Supplemental parenteral nutrition within an enhanced recovery program for open pancreatoduodenectomy for cancer: a pragmatic, multicenter, randomized controlled trial

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Summary

Background The role of supplemental parenteral nutrition (SPN) following pancreatoduodenectomy (PD) in the context of an enhanced recovery program is unexplored. This study aimed to determine whether SPN is superior to early oral feeding alone in reducing postoperative complications.

Methods This pragmatic, multicenter, randomized controlled, trial, across five centers in Italy, enrolled patients aged 18–89 years undergoing open PD for cancer. We excluded patients with an American Society of Anaesthesiology physical status >3 and a preoperative body weight loss of ≥15%. Patients were randomly assigned (1:1) post-operatively to either SPN from day 1 to 5 or no-SPN. All patients were free to begin oral feeding after the operation as desired in the context of a full enhanced recovery after surgery (ERAS) program. The primary outcome was morbidity burden, measured using the comprehensive complication index (CCI). Secondary outcomes included the overall rate of morbidity. Outcomes were assessed up to 90 days postoperatively. Overall, 120 patients per group were required to achieve 80% power and detect at least 30% reduction in the CCI in the SPN group, which was expected to be 23 (median) (interquartile range 21–31). The expected complication rate was 60%, and the type I error rate was set at 5%. Registration at ClinicalTrials.gov (#NCT04438447).

Findings From June 1, 2022, to December 20, 2023, 405 patients were screened for eligibility and 254 patients were randomly allocated to control (no-SPN; n = 129) or treatment (SPN; n = 125) group. All patients were included in the primary and secondary outcome analysis according to the intent-to-treat principle. The median CCI was 20.9 in both arms (median difference 0 [95% CI: −1.07 to 1.7]). The proportion of patients with at least one complication (CCI >0) was similar in both groups [(29.6% vs 29.2%; risk difference 0.4 (95% CI −11.1 to 7.0)]. The overall 90-day morbidity was 67.4% and 63.2% in the no-SPN arm and SPN arm groups, respectively [risk difference −4.2 (95% CI −16.7 to 8.2)]. In high nutritional risk patients (nutritional risk score ≥3), SPN was not protective against the primary outcome when compared with low-risk patients [OR 1.16 (95% CI 0.71–1.91)].

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Interpretation In an ERAS program emphasizing early postoperative oral feeding, SPN does not affect outcome measures, even in patients at high nutritional risk. However, these results do not apply to severely malnourished patients or with critical comorbidities.

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Keywords: Artificial nutrition; ERAS; Pancreatoduodenectomy; Surgery; Outcome; Comprehensive complication index

Research in context

Evidence before this study

Prior to this trial, we performed a systematic literature review using PubMed, Scopus, Embase, and the Cochrane Library database on studies published before June 1, 2022. The search terms included "pancreatoduodenectomy," "cancer," "enhanced recovery after surgery," "morbidity," "supplemental parenteral nutrition" and "peripheral parenteral nutrition" and other synonyms based on these terms. Inclusion criteria were randomized and non-randomized controlled trials and prospective and retrospective comparative studies on supplemental parenteral nutrition (SPN) vs no-SPN associated with early postoperative oral intake in patients undergoing pancreatoduodenectomy in English. The primary outcome was the complication burden as measured by the Comprehensive Complication Index (CCI) and the main secondary outcomes were the overall rate of morbidity, unplanned intensive care admission, and hospital readmission.

Based on the above keywords, we identified no matching studies. For different operations, such as colorectal resections, one randomized trial reported no protective effect of SPN on overall postoperative morbidity (44% in no-SPN group vs 33.7% in SPN group; P = 0.186), whereas another randomized study in patients undergoing a mix of abdominal operations found that the use of early SPN was associated with significant fewer nosocomial infections compared with controls (8.7% vs 18.4%; risk difference, 9.7%; 95% CI, 0.9%–18.5%; P = 0.04). In both studies, patients were allowed early postoperative oral food intake.

Added value of this study

To our knowledge, our study is the first multicenter, randomized trial to compare SPN to no-SPN after pancreatoduodenectomy in patients allowed early postoperative oral food intake in the context of an enhanced recovery protocol. This approach is relevant because oral food alone after such a complex and challenging operation is probably insufficient to cover the energy requirements. Our study provides robust evidence for the futility of adding supplemental calories to what is provided by early oral food intake.

Implications of all the available evidence

Based on the results of this study, we expect that an ERAS protocol with early oral feeding and no supplemental artificial nutrition will become the new standard approach for cancer patients undergoing open pancreatoduodenectomy.

Introduction

Major surgery causes intense changes in metabolism and nutritional status by activating various inflammatory cascades and releasing stress hormones and cytokines. This response appears to be proportional to the extent of operative trauma. Open pancreatoduodenectomy (PD) is recognized as one of the most challenging operations because of the magnitude of dissection and resection, the resultant global stress, and the high morbidity rate.[1] Appropriate tissue healing and maintenance of organ function after such operations are affected by an efficient metabolic response, which in turn, necessitates adequate qualitative and quantitative nutritional substrates. Thus, nutritional support is an essential element of patient care; however, the optimal route and timing of administering nutrients after PD is unclear.[2]

The enhanced recovery after surgery (ERAS) program is considered the gold standard for perioperative care because it minimizes surgery-induced stress and dyshomeostasis[3] with subsequent partial catabolic response, muscle function loss, and limited cellular dysfunction.[4] One of the key ERAS domains for controlling the catabolic reaction is the early postoperative recovery of oral food intake.[5] However, severe surgical morbidity and specific complications of PD, such as delayed gastric emptying (DGE),[6] may compromise oral feeding tolerance. The precise amount of ingested calories and proteins from early oral feeding after PD has not been established. Early oral feeding after PD can

reportedly provide 23% of the protein and 30% of the overall calories required for the first ten postoperative days.[7] These inadequate quantities may lead to postoperative malnutrition, which may be detrimental to postoperative functional recovery.[8] Nevertheless, the implementation of ERAS after PD, with the early resumption of oral feeding, can reduce the rate of postoperative complications compared with traditional care.[9]

In this study, we determined whether administering artificial nutrition close to the recommended requirements by supplemental parenteral nutrition (SPN) early in the postoperative course reduces the morbidity burden in patients treated with an ERAS protocol following open PD for cancer.

