided analysis were accepted as statistically significant. All analyses were performed according to intention to treat and were carried out using Stata (Version15. Statistical software, College station, Texas: StataCorp LLC).

The statistical considerations of changes in FFM were based on earlier studies [30,31] in patients with advanced cancer. Including 40 patients in each randomization group and from base-line to end of trial assuming a change in FFM of four kilograms in the sHPN group and two kilogram in the non-sHPN group, assuming a standard deviation of three kilogram, and a type I error of 0.05 (two-sided) would provide a power of 85% to yield a true difference between the groups. To compensate for drop-out we intended to include 100 patients.

4. Results

4.1. Patient recruitment

A total of 557 patients with incurable gastrointestinal cancer were consecutively approached and screened for inclusion. 323 patients were excluded at screening; while 187 patients refused participation in the RCT (Fig. 1). Forty-seven patients were included in the study, the majority were male (64%) with heterogeneity in diagnosis, pancreatic cancer being most frequent (57%) but equally distributed among the groups. Median age at study inclusion was 67 yrs. Ninety one percent received chemotherapy at inclusion, the two groups being comparable. For more details see (Table 1). Sarcopenia was observed in 38% when defined by muscle function and in 6% when defined by muscle mass.

Nutritional parameters; at baseline there was no difference in BMI or nutritional intake (Table 2). BMI increased during the study, at visit 3 a significant difference (*CI 0.4- 2.9, p < 0.05*) between the groups was found, with a higher BMI in the sHPN group (Table 3).

Energy and protein intake increased in both groups in comparison to baseline (Table 4). The sHPN group did not receive significantly more energy, but the protein provision was significantly higher at visit 2, 3 and 5 (CI 0.38–0.47 p < 0.05). Fluid intake increased and the sHPN group received significantly more fluid at visit 2–4 (*CI 9.2-12.9 p < 0.05*) (Table 5). The number of patients receiving the estimated required energy was stable, whereas the number of patients receiving the required protein was higher in the sHPN-group, but the difference was not significant.

Median provision of supplemental parenteral nutrition was: energy 34 kJ/kg/day, protein 0.44 g/kg and fluid 7.7 ml/kg pr. day.

Three patients in the non-sHPN group accepted a feeding tube to ensure the nutrient intake, but eating difficulties in these patients were more over due to cancer progression and the feeding tube was only used for a short while (<2 weeks) before the patients were declared to be terminal.

Re-admissions and catheter related infections; Mean admission time for the sHPN patients was three days for initiation of treatment with parenteral nutrition. The non-sHPN group was not admitted to the hospital for initiation of the nutritional therapy.

In both treatment groups twenty one percent had more than three re-admissions; the most common reason was infection (21%)

