


BMJ Open Effects of oral immunonutritional supplement on 3-year disease-free survival in gastric cancer patients with pathological stage III after total gastrectomy (CRUCIAL): study protocol of a multicentre, randomised clinical trial

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ABSTRACT

Introduction The nutritional status of patients with gastric cancer (GC) after total gastrectomy continues to deteriorate and lasts a long time after discharge, which is an independent risk factor for mortality. Recent guidelines have recommended appropriate nutritional support after discharge for cancer surgery patients with malnutrition or nutritional risk. The evidence on the efficacy of oral immunonutritional supplement (INS) and its effect on long-term disease-free survival (DFS) in patients with GC is limited. This study was designed to test the hypothesis that oral INS compared to diet alone may improve 3-year DFS of GC patients with pathological stage III after total gastrectomy (Nutrition Risk Screening 2002 score ≥ 3 at discharge).

Methods and analysis This is a pragmatic, open-label, multicentre, randomised controlled study. 696 eligible GC patients with pathological stage III after total gastrectomy will be randomised in a 1:1 ratio to oral INS group or normal diet group for 6 months. The primary endpoint is 3-year DFS after discharge. The following secondary endpoints will be evaluated: 3-year overall survival; unplanned readmission rate at 3 and 6 months after discharge; quality of life, body mass index and haematological index at 3, 6 and 12 months after discharge; incidence of sarcopenia at 6 and 12 months after discharge; and the tolerance to chemotherapy. The adverse events of oral INS will also be evaluated during the intervention.

Ethics and dissemination This study was approved by the ethics committee of Jinling Hospital, Nanjing University (number 2021NZKY-069-01). The present study may validate the effectiveness of oral immunonutritional therapy in improving 3-year DFS for GC patients with pathological stage III after total gastrectomy for the first time. The results of this trial will be disseminated in peer-reviewed journals and at scientific conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a pragmatic, open-label, multicentre, randomised controlled trial providing high quality clinical evidence concerning the efficacy and safety of oral immunonutritional supplement (INS) for gastric cancer (GC) patients with pathological stage III after total gastrectomy.
- ⇒ The data will be handled by an Independent Data Monitoring Committee to ensure the safety of the participants. Oral INS is a well-studied method with a favourable safety profile in previous trials.
- ⇒ This is the first study to evaluate the effect of oral immunonutrition supplementation on long-term disease-free survival in patients with GC after discharge.
- ⇒ Longer survival or recurrence status is not assessed in this study.

Trial registration number NCT05253716.

INTRODUCTION

Malnutrition is common in patients with gastric cancer (GC). It increases postoperative complications, length of stay and cost of treatment and weakens the effect of chemotherapy and quality of life (QoL), as well as shortens long-term survival.¹⁻⁴ In addition to preoperative malnutrition, which most studies are concerned about, the nutritional status after radical gastrectomy will also continue to deteriorate for nearly 1 year; the rate of malnutrition was approximately 30%–50%.^{1 5 6} Due to postoperative

chemotherapy and several other risk factors, including reduced nutritional intake and malabsorption, continuous weight loss, and sarcopenia (an important phenotype of malnutrition) caused by progressive loss of skeletal muscle mass with decreased physical activity persists long after radical gastrectomy.^{7 8} These conditions are more common and severe in patients with pathological stage III GC or after total gastrectomy: the proportion of skeletal muscle loss of $\geq 5\%$ 6 months after surgery has been reported to be up to 51% and 55.4%, respectively.^{9 10} Patients with GC who exhibited $\geq 5\%$ skeletal muscle loss have shown lower 5-year disease-free survival (DFS) rates (33.8% vs 46.2%; $p=0.020$).¹⁰ Moreover, postoperative sarcopenia may persist for approximately 1 year and is significantly related to worse 5-year overall survival (OS) in GC.¹¹ Therefore, reinforced nutritional support should be offered to this patient population, and more attention should be provided.