Methods

Study design

The RASTA study was a pragmatic, multicenter, randomized, controlled trial. It was conducted at five Italian academic institutions with proven pancreatic surgery experience and an established ERAS program. The School of Medicine and Surgery of the Milano-Bicocca University and the pancreas Unit of the San Gerardo Hospital, Monza, Italy, coordinated the trial. The coordinating center was also responsible for monitoring and statistical analysis with the support of the Bicocca Bioinformatics, Biostatistics, and Bioimaging Center of Milano-Bicocca University.

The competent authority approved the study (Italian Drug Agency, AIFA; registration number EudraCT 2020-005483-66; date: September 13, 2021). To comply with Italian legislation, the ethical committee of the coordinating center provided a "not emendable judgment" and approved the protocol (number: 3467; date: February 11, 2022). Ethical Committees for all participating centers successively approved the protocol. The protocol was previously published and is accessible using the following link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10083279/.

Pre-trial training

Before starting patient enrolment, multiple meetings were organized to accomplish the following:

- Correct definition of eligibility, inclusion, and exclusion criteria.
- Agreement on the definition of postoperative complications.
- Training on randomization process and patient instruction on treatment arms.
- Accordance on ERAS elements to be implemented.
- Training of assessors to record the occurrence of the primary and secondary endpoints. Each participating centre nominated two independent outcome assessors. The single-centre principal investigator trained the assessors on the definition of complications during a dedicated pre-trial meeting according to a modified Delphi method. In case of discordance on the endpoint assignment, a third expert intervened to solve the dispute and classify the patient appropriately. Outcome assessors were blinded to treatments.
- Training on how to correctly fill out the case report form.

Participants

Consecutive adult patients (all Caucasian) aged 18 to 89, who were scheduled for elective open pancreatoduodenectomy for any periampullary or pancreatic cancer, were assessed for eligibility. The assessment was done during the prehospitalization visit.

We included patients who met the following characteristics: willingness to participate in the study and able to provide a written informed consent form before any study activities. Also, preoperative normal renal function, blood electrolytes (sodium, potassium, chloride), and coagulation tests were inclusion criteria. We excluded patients with an American Society of Anaesthesiology (ASA) score >3, preoperative severe malnutrition (body weight loss ≥15% in the last six months), ascites, any proven hypersensitivity reaction to parenteral nutrition components, palliative surgery, early postoperative administration of enteral nutrition via a nasoenteric or jejunostomy feeding tube placed during surgery. Gender data were collected using a self-reporting form with the following options: male, female, and other.

Randomization and masking

After enrolment, we randomly allocated patients into two arms. The reasons for exclusion after screening were recorded. Patients were randomly allocated to the SPN or no-SPN group at 8:00 AM on postoperative day 1. Randomization was performed by a computer-generated permuted block sequence. A specific code was generated for each center to achieve equivalent grouping. The allocation ratio was 1:1 with a block size of 4. Concealment was achieved using sealed opaque envelopes. Randomization was stratified by neoadjuvant chemotherapy or chemoradiation therapy and by center. Enrolment was competitive among the centers. A trained surgical resident enrolled the patients and assigned them to the trial groups. The resident was not involved in the remainder of the trial. Surgeons, nurses supplying SPN, and patients were not blinded to the arms, whereas outcome assessors and statisticians were blinded to the grouping.

Procedures

Patients randomized to the treatment arm underwent the full ERAS protocol (details at: https://www.ncbi.

nlm.nih.gov/pmc/articles/PMC10083279) with early oral nutrition plus SPN starting at 8:00 AM of POD 1. Patients were administered a liquid and solid diet, and their progression was based on their will and tolerance. A ready-to-use, all-in-one, 3-bag compartment peripheral parenteral solution (Olimel N4E®, Baxter Italia, SpA, Roma, Italy) containing carbohydrates, lipids, and proteins was used. The solution was infused to deliver 20/25 kcal/kg/day for 5 postoperative days with the addition of intravenous supplementation of vitamins (one vial/day) (Cernevit®, Baxter Italia SpA, Roma, Italy) and trace elements.

In the event of complications preventing the total or partial recovery of oral food intake after postoperative day 5, the SPN was continued or switched to tube enteral feeding based on the decision of the attending surgeon and until clinically indicated. This event was defined as the unplanned use of artificial nutrition.

The administration of SPN was done through a peripheral or central vein catheter, with a delivery rate calculated based on the patient's body weight. The total volume of SPN resulted from calculating the amount of prescribed calories multiplied by body weight.

Patients randomized to the control arm were treated with the same ERAS protocol but without SPN. Consistent with the treatment arm, patients were administered a liquid and solid diet and progressed according to their will and tolerance.

In the event of complications impairing the total or partial recovery of oral food intake after postoperative day 5, patients received SPN or enteral nutrition based on the decision of the attending surgeon and until clinically indicated. This event was defined as the unplanned use of artificial nutrition.

Postoperative capillary blood glucose concentrations were measured every 6 h in all patients. Blood glucose levels >180 mg/dL were treated with insulin (e.g., subcutaneous or continuous intravenous infusion). The participating centers selected the open PD technique and analgesia methods according to their standards. All patients received venous thrombosis and antibiotic prophylaxis. The data were anonymously collected and entered into an electronic, dedicated, password-protected Microsoft Excel spreadsheet with a double entry to ensure the consistency of the records. The electronic registry was identical at all centers, each with its own dataset. Subject identification was done only by a randomization code. In the event of missing or implausible data, queries were mailed to the participating centers to obtain integrations or corrections.

Outcomes

The primary endpoint of the trial was the complication burden within 90 days following surgery. The complication burden was assessed using the comprehensive complication index (CCI),[10] which incorporates all complications and their severity as defined by the Clavien–Dindo classification and summarizes postoperative morbidity with a numerical scale ranging from 0 (no complication) to 100 (death). Primary and secondary outcomes were assessed locally. Patient chart evaluation and data entry for outcome recording were done by trained assessors (selected at each center) who were not directly involved in patient care and thus were blind to patient allocation.

The definition and grading of specific complications of PD, such as pancreatic fistula, DGE, biliary fistula, hemorrhage, and Clavien–Dindo scores, are summarized in Supplementary Material (page 2–8). Secondary outcome measures included mean daily calories delivered by SPN, unplanned artificial nutrition, 90-day severity and complication rate, cardiac, pulmonary, and urinary complications, surgical site infections, multidrug-resistant bacteria infections, postoperative pancreatic fistula, delayed gastric emptying, postoperative hemorrhage, biliary fistula, enteric fistula, blood transfusion, reoperation, unplanned intensive care unit admission, blood glucose levels, Δ plasma prealbumin levels (baseline, postoperative days 1 and 6), opioid use, resumption of bowel function, Δ body weight (admission–discharge), length of stay (LOS), 90-day mortality, and 90-day unplanned hospital readmission.