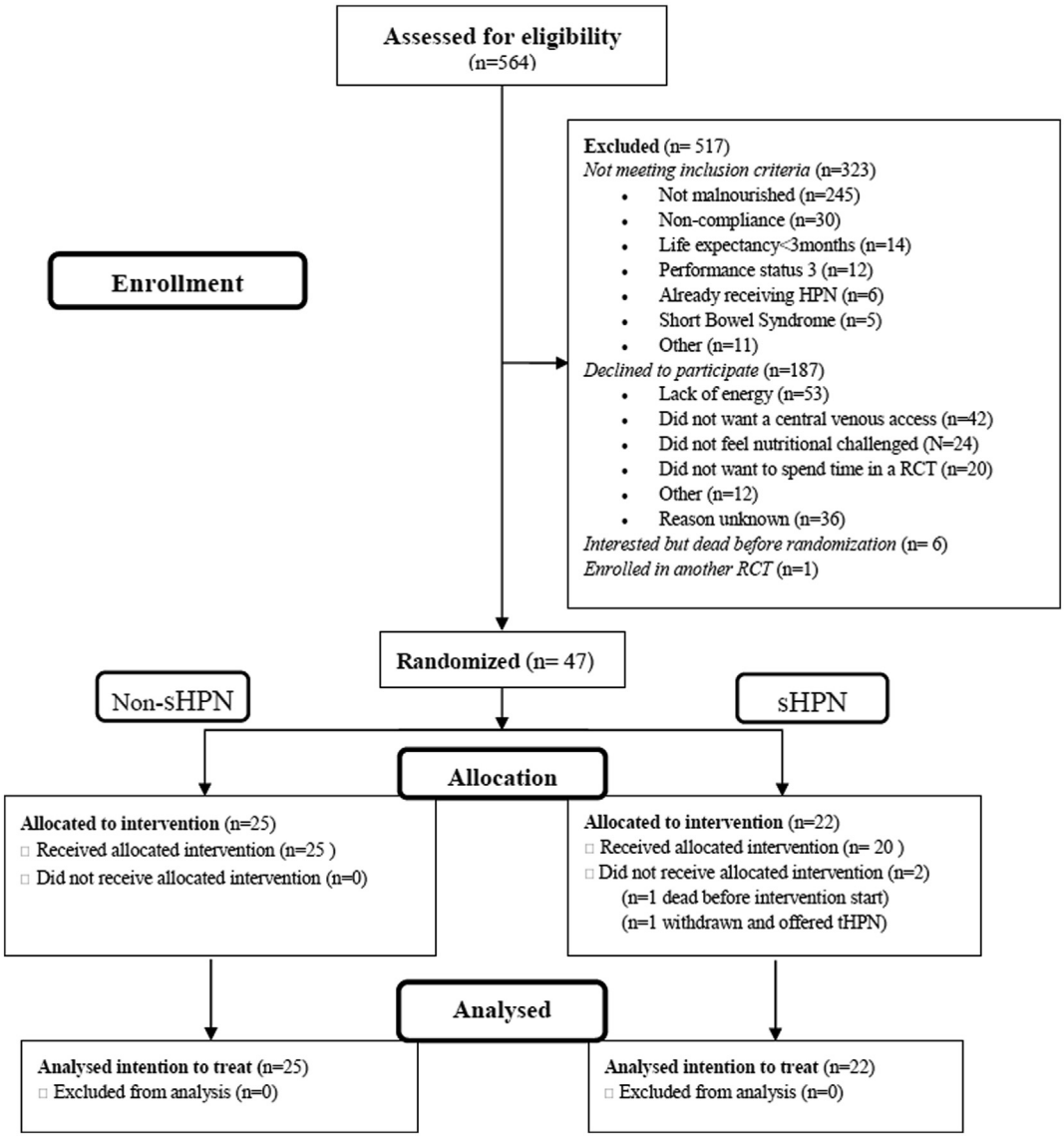

Fig. 1. Consort flow diagram.

the majority not related to the central venous access. Two patients were admitted to the hospital with catheter related infection during the study, though there were no episodes of severe catheter related bloodstream infection. Forty seven percent were admitted and died in hospital or at hospice.

4.2. Primary outcome

The FFM variation differed between the two groups, the difference being significant at visit 3 ($p < 0.01$) (Fig. 2). Mean FFM and FFMI evaluated by BIA in the non-sHPN group *decreased* during the study time as opposed to the mean FFM and FFMI in the sHPN group where the values *increased* from baseline to visit 5. At twelve weeks (visit 3) 40% in the non-sHPN group versus (69%) in the sHPN group had increased FFM. Changes in FFM and FFMI were compared using the linear mixed model and the difference in FFM (6.44 kg) and FFMI (2.03 kg/m^2) were significant ($p < 0.01$) after 12 weeks (Table 5). The variation observed was not caused by individual differences but by variation between the groups. Neither baseline BMI, age, mGPS nor sex predicted FFM gain when tested in the logistic regression.

4.3. Secondary outcomes

Handgrip strength improved from baseline to last visit in both treatment groups. In the mixed model handgrip did not change significantly at any time point and there was no significant difference between the two groups. Patients performed better in 6MWT over time, but the variation found was mainly due to individual variation. In the mixed model the changes were insignificant between the groups. The FFM and FFMI estimate measured by skinfold *decreased* in the non-sHPN group and an *increase* was observed in the sHPN group. Differences were significant at visit 3 ($p < 0.05$) and 5 ($p < 0.05$) (Table 3).

4.3.1. Quality of life

All patients accepted completion of the questionnaire and all managed to answer the questions without assistance. At twelve weeks (visit 3) 9% in the non-sHPN group versus 57% in the sHPN group expressed increase in overall QoL (Table 6). A significant difference ($p < 0.05$) in mean overall QoL was found after 12 weeks, at visit 3 (+16.0) in favour of the sHPN group (Table 5).

