A fish oil-enriched food for special medical purpose in Chinese patients with gastrointestinal tumor undergoing surgery: A multicenter, randomized, active-controlled, non-inferiority phase III trial

doi: 10.6133/apjcn.202604/PP.0004
Published online: March 2026

Running title: FSMP vs. TPF-T in GI tumor nutrition

Jianchun Yu MD[1], Wei Chen MD[2], Gang Xiao MD[3], Qi An MD[3], Ziyu Li MD[4], Bin Liang MD[5], Yuanxin Li MD[6], Dongbing Zhao MD[7], Junsheng Peng MD[8], Yanbing Zhou MD[9], Guole Lin MD[1], Weiming Kang MD[1], Zijian Li MD[3], Chao Yan MD[4], Yuanpei Lin MD[5], Changzhen Zhu MD[6], Hu Ren MD[7], Yijia Lin MD[8], Yulong Tian MD[9]

[1]Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[2]Department of Clinical Nutrition, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[3]Department of General Surgery, Beijing Hospital, National Center of Gerontology, National Clinical Research Center for Gerontology, The Key Laboratory of Geriatrics of National Health Commission, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China
[4]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Ward I of the Gastrointestinal Cancer Center, Peking University Cancer Hospital and Institute, Beijing, China
[5]Department of Gastrointestinal Surgery, Peking University People's Hospital, Beijing, China
[6]Department of Gastrointestinal Surgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China
[7]Department of Pancreatic and Gastric Surgical Oncology, National Cancer Center/National Clinical Research for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[8]The Sixth Affiliated Hospital, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Disease, Guangzhou, China
[9]Department of Gastrointestinal Surgery, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Authors' email addresses and contributions:
JY: yu-jch@163.com, yujch@pumch.cn
Contribution: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; and Writing - review & editing.

WC: chenw@pumch.cn, txchenwei@sina.com

Contribution: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; and Writing - review & editing.

GX: xgbj@sina.com, xiaogang0549@bjhmoh.cn
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

QA: anqi3651@bjhmoh.cn, Doctor_an11@126.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

ZL: ziyu_li@hsc.pku.edu.cn, ligregory@outlook.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

BL: liangbin@pkuph.edu.cn, 13681444694@163.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

YL: lyxa01633@btch.edu.cn, liyuanxin1966@163. com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

DZ: dbzhao@cicams.ac.cn, dbzhao2003@sina.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

JP: pengjsh@mail.sysu.edu.cn, pengsir1010@126.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

YZ: zhouyanbing@qduhospital.cn, zhouyanbing999@aliyun.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Writing - review & editing.

GL: lingl@pumch.cn, linguole@126.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

WK: Kangwm@pumch.cn
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

ZL: lizijian4839@bjhmoh.cn, zyzhj90@126.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

CY: yanchao_mail@163.com (ORCID: 0000-0001-7622-5730)
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

YL: yanchao@bjmu.edu.cn, linyuanpei1989@163.com
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

CZ: zzza02492@btch.edu.cn, 13552587121@163.com

Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

HR: renhu0001@163.com (ORCID: 0000-0001-7274-287X)
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

YL: linyj3@mail.sysu.edu.cn
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

YT: 15269611858@139.com (ORCID: 0000-0003-3592-1064)
Contribution: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Writing - review & editing.

Corresponding Author: Dr Jianchun Yu, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Peking Union Medical College Hospital, 1 Shuaifuyuan Road, Dongcheng District, Beijing, China. Tel: 13801310449. Email: yu-jch@163.com

ABSTRACT

Background and Objectives: This study aimed to evaluate the safety and efficacy of a fish oil-enriched food for special medical purposes (FSMP, ProSure) compared to an oncology-specific enteral nutrition product (TPF-T). **Methods and Study Design:** This multicenter, randomized, open-label, non-inferiority phase III trial (NCT05301556) included patients with gastrointestinal tumors scheduled for surgery and at high risk for malnutrition. Participants were randomized 1:1 to receive either FSMP or TPF-T as a sole nutritional source from 4±2 days before surgery to 9±3 days postoperatively. The primary endpoint was the change in serum pre-albumin levels from baseline to 9±3 days post-surgery (non-inferiority margin: 20.807 mg/L). **Results:** Of the 325 patients randomized (FSMP: n = 162; TPF-T: n = 163), FSMP demonstrated non-inferiority to TPF-T in maintaining serum pre-albumin levels in the perioperative patients (least square [LS] mean difference: 6.9 mg/L, 95% CI: -5.0 to 18.8). FSMP showed a greater reduction in serum triglycerides (LS mean difference: -0.133 mmol/L, 95% CI: -0.239 to -0.027, p = 0.014), while comparable changes in other lipid parameters, serum albumin, body weight, or grip strength from baseline to 9±3 days post-surgery, and the length of hospital stay were observed between groups (all p >0.05). The most common treatment-emergent adverse events were gastrointestinal disorders, including abdominal distension (FSMP: 17.3% vs. TPF-T: 18.4%), diarrhea (21.0% vs. 11.0%), and nausea (6.8% vs. 5.5%). **Conclusions:** ProSure, an FSMP, when used as a sole nutritional source, is not inferior to TPF-T in maintaining perioperative nutritional status in patients with gastrointestinal tumors, demonstrating comparable efficacy and safety.

Key Words: gastrointestinal neoplasms, malnutrition, perioperative care, enteral nutrition, eicosapentaenoic acid

INTRODUCTION

Malnutrition is a prevalent and severe complication among patients with gastrointestinal tumors, driven by the impact of both the tumor itself and the effects of anti-tumor therapies.[1] Surgical resection, the cornerstone of curative treatment for gastrointestinal tumors, often exacerbates these issues due to postoperative gastrointestinal dysfunction, which manifests as bowel wall edema, dysmotility, and gut injury, further compromising nutritional status.[2-5] The prevalence of malnutrition in this population is linked to adverse outcomes, including impaired quality of life, delayed wound healing, and increased risk of postoperative complications, such as in-hospital infections, prolonged hospitalization, and higher in-hospital

mortality rates.1 Given these challenges, perioperative nutritional support, particularly preoperative optimization, plays a critical role within Enhanced Recovery After Surgery (ERAS) protocols to reduce adverse outcomes. Moreover, serum pre-albumin has emerged as a reliable biomarker for evaluating nutritional status and serves as a prognostic indicator in these patients.[6, 7] Therefore, optimizing perioperative nutrition support strategies, including maintaining or improving serum pre-albumin levels, is critical for enhancing surgical outcomes in this vulnerable patient group.[8]

Conventional nutritional strategies, including oral nutritional supplements, enteral nutrition (EN), and parenteral nutrition, play a vital role in preventing adverse pathophysiological changes associated with malnutrition.[9, 10] Among these, early initiation of EN is particularly advantageous compared with total parenteral nutrition, as it has been shown to shorten hospital stay, increase serum albumin levels,[11] and decrease postoperative infection risk.[12] Beyond providing essential calories and protein, advanced EN formulations enriched with long-chain polyunsaturated fatty acids (LCPUFAs) and non-essential amino acids such as glutamine have demonstrated additional benefits in surgical oncology. Meta-analyses have revealed that EN supplements containing omega-3 fatty acids and glutamine can significantly elevate levels of key nutritional biomarkers, including pre-albumin, immunoglobulin M (IgM), and immunoglobulin G (IgG), while also reducing the incidence of postoperative complications.[13-15]