The day of hospital discharge was based on individual clinical judgment; however, LOS was also calculated by achieving pre-specified discharge criteria (full patient mobilization, pain controlled by oral analgesics, and tolerance to oral feeding). In particular, a visual analog pain scale ≤ 2 had to be achieved for safety discharge. This was defined as time to functional recovery.

Post-discharge follow-up occurred through weekly outpatient visits. Also, telephone and web-based interviews were allowed to monitor the patient's state of health. When warning signs of potential complications were identified, patients were directed to the hospital where the operation was performed for further evaluation. Follow-up ended 90 days after the operation.

Safety issues

An ad interim analysis was planned at the achievement of 50% of the study power. The study had to be stopped in case of an increase over 30% of the expected median CCI in either group. The study had to be stopped in case of death or a life-threatening experience related to the use of SPN or a persistent or significant disability/incapacity exceeding 5% of the population in both groups. A Data and Safety Monitoring Board oversaw and monitored the trial to ensure participant safety and the validity and integrity of the data. Additional safety issues included the number of patients not tolerant to a solid diet after POD 7, the rate of insulin use, and the

frequency of intravenous correction of electrolyte levels (sodium, potassium, chlorite, magnesium, and calcium) during the postoperative course.

Statistical analysis

A sample size of 120 patients per group was necessary to provide 80% power and to detect at least a 30% reduction in the CCI, which was expected to be approximately 23 (median) (IQR 21–31) in complicated patients of the control group. The hypothesized reduction of 30% was based on sound clinical relevance, meaning that such a reduction may have a consistent and significant impact on the postoperative course with advantages on quality of life, shorter length of hospitalization, and a relevant decrease of health care burden and resources. The median CCI of 23 was derived from a previous publication.[11] The complication rate for this type of surgery was expected to be 60%. A Mann–Whitney U test was considered, standard deviation of 18.5 for both groups was assumed and the type I error rate was fixed at 5% (two tails).

The primary endpoint (CCI) was a continuously skewed variable, but in the performed statistical analyses, it was also considered a normally distributed variable (after log-transformation, normality was assessed by visual inspection of the histogram) and as a binary variable (CCI >20.9 vs ≤ 20.9). For the primary and secondary binary endpoints, the risk difference with a corresponding 95% confidence interval (Wald method) was calculated. For the numerical endpoints, the difference in the location parameter (i.e., median difference) between the two groups or the mean difference with a corresponding 95% confidence interval was calculated (percentile method based on 10,000 bootstrap replications for the median difference and interval based on the T distribution for the mean difference). Chi-square tests (for categorical variables), Mann–Whitney U tests (for skewed numerical variables), or independent T-tests (for normally distributed numerical variables) were adopted to evaluate univariate associations.

A multivariable modified (i.e. robust standard errors with sandwich estimator) Poisson regression model was used to identify the factors associated with the primary endpoint (CCI >20.9 vs ≤ 20.9) and to evaluate the treatment effect, adjusting for possible residual confounders. Using the modified Poisson model, the effect of SPN over the controls on the CCI was also examined within pre-specified subgroups to account for potential effect modification. The selection of predictors was not based on an automated algorithm but only on previous knowledge and clinical interest. All predictors used were pre-specified in the protocol. The risk factors for this analysis were nutritional risk screening-2002 (NRS-2002, ≥3), body mass index (>30), gender (male), age (>70 years), Charlson comorbidity index (>4), ASA score (=3), estimated blood loss (≥500 mL), surgery duration (>360 min), biliary stenting, diabetes, pylorus-preserving PD (vs Whipple), pancreatic cancer (vs other malignancies), fistula risk score (≥7), delayed gastric emptying (grades B and C), postoperative pancreatic fistula (grades B and C), use of postoperative oral nutritional supplements, and preoperative weight loss (>0%). Similarly, multivariable and subgroup analyses were carried out using the linear regression model for the log-transformed CCI. All regression analyses were run also modelling quantitative variables using natural cubic splines with 3 inner knots (quartiles) and 2 boundary knots (minimum and maximum).

Assumptions of normality and homogeneity of variance of residuals were assessed by visual inspection of, respectively, the normal Q–Q plot and the spread–location plot. For all multivariable models, adjustment by center was performed using clustered standard errors.

ERAS compliance to pre/intraoperative domains was defined as the implementation of at least 70% of the items, whereas ERAS overall compliance was defined as the implementation of at least 70% of the pre/intra or postoperative items. All analyses were performed based on the principles of "intent-to-treat" using R software (R Foundation for Statistical Computing, Vienna, Austria). There were no missing data in any of the predictors included in the analysis, nor in the outcomes. Therefore, no method for handling missing values was needed. The trial was registered at ClinicalTrials.gov (#NCT04438447; date: June 16, 2020).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 1st, 2022, to December 20th, 2023, 405 patients were assessed for trial eligibility. Based on the used exclusion criteria, 151 patients were not considered eligible. The detailed reasons are specified in Fig. 1. A total of 254 patients were enrolled and randomized to the control (no-SPN group; n = 129) or treatment (SPN; n = 125) groups. There was no treatment discontinuation or dropout at any stage and no loss to follow-up. Thus, all patients were included in the analyses for primary and secondary outcome measures based on the intent-to-treat principle. The trial was closed on March 20th, 2024.

Baseline participant demographic information is listed in Table 1. Specific surgery-related risk factors for postoperative complications, including preoperative biliary stenting, type of pancreatic anastomosis, Wirsung duct diameter, pancreatic texture, blood loss, intraoperative blood transfusion, operative time,