The most recent guideline recommends appropriate postdischarge nutritional support for surgical cancer patients with nutritional risks or those who are already malnourished, and several guidelines have recommended oral nutritional supplement (ONS) as the preferred approach.^{12 13} The limited available evidence suggests that consecutive ONS for 3 months postdischarge has a positive effect on maintaining weight, reduces the risk of sarcopenia and improves chemotherapy tolerance for GC after surgery.^{14 15} Although ONS can effectively prolong median OS for metastatic GCs,¹⁶ its effect on survival outcomes of GC patients with pathological stage III after total gastrectomy remains unclear. Omega-3 polyunsaturated fatty acids (ω -3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) are commonly used as nutrients for immunity. Ryan *et al* found that enteral nutrition enriched with 2.2 g of EPA/day can maintain skeletal muscle mass after esophagectomy.¹⁷ Furthermore, recent preclinical studies have shown that ω -3 PUFAs can also inhibit GC-related cell growth and metastasis.^{18–20} However, to our knowledge, studies on DFS after oral immunonutritional supplement (INS) after surgery for advanced GC are lacking.

The objective of this pragmatic, multicentre, randomised clinical trial is to evaluate the efficacy of the postoperative oral INS for 6 months and its effect on 3-year DFS, 3-year OS, weight maintenance, sarcopenia, QoL, chemotherapy tolerance and unplanned readmission of GC patients with pathological stage III after total gastrectomy. We hypothesise that oral INS will have significantly more benefits than diet alone for the above patients with nutritional risk at discharge.

METHODS AND ANALYSIS

Standard protocol approval, registration and patient consent

This study will be conducted in accordance with good clinical practice and ethical standards set out in the Declaration of Helsinki of 1964 and its subsequent amendments. The study protocol (version 2.0) was approved by the

Ethics Committee of Jinling Hospital (Nanjing, China; 17 December 2021; approval number 2021NZKY-069-01). The medical personnel of the participating institutions will obtain written informed consent from all the patients enrolled in the study, and clarify that they can withdraw at any time without providing a reason and without any effect on their current or future care. The translated patient consent form is available in online supplemental file 1.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Design and randomisation

This study is initiated by the investigator and will be designed as a pragmatic, multicentre, open-label, randomised and controlled clinical trial. Eligible patients will be randomly assigned to the INS or control group (C) using a 1:1 ratio. Centralised permuted block randomisation will be implemented using the mobile client-based *Randomization Allocation Tool* (RAT),²¹ with stratification by trial centre (13 tertiary general hospitals in China), pathological stage of TNM (IIIA or IIIB or IIIC) and Laurén classification (intestinal type or not). If a participant is qualified for the trial and has signed the written informed consent, the investigator authorised by each centre can input the relevant information into the RAT. The assigned group will be immediately fed back to the interface on the mobile client of the investigator. Participants will accept the specified treatment.

Subjects

Prior to surgery, the principal investigator at each study centre will be responsible for recruiting subjects. Patients will be enrolled in the study when they volunteer and meet the following criteria: consecutive adults (18 years of age or more) patients with GC who have undergone radical total gastrectomy with pathological TNM stage III and Nutrition Risk Screening 2002 (NRS2002) score of ≥ 3 and the Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 at discharge. Patients will be excluded for the following: inability to oral or consume ONS; previous receipt of neoadjuvant chemotherapy; pregnancy; palliative surgery or gastric stump cancer or Borrmann type IV; inability to discontinue oral anticoagulants; AIDS (HIV positive or $CD4 < 200/mm^3$); severe cardiovascular disease that includes chronic heart failure, angina pectoris, myocardial infarction, arrhythmias (such as atrial fibrillation) or uncontrolled hypertension; severe liver and kidney diseases including active hepatitis, cirrhosis and uraemia; diabetes with complications or uncontrolled by medications; previous use of fish oil capsule > 2 times/week; contraindications for fish oil capsule; incomplete grip strength measurement and 5-time chair stand test; and previous enrolment in other studies within the same hospital admission.

Discharge criteria

The discharge criteria are similar for the two groups. They include the ability to mobilise and self-care; oral tolerance of semi-liquid food; tube feeding is not required; and no complications requiring hospital treatment. The patient can be discharged when they meet these criteria, and the time of discharge will be recorded.²²

Assessments

General demographic (gender, age and body mass index (BMI)) and clinical data, including the American Society of Anesthesiologists score, the Charlson Comorbidity Index, surgical methods (laparoscopy and laparotomy), pathological stage of TNM (IIIA, IIIB and IIIC), Laurén classification (intestinal and non-intestinal type), and tumour size and location will be collected before discharge after radical gastrectomy. The pathological terms and classification used in this study are compiled using the eighth edition of the American Joint Committee on Cancer staging system.²³ In addition to the NRS2002 (score range from 0 to 7, 3 or higher are considered nutritional risk) and ECOG (the performance status was classified into 0–5 grades: 0=asymptomatic, 1=symptomatic but completely ambulatory, 2=ambulatory and capable of all self-care, 3 or 4=generally considered unsuitable for chemotherapy) scores acquired at discharge, the following indicators will be evaluated.