Fish oil-enriched nutritional supplements have shown promise in improving clinical outcomes in oncology patients by enhancing acute-phase protein levels, such as albumin, pre-albumin, and transferrin, while simultaneously reducing tumor-associated factors, including tumor necrosis factor-alpha (TNF-alpha), and pro-inflammatory cytokines like interleukin-6 (IL-6). These supplements have demonstrated positive effects on body weight, nutritional status, and quality of life, particularly in patients with cancer cachexia and systemic inflammation.[15-18] Furthermore, among surgical patients, they support both preoperative nutritional optimization and postoperative recovery 19, 20. Despite these benefits, previous studies have primarily assessed fish oil-enriched supplements as adjuncts to standard dietary intake, limiting their evaluation as a sole nutritional source in perioperative settings.[17, 21] Thus, the efficacy and safety of fish oil-enriched formulations as exclusive enteral nutritional support in patients undergoing surgery for gastrointestinal tumors remain underexplored, particularly within the Chinese population.

To address this gap, we designed a multicenter, randomized, active-controlled, non-inferiority clinical trial to assess the efficacy of an upgraded fish oil-enriched food for special

medical purposes (FSMP) specifically tailored to meet the nutritional requirements and preferences of Chinese patients. The primary objective of this trial is to evaluate the safety and efficacy of a fish oil-enriched FSMP when used as a sole nutritional source in patients undergoing surgery for gastrointestinal tumors.

MATERIALS AND METHODS

Study design and participants

This study was a randomized, active-controlled, open-label, multicenter, non-inferiority phase III clinical trial conducted in patients with gastrointestinal tumors with risks for malnutrition and scheduled for surgical resection. Eligible patients were adults aged 18 to 75 years with histologically or radiologically confirmed upper or lower gastrointestinal tumors, a Nutritional Risk Screening 2002 (NRS-2002) score of 3 or higher, and a body mass index (BMI) between 18.5 and 30 kg/m². Female participants were required to be non-pregnant and non-lactating, with at least 6 weeks postpartum prior to screening. Key exclusion criteria included a life expectancy of less than 3 months, contraindications to enteral nutrition deemed uncorrectable by the investigator, recent use of parenteral nutrition, or transfusion of plasma, red blood cells, albumin, or amino acids within 1 week before screening. Patients with serum albumin levels <2.5 g/dL, moderate to severe anemia (hemoglobin <90 g/L), plans for endoscopic tumor resection or palliative surgery, or significant organ dysfunction, including renal, hepatic, or cardiac insufficiency, as well as those with recent major cardiovascular or cerebrovascular events within 6 months, were also excluded. Additionally, patients receiving tumor immunotherapy or substances known to profoundly modulate immune function and metabolism were not eligible.

The study was conducted in compliance with the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000) and the International Council for Harmonisation Good Clinical Practice guidelines. The study protocol was approved by the Ethical Committee of all participating centers (the ethical approval numbers for the leading site, Peking Union Medical College Hospital, are HS2021050 and KS2021611), and written informed consent was obtained from all participants. This trial was registered at ClinicalTrials.gov (NCT05301556).

Procedure

Participants were randomized in a 1:1 ratio using a dynamic minimization algorithm into two groups: the experimental group received a fish-oil-enriched food for special medical purpose (FSMP, ProSure, Abbott) and the control group received a comparable oncology-specific EN

product registered as a drug in China (TPF-T, Fresenius). Randomization was stratified by tumor location (upper vs lower gastrointestinal tract) and the intended surgical approach (laparoscopic vs open surgery). Due to the distinct formulations of the two products (powder vs liquid), a non-blinded design was employed.

Both products were administered as a single nutritional source through oral or tube feeding, beginning 4 ± 2 days before surgery and continuing until 9 ± 3 days postoperatively. The product used in the FSMP group provided 1.3 kcal/ml energy density, with 28.31 g/100 g of protein, 2.1 g/100 g of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA), and 3.19 g/100 g of glutamine. In comparison, TPF-T offered a similar energy density of 1.3 kcal/mL, with 5.85 g/100 mL of protein and 0.3 g/100 mL of omega-3 fatty acids. A detailed nutrient composition of both products is provided in Supplementary Table 1. Energy requirements for each participant were calculated based on a target of 25-30 kcal/kg ideal body weight (IBW, height [cm] - 105) daily, with adjustments for age, gender, and physical activity level. Before surgery, TPF-T or FSMP provided all the daily target energy needed by participants. During the postoperative period, participants received the allocated intervention at incremental energy targets according to postoperative tolerance: 20% of target energy intake on day 2 post-surgery, 30-80% on days 3-5, and up to the full target intake by day 6. No energy target was required on the surgery day and on day 1 post-surgery. Both products were administered from baseline until day 9±3 days postoperatively, after which participants were transitioned to routine nutritional support as determined by their clinical team.

Concomitant use of medications and supplements that could influence metabolism, such as steroids, growth hormones, anti-inflammatory fat emulsions, and other omega-3 fatty acid, protein, glutamine, or arginine-containing products, was prohibited throughout the study period. Postoperative parenteral nutrition was only allowed for fluid replacement purposes.

Endpoints

The primary endpoint was the change in serum pre-albumin levels from baseline to 9 ± 3 days post-surgery. Secondary endpoints included changes in serum pre-albumin from baseline to 1 day before surgery/the day of surgery and to 1 day post-surgery, and changes in serum albumin, C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR) from baseline to 1 day before surgery/surgery day, 1 day, and 9 ± 3 days post-surgery. Other endpoints included changes in body weight, NRS-2002 score, fasting blood glucose, serum triglycerides (TG), total cholesterol (TC), grip strength, and Eastern Cooperative Oncology Group performance status (ECOG PS) from baseline to 9±3 days post-surgery, along with length of

hospital stay and product intake compliance. Product intake compliance was defined as the proportion of participants consuming at least 75% of their prescribed daily target energy for at least 7 days during the study period (excluding the day of surgery and 1 day post-surgery).

Safety endpoints included the incidence of adverse events (AEs) and serious adverse events (SAEs), vital signs, gastrointestinal tolerance (assessed using the Gastrointestinal Function Assessment Form), and incidence of feeding tube-related complications, such as nasal mucosa injury, tube blockage, and stoma site infections. Laboratory abnormalities were also monitored. Safety evaluations were performed at baseline, on 1 day before surgery/the day of surgery, at 1 day, and 9 ± 3 days post-surgery.

Statistical analysis

The primary analysis was based on a non-inferiority framework, using a non-inferiority margin of 20.807 mg/L for the change in serum pre-albumin levels from baseline to 9 ± 3 days post-surgery. This non-inferiority margin was predefined based on previously published data from a study comparing TPF-T with normal diet in patients undergoing surgery for gastrointestinal malignancies,[22] and clinical judgment regarding the minimal clinically meaningful difference in pre-albumin change. With a common standard deviation (SD) of 52.26 mg/L,[22] a sample size of 100 participants per group provided 80% power to detect a difference of 20.807 mg/L using a two-sided 0.05 significance level (nQuery Advisor® Version 7.0). To account for potential dropouts, the final sample size was set at a maximum of 175 participants per group.