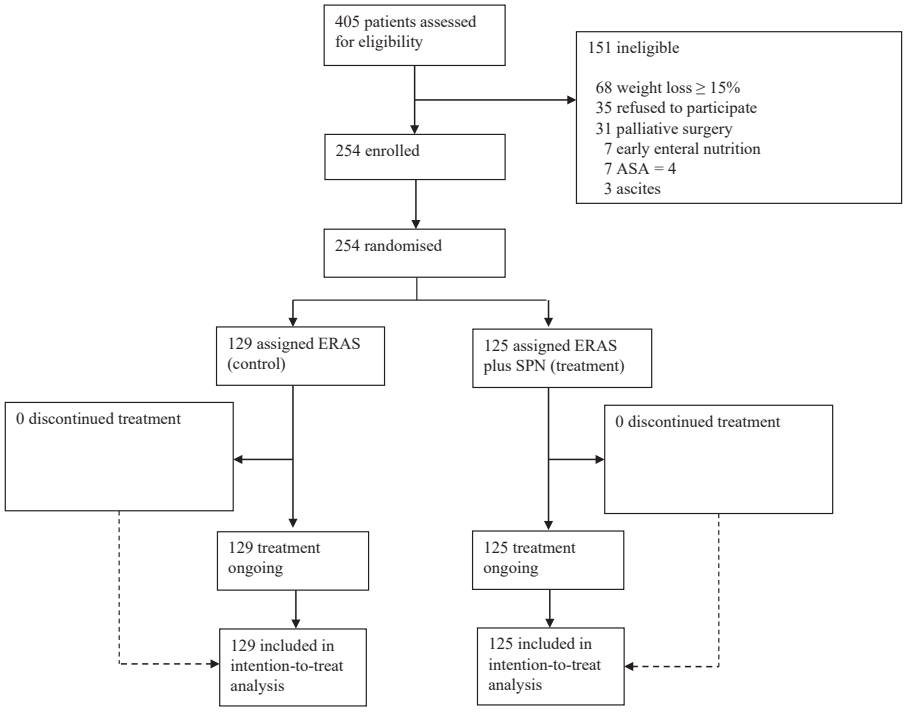

Fig. 1: Trial profile. ERAS, Enhanced recovery after surgery; SPN, supplemental parenteral nutrition.

surgical field contamination, and vascular resection, were evaluated. The two groups were balanced for all of these parameters. Approximately 28% of the patients were defined as high nutritional risk by the NRS-2002 (≥3), whereas 42% of the population had some degree of preoperative weight loss even though the median weight loss was 0.

The median CCI was 20.9 in both arms, with a median difference of 0 (95% CI: −1.7; 1.7, P = 0.831) (Table 2). Similarly, the log CCI, the proportion of patients with at least one complication (CCI >0), and the proportion of patients with a CCI >20.9 were not significantly different between the two arms. The visual distribution of individual patient CCI with box and whisker plots is shown in Supplementary Material (page 9).

Several pre-specified secondary endpoints were evaluated (Table 3). The treatment group exhibited a significantly lower probability of having an indication for unplanned artificial nutrition and higher blood glucose levels between POD 2 and 5, but without a significantly increased use of insulin therapy (68.2% in controls vs 71.2% in the SPN group; P = 0.704). Patients in the treatment group presented with significantly higher levels of prealbumin at POD 2–5 (all P < 0.05), with a positive delta (P = 0.041). The essential variables of outcome, such as overall morbidity, clinically relevant pancreatic fistula (grades B and C), major complications (Clavien-Dindo score ≥3), surgical site infections, reoperations, unplanned admission to intensive care unit, mortality, readmission, and LOS, were not statistically different between the two groups.

Because both groups adhered to the ERAS protocol, we evaluated and compared the rate of compliance to all ERAS domains to exclude potential bias between groups (Table 4). None of these comparisons showed significant differences. In particular, patients in both groups resumed an oral liquid diet at a median POD 1 and a solid diet at POD 3, whereas 83.7% of the control group vs 83.1% of the treatment group tolerated a solid diet within POD5 [risk difference −0.6 (95% CI−11.3; 8.7)]. Compliance with the ERAS protocol >70% was 87.6% vs 91.2% [risk difference 3.6 (95% CI −4.7; 11.9)] in the control and treatment groups, respectively.

There was no significant difference in safety issues (Supplementary Material page 10). Supplementary Material (page 11 and 12) depict the risk ratios and the mean difference with 95% CI of the subgroup analyses. Box A shows the results of the Poisson regression model for a CCI >20.9, whereas box B shows the results of the linear regression model for a log-transformed CCI. There were no treatment advantages in any of the subgroups studied. In particular, for patients at high nutritional risk (NRS-2002 ≥ 3), documented weight loss, delayed gastric emptying, at very high risk of pancreatic fistula (FRS ≥7), and with clinically relevant pancreatic fistula (grades B and C), the treatments and controls exhibited similar risk ratios

with the correspondent 95% CI of the odds ratio including 1. Similar results were obtained by linear regression analysis.

Further subgroup analyses were run to evaluate whether patients who received unplanned artificial nutrition had different outcomes in the two groups (Supplementary Material, page 13). Patients who received unplanned artificial nutrition exhibited a higher CCI and more patients had a CCI >20.9 compared with those who did not receive artificial nutrition. However, median CCI, Log CCI, number of patients with CCI >20.9, and duration of artificial nutrition were not significantly different between the control and treatment groups in the subgroup who received unplanned artificial nutrition. For patients receiving unplanned artificial nutrition, 13.5% in the control group vs 14.8% in the treatment group (P = 1) were fed through a nasoenteric or a jejunostomy feeding tube.

Univariable and multivariable Poisson and linear regression analyses were done to identify risk factors for the primary outcome (Supplementary Material, page 14). Panel A describes the covariates for CCI >20.9 and panel B for log CCI. Body mass index >30, age >70 y, diabetes and Wirsung stenting were significant factors for CCI >20.9. A fistula risk score ≥7 was also an important risk factor for CCI >20.9 (RR 1.682 [95%CI 1.081–2.619]) but without reaching statistical significance (P = 0.073). When quantitative variables were modelled using cubic splines, fistula risk score remained the most important predictive variable both for CCI >20.9 (likelihood ratio test P = 0.011) and for log (CCI) (likelihood ratio test P < 0.001) (Supplementary Material pages 15–17).

We also analysed the distribution of the comprehensive complication index by center and study group to exclude a center-mediated effect on the primary outcome (Supplementary Material, page 18). No significant effect among center within each of the two study groups and between study groups within each center was observed.

The arms were well-balanced in terms of pathology characteristics (Supplementary Material, page 19).