Sarcopenia

Sarcopenia is diagnosed as low skeletal muscle mass plus low skeletal muscle strength or low physical performance, according to the criteria of the Asian Working Group for Sarcopenia 2019 criteria.²⁴ Abdominal CT images will be selected to calculate the skeletal muscle index of the third lumbar spine (L3MI). Low skeletal muscle mass is defined as $L3MI < 40.8 \text{ cm}^2/\text{m}^2$ for men and $L3MI < 34.9 \text{ cm}^2/\text{m}^2$ for women, according to our previously published study.²⁵ Patients will hold the dynamometer (EH101, China) with maximum force in the dominant hand, and the experiment will be carried out three consecutive times. The maximum value measured after each interval of 1 min is grip strength²⁶; low skeletal muscle strength is defined as grip strength $< 28.0 \text{ kg}$ for men and grip strength $< 18.0 \text{ kg}$ for women. Physical performance will be assessed using a 5-time chair stand test; low physical performance will be defined as a 5-time chair stand test result of $\geq 12 \text{ s}$. Sarcopenia will be assessed preoperatively and 6 and 12 months after discharge.

Anthropometric indicators

Body weight and BMI, calculated as weight (kg)/height (m^2), will be collected at discharge and 3, 6 and 12 months after discharge.

Haematological indicators

Haematological indicators including albumin, prealbumin and haemoglobin will be assessed at discharge and 3, 6 and 12 months after discharge.

Quality of life

QoL will be assessed at discharge and 3, 6 and 12 months after discharge using the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30). The EORTC QLQ-C30 questionnaire consists of 30 items, which can evaluate QoL from a multidimensional perspective and better reflect the connotation of QoL for patients with cancer.²⁷

ω -3 PUFA intake for the diet

The Food Frequency Questionnaire (FFQ) will be developed to assess the dietary intake of ω -3 PUFAs to rule out its influence on the trial results. FFQ will be completed at baseline, the third month of the intervention and the end of the intervention.

Toxicity and tolerability of chemotherapy

Chemotherapy toxicity will be monitored at the end of each cycle during chemotherapy by the investigators and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). In addition, chemotherapy intolerance (defined as the presence of reduction, delay or termination) will be assessed and documented.²⁸

Tumour recurrence assessments

A minimum follow-up for tumour recurrence assessments of 36 months will be required for each patient. They will include (1) CT or MRI of the chest and abdomen repeated every 6 months for 3 years; (2) tumour marker assessments, including carcinoembryonic antigen and carbohydrate antigen 19-9, assessed at the same frequency as CT or MRI; and (3) mandatory annual endoscopy during follow-up.

Adverse complications and events

All adverse complications and events attributed to interventions (gastrointestinal side effects, such as nausea, vomiting, diarrhoea, abdominal pain, abdominal distention and constipation), including unplanned hospitalisations, will be recorded.

ω -3 PUFA measurement

The red blood cells (RBCs) slurry will be obtained after centrifugation at 700g/min and 4°C for 10 min within 3 hours of extraction of 10 mL of venous blood with an EDTA anticoagulant tube during fasting at 07:00.^{29 30} The isolated RBCs will be stored at -80°C to determine the content of fatty acids (FA). We will measure FAs by liquid chromatography tandem mass spectrometry,³¹ and the data will be presented by measuring EPA and DHA as a percentage of the total FA content. Measurements will be taken before the intervention and at the end of the intervention.

A trained team that includes a gastrointestinal surgeon, an oncologist, a dietitian and an oncology specialty nurse at each research centre will evaluate all of these indicators.