The full analysis set (FAS) included all randomized participants who received at least one dose of the study product. Per protocol set (PPS) comprised those in the FAS who adhered to the protocol without major deviations and completed all required assessments, which was the primary analysis set for efficacy. The safety set (SS) consisted of participants who received at least one dose and underwent post-dose safety evaluations.

Analysis of covariance (ANCOVA) was used to assess the primary endpoint, adjusting for baseline values, study site, and randomization stratification factors. Non-inferiority was concluded if the lower bound of the two-sided 95% confidence interval (CI) of the intergroup difference (FSMP – TPF-T) was greater than -20.807 mg/L. Subgroup analyses were performed for predefined factors, including tumor location and surgical method. Given the clinical importance of both systemic inflammation and nutritional status recovery after surgery, post hoc analyses focused on exploratory assessments of CRP and body weight across subgroups in both FAS and PPS. Other continuous endpoints were analyzed using

ANCOVA, while categorical outcomes were evaluated using Chi-square or Fisher's exact tests as appropriate. Multiple imputation for missing data was performed only for the primary endpoint as a post-hoc sensitivity analysis, while no imputation was applied to other endpoints. All analyses were conducted using SAS version 9.4 or higher. *p*-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Between July 4, 2022, and January 9, 2024, a total of 337 patients were screened, of whom 325 were randomized into the study. Ultimately, 253 patients completed the study, with AEs being the most common reason for withdrawal (13.6%). One hundred and sixty-two participants in the FSMP group and 163 in the TPF-T group were included in the FAS, with 100 participants in each group forming the PPS (Figure 1).

The median age was 61 years (range: 31-75 years), and the majority of participants were male (65.2%). The mean BMI was 24.28 kg/m² (SD: 2.87). Most patients (62.8%) had lower gastrointestinal tumors, while 37.2% had tumors located in the upper gastrointestinal tract. The vast majority of patients (98.2%) underwent laparoscopic surgery, while only 1.8% underwent laparotomy. Nutritional status at baseline, as assessed by the Patient-Generated Subjective Global Assessment (PG-SGA), indicated that 75.1% of patients were moderately malnourished, and 19.7% were severely malnourished. The baseline characteristics were comparable between the groups (Table 1).

Pre-albumin

On day 9±3 post-surgery, the primary endpoint analysis in the PPS demonstrated the mean change from baseline was -60.8 mg/L (standard error [SE]: 12.0) and -67.7 mg/L (SE: 11.4) in the FSMP and control groups, respectively, with a least square (LS) mean difference of 6.9 mg/L (SE: 6.02) between the FSMP and control groups. The 95% CI ranged from -5.0 to 18.8 mg/L, which exceeded the pre-specified non-inferiority margin of -20.807 mg/L, thereby confirming the non-inferiority of FSMP relative to TPF-T in maintaining nutrition status. Similarly, the LS mean difference between the two groups was 7.3 mg/L (SE: 5.50) with a 95% CI of -3.5 to 18.2 mg/L in the FAS, also meeting the non-inferiority criteria.

In the PPS, the mean change from baseline was 8.1 mg/L (SE: 7.90) and 9.6 mg/L (SE: 7.47) in the FSMP and control groups, respectively, on the visit of 1 day before surgery/the day of surgery, with a between-group difference of -1.5 mg/L (95% CI: -8.9 to 5.8 mg/L). On

day 1 post-surgery, the mean change from baseline was -37.6 mg/L (SE: 7.14) in the FSMP group and -40.2 mg/L (SE: 6.78) in the control group, yielding a between-group difference of 2.6 mg/L (95% CI: -4.0 to 9.3 mg/L) (Table 2). A post-hoc multiple imputation analysis for the primary outcome in the FAS revealed similar results (Supplementary Table 2). The subgroup analysis confirmed the non-inferiority of FSMP to TPF-T in maintaining nutrition status across various subpopulations and time points, including patients with upper and lower gastrointestinal tumors, and those undergoing laparoscopy (Supplementary Table 3).

Other secondary efficacy endpoints

The results of other secondary endpoints in PPS and FAS are detailed in Table 3. In PPS, the between-group difference of change from baseline in serum albumin levels was -0.23 g/L (95% CI: -1.10, 0.63; p = 0.599) at 9±3 days post-surgery. Similarly, the difference in body weight change was 0.35 kg (95% CI: -0.14, 0.85; p = 0.160). Furthermore, no statistically significant difference was found in the subgroup analysis of body weight (Supplementary Figure S1). NRS-2002 scores showed a similar change of 0.6 (SD: 0.87) in the FSMP group compared to 0.7 (SD: 0.91) in the control group (p = 0.635) (Table 3).

For inflammatory markers, the between-group difference of CRP increase was -3.69 mg/L (95% CI: -11.34, 3.97; p = 0.343). For subgroup analysis, no statistically significant difference was found in the upper gastrointestinal tumor subgroup. However, within the lower gastrointestinal tumor subgroup, compared with the control group (37.2 mg/L, SE: 10.3), the CRP increase in the FSMP group (21.9 mg/L, SE: 10.6) at 1 day post-surgery was significantly lower, and the between-group difference was -7.93 mg/L (95% CI: -14.72, -1.14; p = 0.022) (Supplementary Figure S1). The increase of NLR was 1.75 (SE: 0.584) in the FSMP group versus 1.68 (SE: 0.551) in the control group, with a between-group difference of 0.07 (95% CI: -0.51, 0.65; p = 0.814).

Fasting blood glucose levels showed a change of 0.49 mmol/L (SE: 0.307) in the FSMP group versus 0.37 mmol/L (SE: 0.290) in the control group, with a between-group difference of 0.12 mmol/L (95% CI: -0.18, 0.42; p = 0.436). Notably, the reduction in serum TG was significantly greater in the FSMP group (-0.337 mmol/L, SE: 0.114) compared to the control group (-0.205 mmol/L, SE: 0.108), with a between-group difference of -0.133 mmol/L (95% CI: -0.239, -0.027; p = 0.014). TC showed a similar decrease in the two groups, with a between-group difference of -0.160 mmol/L (95% CI: -0.330, 0.010; p=0.065).

The decrease of grip strength was similar between the FSMP group and control group, with a difference of -0.78 kg (95% CI: -2.61, 1.05; p = 0.401). For ECOG PS, 76% of patients in

the FSMP group maintained a score of 0 compared to 75% in the control group at 9±3 days post-surgery (p >0.999). Length of hospital stay was comparable between the two groups in the PPS (p = 0.286), and in the FAS, a trend of fewer days of hospital stay was found in the FSMP group compared to the control group (16.8 vs. 18.9 days, p = 0.057). When adjusted with baseline severity of disease (tumor stage), significantly fewer days of hospital stay were found in the FSMP group compared to the control group in the FAS (p = 0.023). Nutritional compliance was similar, with 83.3% in the FSMP group and 79.1% in the control group achieving an overall product intake compliance of ≥75% (p = 0.562).