Variables	Control N = 129	Treatment N = 125
Age, years (mean (SD))	67 (11)	68 (10)
Sex, Female	65 (50.4)	53 (42.4)
Body weight, kg (mean (SD))	68 (13)	69 (13)
Height, cm (mean (SD))	168 (10)	167 (9)
Body mass index, kg/m^2 (mean (SD))	24.3 (3.4)	24.5 (4.1)
Nutritional risk score-2002		
0	42 (32.8)	50 (40)
1	31 (24.2)	22 (17.6)
2	20 (15.6)	20 (16.0)
3	22 (17.2)	18 (14.4)
4	8 (6.2)	8 (6.4)
5	3 (2.3)	4 (3.2)
6	2 (1.6)	3 (2.4)
Nutritional risk score-2002 ≥ 3	35 (27.3)	33 (26.4)
% body weight loss	0 [0, 7]	0 [0, 6.3]
Any body weight loss	57 (44.2)	51 (40.8)
Charlson comorbidity index	5 [3, 6]	5 [4, 6]
Smoker		
Former	19 (14.7)	25 (20)
Active	29 (22.5)	30 (24)
Diabetes	30 (23.2)	22 (17.6)
Cardiac disease		
Ischemic	14 (10.9)	10 (8)
Other	8 (5.4)	10 (7.2)
Hypertension	76 (58.9)	57 (45.6)
Pulmonary disease		
COPD	8 (6.2)	4 (3.2)
Other	4 (3.1)	6 (4.8)
ASA classification		
1	18 (14)	20 (16)
2	62 (48.1)	66 (52.8)
3	49 (38)	39 (31.2)
Haemoglobin, g/L	124 [114, 134]	124 [117, 135]
Glycated hemoglobin, mmol/mol	38 [35, 44.5]	36 [33, 41]
Prealbumin, mg/dL	18 [14, 23.7]	20 [16, 24]
Albumin, g/L	40.4 [37, 43]	41 [37.6, 43.4]
Total bilirubin, mg/dL	0.7 [0.43, 1.50]	0.74 [0.46, 1.62]
C-reactive protein, mg/dL	0.84 [0.32, 2.1]	0.80 [0.3, 2.5]
Jaundice	66 (51.2)	64 (51.2)
Biliary stenting		
Plastic	20 (15.5)	18 (14.4)
Metallic	56 (43.4)	50 (40)
Neoadjuvant chemotherapy	49 (38.0)	48 (38.4)
Gem-based	19 (14.7)	12 (9.6)
FOLFIRINOX	23 (17.8)	21 (16.8)
PEX-G	4 (3.1)	14 (11.2)
Other	3 (2.3)	1 (0.8)
Type of surgery		
Whipple	34 (26.4)	26 (20.8)
Pylorus-preserving	95 (73.6)	99 (79.2)
Pancreatic anastomosis		
Jejunal	127 (98.4)	124 (99.2)
Gastric	2 (1.6)	1 (0.8)
Wirsung duct diameter, mm	4 [3, 5]	4 [3, 5]
Wirsung duct stenting		
External	20 (15.5)	20 (16.0)

(Table 1 continues on next page)

Discussion

In this trial, we found no difference in the postoperative complication burden, measured as CCI, between patients who received SPN compared with those who did not after undergoing open PD in the context of an ERAS program. The use of SPN to approximate recommended energy and protein goals did not affect the primary outcome measure or pre-specified key secondary outcomes, including reoperation, surgical site infection, unplanned admission to ICU, duration of hospitalization, and readmission. Similarly, the subgroup analyses, made to scrutinize data and identify

Variables	Control N = 129	Treatment N = 125
(Continued from previous page)		
Internal	6 (4.7)	5 (4.0)
Pancreatic texture		
Soft	67 (52.3)	64 (51.6)
Hard	61 (47.7)	60 (48.4)
Fistula risk score	3 [1, 5]	3 [1, 5]
Vascular resection	20 (15.5)	17 (13.6)
Estimated blood loss, mL	300 [200, 500]	300 [200, 500]
Intraoperative contamination	3 (2.3)	3 (2.4)
Intraoperative hypothermia	8 (6.2)	3 (2.4)
Intraoperative transfusion	24 (18.6)	21 (16.8)
Type of perioperative analgesia		
TAP block	13 (13.4)	11 (12.0)
Epidural	52 (53.6)	52 (56.5)
Wound catheter	32 (33)	28 (30.4)
Operative time, min	445 [378, 506]	415 [35, 480]
Abdominal drains	128 (99.2)	122 (97.6)

Values are medians [interquartile range] or numbers (%). ASA, American Society of Anaesthesiology; Gem, Gemcitabine; COPD, Chronic obstructive pulmonary disease; TAP, Transversus abdominal plan; FOLFIRINOX, leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, oxaliplatin; PEX-G, cisplatin, epirubicin, capecitabine, gemcitabine.

Table 1: **Baseline and operative characteristics.**

patient subpopulations that may have benefited from treatment, such as subjects with multiple comorbidities, clinically relevant pancreatic fistula, delayed gastric emptying, and biliary stenting revealed no significant benefits when adding SPN to early oral food intake. It should be emphasized that these results have been achieved in patients with high compliance with the ERAS protocol.

We excluded patients with preoperative weight loss ≥15% for ethical reasons. According to the GLIM criteria,[12] this cohort suffers from severe malnutrition, and per the ESPEN guidelines,[13] should receive both pre- and postoperative medical nutrition. The study design did not permit any perioperative nutritional treatment; therefore, including severely malnourished patients would have constituted a serious violation of both guidelines and ethical principles, exposing these patients to a significant and unacceptable increased risk of morbidity and mortality.

However, we conducted subgroup analyses on patients with high nutritional risk (NRS ≥3) and those with weight loss between 1% and 14%. In these subgroups as well, SPN did not significantly modify the primary outcome.

Similarly, patients with an ASA score >3 were considered at extremely high risk for morbidity and mortality following PD. In clinical practice, patients with an ASA score of 4 are generally not considered appropriate candidates for this type of surgery. For example, in one of the largest published series on PDs,[1] ASA 4 patients comprised only 0.2% of the entire cohort, indicating that—except in very rare cases—such patients are not suitable for major pancreatic resections. Consistently, in our series, patients with ASA 4 accounted for less than 1% of the population screened for eligibility.