Table 1 Nutrient contents of the iVital Energy

Items	100mL	NRV%
Energy, kcal	150	7
Proteins (%)	27	–
Carbohydrates (%)	34	–
Fats (%)	39	–
Proteins, g	10	17
Fats, g	6.7	11
Saturated fatty acid, g	0.6	–
Monounsaturated fatty acid, g	4.9	–
Polyunsaturated fatty acids, g	1.2	–
Carbohydrates, g	12.4	4
Vit A, µg	81	10
Vit D, µg	2.5	50
Vit E, mg	3.75	27
Vit B ₁ , mg	0.14	10
Vit B ₆ , mg	0.13	9
Vit C, mg	18.8	19
Sodium, mg	55	3
Phosphorus, mg	120	17
Potassium, mg	130	7
Magnesium, mg	14	5
Calcium, mg	205	26
Iron, mg	1.8	12
Zinc, mg	2	13
Selenium, µg	13.5	27

NRV, nutrient reference values.

Treatment

A team of experienced surgeons who have performed at least 50 GC surgeries in the last calendar year will perform GC surgery in each participating centre. Total gastrectomy and standard D2 lymph node dissection will be performed, and more than 15 lymph nodes will be dissected. All patients will receive nutritional counselling at discharge and at the beginning of each cycle of adjuvant chemotherapy.

All enrolled patients will be randomised into two groups within 24 hours before discharge: (1) INS group and (2) C group. In the INS group, patients will consume two bottles per day of a high-calorie, high-protein ONS (iVital Energy (vanilla, 200mL per bottle, 1.5 kcal per mL), Fresenius Kabi, Germany) and three capsules of marine fish oil (webber naturals (1.425g of fish oil per capsule, containing 0.6g of EPA and 0.3g of DHA), Canada) per day after discharge for 6 months, in addition to diet. In the C group, patients will receive nutritional counselling and dietary modifications; the intake of protein-rich foods will increase. ONS will also be considered when a dietitian evaluates the medical needs of a patient.

The detailed composition of iVital Energy is provided in [table 1](#). The number of supplements consumed will be counted daily. The researchers will monitor compliance by telephone every week and check the records at each follow-up. In addition, participants will be asked to bring back the remaining iVital Energy and fish oil capsules at each follow-up visit for counting to measure compliance. Any gastrointestinal side effects will also be recorded to determine the safety of ONS and fish oil consumption.

Anticancer treatments

Patients will receive 6–8 cycles of fluorouracil-based adjuvant chemotherapy from 3 to 4 weeks after discharge. Oncologists will decide on a specific treatment regimen (fluorouracil combined with platinum, fluorouracil combined with paclitaxel or fluorouracil combined with platinum and paclitaxel) and duration of treatment.

Endpoints

The primary endpoint will be a 3-year DFS postdischarge after radical gastrectomy. DFS is defined as the time from randomisation to tumour recurrence of primary cancer, new GC, distant metastases or death from any cause, whichever comes first.³²

The following secondary endpoints will also be evaluated: 3-year OS; unplanned readmission rate (one or more) at 3 and 6 months after discharge; QoL (EORTC QLQ-C30 score), weight, BMI and haematological index at 3, 6 and 12 months after discharge; incidence of sarcopenia at 6 and 12 months after discharge; and the tolerance to chemotherapy.

The safety of ONS and the fish oil capsule will be evaluated during the intervention by monitoring vital signs (heart rate, pulse, blood pressure, respiration rate) and the incidence of gastrointestinal side effects, as mentioned above.

[Table 2](#) provides a summary of the assessments and related endpoints that will be investigated during the study. The flowchart of the CRUCIAL (effects of oral immunonutritional supplement on 3-year disease-free survival in gastric cancer patients with pathologic stage III after total gastrectomy) trial is shown in [figure 1](#).

Benefit for participants

All patients will receive an early nutritional assessment and counselling. The nutritional status of the patients will be regularly monitored. Medical interventions will be provided for any adverse effects during nutritional support.