Safety

The mean total accumulated perioperative product calories were 10,403.60 kcal (SD: 3968.22) in the FSMP group and 9,828.65 kcal (SD: 3901.71) in the control group (p = 0.189). The mean preoperative exposure time was 3.8 days for both groups (FSMP: 3.8 [SD: 1.20] vs. TPF-T: 3.8 [SD: 1.08]; p = 0.661). Gastrointestinal intolerance was also similar between groups at the final visit, with 79.0% of participants in the FSMP group and 78.5% in the control group maintaining a baseline score of 0. Feeding tube-related complications were infrequent in both groups, with a low incidence reported (FSMP: 1.2% vs. TPF-T: 0.6%).

A total of 16 SAEs occurred in 14 (8.6%) participants in the FSMP group, all unrelated to FSMP, compared to 30 SAEs in 29 (17.8%) participants in the control group. Non-SAEs were reported in 62.3% of participants in the FSMP group and 54.6% in the control group. The most frequently reported treatment-emergent adverse events (TEAEs) were gastrointestinal disorders (FSMP: 46.3% vs. TPF-T: 40.5%), including abdominal distension (17.3% vs. 18.4%), diarrhea (21.0% vs. 11.0%), and nausea (6.8% vs. 5.5%). The incidence of TEAEs leading to dose reductions was similar between the FSMP and control groups (3.1% vs. 1.6%), as was the incidence of TEAEs leading to dose discontinuation (14.2% vs. 17.2%) and study withdrawal (11.7% vs. 14.7%).

DISCUSSION

This study demonstrated that the use of ProSure, an FSMP, as a single nutritional source in patients with gastrointestinal tumors undergoing surgery at risk of malnutrition, was not inferior to the standard oncology-specific EN (TPF-T) in maintaining serum pre-albumin levels by day 9 ± 3 post-surgery. The findings were consistent across all time points, including the day of surgery and day 1 post-surgery, indicating comparable efficacy in perioperative nutritional support between ProSure and TPF-T. Additionally, both groups

exhibited similar results in terms of other key parameters such as albumin levels, body weight, grip strength, and inflammatory markers. These results suggest that ProSure can serve as an effective perioperative nutritional option for patients at risk of malnutrition undergoing gastrointestinal tumor surgery.

Surgical resection often exacerbates the gastrointestinal dysfunction and further compromises nutritional status in patients with gastrointestinal tumors. In a study evaluating nutrition support in patients undergoing gastrectomy, a significant postoperative decrease in pre-albumin and albumin levels was observed on day 3 (about 85-90 mg/L in pre-albumin, and 3-8 g/L in albumin), followed by an increase on day 5, with a decrease of about 60 mg/L and 1.5 g/L in pre-albumin and albumin decrease from baseline, respectively.[23] In a randomized controlled trial comparing the efficacy of EPA-enriched EN with standard EN in patients undergoing esophagectomy, both groups experienced a significant decline in albumin levels immediately after surgery, followed by a gradual recovery.16 These results mirror the pattern observed in our study, that both the FSMP and control groups exhibited a decline in serum pre-albumin levels shortly after surgery. The absolute decrease in pre-albumin was smaller in the present study compared to previous studies. This disparity is likely attributable to differences in nutritional protocols, as evidenced by a recent trial comparing the efficacy of an immunonutrition formula to a standard TPF-T in alleviating pre-albumin reduction and body weight loss in a comparable patient population. However, no conclusion could be drawn due to the disparity in study design and population. As recommended by most ERAS Society Guidelines,[24] perioperative nutrition care, as used in the present study, might optimize surgical recovery in patients at risk of malnutrition.[25] In the meantime, the present study demonstrated that the upgraded FSMP is comparable to a standard TPF-T in maintaining nutritional outcomes among malnourished patients with gastrointestinal tumors undergoing surgery, especially a trend of superior nutritional supplementation efficacy with FSMP compared to TPF-T on surgery day in patients with upper gastrointestinal tumors. The secondary endpoint analysis also revealed comparable outcomes between FSMP and TPF-T in terms of serum albumin, grip strength, body weight, and inflammatory markers, with a significantly reduced length of hospital stay, underscoring their similar nutritional and metabolic effects during the perioperative period and possible clinical benefit.

Endogenous bioactive lipids are part of a complex network that modulates a plethora of cellular and molecular processes, including inflammation.[26, 27] Studies showed that a high-fat and high-cholesterol diet promotes intestinal inflammation.[28] Considering the involvement of endogenous lipids in the pathogenic inflammatory processes, we observed the change of lipid

and inflammation parameters in this study. Notably, FSMP demonstrated a significantly greater reduction in serum TG levels compared to TPF-T, suggesting a unique impact on lipid metabolism. This finding is consistent with previous research indicating that omega-3 fatty acid-enriched EN formulations can modulate lipid profiles and reduce systemic inflammation. For example, a study on esophageal cancer surgery patients receiving EPA-enriched EN reported a preservation of lean body mass and an attenuation of inflammatory cytokines such as TNF-α, IL-6, and interleukin-8.16 Thus, the lipid-lowering effect of FSMP may offer additional benefits in managing dyslipidemia and systemic inflammation in malnourished cancer patients. Furthermore, the observed difference in CRP increase between the two groups within the lower gastrointestinal tumor subgroup also suggests that FSMP may have an anti-inflammatory advantage compared to the TPF-T. However, parameters related to immune function (e.g., NLR) were comparable between the two groups, possibly due to an underpowered sample size for the detection of differences, limited follow-up duration, and confounders, which need to be further validated.

The safety profile of FSMP was comparable to the standard enteral nutrition product in patients undergoing gastrointestinal tumor surgery, with similar overall incidences of AEs and SAEs in both groups. Diarrhea was more frequent in the FSMP group (21.0% vs. 11.0% in control), but most of these events were mild and self-limiting. Interestingly, the control group showed a higher, albeit low, incidence of anastomotic leakage (6.1% vs. 2.5%). Larger studies are needed to determine if these differences are clinically significant. Importantly, in an analysis of 8 clinical trials, LCPUFAs did not affect blood coagulation parameters and bleeding manifestations.[29] Consistently, in the present study, no coagulation-related safety concerns were noted with the high-dose EPA in ProSure, when using it as a sole source of nutrition, which aligns with previous studies.[16, 29, 30] Although a certain degree of gastrointestinal intolerance was observed in both groups, likely attributable to surgical alterations in anatomy and functional impairments following gastrointestinal oncology surgery, overall tolerance was comparable between the groups. The lipid-lowering effect in the FSMP group, reflected in a greater reduction in TG, did not result in adverse metabolic outcomes. These results suggest that ProSure is a safe option for perioperative nutrition in surgical patients with a risk of malnutrition. However, more studies are desired to further confirm its long-term safety and efficacy.