The value of postoperative SPN in surgical cancer patients has not been established. One randomized clinical trial (RCT) in 80 patients with gastric cancer showed the benefits of SPN on surrogate endpoints, such as protein synthesis, quality of life, well-being, and immune function, when compared to intravenous fluid administration.[14] One RCT enrolling 27 patients with gastroesophageal cancer reported a significant reduction of the 90-day postoperative mortality rate in patients receiving SPN compared with intravenous fluids.[15] The results of another large RCT demonstrated that in patients undergoing mostly gastric and colorectal resections and intolerant to early enteral tube feeding, postoperative SPN initiated within 3 days was associated with a significant reduction of infectious complications compared with late SPN initiation.[16] A recent meta-analysis concluded that SPN had no significant advantages on infectious and non-infectious morbidity, and surgical site infections compared with intravenous fluid administration.[17] The different study designs, population, perioperative care, and outcome measures of the above trials make the comparison with our study challenging. Yet, a single-center, pragmatic,

Variables	Control N = 129	Treatment N = 125	Median difference (95% CI) or Mean difference (95% CI) or Geometric mean ratio (95% CI) or Risk difference (95% CI)	P
CCI	20.9 [0, 37.2]	20.9 [0, 37.2]	0[a] (−1.7; 1.7)	0.83
Log CCI	2.72 (1.12)	2.74 (1.15)	0.02[b] (−0.27; 0.3)	0.89
			0.98[c] (0.74; 1.30)	
CCI in patients with CCI >0	29.6 [20.9, 43.5]	29.2 [20.9, 42.5]	0.4[a] (−11.1; 7)	0.99
CCI >20.9	56 (43.4)	59 (47.2)	3.8[d] (−9.2; 16.8)	0.63

CCI, Comprehensive complication index. Values are medians [interquartile range] or numbers (%). [a]Median difference. [b]Mean difference. [c]Geometric mean difference. [d]Risk difference.

Table 2: **Primary outcome.**

Variables	Control N = 129	Treatment N = 125	Risk difference (95% CI) or Median difference (95% CI)	P-value
Daily calories per kilogram	NA	21.3 [17.8, 24.2]	NA	NA
Unplanned artificial nutrition	83 (64.3)	62 (49.6)	14.7 (1.9; 27.6)	0.025
Prealbumin POD 1, mg/dL	13 [10.5, 14.5]	13 [11, 17]	0 (−2; 0)	0.13
Prealbumin POD 6, mg/dL	11 [8, 14]	13 [9, 16]	2 (−1; 3.5)	0.0026
Delta Prealbumin baseline-POD1, mg/dL	−3 [−7, −1]	−5 [−8, −1.2]	−2 (−5; 0)	0.201
Delta Prealbumin baseline-POD6, mg/dL	−4 [−9, −2]	−4 [−8.5, 0]	0 (−3; 3)	0.56
Delta Prealbumin POD1-POD6, mg/dL	−1 [−3, 1]	1 [−4, 3]	2 (−1; 3)	0.041
Blood glucose level POD1, mg/dL	151 [122, 176]	150 [130, 184]	−1 (−15; 12)	0.22
Blood glucose level POD2, mg/dL	124 [99, 144]	142 [122, 169]	18 (8.5; 27)	<0.0001
Blood glucose level POD3, mg/dL	116 [95, 140]	137 [120, 171]	21 (11; 29.5)	<0.0001
Blood glucose level POD4, mg/dL	113 [100, 135]	133 [117, 162]	20 (9; 29.5)	<0.0001
Blood glucose level POD5, mg/dL	117 [101, 152]	132 [115, 155]	15 (5; 23)	0.005
Resumption of bowel function, day				
Gas	2 [2, 3]	2 [2, 3]	0 (−1; 1)	0.40
Stools	4 [3, 5]	4 [3, 5]	0 (−1; 1)	0.93
90-d morbidity	87 (67.4)	79 (63.2)	−4.2 (−16.7; 8.2)	0.56
Pancreatic fistula				
BL	13 (10.1)	14 (11.2)	1.1 (−7.3; 9.5)	0.54
B	29 (22.5)	25 (20)	−2.5 (−13.3; 8.4)	
C	1 (0.8)	4 (3.2)	2.4 (−1.8; 6.6)	
Biliary fistula				
A	7 (5.4)	9 (7.2)	1.8 (−5.0; 8.5)	0.47
B	1 (0.8)	3 (2.4)	1.6 (−2.2; 5.5)	
C	0 (0)	1 (0.8)	0.8 (−1.5; 3.1)	
Enteric fistula	3 (2.3)	2 (1.6)	−0.7 (−4.9; 3.4)	1
Postoperative hemorrhage				
A	9 (7)	7 (5.6)	−1.4 (−8.1; 5.4)	0.50
B	6 (4.7)	7 (5.6)	0.9 (−5.3; 7.2)	
C	0 (0)	2 (1.6)	1.6 (−1.4; 4.6)	
Blood transfusion	37 (28.7)	37 (29.6)	0.9 (−11; 12.9)	0.98
Delayed gastric empting				
A	16 (12.4)	16 (12.8)	0.4 (−8.2; 9)	0.98
B	9 (7.0)	8 (6.4)	−0.6 (−7.3; 6.1)	
Surgical site infection				
Incisional	21 (16.3)	13 (10.4)	−5.9 (−15; 3.2)	0.39
Organ/space	26 (20.2)	27 (21.6)	1.4 (−9.3; 12.2)	
Infection with MDR bacteria	37 (28.7)	31 (24.8)	−3.9 (−15.5; 7.8)	0.58
Cardiac complication	9 (7.0)	9 (7.2)	0.2 (−6.3; 6.8)	1
Pulmonary complication	11 (8.5)	8 (6.4)	−2.1 (−9.4; 5.1)	0.89
Urinary tract infection	7 (5.4)	6 (4.8)	−0.6 (−6.7; 5.4)	1
Acute kidney injury	10 (7.8)	7 (5.6)	−2.2 (−9.1; 4.8)	0.66
Relaparotomy	7 (5.4)	10 (8.0)	2.6 (−4.4; 9.5)	0.57
Unplanned ICU admission	13 (10.1)	16 (12.8)	2.7 (−5.9; 11.3)	0.63
Severity of complication (Clavien-Dindo score)				
1	13 (10.1)	14 (11.2)	1.1 (−7.3; 9.5)	0.99
2	49 (38.0)	46 (36.8)	−1.2 (−13.9; 11.5)	
3A	15 (11.6)	17 (13.6)	2 (−7; 10.9)	
3B	5 (3.9)	4 (3.2)	−0.7 (−5.9; 4.5)	
4A	3 (2.3)	3 (2.4)	0.1 (−3.7; 3.9)	
4B	2 (1.6)	3 (2.4)	0.8 (−3.4; 5.1)	
90-d mortality	2 (1.6)	4 (3.2)	1.6 (−2.9; 6.2)	0.65
Delta body weight, kg	−3 [5, 0]	−3 [−5, 0]	0 (−2; 0.5)	0.64
Length of stay, day	12 [9, 19]	12 [8, 20]	0 (−5; 1)	0.95
Functional recovery, day	11 [8, 18]	12 [7, 18]	1 (−2; 3)	0.94
90-d unplanned hospital readmission	12 (8.3)	12 (9.3)	1 (−4.6; 10.1)	0.72

Values are medians [interquartile range] or numbers (%). NA, not applicable; BL, Biochemical leak; POD, Postoperative day; MDR, multidrug resistant; ICU, Intensive care unit.

