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Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors: protocol for a single-center randomised controlled trial

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Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors: protocol for a single-center randomised controlled trial

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ABSTRACT

Introduction

Postoperative pancreatic fistula (POPF) remains one of the main complications following pancreatic resection. Despite the low postoperative mortality caused by pancreatic fistula, the readmission and intervention rates in patients with pancreatic fistula are still considerable. At present, there have been abundant studies on pancreatic fistula after pancreaticoduodenectomy, but few studies on feeding protocol after distal pancreatectomy or enucleation of pancreatic tumors. We designed this trial to test the hypothesis that early feeding does not increase the incidence of postoperative pancreatic fistula and has a better influence on the long-term prognosis in patients who undergo distal pancreatectomy or enucleation.

Methods and analysis

This is a prospective randomised controlled trial conducted in a single center. A total of 106 patients undergoing distal pancreatectomy or enucleation of pancreatic tumors will be recruited with informed consent. They are randomly assigned to either an early or a late feeding group. In the early feeding group, each included patient begins oral feeding on postoperative day (POD) 3, and in the late feeding group, patients begin oral feeding on the POD7. The primary outcome is the incidence of clinically relevant postoperative pancreatic fistula (CR-POPF). Secondary outcomes include the length of postoperative hospital stay, readmission rate, postoperative complications and indicators of long-term prognosis.

Ethics and dissemination

The research ethics committee of the Peking University Third Hospital approved the study (M2021395). Findings will be disseminated in a peer-reviewed journal and in national and/or international meetings to guide future practice.

Trial registration number ChiCTR2100053978

Strengths and limitations of this study

1. This study is the first randomised controlled trial to provide robust evidence comparing the two feeding regimens studied for management after distal pancreatectomy and enucleation of pancreatic tumors since ISGPS redefined and updated the classification of pancreatic fistula in 2016.
2. Due to practical reasons, the patients and the clinicians administering the treatment in the study can not be blinded to the assignment of the groups, although the principal investigator and clinicians conducting the follow-up evaluation are blinded.
3. The study included patients with different pancreatic tumor diagnoses and prognoses, which may have been too broad a choice.

INTRODUCTION

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. The International Study Group of Pancreatic Surgery (ISGPS) classifies POPF into three risk levels in 2005.[1] In 2016, ISGPF revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer included in the pancreatic fistula.[2] The definition of grade C pancreatic fistula is more strict. The occurrence of postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even death.[3-5]

Distal pancreatectomy and enucleation are the standard treatment for pancreatic body and tail tumors. Compared with pancreatoduodenectomy, although distal pancreatectomy and enucleation are less difficult, the reported incidence of clinically relevant pancreatic fistula remains at 6%-34% due to the anatomical characteristics of the pancreas and the physiological characteristics of the patient.[6] [7] Despite the low mortality caused by pancreatic fistula, there's still a considerable percentage of patients suffering from readmission and percutaneous drainage.[8-10]

For the prevention of pancreatic fistula after distal pancreatectomy and enucleation, there are still some controversies in intraoperative procedures, early postoperative nutritional support, the timing of drainage tube removal, and the use of somatostatin analogs. Since fasting is an essential condition for inhibiting pancreatic secretion in patients with postoperative pancreatic fistula, the necessity of "nil per os" (NPO) has been emphasized in the past.[10] However, long-term intravenous nutrition can cause dysbiosis and lead to metabolic adverse events.[11] It has been confirmed that early enteral nutrition helps maintain gastrointestinal integrity and immune capacity.[12] [13] Recently, American Gastroenterological Association (AGA) update the clinical practice in patients with pancreatic necrosis, this expert review recommended that enteral feeding should be initiated early to decrease the risk of infected necrosis. In patients without nausea, vomiting, and no signs of severe ileus, a trial of oral nutrition is recommended immediately.[14]