It is important to acknowledge certain limitations of our study. The relatively short follow-up period may have precluded the detection of long-term nutritional and clinical benefits, and the open-label design could have introduced bias despite efforts to standardize outcome

assessments. Notably, blinding of participants and investigators was not feasible due to the study products differences in formulation, taste, and mode of preparation, consistent with previous studies using similar interventions.[20, 31] Though it may have influenced the reporting and assessment of patient-reported gastrointestinal tolerance and product acceptability, despite the use of standardized assessment tools and objective criteria, the primary endpoint and key secondary endpoints were laboratory-based or objective, which are less susceptible to expectation bias. The attrition rate exceeded 20%, which was similar with previous studies of omega-3-enriched nutritional interventions and largely attributable to postoperative TEAEs,[16, 21, 32] the PPS included 100 participants per group as prespecified in the sample size calculation, thereby preserving the target statistical power. In addition, multiple imputation was performed on the FAS, yielding consistent results that further support the robustness of our conclusions. Furthermore, our study did not assess immune-related biomarkers such as lymphocyte subsets, which have been highlighted in other studies as important indicators of immunomodulatory effects of specialized nutritional products. Future research incorporating these parameters, along with longer follow-up durations, is warranted to fully elucidate the role of fish oil-enriched FSMP in surgical oncology.

Conclusion

In this randomized controlled trial involving patients undergoing surgery for gastrointestinal tumors with risk of malnutrition, ProSure, a fish oil-enriched FSMP, offers non-inferiority in overall nutritional benefits to the standard oncology-specific product, TPF-T. Importantly, the safety profiles of ProSure and TPF-T were similar, confirming ProSure's tolerability as a sole nutritional source in this population. Given these findings, ProSure represents a viable and effective nutritional support option for patients with gastrointestinal tumors undergoing surgery, particularly those at risk for malnutrition, with its distinct taste profile also providing an alternative for individualized patient choice. For patients with combined gastrointestinal dysfunction and poor tolerance, adjunct use of digestive enzymes and probiotics, along with reduced application of antibiotics and acid suppressants, may help improve tolerance and merits further investigation.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

ACKNOWLEDGEMENTS

We thank Abbott China Research and Development Center for their involvement in the study design, data collection and analysis, and preparation and review of the manuscript. We thank all study sites and research staff who provided support to this research project. We thank all of the patients who participated in this research.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declared no conflict of interest.

This research project is solely funded by Abbott Laboratories Trading (Shanghai) Co., Ltd.

REFERENCES

1. 1. Arends J. Malnutrition in cancer patients: Causes, consequences and treatment options. Eur J Surg Oncol. 2024;50:107074. doi:10.1016/j.ejso.2023.107074
2. GlobalSurg C, Surgery NGHUoG. Impact of malnutrition on early outcomes after cancer surgery: an international, multicentre, prospective cohort study. Lancet Glob Health. 2023;11:e341-e9. doi:10.1016/S2214-109X(22)00550-2
3. Duran Poveda M, Suarez-de-la-Rica A, Cancer Minchot E, Ocon Breton J, Sanchez Pernaute A, Rodriguez Caravaca G, et al. The Prevalence and Impact of Nutritional Risk and Malnutrition in Gastrointestinal Surgical Oncology Patients: A Prospective, Observational, Multicenter, and Exploratory Study. Nutrients. 2023;15:3283. doi:10.3390/nu15143283
4. Kenny E, Samavat H, Touger-Decker R, Parrott JS, Byham-Gray L, August DA. Adverse perioperative outcomes among patients undergoing gastrointestinal cancer surgery: Quantifying attributable risk from malnutrition. JPEN J Parenter Enteral Nutr. 2022;46:517-25. doi:10.1002/jpen.2200
5. Kiss N, Prado CM, Daly RM, Denehy L, Edbrooke L, Baguley BJ, et al. Low muscle mass, malnutrition, sarcopenia, and associations with survival in adults with cancer in the UK Biobank cohort. J Cachexia Sarcopenia Muscle. 2023;14:1775-88. doi:10.1002/jcsm.13256
6. Bouletreau P, Chassard D, Allaouchiche B, Dumont JC, Auboyer C, Bertin-Maghit M, et al. Glucose-lipid ratio is a determinant of nitrogen balance during total parenteral nutrition in critically ill patients: a prospective, randomized, multicenter blind trial with an intention-to-treat analysis. Intensive Care Med. 2005;31:1394-400. doi:10.1007/s00134-005-2771-5
7. Zhou J, Hiki N, Mine S, Kumagai K, Ida S, Jiang X, et al. Role of Prealbumin as a Powerful and Simple Index for Predicting Postoperative Complications After Gastric Cancer Surgery. Ann Surg Oncol. 2017;24:510-7. doi:10.1245/s10434-016-5548-x
8. Sanchez Leon RM, Rajaraman A, Kubwimana MN. Optimizing Nutritional Status of Patients Prior to Major Surgical Intervention. Methodist Debakey Cardiovasc J. 2023;19:85-96. doi:10.14797/mdcvj.1248

9. Gustafsson UO, Rockall TA, Wexner S, How KY, Emile S, Marchuk A, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations 2025. Surgery. 2025;184:109397. doi:10.1016/j.surg.2025.109397
10. Weimann A, Bezmarevic M, Braga M, Correia M, Funk-Debleds P, Gianotti L, et al. ESPEN guideline on clinical nutrition in surgery - Update 2025. Clin Nutr. 2025;53:222-61. doi:10.1016/j.clnu.2025.08.029
11. Zhao XF, Wu N, Zhao GQ, Liu JF, Dai YF. Enteral nutrition versus parenteral nutrition after major abdominal surgery in patients with gastrointestinal cancer: a systematic review and meta-analysis. J Investig Med. 2016;64:1061-74. doi:10.1136/jim-2016-000083
12. Li K, Wang D, Zhang X, Yang J, Chen X. Efficacy of early enteral nutrition versus total parenteral nutrition for patients with gastric cancer complicated with diabetes mellitus: A systematic review and meta-analysis. Nutr Diet. 2022;79:129-39. doi:10.1111/1747-0080.12721
13. Shen J, Dai S, Li Z, Dai W, Hong J, Huang J, et al. Effect of Enteral Immunonutrition in Patients Undergoing Surgery for Gastrointestinal Cancer: An Updated Systematic Review and Meta-Analysis. Front Nutr. 2022;9. doi:10.3389/fnut.2022.941975
14. Fu H, Li B, Liang Z. Effect of enteral immunonutrition compared with enteral nutrition on surgical wound infection, immune and inflammatory factors, serum proteins, and cellular immunity in subjects with gastric cancer undergoing a total gastrectomy: A meta-analysis. Int Wound J. 2022;19:1625-36. doi:10.1111/iwj.13763
15. Yu K, Zheng X, Wang G, Liu M, Li Y, Yu P, et al. Immunonutrition vs Standard Nutrition for Cancer Patients: A Systematic Review and Meta-Analysis (Part 1). JPEN J Parenter Enteral Nutr. 2020;44:742-67. doi:10.1002/jpen.1736
16. Ryan AM, Reynolds JV, Healy L, Byrne M, Moore J, Brannelly N, et al. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. Ann Surg. 2009;249:355-63. doi:10.1097/SLA.0b013e31819a4789
17. Fearon KC, Von Meyenfeldt MF, Moses AG, Van Geenen R, Roy A, Gouma DJ, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut. 2003;52:1479-86. doi:10.1136/gut.52.10.1479
18. Barber MD, Ross JA, Preston T, Shenkin A, Fearon KC. Fish oil-enriched nutritional supplement attenuates progression of the acute-phase response in weight-losing patients with advanced pancreatic cancer. J Nutr. 1999;129:1120-5. doi:10.1093/jn/129.6.1120
19. Homan van der Heide JJ, Bilo HJ, Donker AJ, Wilmink JM, Sluiter WJ, Tegzess AM. The effects of dietary supplementation with fish oil on renal function and the course of early postoperative rejection episodes in cyclosporine-treated renal transplant recipients. Transplantation. 1992;54:257-63.
20. Sittitrai P, Ruenmarkkaew D, Booyaprapa S, Kasempitakpong B. Effect of a perioperative immune-enhancing diet in clean-contaminated head and neck cancer surgery: A randomized controlled trial. Int J Surg. 2021;93:106051. doi:10.1016/j.ijsu.2021.106051