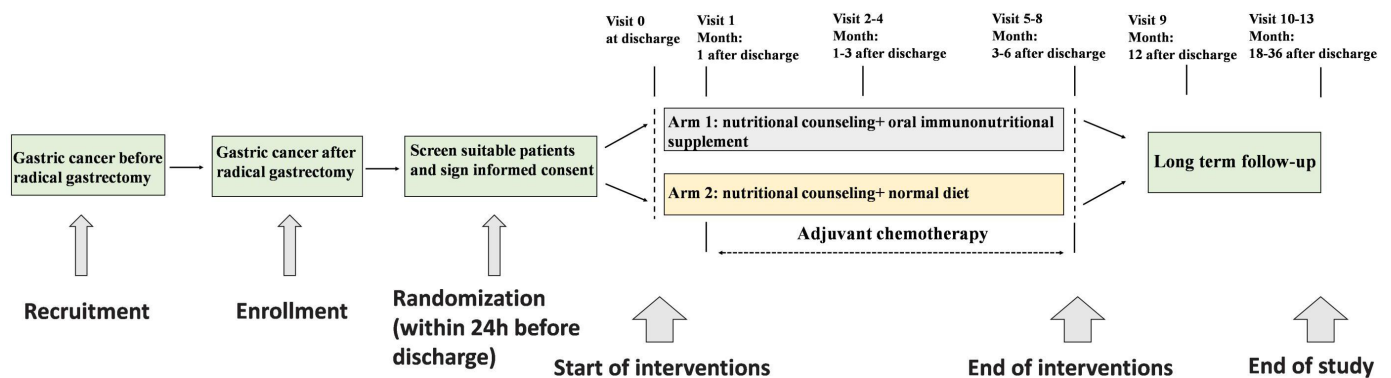
Potential risks and burdens for research participants

ONS and fish oil capsules may cause discomfort or expose patients to an increased risk of gastrointestinal intolerance, which will be recorded and promptly provided medical treatment. The ONS product in this study is vanilla, which is internationally well accepted and tolerated, as reported in previous studies.³³ As indicated in the ESPEN guidelines in 2016, fish oil and ω-3 FA were mainly well tolerated.³⁴ Furthermore, the combined dose of the

Table 2 Summary of scheduled assessment and follow-up during the study

	Visit 0	Visit 1–8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Evaluations	Discharge	Month: 0–6 after discharge	Month: 12 after discharge	Month: 18 after discharge	Month: 24 after discharge	Month: 30 after discharge	Month: 36 after discharge
Informed consent	X						
Inclusion/exclusion criteria	X						
Randomisation	X						
Demographic data	X						
Clinical data	X						
Blood sample	X	X					
BMI	X	X	X				
Sarcopenia	X	X	X				
Haematological indicators	X	X	X				
QoL (EORTC QLQ-C30)	X	X	X				
ω -3 PUFAs intakes in diet	X	X					
Chemotherapy tolerance		X					
Chemotherapy toxicity		X					
Adherence to interventions		X					
Adverse events		X					
Unplanned readmission		X					
CT or MRI		X	X	X	X	X	X
Tumour markers		X	X	X	X	X	X
Endoscopy			X		X		X
DFS							X
OS							X

BMI, body mass index; DFS, disease-free survival; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life questionnaire; OS, overall survival; QoL, quality of life.


Figure 1 Flowchart of the CRUCIAL (effects of oral immunonutritional supplement on 3-year disease-free survival in gastric cancer patients with pathologic stage III after total gastrectomy) trial.

EPA and DHA supplement was up to 5g/day, which did not increase the risk of spontaneous bleeding episodes or bleeding complications.³⁵ Therefore, there are no safety concerns for adults regarding the dose of fish oil in this study.

Statistical methods

Sample size

The sample size was calculated according to the primary endpoint using PASS V.15.0 software (NCSS, Kaysville, Utah, USA). Based on relevant data available in the previous literature, the 3-year DFS after total gastrectomy for stage III GC was 36.2%.³⁶ Assuming this type of patient received only nutritional counselling in the control group, the 3-year DFS was similar, that is, 36%. Taking into account a study power of 80%, an alpha error level at two tails of 5%, and an expected 3-year DFS of 46% in the INS group, 696 patients (348 in each group) will have to be enrolled to allow for a dropout rate of 5% or withdrawal.

Statistical analyses

Analyses of primary and secondary endpoints will be based on the intention-to-treat principle. Survival curves will be estimated using the Kaplan-Meier method and compared with the results of log-rank tests in time-to-event analyses. The HRs and 95% CIs will be derived using Cox proportional hazards models. For the primary endpoint of the 3-year DFS, an additional prespecified analysis of the multivariate Cox proportional hazards model will be used to evaluate the consistency of the group effect. This model will account for clinically important baseline characteristics, including trial centre, age, sex, Laurén type, sarcopenia, N stage, T stage and TNM (Tumor-Node-Metastasis) stage. The proportional hazards assumption will be evaluated using scaled Schoenfeld residuals. Prespecified subgroup analyses will include age (≥ 65 vs < 65 years old), sex (men vs women), Laurén type (intestinal type vs non-intestinal type), sarcopenia (yes vs no), N stage (N0 vs N1 vs N2 vs N3), T stage (T1 vs T2 vs T3 vs T4) and TNM stage (IIIA vs IIIB vs IIIC). Cox proportional hazards models with additional interaction variables of the subgroup and group factors will be constructed to estimate the p values of interactions in these subgroup analyses.