In recent years, with the continuous deepening of the concept of enhanced recovery after surgery (ERAS), an increasing number of novels have reported that enhanced recovery does not increase the incidence of postoperative pancreatic fistula and other complications, but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients.[15] [16] However, most of the previous studies focused on the pancreaticoduodenectomy[17-21] and only a small number of researches on distal pancreatectomy. [22] [23] Pecorelli et al. performed an observational case-control study to assess the feasibility and safety of enhanced recovery programme for laparoscopic distal pancreatectomy and to analyze its financial impact compared to traditional management.[6] But the key elements of enhanced recovery programmes include not only early oral feeding but also some other perioperative care. It can not prove directly whether early enteral nutrition plays a real role in accelerating recovery in these patients. In the study of Fujii et al., patients who developed POPF after distal pancreatectomy were randomly assigned to the dietary intake group or the no dietary intake group, and each group consisted of 15 patients.[24] Patients in the no dietary

intake group fasted until drain removal. In the dietary intake group, food intake was started on postoperative day (POD) 6. The final results showed that no significant differences were found in the length of drain placement, POPF-related intra-abdominal hemorrhage, other complications, or the length of postoperative hospital stay between the two groups.

Therefore, evidence regarding whether early oral intake can be tolerated in patients undergoing distal pancreatectomy or enucleation remains to be further explored from large randomised controlled trials.

MATERIALS AND METHODS

Study design and setting

This prospective randomised controlled trial is conducted at the Department of General Surgery, Peking University Third Hospital, Beijing, China. The Department of General Surgery offers conventional treatment and care to adult patients with liver, pancreas, biliary tract, gastrointestinal, thyroid, and breast diseases. Annually, the number of pancreatectomy can amount to 150.

Sample size estimation

In this study, the occurrence of clinically relevant postoperative pancreatic fistula (CR-POPF) is the main observation index. According to the previous literature,[7] the sample size is calculated by PASS software. The incidence of postoperative pancreatic fistula in the early feeding group and the late feeding group was 6.8% and 26.3%, respectively. With a type I error (α=0.05) and type II error (β=0.2), taking into account a dropout of 20%, 53 patients will be expected to be included in each group. Taken together, we will recruit a total of 106 patients for this trial.

Randomisation

Randomisation is performed after distal pancreatectomy and enucleation of pancreatic tumor. Researchers use a random number generator to generate a randomization scheme. According to the predetermined randomization scheme, eligible patients are randomised to 1:1 to either the early feeding group or the late feeding group.

Blinding

This is a non-blinded study. Because of the nature of the intervention, neither patients nor clinicians can be blinded to the allocation. The principal investigator and clinicians conducting the follow-up evaluation are not involved in the treatment of the patients and are blinded to the allocation. All statistical analyses will be performed blinded to group allocation.

Selection of subjects

Inclusion criteria include: (1) Patients who undergo open or minimally invasive distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, and enucleation of pancreatic tumor between December 2021 and June 2023; (2) The preoperative diagnosis is clear and surgical treatment is feasible; (3) No absolute surgical contraindications; (4) All patients and authorised surrogates should be informed about the risks and benefits of surgery, and sign the informed consent.

Exclusion criteria include: (1) Patients cannot tolerate surgery, such as with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency; (2) Poor compliance of patients and their

authorised surrogates; (3) Patients with combined gastrointestinal resection; (4) Enrolled in another trial.

Treatment procedures

After obtaining written informed consent, randomization is carried out as described above. For each included patient the following baseline characteristics will be collected: age, gender, height, weight, complication, preoperative laboratory or imaging examinations, and American Society of Anesthesiologists (ASA) classification (I-IV). Data on type of surgery (distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, and enucleation), type of surgical intervention (robot-assisted, laparoscopic, open), operative time, intraoperative blood loss, tumor localization, pancreas texture, pancreatic thickness, and diameter of the pancreatic duct.All patients included in the study will receive routine treatment regimens perioperatively, including inhibition of pancreatic secretion, acid inhibition, perioperative antibiotic, fluid therapy, and nutritional support during water deprivation and fasting. The patients in the early feeding group start oral feeding on POD3, and the patients in the late feeding group begin oral feeding on POD7. The patient's body temperature, pain scoring (visual analogue scale, VAS), ambulation, flatus and defecation, and dietary status will be recorded daily. The patient's nutritional status (BMI/PNI) is regularly monitored. The routine postoperative examination is arranged as follows: hemoglobin (Hb) concentration, white blood cell counts, serum amylase levels, amylase levels in drainage fluid, etc., and other laboratory or imaging examinations may be performed according to the needs of disease to assist in evaluating the position of the drainage tube.