21. Barber MD, Ross JA, Voss AC, Tisdale MJ, Fearon KC. The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. Br J Cancer. 1999;81:80-6. doi:10.1038/sj.bjc.6690654
22. Huang ZJ, Chen BS, You J, Wu BL, Jiang L, Feng QZ, et al. [The clinical significance of preoperative enteral immune nutrition in patients with malignant gastrointestinal tumors]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2014;45:167-70.
23. Li K, Xu Y, Hu Y, Liu Y, Chen X, Zhou Y. Effect of Enteral Immunonutrition on Immune, Inflammatory Markers and Nutritional Status in Gastric Cancer Patients Undergoing Gastrectomy: A Randomized Double-Blinded Controlled Trial. J Invest Surg. 2020;33:950-9. doi:10.1080/08941939.2019.1569736
24. Powers BK, Ponder HL, Findley R, Wolfe R, Patel GP, Parrish RH, 2nd, et al. Enhanced recovery after surgery (ERAS((R))) Society abdominal and thoracic surgery recommendations: A systematic review and comparison of guidelines for perioperative and pharmacotherapy core items. World J Surg. 2024;48:509-23. doi:10.1002/wjs.12101
25. Ding D, Feng Y, Song B, Gao S, Zhao J. Effects of preoperative and postoperative enteral nutrition on postoperative nutritional status and immune function of gastric cancer patients. Turk J Gastroenterol. 2015;26:181-5. doi:10.5152/tjg.2015.3993
26. Calder PC, Waitzberg DL, Klek S, Martindale RG. Lipids in Parenteral Nutrition: Biological Aspects. JPEN J Parenter Enteral Nutr. 2020;44 Suppl 1:S21-S7. doi:10.1002/jpen.1756
27. Leuti A, Fazio D, Fava M, Piccoli A, Oddi S, Maccarrone M. Bioactive lipids, inflammation and chronic diseases. Adv Drug Deliv Rev. 2020;159:133-69. doi:10.1016/j.addr.2020.06.028
28. Xu F, Yu Z, Liu Y, Du T, Yu L, Tian F, et al. A High-Fat, High-Cholesterol Diet Promotes Intestinal Inflammation by Exacerbating Gut Microbiome Dysbiosis and Bile Acid Disorders in Cholecystectomy. Nutrients. 2023;15. doi:10.3390/nu15173829
29. Jeansen S, Witkamp RF, Garthoff JA, van Helvoort A, Calder PC. Fish oil LC-PUFAs do not affect blood coagulation parameters and bleeding manifestations: Analysis of 8 clinical studies with selected patient groups on omega-3-enriched medical nutrition. Clin Nutr. 2018;37:948-57. doi:10.1016/j.clnu.2017.03.027
30. Fradet S, Pelletier JF, Singbo N, Lacombe L, Toren P, Lodde M, et al. Effects of omega-3 fatty acids supplementation on perioperative blood loss and complications after radical prostatectomy. Clin Nutr ESPEN. 2022;47:221-6. doi:10.1016/j.clnesp.2021.12.011
31. Yu J, Xiao G, Zhou Y, Ye Y, Liang H, Lin G, et al. Efficacy and safety of using an enteral immunonutrition formula in the enhanced recovery after surgery protocol for Chinese patients with gastrointestinal cancers undergoing surgery: A randomized, open-label, multicenter trial (healing trial). Chin Med J (Engl). 2025:2847-9. doi:10.1097/cm9.0000000000003676
32. Sim E, Kim JM, Lee SM, Chung MJ, Song SY, Kim ES, et al. The Effect of Omega-3 Enriched Oral Nutrition Supplement on Nutritional Indices and Quality of Life in Gastrointestinal Cancer Patients: A

Randomized Clinical Trial. Asian Pac J Cancer Prev. 2022;23:485-94. doi:10.31557/apjcp.2022.23.2.485.

Table 1. Baseline characteristics of patients

Characteristics	Total (N=325)	FSMP group (n=162)	Control group (n=163)
Age, year, median (range)	61.0 (31, 8)	62.0 (31, 8)	61.0 (34, 8)
Male, n (%)	212 (65.2)	106 (65.4)	106 (65.0)
BMI, kg/m^2, mean (SD)	24.3 (2.87)	24.4 (2.83)	24.2 (2.91)
Location of tumor, n (%)			
Upper gastrointestinal tract	121 (37.2)	59 (36.4)	62 (38.0)
Lower gastrointestinal tract	204 (62.8)	103 (63.6)	101 (62.0)
Type of tumor, n (%)			
Malignant (excluding GIST)	290 (89.2)	145 (89.5)	145 (89.0)
Benign (excluding GIST)	12 (3.7)	5 (3.1)	7 (4.3)
GIST	22 (6.8)	12 (7.4)	10 (6.1)
Benign	12 (3.7)	7 (4.3)	5 (3.1)
Malignant	10 (3.1)	5 (3.1)	5 (3.1)
Missing	1 (0.3)	0	1 (0.6)
Type of surgery, n (%)			
Laparoscopy	319 (98.2)	160 (98.8)	159 (97.5)
Laparotomy	6 (1.8)	2 (1.2)	4 (2.5)
PG-SGA score, median (range)	5.0 (1, 20)	5.0 (1, 20)	5.0 (1, 18)
Well-nourished	15 (4.6)	9 (5.6)	6 (3.7)
Moderately malnourished	244 (75.1)	122 (75.3)	122 (74.8)
Severely malnourished	64 (19.7)	30 (18.5)	34 (20.9)
Missing	2 (0.6)	1 (0.6)	1 (0.6)

BMI, body mass index; SD, standard deviation; GIST, gastrointestinal stromal tumor; PG-SGA, patient-generated subjective global assessment.