Table 1
Baseline characteristics of the 47 participating patients.

	Total Median (Range) N (%)	Non-sHPN group Median (Range) N (%)	sHPN group Median (Range) N (%)
All patients	47	25	22
Sex			
N = women	17 (36)	10 (40)	7 (32)
Age	66.9 (41.5–88.2)	65.9 (43.3–88.2)	67.4 (41.5–81.6)
Performance status			
0	6 (13)	5 (20)	1 (5)
1	25 (53)	13 (52)	12 (54)
2	16 (34)	7 (28)	9 (41)
Tumour site			
Oesophagus	2 (4)	1 (4)	1 (5)
Stomach	9 (19)	4 (16)	5 (22)
Duodenum	2 (4)	1 (4)	1 (5)
Pancreas	27 (58)	14 (56)	13 (59)
Bile duct	2 (4)	1 (4)	1 (5)
Colorectal	5 (11)	4 16)	1 (5)
Chemotherapy at inclusion	43 (91)	23 (92)	20 (91)
Smoking			
Current	13 (28)	9 (36)	4 (18)
Former	22 (47)	11 (44)	11 (50)
Never	12 (25)	5 (20)	7 (32)
Alcohol			
<7	40 (85)	19 (76)	21 (95)
7–14	7 (15)	6 (24)	1 (5)
Study completion			
Visit 1 (Baseline)	47	25 (100)	22 (100)
Visit 2 (6 weeks)	36	20 (80)	16 (73)
Visit 3 (12 weeks)	25	11 (44)	14 (64)
Visit 4 (18 weeks)	22	10 (40)	12 (55)
Visit 5 (24 weeks)	17	9 (36)	8 (36)
Reasons for not completing study			
Death	28 (60)	15 (60)	13 (59)
Complications	1 (2)	1 (4)	–
Non-compliance	1 (2)	1 (4)	–

Table 2
Baseline nutritional characteristics.

	Total Median (Range) N (%)	Non-sHPN group Median (Range) N (%)	sHPN group Median (Range) N (%)
All patients	47	25	22
BMI	*21.3 (14.8–35.7)*	*21.3 (15.9–29.6)*	*21.6 (14.8–35.7)*
15–18.5 (underweight)	8 (17)	5 (20)	3 (14)
18.5–24.9 (normal weight)	33 (70)	17 (68)	16 (72)
25.0–35.0 (overweight)	6 (13)	3 (12)	3 (14)
24 h recall 75% of established needs			
Energy	43 (93)	23 (92)	20 (95)
Protein	22 (48)	12 (48)	10 (48)
Fluids	32 (70)	16 (64)	16 (76)
Weightloss prior to inclusion			
<5%	8 (17)	7 (28)	1 (5)
5-10%	10 (22)	4 (16)	6 (27)
>10%	29 (61)	14 (56)	15 (68)
Sarcopenia*			
BIA	3 (6)	1 (4)	2 (9)
Handgrip	18 (38)	9 (36)	9 (41)
mGPS (0–2)**			
0	17 (36)	8 (32)	9 (41)
1	15 (32)	8 (32)	7 (32)
2	15 (32)	9 (36)	6 (27)
Glucocorticoid treatment	19 (40)	12 (48)	7 (32)
Central Venous Access			
tCVC	15 (72)	–	15 (72)
Port A Cath	3 (14)	–	3 (14)
Picc-Line	3 (14)	–	3 (14)
HPN Administration			
Home care nurse	10 (48)	–	10 (48)
Patient	7 (33)	–	7 (33)
Relative	4 (19)	–	4 (19)
Continued HPN after study completion	7 (33)		7 (33)

* Sarcopenia = loss of muscle mass and function.
** mGPS = Modified Glasgow Prognostic Score (0 = albumin>35,crp<10, 1CRP>10, albumin>35, 2 = CRP>10, Alb<35). N= number of missing values at each time point.

Besides significant differences in overall QoL, significant improvements in QoL parameters were found in the answers on nausea, depression and constipation. At visit 3 and 4 patients in the sHPN group claimed to feel less nausea ($p = 0.03$). As well they felt significant less depressed, at visit 3 ($p = 0.03$). The score for constipation was significantly higher in patients receiving sHPN at visit 5 ($p < 0.01$). We found no significant differences in the remaining QoL parameters, especially no differences were found for “troubles sleeping”, “physical impairment” or “dependency”.