The normality of the continuous variable will be assessed using the Shapiro-Wilk test. Continuous variables will be presented as means with SD or medians with IQRs, and categorical variables will be shown as frequencies and percentages. The Student's t-test will be used for the analysis of continuous variables of normal distribution, and Wilcoxon rank-sum test will be used for the analyses of continuous non-normal distribution or ranking data. The χ^2 test or Fisher's exact test will be used for the analyses of categorical variables.

For the superiority assessment of the primary endpoint of the 3-year DFS, a two-sided p value of less than 0.05 will be considered statistical significance. Due to the potential

for type I error due to multiplicity, any other inferences drawn from p values, or 95% CIs will not be reproducible and should be interpreted as exploratory.

All statistical analyses will be performed using SAS software, V.9.4 (SAS Institute) by independent statisticians masked in the allocation of the treatment group.

Study administration

The Clinical Endpoint Committee (CEC) is an independent group of five experts that includes one pathologist, two radiologists and two clinical specialists. Recurrence of the primary endpoint will be assessed by the CEC, who are masked from the treatment assignment, based on medical history and physical examination combined with imaging evaluation, cytology or tissue biopsy findings.

Recruiting process

The trial was registered on 24 February 2022. The first patient was randomised on 1 August 2022. So far, 76 patients had been randomised, and the enrolment keeps to the flowchart.

Data management

The investigators are responsible for the accuracy and timely entry of the data into the electronic case report form (eCRF) according to the study protocol. The study monitor will review the eCRFs and other study documents, and verify the primary data. The final confirmed data set will be locked and analysed by the trial statistician. In principle, the data set locking cannot be modified. The investigators must keep research documents for a specified period by the regulatory requirements.

ETHICAL AND DISSEMINATION

This study was approved by the ethics committee of Jinling Hospital. We will not begin recruiting at other participating centres of the trial until the local ethics committee approves the study. Site ethical approvals were obtained from ethics committees of the First Affiliated Hospital of Nanjing Medical University, the Second Affiliated Hospital of Nanjing Medical University, the Affiliated Cancer Hospital of Nanjing Medical University, Nanjing Jiangning Hospital, Zhenjiang First People's Hospital, The Third Affiliated Hospital of Soochow University, Changzhou Second Hospital, The First Affiliated Hospital of Soochow University, The Second Affiliated Hospital of Soochow University, The Affiliated Wuxi People's Hospital of Nanjing Medical University and Yixing People's Hospital. The results of the study will be presented at national and international medical meetings. Meanwhile, the results will be published in prestigious peer-reviewed medical journals.

DISCUSSION

Malnutrition can occur at any stage during the development, progression and treatment of GC.³⁷ After surgical resection of the tumour, the incidence of malnutrition is

30%–50% after discharge, which is still common.⁶ Malnutrition is more pronounced in patients with pathological stage III GC or after total gastrectomy,^{1 38 39} which will significantly shorten long-term survival.^{40 41} A previous randomised controlled trial has demonstrated nutritional support was a feasible approach to increase the median OS of patients with stage IV GC from 11.9 to 14.8 months.¹⁶ However, oral INS after discharge is mostly concentrated in nutritional status or inflammatory response in patients with advanced GC,⁴² and lacks high-quality evidence on long-term DFS and OS, which still requires confirmation.

The ONS is the preferred form of nutritional support for energy and nutrients for specific medical purposes.⁴³ A previous multicentre randomised controlled trial had demonstrated high tolerability and compliance with long-term oral ONS after GC surgery.⁴⁴ Several studies have found that ONS can reduce the incidence of sarcopenia, improve some parameters of QoL, improve chemotherapy tolerance¹⁵ and delay weight loss after total gastrectomy.^{45 46} However, the duration of ONS is usually shorter (6–12 weeks), resulting in a difference in weight maintenance and gradual decline after 6 months that is insignificant 1 year after surgery compared with the results of the standard diet.¹⁴ This study will ensure that long-term nutritional support (6 months) is provided to patients with a nutritional risk assigned to the INS group after discharge, and improve nutritional status and QoL for 12 months after surgery.