Table 2. Serum pre-albumin levels

Outcomes	FAS				PPS			
	FSMP group (n=162)	Control group (n=163)	95%CI	*p* value	FSMP group (n=100)	Control group (n=100)	95%CI	*p* value
Primary endpoint (9±3 days post-surgery)			-3.5, 18.2	0.184			-5.0, 18.8	0.255
Baseline, mg/L, mean (SD)	234 (55.9)	236 (57.5)			234 (46.0)	244 (58.9)		
9 ± 3 days post-surgery, mg/L, mean (SD)	171 (52.6)	165 (56.1)			176 (43.6)	173 (55.3)		
Change from baseline, mg/L, LS mean (SE)	-57.5 (11.3)	-64.9 (11.1)			-60.8 (12.0)	-67.7 (11.4)		
Difference between groups, mg/L, LS mean (SE)	7.3 (5.50)				6.9 (6.02)			
Secondary endpoint			-5.0, 7.0	0.737			-8.9, 5.8	0.680
1 day before surgery/Surgery day, mg/L, mean (SD)	238 (53.3)	244 (56.5)			240 (48.0)	249 (58.1)		
Change from baseline, mg/L, LS mean (SE)	9.3 (6.21)	8.3 (6.11)			8.1 (7.90)	9.6 (7.47)		
Difference between groups, mg/L, mean (SE)	1.0 (3.04)				-1.5 (3.73)			
1 day post-surgery, mean (SD)	192 (45.2)	194 (48.7)	-2.5, 9.1	0.268	194 (41.0)	198 (48.9)	-4.0, 9.3	0.439
Change from baseline, mg/L, LS mean (SE)	-40.9 (5.86)	-44.1 (5.77)			-37.6 (7.14)	-40.2 (6.78)		
Difference between groups, mg/L, mean (SE)	3.3 (2.95)				2.6 (3.38)			

FAS: full analysis set; PP: per protocol; LS: least squares; SE: standard error; CI: confidence interval; SD: standard deviation.

Table 3. Other efficacy outcomes

Outcomes	FAS				PPS			
	FSMP group (n=162)	Control group (n=163)	95%CI	*p* value	FSMP group (n=100)	Control group (n=100)	95%CI	*p* value
Albumin			-1.22, 0.45	0.364			-1.10, 0.63	0.599
Baseline, g/L, mean (SD)	40.5 (4.05)	40.4 (3.86)			40.5 (3.90)	40.7 (4.04)		
9±3 days post-surgery, g/L, mean (SD)	36.4 (4.62)	36.9 (4.69)			37.0 (4.09)	37.4 (4.52)		
Change from baseline, g/L, LS mean (SE)	-4.85 (0.879)	-4.47 (0.863)			-5.88 (0.881)	-5.65 (0.835)		
Difference between groups, g/L, LS mean (SE)	-0.39 (0.424)				-0.23 (0.438)			
Body weight			-0.34, 0.51	0.702			-0.14, 0.85	0.160
Baseline, kg, mean (SD)	67.9 (10.9)	68.2 (11.3)			67.4 (10.7)	69.1 (11.7)		
9±3 days post-surgery, kg, mean (SD)	65.8 (10.5)	66.0 (10.8)			65.4 (10.6)	66.7 (11.2)		
Change from baseline, kg, LS mean (SE)	-1.22 (0.446)	-1.30 (0.435)			-0.77 (0.502)	-1.12 (0.476)		
Difference between groups, kg, LS mean (SE)	0.08 (0.217)				0.35 (0.252)			
NRS-2002 score				0.848				0.635
Baseline, mean (SD)	3.4 (0.61)	3.3 (0.55)			3.4 (0.67)	3.3 (0.48)		
9±3 days post-surgery, mean (SD)	4.0 (0.98)	4.0 (0.96)			4.0 (0.98)	3.9 (0.97)		
Change from baseline, mean (SD)	0.7 (0.88)	0.7 (0.92)			0.6 (0.87)	0.7 (0.91)		
CRP			-11.0, 10.2	0.945			-11.34, 3.97	0.343
Baseline, mg/L, mean (SD)	3.26 (6.46)	4.63 (14.5)			2.16 (2.75)	3.38 (8.03)		
9±3 days post-surgery, mg/L, mean (SD)	35.5 (47.8)	37.3 (46.1)			24.6 (22.4599)	30.1 (32.5)		
Change from baseline, mg/L, LS mean (SE)	33.7 (10.9)	34.1 (10.8)			27.9 (7.77)	31.6 (7.43)		
Difference between groups, mg/L, LS mean (SE)	-0.374 (5.38)				-3.69 (3.88)			
NLR			-0.206, 1.067	0.184			-0.509, 0.646	0.814
Baseline, mean (SD)	2.17 (1.18)	2.36 (1.41)			1.95 (0.939)	2.23 (1.33)		
9±3 days post-surgery, mean (SD)	4.03 (3.79)	3.83 (2.33)			3.38 (2.58)	3.56 (2.10)		
Change from baseline, LS mean (SE)	1.85 (0.663)	1.42 (0.648)			1.75 (0.584)	1.68 (0.551)		
Difference between groups, LS mean (SE)	0.430 (0.323)				0.069 (0.293)			

FAS: full analysis set; PPS: per protocol set; LS: least squares; SE: standard error; SD: standard deviation; CI: confidence interval; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; ECOG PS: eastern cooperative oncology group performance status.

Table 3. Other efficacy outcomes (cont.)

Outcomes	FAS				PPS			
	FSMP group (n=162)	Control group (n=163)	95%CI	*p* value	FSMP group (n=100)	Control group (n=100)	95%CI	*p* value
Blood glucose			-0.28, 0.53	0.539			-0.18, 0.42	0.436
Baseline, mmol/L, mean (SD)	5.37 (1.15)	5.23 (0.81)			5.39 (1.31)	5.27 (0.82)		
9±3 days post-surgery, mmol/L,mean (SD)	6.15 (1.98)	5.96 (1.74)			5.87 (1.45)	5.65 (1.06)		
Change from baseline, mmol/L,LS mean (SE)	1.04 (0.421)	0.91 (0.412)			0.49 (0.307)	0.37 (0.290)		
Difference between groups, mmol/L,LS mean (SE)	0.13 (0.205)				0.12 (0.153)			
Triglycerides			-0.187, 0.008	0.071			-0.239, -0.027	0.014
Baseline, mmol/L, mean (SD)	1.60 (1.14)	1.61 (1.13)			1.51 (1.00)	1.58 (0.754)		
9±3 days post-surgery, mmol/L,mean (SD)	1.28 (0.537)	1.37 (0.509)			1.25 (0.500)	1.39 (0.467)		
Change from baseline, mmol/L,LS mean (SE)	-0.287 (0.101)	-0.197 (0.099)			-0.337 (0.114)	-0.205 (0.108)		
Difference between groups, mmol/L,LS mean (SE)	-0.090 (0.050)				-0.133 (0.054)			
Total cholesterol			-0.257, 0.046	0.173			-0.330, 0.010	0.065
Baseline, mmol/L, mean (SD)	4.66 (0.985)	4.67 (0.933)			4.68 (0.976)	4.71 (0.870)		
9±3 days post-surgery, mmol/L,mean (SD)	4.09 (0.874)	4.21 (0.892)			4.15 (0.885)	4.31 (0.781)		
Change from baseline, mmol/L,LS mean (SE)	-0.552 (0.157)	-0.447 (0.154)			-0.528 (0.183)	-0.368 (0.173)		
Difference between groups, mmol/L,LS mean (SE)	-0.105 (0.077)				-0.160 (0.086)			
Length of hospital stay				0.057				0.286
Days, mean (SD)	16.8 (6.37)	18.9 (9.60)			16.7 (6.47)	18.0 (9.24)		
ECOG PS								
Baseline, n (%)				0.392				0.390
0	139 (85.8)	145 (89.0)			95 (95.0)	92 (92.0)		
1	23 (14.2)	18 (11.0)			5 (5.0)	8 (8.0)		
9±3 days post-surgery, n (%)				0.524				>0.999
0	106 (65.4)	106 (65.0)			76 (76.0)	75 (75.0)		
1	40 (24.7)	40 (24.5)			22 (22.0)	22 (22.0)		
2	7 (4.3)	6 (3.7)			2 (2.0)	2 (2.0)		
3	1 (0.6)	5 (3.1)			0	1 (1.0)		
4	0	1 (0.6)			0	0		
missing	8 (4.9)	5 (3.1)			0	0		

FAS: full analysis set; PPS: per protocol set; LS: least squares; SE: standard error; SD: standard deviation; CI: confidence interval; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; ECOG PS: eastern cooperative oncology group performance status.