4.3.2. Overall survival

Median overall survival was 169 (CI 88–295) days in the non-sHPN group versus 168 (CI 80–268) days in the sHPN group. At six months 44% of patients in the non-sHPN group and 50% in the sHPN group were still alive. Twenty percent were still alive at one year in the non-sHPN group and 14% in the sHPN group (Fig. 3). We found no significant difference in overall survival between the two groups. In the univariate cox regression analyses, baseline handgrip strength, mGPS and BMI were predictive for survival. None of the variables were significant predictors of survival when included in the multivariate model with age and sex.

4.4. Drop outs during the study

Completion of all five visits in the study was accomplished by 17 (36%) patients. Main reason for non-completion was death before end of study (60%). No patients were lost to follow up.

5. Discussion

In this randomized controlled trial we investigated the effect of sHPN in patients with incurable GI cancer. FFM and overall QoL improved in patients receiving sHPN compared to the patients not receiving the supplement. Improved physical function was documented in both groups using handgrip and 6MWT, but without difference between the groups. Overall survival was comparable in the two groups. Although dietetic counselling aimed to ensure a sufficient intake of nutrients and fluids, not all patients reached the goal for protein. Unfortunately, we were unable to include the estimated number of patients. However, the intervention appeared to prevent the acceleration of further weight loss and muscle waste. FFM increased in numerous patients; 40–67% in the non-sHPN group and 47–69% in the sHPN group, at different time points. The rise in FFM appeared earlier in the sHPN group than in the non sHPN group. There was a significant, although temporary, difference in FFM after 12 weeks, which may imply a positive effect of the sHPN.

Most studies on sHPN in cancer patients have reported on FFM, function, survival, or QoL. Our aim was to study the effect of nutritional therapy on both FFM and function while ensuring the nutritional components. Even though we found an improvement in FFM and a significant higher protein provision in the sHPN group the enhanced physical function was not significantly higher in this group. Significant increase in handgrip strength may have been undetectable due to the limited sample size. The results of the 6MWT were unreliable, affected by non-ignorable missing values, linked to the outcome and the variance found was attributable to

Table 3
Exact values in median (range) for outcome variables.

	Patients Evaluated	Non-sHPN Median (Range)	sHPN Median (Range)
BMI (kg/h^2)			
Baseline	46 (25 + 21)	21.3 (15.9–29.6)	21.5 (14.8–35.7)
Visit 2	36 (20 + 16)	21.0 (14.4–29.8)	22.2 (16.1–36.8)
Visit 3	25 (11 + 14)	19.5 (15.9–29.8)	22.7 (16.5–38.8)
Visit 4	22 (10 + 12)	22.9 (15.8–31.7)	23.7 (16.9–34.8)
Visit 5	17 (9 + 8)	22.9 (15.6–31.6)	23.5 (18.9–31.6)
FFM (BIA) (kg)			
Baseline	43 (22 + 21)	48.6 (35.7–59.0)	48.1 (26.8–56.5)
Visit 2	32 (17 + 15)	45.8 (37.7–60.3)	50.4 (35.0–63.6)
Visit 3	23 (10 + 13)	45.6 (40.2–53.6)	55.2 (34.9–66.7)
Visit 4	18 (7 + 11)	49.8 (35.1–62.9)	54.9 (38.1–69.9)
Visit 5	16 (9 + 7)	44.4 (33.9–64.2)	50.3 (41.1–58.6)
FFMI (BIA) (kg/h^2)			
Baseline	43 (22 + 21)	16.6 (12.2–19.5)	16.6 (11.3–21.1)
Visit 2	32 (17 + 15)	16.2 (13.4–19.6)	17.6 (13.9–23.5)
Visit 3	23 (10 + 13)	15.8 (13.7–18.9)	17.9 (14.0–26.8)
Visit 4	18 (7 + 11)	16.9 (12.4–19.5)	18.6 (15.3–21.8)
Visit 5	16 (9 + 7)	16.9 (12.0–19.1)	18.2 (15.5–19.7)
Handgrip (kg)			
Baseline	47 (25 + 22)	24.8 (10.8–51.8)	28.6 (7.2–51.3)
Visit 2	36 (20 + 16)	30.0 (13.1–49.1)	32.7 (19.8–54.0)
Visit 3	25 (11 + 14)	28.4 (21.2–54.0)	33.1 (19.4–55.4)
Visit 4	21 (10 + 11)	28.9 (9.9–61.2)	33.8 (22.5–59.9)
Visit 5	17 (9 + 8)	27.5 (15.8-67-5)	39.0 (24.3–59.4)
6MWT (meters)			
Baseline	43 (23 + 20)	436 (60–651)	431 (240–775)
Visit 2	30 (17 + 13)	449 (120–627)	526 (240–817)
Visit 3	16 (7 + 9)	490 (399–602)	574 (474–855)
Visit 4	16 (8 + 8)	453 (240–663)	601 (360–844)
Visit 5	11 (5 + 6)	495 (300–668)	610 (529–861)