Table 3: **Secondary outcomes.**

Variables	Control N = 129	Treatment N = 125	Risk difference (95% CI) or Median difference (95% CI)	P-value
Preoperative				
Patient education	125 (99.2)	125 (100)	0.8 (−0.7; 6.9)	1
Oral carbohydrate load	60 (61.2)	63 (64.3)	3.1 (−9.2; 17.0)	0.77
No fasting	129 (100)	125 (100)	–	NA
No bowel preparation	126 (97.7)	124 (99.2)	1.5 (−2.3; 5.3)	0.64
No long acting benzodiazepines	94 (74.6)	91 (73.4)	−1.2 (−11.1; 10.9)	0.94
Intraoperative				
Prevention PONV	123 (97.6)	122 (98.4)	0.8 (−3.1; 7.6)	1
Active warming	121 (93.8)	122 (97.6)	3.8 (−1.9; 9.5)	0.24
Fluid balance, mL	1325 [187, 2524]	1410 [290, 3025]	85 (−710; 750)	0.78
Goal-directed fluid therapy	60 (46.5)	61 (48.8)	2.3 (−10.8; 15.4)	0.81
ERAS compliance pre/intra domains >70%	118 (91.5)	121 (96.8)	5.3 (−1.2; 11.8)	0.12
Postoperative				
Prokinetics drugs	93 (73.8)	95 (76.6)	2.8 (−7.6; 15.5)	0.71
Early mobilization, day	1 [1, 2]	1 [1, 2]	0 (−1; 1)	0.95
Patients with early mobilization > POD 1	45 (35.7)	44 (35.2)	−0.5 (−11.7; 12.4)	1
Full mobilization, day	3 [2, 5]	3 [2, 5]	0 (−1; 1)	0.90
Patients with full mobilization > POD 3	47 (37.6)	48 (38.7)	1.1 (−10.7; 14.7)	0.96
NGT removal, day	1 [0, 1]	0 [0, 1]	−1 (−1; 0)	0.089
Patients with NGT > POD 1	14 (10.9)	7 (5.6)	−5.3 (−12.8; 2.2)	0.20
Resumption liquid diet, day	1 [1, 2]	1 [1, 1]	0 (0; 0)	0.27
Patients not tolerating liquid diet > POD 1	36 (27.9)	26 (20.8)	−7.1 (−18.4; 4.2)	0.24
Use of oral nutritional supplements	33 (25.6)	28 (22.4)	−3.2 (−14.5; 8.1)	0.66
Resumption of solid diet, day	3 [2, 4]	3 [2, 5]	0 (−1; 1)	0.45
Patients tolerating solid diet within day 5	108 (83.7)	103 (83.1)	−0.6 (−11.3; 8.7)	1
Amount of postoperative IV fluids (until POD 5), mL	6600 [5500, 10,000]	4600 [2500, 10,973]	−2000 (−4000; 3500)	0.38
Stop IV fluids, day	5 [4, 8.5]	5 [4, 7]	0 (−1; 1)	0.20
Patients with stop IV fluid > POD 5	41 (32.3)	56 (45.9)	13.6 (0.4; 25.7)	0.038
Urinary catheter removal, day	3 [2, 4]	3 [2, 4]	0 (−2; 2)	0.62
Patients with urinary catheter > POD 3	47 (37)	38 (31.1)	−5.9 (−18.4; 6.3)	0.40
Abdominal drain removal, day	6 [3, 16]	6 [4, 15]	0 (−2; 2)	0.69
Opioid use	74 (57.4)	64 (51.2)	−6.2 (−19.2; 6.9)	0.39
Overall ERAS compliance >70%	113 (87.6)	114 (91.2)	3.6 (−4.7; 11.9)	0.47

Values are medians [interquartile range] or numbers (%). NA, not applicable; ERAS, Enhanced recovery after surgery; PONV, postoperative nausea and vomiting; NGT, naso-gastric tube; IV, intravenous; POD, postoperative day.

Table 4: **Compliance to ERAS domains.**

randomized controlled trial with 158 subjects was performed comparing the influence of peripheral parenteral vs conventional fluid therapy on postoperative complications in colorectal surgery patients in the contest of an ERAS program. No significant protective effect of parenteral nutrition on postoperative morbidity was observed.[18]

The precise amount of calories and proteins ensured by early oral food intake after PD has not been established. Within two weeks after PD, patients allowed early oral feeding received a mean of 30% of their energy goals and 23% of their protein requirements.[7] In another study, the median oral energy intake of patients after PD was approximately 600 kcal per day,[19] which is very low compared with the recommended target. This limited intake, if perpetuated for a long period, may result in a high risk of developing malnutrition with the related increased morbidity.[8] The application of an ERAS protocol may facilitate a much better postoperative food tolerance with a subsequent reduced risk of undernutrition.[5] Nevertheless, the nutritional targets based on the ERAS protocol for solid and liquid food were reached in approximately 50% of the patients undergoing PD.[20] More recent prospectively collected data in 346 patients undergoing pancreatic resection with an established ERAS program showed similar results. Within seven postoperative days, energy and protein oral intake goals were reached in 30% and 29% of the patients, respectively.[21]

Based on poor postoperative oral intake and the frequently reported preoperative nutritional derangements of surgical cancer patients, European[12] and

American[22] Clinical Nutrition Society guidelines recommend immediate artificial nutritional support after major abdominal surgical procedures. However, the results of small randomized trials[23] and large retrospective studies[24] suggest that preventing caloric and nitrogen shortage through early enteral tube feeding does not provide any significant clinical advantages compared with early oral feeding. These results have been confirmed by a meta-analytic approach.[25] The two upcoming NUTRIWHI[26] and ENE-PAN[27] trials, designed for patients undergoing PD with an ERAS pathway, will challenge the hypothesis of superiority of early enteral or total parenteral nutritional support over early oral feeding. Unlike these trials, the backbone of the treatment arm in the RASTA study was SPN and not enteral nutrition or total parenteral nutrition. The choice of peripheral SPN was based on the fact that most patients undergoing PD within an ERAS protocol do not usually require a central venous catheter and a feeding jejunostomy or a nasoenteric tube is recommended in selected scenarios, such as reoperations, the occurrence of complications affecting oral nutrition, or severe preoperative malnutrition.[28] Moreover, peripheral parenteral nutrition enables the precise delivery of the prescribed energy at the beginning of the infusion, whereas enteral tube feeding requires several days to reach the caloric target because of limited tolerance during the early postoperative period.[29]