Table 3. Other efficacy outcomes (cont.)

Outcomes	FAS				PPS			
	FSMP group (n=162)	Control group (n=163)	95%CI	*p* value	FSMP group (n=100)	Control group (n=100)	95%CI	*p* value
Grip strength			-2.22, 0.62	0.267			-2.61, 1.05	0.401
Baseline, kg, mean (SD)	32.2 (10.5)	31.9 (10.7)			32.0 (11.2)	33.1 (11.6)		
9±3 days post-surgery, kg, mean (SD)	29.3 (9.78)	30.0 (9.92)			29.0 (9.57)	30.6 (10.2)		
Change from baseline, kg, LS mean (SE)	-2.67 (1.47)	-1.87 (1.44)			-3.95 (1.86)	-3.17 (1.76)		
Difference between groups, kg, LS mean (SE)	-0.80 (0.720)				-0.78 (0.926)			
Compliance ≥75%				0.562			-	-
n (%)	135 (83.3)	129 (79.1)			-	-		

FAS: full analysis set; PPS: per protocol set; LS: least squares; SE: standard error; SD: standard deviation; CI: confidence interval; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; ECOG PS: eastern cooperative oncology group performance status.

Table 4. Treatment-emergent adverse events (TEAEs) with incidence greater than 3% in any group

Events, n (%)	FSMP group (n=162)	Control group (n=163)
Abdominal distension	28 (17.3)	30 (18.4)
Diarrhea	34 (21.0)	18 (11.0)
Nausea	11 (6.8)	9 (5.5)
Abdominal pain	7 (4.3)	8 (4.9)
Vomiting	8 (4.9)	4 (2.5)
Hypoproteinemia	7 (4.3)	7 (4.3)
Hypoalbuminemia	7 (4.3)	6 (3.7)
C-reactive protein increased	7 (4.3)	15 (9.2)
Neutrophil count increased	7 (4.3)	6 (3.7)
WBC counts increased	6 (3.7)	6 (3.7)
ALT increased	5 (3.1)	6 (3.7)
AST increased	3 (1.9)	5 (3.1)
Pneumonia	7 (4.3)	2 (1.2)
Abdominal infection	1 (0.6)	5 (3.1)
Cough	10 (6.2)	8 (4.9)
Anaemia	8 (4.9)	11 (6.7)
Pyrexia	6 (3.7)	16 (9.8)
Anastomotic leak	4 (2.5)	10 (6.1)
Incision site pain	7 (4.3)	2 (1.2)
Insomnia	6 (3.7)	13 (8.0)
Hepatic function abnormal	3 (1.9)	7 (4.3)

TEAE: treatment-emergent adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; WBC: white blood cell.

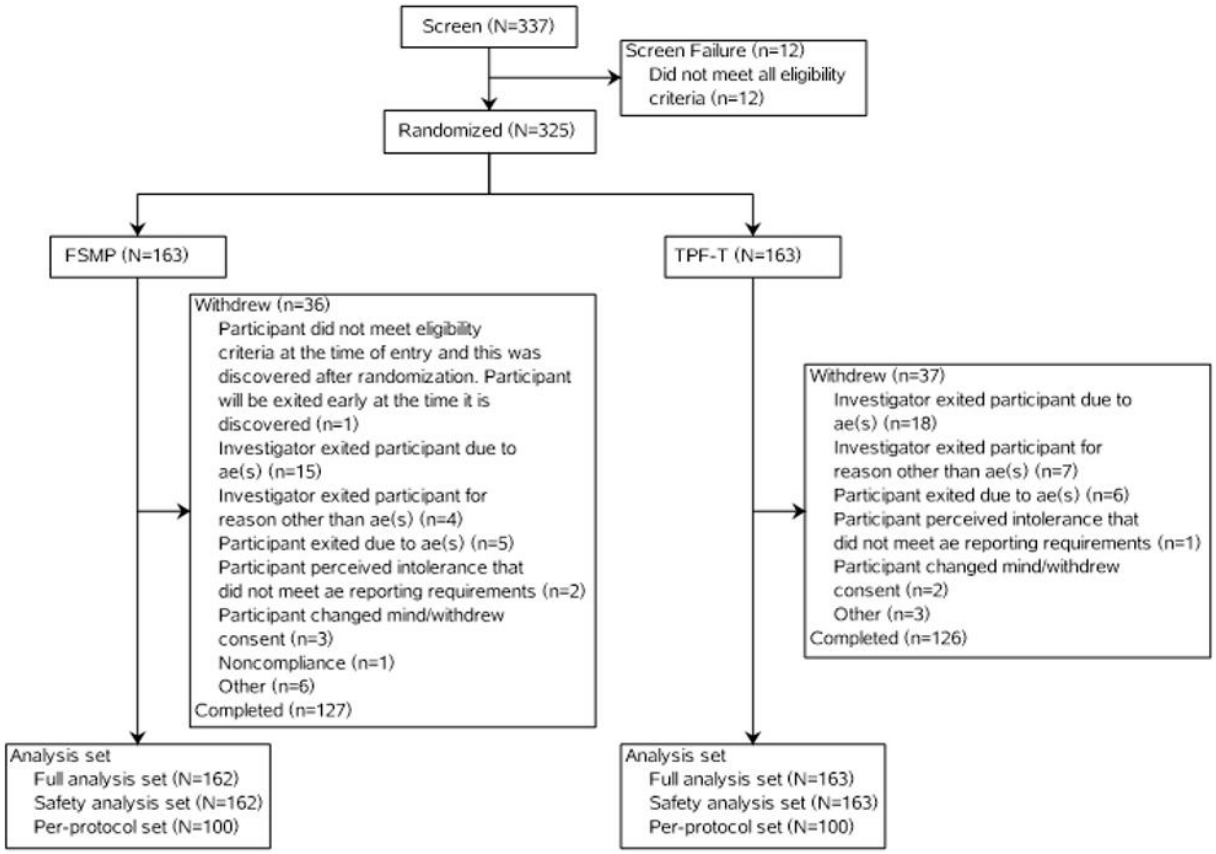

Figure 1. Patient flowchart.