individual differences rather than to difference between the groups.

A retrospective study from 2015 [32] including 304 pancreatic cancer patients receiving oncologic treatment demonstrated benefit on survival of systematic nutritional interventions despite an evidence of tumour progression. In our study we found no difference in survival between the study groups. The study by Lundholm et al. [7] tested a supplemental PN in weight-losing patients with cancer undergoing multimodal palliation including COX inhibitors, erythropoietin, and insulin. In that study on 309 patients with solid tumours (primarily gastrointestinal cancer), with an expected survival of at least six months, patients randomized to receive sHPN improved in energy balance, increased their body fat, had greater maximum exercise capacity and prolonged survival. In our study the variance found in ingested nutrients was primarily between individuals which could reflect the small sample size. Improvement of QoL and nutritional status in patients with cancer receiving sHPN was demonstrated in a longitudinal study by Vashi et al. [6], in which improvement of overall QoL was found after twelve weeks. A longitudinal observational study [33] on patients with incurable cancer receiving HPN due to obstructive disease in the intestine, reported on an improvement in overall QoL during the four months study. This corresponds well with our findings, with significant improved overall QoL after 12 weeks in the sHPN group. Hereafter, the increase stabilised and did not differ significantly between the groups. The weight loss in patients with cancer is a major concern to patients and their relatives and HPN can provide the nutritional requirement and lift the burden from the carers [34]**.** Orreval et al. [35] reported a positive impact on QoL in patients with cancer receiving HPN, mainly related to increased functional capacity and less worries about potential weightloss or eating disabilities.

The present study is the first, to our knowledge, using linear mixed models to study the longitudinal effects of sHPN on FFM in patients with incurable cancer. One of the advantages with the mixed model is the ability to study the effect over time in a group with restricted overall survival, where the intervention possibly might have a time limited palliative effect and no improvement of overall survival.

Great variability exists for the different BIA equations, which is often evaluated on healthy people and not on cancer patients. When used in a longitudinal study under standard conditions, we accepted the limitations and the interpersonal changes as tolerable. The manufactured equation in the Maltron BIA scanner was not available and may be a source of uncertainty given the calculated FFM. Consequently, FFM was estimated using the equation by Schols et al. [36], which was recently tested superior in a cohort of patients with colorectal cancer. Schols equation having the highest agreement with DXA measured FFM [37]. Three patients in the study had BMI less than 16 and one had BMI >35 and 21% had slight oedema at baseline which may have influenced the BIA measured FFM.

Weight loss was prominent in our study; whereas BIA defined sarcopenia was infrequent, implicating that the cachexia was a result of weight rather than loss of muscle mass. At baseline three (6%) patients fulfilled the criteria of sarcopenia defined by muscle mass, and 18 (38%) defined by function. In a previous study in

Table 4
Nutritional intake of non-protein calories, protein and fluids, median (range) from baseline to visit 5.