Another unexpected result of the present trial was the lack of benefits of SPN in patients who received unplanned artificial nutrition, which was defined as the need to start (in the control arm) or continue (in the treatment arm) artificial nutrition after postoperative day 5. Unplanned artificial nutrition was likely prescribed to those patients who developed a severe complication or intolerant to oral feeding. The median CCI of this subgroup was around 40 vs 9 in patients not receiving unplanned artificial nutrition, and a CCI >20.9 was observed in approximately 75% vs 22% of patients not receiving unplanned artificial nutrition. This indicates that supplementing calories and nitrogen from the first postoperative day had no protective effect, even in patients who developed a severe complication later on. We speculate that patients undergoing open PD may have metabolic pathways similar to critically ill patients in whom permissive underfeeding is not detrimental.[30,31] We hypothesized that the calorie and protein deficiency induced by insufficient oral intake may be replaced by endogenous energy production and muscle protein breakdown. These mechanisms allow for appropriate tissue healing, maintenance of organ function, and functional recovery. An alternative assumption is that the substrates delivered by SPN are only partially utilized. Yet, we observed a statistically improved synthesis of short half-life proteins in the SPN group, but this did not translate into any measurable change in outcome. Another hypothesis is that the control group may have experienced complications due to insufficient oral intake while the SPN group may have suffered from overfeeding-related morbidity so that the true protective effect of SPN could have been obscured. However, median CCI, overall morbidity, major morbidity, and mortality rates observed in our study are consistent with those reported in large international series involving patients undergoing pancreatoduodenectomy worldwide.[32] This consistency suggests that neither potential undernutrition in the control group nor possible overfeeding in the SPN group had a significant impact on the study outcomes.

This study had several limitations. The amount of calories delivered during early oral feeding was not measured. Therefore, whether patients reached their nutritional needs using this approach is unknown; however, previous studies showed that oral feeding alone was largely insufficient to cover the energy target following PD.[19–21] RASTA was a pragmatic trial designed to mimic routine clinical practice. In this scenario, quantifying energy intake by hospital food servings for each surgical patient is practically impossible. To achieve this goal, the exact amount of proteins and calories in each meal must be calculated and then recalculated by subtracting the leftovers to obtain a precise intake measure.

By choosing a pragmatic study design, explanatory insights on the lack of protective effect of SPN could not be addressed. Explanatory studies are mainly design to establish causal mechanisms such as biological or physiological phenomena, under controlled conditions. Often the participants are highly selected to reduce variability and the outcome measures are surrogate or intermediate biological endpoints. In alternative, the purpose of pragmatic studies is to determine whether an intervention works in real-world settings mimicking as close as possible the routine clinical practice. To do so the interventions are applied as it would be in usual care, with flexibility and the outcomes are clinically meaningful as in our case the burden of complications after open PD.

The second limitation is the lack of blindness because of the nature of the study. We tried to minimize this potential confounding effect by having outcome assessors and statisticians blinded to treatment. While outcome assessors were blinded, performance bias remains possible. A third limitation was the exclusion of patients with severe preoperative malnutrition, so the trial findings do not apply to this category of patients. To gain more insight into nutritional high risk patients, post-hoc subgroup analyses (NRS-2002 $\geq$ 3 and weight loss between 1% and 14%) were performed, in which no additional benefit of SPN could be identified. These results should be interpreted cautiously since subgroup analyses may suffer from

type II errors and therefore be underpowered. Another possible drawback is the use of a single parenteral formulation. Therefore, whether different compositions of the parenteral bag may have had an impact on the outcome could not be ruled out. Finally, the surgical technique for open PD was not standardized and this may represent a potential confounder in the resulting analyses. To explore this confounder, we analysed the center-specific effect on the primary outcome and no significant differences among centers within each of the two study groups and between study groups within each center were found. We also acknowledge that the originally planned analysis of repeated events (complications) using Nelson-Aalen estimator and incidence rates which was reported in the study protocol was not carried out because it did not provide any added value to the study results.

It will be important that future long-term analyses will address patient nutritional status, quality of life, functional recovery and survival.

The major strength of this study is the novel design and the implementation of a full ERAS program that should be considered the standard of care following PD.

In conclusion, this randomized trial provides evidence for the futility of early parenteral nutrition supplementation in terms of postoperative morbidity burden when an early food intake policy is applied in the context of the ERAS protocol. The results also appear valid for nutritional high risk patients and for patients with preoperative weight loss <15%. We expect these results to be practice-changing and stimulate the revision of international guidelines on artificial nutrition in patients undergoing major abdominal operations. Our findings do not apply to severely malnourished patients or with critical comorbidities.

Contributors

LG, SP, GC, NP, IF, MS, DPB were involved in study conceptualisation and design. All authors were involved in data acquisition. LG, SP, GC, NP, IF, MS, AF, EV, SR, SC, AP, GG, CC, GM, AV, EP, DPB had full access to all the data and verified the data. LG, SP, GC, NP, IF, MS, DPB did the analyses and interpretation of data. MB, GM, AG, RS, AZ, MF, GB provided supervision during conceptualisation, design, data acquisition, data analyses, data interpretation, drafting of the manuscript, and final approval. LG, SP, GC, NP, IF, MS, DPB wrote the original manuscript draft. All authors revised the manuscript critically for important intellectual content and provided final approval of the version to be published. All authors had full access to the data and verified the data, and had final responsibility for the decision to submit for publication.

Data sharing statement

De-identified individual participant data collected in the RASTA trial can be made available upon request by contacting the principal investigator (LG), who will review all requests. There are no date restrictions on the availability of data. The RASTA investigators will be allowed to approve all research performed with the shared data.

Declaration of interests

LG received speaker honoraria from BBraun and travel grant from Akern, MS, received speaker honoraria from Akern, SP received consultancy honoraria from AlphaTau Medical and from ClearNote Heath and speaker honoraria from Fresenius Kabi. GM received consultancy honoraria from OncoSil. All other authors declare no competing interests.

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The authors take full responsibility for the integrity and completeness of the data and the content of this article.

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Appendix A. Supplementary data

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