Omega-3 PUFAs, as immunological nutrients, do not only prevent cardiovascular events⁴⁷; they fight sarcopenia by reducing insulin resistance, improving mitochondrial function, inhibiting the inflammatory response and activating the mTOR pathway.¹⁸ Smith *et al* confirmed that oral administration of fish oil (1.86 g/day EPA+1.5 g/day DHA) for 6 months delayed the loss of muscle mass and function, and prevented sarcopenia in healthy older adults without severe adverse events related to ω -3 PUFA.⁴⁸ Preclinical studies have confirmed that ω -3 PUFAs can inhibit GC progress by inducing apoptosis of GC cells in various ways.^{19 20 49 50} In addition, a randomised controlled trial has shown that 2 g/day ω -3 PUFAs during neoadjuvant chemotherapy can improve the pathological response rate and the subsequent R0 resection rate.⁵¹ Moreover, ω -3 PUFAs also play a synergistic role with cisplatin to enhance its inhibitory effect on GC.⁵² In this study, the nutrition and antitumour recurrence effects of ω -3 PUFAs can be fully played under the premise of ensuring safety.

Several studies have attempted to determine whether nutritional support can improve long-term survival for patients with GC after discharge. A nationwide cohort study (n=1771, including 218 gastric patients) in France did not show significant improvement in OS (mean follow-up of 33±20 months, p=0.19) after 45 days of oral immunonutrition before digestive oncological surgery relative to a normal diet.⁵³ During the postoperative period, a small prospective controlled randomised study (n=98) found that enteral immunonutrition (including

arginine, glutamines and ω -3 PUFAs) continued for 6 days in patients with GC did not significantly prolong 6-month (p=0.24) OS and 1-year OS (p=0.83) compared with conventional enteral nutrition.⁵⁴ The beneficial effects of immune modulated enteral nutrition were too weak to be significant in these patients because malnourished patients (population who needed nutritional support) were excluded. However, in a randomised controlled trial involving 99 patients with GC treated with enteral nutrition, postoperative enteral immunonutrition lasting 7 days had a positive effect on 6-month OS (HR=0.25, p=0.049) only in malnourished stage IV GC patients.⁵⁵ The three studies did not demonstrate that nutritional support had a positive effect on long-term survival of advanced GC, due to the exclusion of appropriate patients and the short duration of intervention. More importantly, the primary outcome did not involve DFS. In the present study, we expect that ONS combined with ω -3 PUFAs will reduce postoperative recurrence, improve long-term DFS and OS by reducing sarcopenia, and improve tolerance and efficacy of chemotherapy.

To our knowledge, this is the first study to investigate the efficacy of oral INS, based on 3-year DFS, 3-year OS, 1-year nutritional status and QoL, in a population of specific GCs, with the expectation of developing new therapeutic strategies to improve the efficacy of anticancer therapy. At the same time, compared with previous studies, patients will be able to receive oral INS/nutritional counselling longer after discharge to cope with the postoperative chemotherapy in this study. Furthermore, although iVital Energy and fish oil capsules are taken separately, they provide more ω -3 PUFAs than other immunonutritional preparations, potentially providing more benefit to patients. However, there are some limitations to this study. First, patients receiving preoperative chemotherapy before gastrectomy will be excluded from this study, excluding these patients will reduce the 'generalisability' and applicability of the study findings to Western patients. Second, the results of this study may not apply to all patients with GC. Finally, longer survival or recurrence status is not assessed in this study.

In conclusion, the positive results of this multicentre clinical trial will further stimulate larger international randomised trials, which can improve the quality of supportive care for patients with cancer and increase access to patients who may benefit from nutritional support in the nonsurgical oncological setting.

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Contributors During the study, DZ and YL contributed equally as first authors. DZ, YL, LZ, XG and XW developed the study concept and drafted the manuscript. DZ, ML and YL are responsible for the randomisation of patients. DZ, XX, HX, GangL, KY, JZuo, YugangW, JQ, JZhou, KD, YongW, ZT, CJ, WW, ZS and GuoliL are responsible for recruiting, managing the treatment of the patients and collecting data. All authors have read and approved of the final manuscript.

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