	Patients Evaluated	Non-sHPN Median (Range)	sHPN Median (Range)	sHPN including HPN
Energy (kJ/kg/d)				
Baseline	46 (25 + 21)	131.7 (92.6–239)	158.8 (24.6–249.5)	158.8 (24.6–249.5)
Visit 2	36 (20 + 15)	148.8 (10.8–266.3)	125.6 (57.0–300.9)	158.2 (90.0–334.5)
Visit 3	26 (12 + 14)	130.0 (24.3–332.6)	126.2 (30.0–290.7)	160.5 (63.8–320.0)
Visit 4	22 (10 + 11)	168.9 (83.3–303.3)	168.1 (70.9–244.5)	196.0 (107.0–283.3)
Visit 5	17 (9 + 8)	153.3 (91.6–228.5)	130.9 (59.9–320.9)	167.8 (98.4–348.7)
Protein(g/kg/d)				
Baseline	46 (25 + 21)	1.11 (0.33–2.32)	1.18 (0.13–1.76)	1.18 (0.13–1.76)
Visit 2	36 (20 + 15)	1.16 (0.60–2.19)	1.08 (0.42–2.44)	1.52 (0.85–2.81)
Visit 3	26 (12 + 14)	1.10 (0.32–2.84)	1.39 (0.44–2.11)	1.81 (0.88–2.48)
Visit 4	21 (10 + 11)	1.16 (0.65–2.84)	1.34 (0.65–2.14)	1.79 (1.07–2.51)
Visit 5	17 (9 + 8)	1.10 (0.69–1.69)	1.12 (0.45–2.29)	1.57 (0.94–2.65)
Fluids (ml/kg/d)				
Baseline	46 (25 + 21)	29.1 (4.4–57.6)	30.2 (11.2–43.8)	30.2 (11.2–43.8)
Visit 2	36 (20 + 15)	30.1 (13.5–55.9)	32.3 (21.0–54.3)	41.6 (27.9–63.1)
Visit 3	26 (12 + 14)	30.8 (16.0–65.7)	30.8 (17.5–80.5)	37.4 (24.0–88.2)
Visit 4	22 (10 + 11)	38.9 (7.7–49.7)	36.4 (18.2–56.0)	42.3 (25.9–65.5)
Visit 5	17 (9 + 8)	34.0 (16.1–68.4)	31.2 (16.3–37.6)	38.9 (24.9–44.2)

Table 5
Mean difference in outcome *between* sHPN and non-sHPN from baseline to visit five. Differences accounting for the baseline value when tested using the linear mixed model.

Mean difference	Baseline	Visit 2	Visit 3	Visit 4	Visit 5
Baseline – Visit 5		(6 weeks)	(12 weeks)	(18 weeks)	(24 weeks)
BMI (kg/m^2)	0.26 [−2.6, 2.1] *(N = 0)*	0.43 [−0.7, 1.6] *(N = 0)*	1.65 [0.4, 2.9]* *(N = 0)*	−4.9 [−1.9, 1.0 *(N = 0)*	−0.66 [−2.1,0.8] *(N = 0)*
FFM/kg (BIA)	−0.30 [−4.1, 4.7] *(N = 3/1)*	1.73 [−1.4, 4.9] *(N = 3/1)*	6.44 [2.9, 10.0]** *(N = 3/1)*	3.39 [−0.6, 7.4] *(N = 3/1)*	1.66 [−2.4, 5.7] *(N = 3/1)*
FFMI(kg/m^2) (BIA)	0.04 [−1.3, 1.2] *(N = 3/1)*	0.51 [−0.6, 1.6] *(N = 3/1)*	2.03 [0.8, 3.3]** *(N = 3/1)*	0.95 [−0.5,2.4] *(N = 3/1)*	0.32 [−1.2, 1.8] *(N = 3/1)*
FFM/kg (skinfold)	−2.49 [−2.6, 7.6] *(N = 0)*	2.30 [−0.6, 5.2] *(N = 0)*	4.20 [0.9, 7.5]* *(N = 0)*	1.88 [−1.6, 5.4] *(N = 0)*	4.15 [0.4, 7.9]* *(N = 0)*
FFMI (kg/m^2) (skinfold)	−0.97 [−0.4, 2.3] *(N = 0)*	0.66 [−2.8, 1.6] *(N = 0)*	1.21 [0.1, 2.3]* *(N = 0)*	0.50 [−0.6, 1.6] *(N = 0)*	1.51 [0.3, 2.7]* *(N = 0)*
Handgrip/kg	3.07 [−9.9, 3.7] *(N = 0)*	−0.39 [−5.0, 4.24] *(N = 0)*	−0.08 [−5.2, 5.1] *(N = 0)*	1.29 [−4.1, 6.7] *(N = 0/1)*	−1.10 [−6.7, 4.6] *(N = 0)*
6MWT/meter	28.51 [−110.2, 53.2] *(N = 2/2)*	−4.99 [−45.6, 35.6] *(N = 3/3)*	42.57 [−3.3, 88.4] *(N = 4/5)*	32.22 [−13.8, 78.3] *(N = 2/4)*	31.56 [−18.8, 81.9] *(N = 4/2)*
Overall QoL	−4.1 [−7.9, 16.1] *(N = 0)*	2.44 [−11.0,15.9] *(N = 0)*	16.00 [0.6, 31.4]* *(N = 0)*	15.4 [−0.8, 31.6] *(N = 0)*	7.02 [−10.9, 24.9] *(N = 0)*
24h recall energy(kJ/kg/d)	9.7 [−35.5, 16.0] *(N = 1/0)*	29.7 [−14.0, 73.3] *(N = 1/0)*	2.9 [−4.6, 51.5] *(N = 1/0)*	12.9 [−39.4, 65.2] *(N = 1/0)*	35.2 [−21.2, 91.6] 0.5 *(N = 1/0)*
24h recall protein (g/kg/d)	0.02 [−0.3, 0.2] *(N = 1/0)*	0.43 [0.1, 0.8]* *(N = 1/0)*	0.38 [0.1, 0.8]* *(N = 1/0)*	0.22 [−0.2,0.6] *(N = 1/0)*	0.47 [0.1, 0.9]* *(N = 1/0)*
24h recall fluids (ml/kg/d)	−1.4 [−5.2, 7.8] *(N = 1/0)*	9.2 [2.0, 16.3]* *(N = 1/0)*	9.4 [1.4, 17.4]* *(N = 1/0)*	12.9 [4.21,2.6]** *(N = 1/0)*	3.2 [−6.2,12.6] *(N = 1/0)*

N = number of missing values at each time point. *p < 0.05, **p < 0.01.
FFM=Fat Free Mass, FFMI= Fat Free Mass Index, 6MWT = Six Minutes Walking Test.
Baseline; No significant difference.

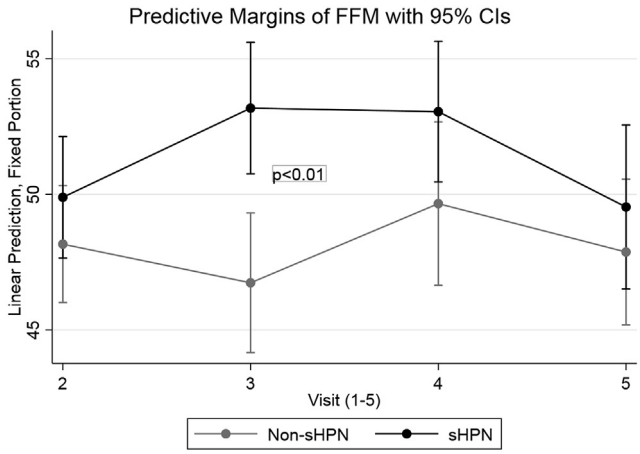

Fig. 2. Predictive Margins of fat free mass (FFM) estimated using BIA. Significant difference is present at visit 3 (after 12 weeks) when tested using the mixed model.

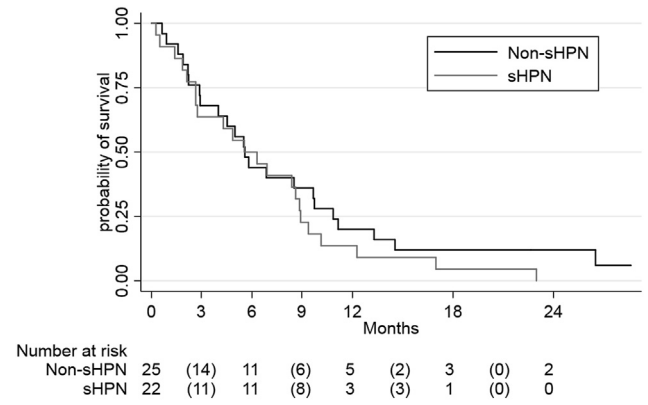

Fig. 3. Overall survival in patients treated with supplementary HPN (sHPN) and in patients not receiving HPN (non-sHPN).

Table 6
Exact values in mean (±sd) for the overall QoL score in EORTC QLQ-C15-PAL.

	Patients Evaluated	Non-sHPN Mean (sd)	sHPN Mean (sd)
Overall QoL			
Baseline	47 (25 + 22)	64 ± 17	60 ± 23
Visit 2	36 (20 + 16)	65 ± 21	67 ± 23
Visit 3	25 (11 + 14)	53 ± 14	69 ± 23
Visit 4	22 (10 + 12)	60 ± 21	78 ± 26
Visit 5	17 (9 + 8)	56 ± 18	69 ± 24

advanced pancreatic cancer patients receiving chemotherapy BMI did not have any impact on survival whereas sarcopenia at diagnosis and loss of muscle mass during chemotherapy were independently associated with survival [38]. A recent study on 67 metastatic colorectal cancer patients showed significant loss of muscle mass during chemotherapy and a significant worse overall survival if the weight loss was more than nine percent [39]. In our study, the BMI remained stable or increased from baseline throughout the study, and we found no association between mortality and FFM. Some patients may have had refractory cachexia at baseline, which may have made it impossible to achieve any improvement in FFM or physical function. Well aware that many patients were cachectic at time of inclusion, we intended not to regulate the inflammatory response with medical intervention but solely with nutrients. However, numerous patients were treated with glucocorticoid, which may hamper muscle generation [40].

One of the major limitations in our study was the challenge of inclusion, with a large group of patients not wanting to participate. The large number of refusals, for different reasons, was unexpected and it weakens the external validity. In previous studies it has proven difficult to persuade palliative care patients to participate in randomized trials, if any risk of side effects, if the study involves complex interventions or if the patient does not get support to participate from their relatives [41,42]. Consequently it can be difficult to predict if our study population is representative. However, bearing in mind that the patients offered participation were not severely hypophagic, included when nutritionally at risk, NRS ≥2, it was interesting that 34% did not want to participate; some not wanting a central venous access and some were not feeling nutritional challenged. Secondly, the population studied was remarkably fragile and before the end of study more than half of the patients were dead. Completion of all five visits in the study was only accomplished by 17 (36%) patients. In our power calculation we estimated 80% to be able to complete the study, but in reality only 36% accomplished the study visits, and caution must be taken when interpreting the results.

In the study we decided to provide dietician advice and HPN as a supplement to the oral intake, opting to realise the estimated nutritional goals. The reason for choosing HPN as the choice of therapy at an earlier stage than usually recommended was carefully

considered. Since most patients were receiving chemotherapy, side effects with gastrointestinal toxicity were expected. The gastrointestinal toxicity was expected to have major impact on the gastrointestinal tract and could worsen the intake, nausea and dysphagia. Furthermore, all patients were living at home, few still working, and a nasal tube would therefore be impractical an unattractive during length of the study.

Our results are interesting, but should be considered for hypothesis generating; to further explore the signals observed in this study future studies should focus on the prevention of the decline in muscle mass and function. A combination of nutritional intervention, physical training and modulation of inflammation should probably be applied. Furthermore, it should be considered if a randomized nutritional study is feasible in patients with limited survival, were the patients recruited may be a very selected group not representative of the general population.

From the results we suggest that improved FFM and FFMI may be obtained in patients with incurable GI cancer, that sHPN is feasible although it may not be requested by many patients. Notwithstanding the relatively limited sample, it seems possible to increase nutritional intake, BMI, FFM and perhaps muscle function although not all findings turned out to be significant.

6. Conclusion

Findings from this study suggest that sHPN temporally have a preventive effect on loss of FFM in patients with incurable gastrointestinal cancer. sHPN may have a positive effect on overall QoL and it may be considered if sHPN should be offered in carefully selected patients with incurable cancer. We found no increased risk of adverse events or death when offering sHPN but on the other hand a significant advantage in function or overall survival was not identified. However, with a small sample size, caution must be applied, as the findings might not be solid.

Data availability

Data is available from OPEN, Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark. We are under signed contractual obligation to share the data through OPEN. Interested researchers can email to open@rsyd.dk for further information about data access.

Statement of authorship

SRO, BW, PP and JK designed the study. SRO collected the data and analysed and interpreted data in close collaboration with BW, PP and JK. SRO, BW, PP and JK drafted the manuscript. All authors read and approved the final draft of the article.

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Conflicts of interest

Primary investigator participated in the Nordic training program in clinical nutrition Nordic Nutrition Academy (NNA), realized in a partnership with Baxter, Nestlé and Karolinska Institute. Sip feeding products were provided by Nestlé. Funding for the study was received from Baxter Healthcare Corporation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.12.011.

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