Discharge criteria: no fever, abdominal pain, and distension; no need for surgery-related perioperative treatment; the patient has tolerated the solid food and can move normally; no signs of infection; independently mobile at the preoperative level. The wound is not suppurative, infected, or dehisced. Patients may discharge with or without the abdominal drainage tube.

Follow-up on complications, survival, and quality of life will be continued through outpatient visit, telephone, and other means every 3 months for the first year and then every 6 months. All patients are followed up for 3 years or until recurrence, metastasis, or death. The study pathway is illustrated in figure 1.

Outcome measures

The primary outcome measures:

The primary endpoint is CR-POPF. According to the definition proposed by ISGPS in 2017,[1] POPF is defined as 3 times higher than the upper limit of serum amylase in the drainage fluid on or after POD3. The triple value of the upper limit is 330 U/L. CR-POPF, associated with a clinically relevant development or condition related directly to the POPF, is including grade B and grade C POPF. Grade B: Continuous drainage for more than 3 weeks, positive findings of abdominal ultrasonography or CT, complicated with therapeutic agents and less-invasive treatment including percutaneous, endoscopic, or angiographic interventional procedures; Grade C: Reoperation is needed or organ failure occurs, sepsis or death associated with

pancreatic fistula.

The secondary outcome measures:

The secondary outcomes include readmission rate, length of postoperative hospital stay, length of drainage, hospitalization expenses, time to start adjuvant therapy postoperatively, disease-free survival (DFS), overall survival (OS), postoperative recurrence and metastasis, the rate of pancreatic pseudocyst, peripancreatic effusion, and other perioperative complications, such as abdominal abscess, delayed gastric emptying, post-pancreatectomy hemorrhage, and pulmonary complication.

Data collection and management

The investigators will study the instructions for data collection before the trial starts. All data collected will be stored in an electronic case report form (eCRF). Original medical records are collected and cannot be changed by anyone. The original record should not show any correction and can only be accompanied by an explanation, date, and physician signature.

Data analysis

IBM SPSS Statistics 24.0 (IBM, Chicago, IL, USA) will be used as statistical software. Participants with missing primary or secondary outcome data are excluded. Continuous variables will be expressed as mean ± standard deviation, and comparison between groups will be performed by Students' t-test or Mann-Whitney U test. Categorical variables will be expressed as rate and percentage, χ^2 test will be used for comparison between groups, Kaplan-Meier survival curve will be used to analyze the distribution of DFS, and a log-rank test is used to compare the significance of survival between subgroups. Multivariate survival is analyzed using Cox regression analysis. Linear correlation analysis will be used to test the correlation between variables. It will be considered statistically significant when P values of less than 0.05.

Assessment of safety

Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients. Patients need to attend the out-patient clinic to follow up and undergo some necessary examinations after hospital discharge.

Confidentiality

All patients' data are kept confidential and not disclosed. The patient's information will be represented by a unique number, and the coded information will be properly stored in the center. When the research information and data obtained from this study are published in scientific conferences or scientific journals, the identity of patients will not be disclosed.

Discussion

Pancreatic fistula is a common complication after pancreatic surgery, which can increase the risk of other postoperative complications and even lead to death. Previous studies have shown that early enteral nutrition does not aggravate POPF and did not prolong drain placement or hospital stay in patients with POPF after pancreatectomy. [21 24 25] Our center is relatively conservative in terms of diet and drainage tube removal time. In our center, all patients usually start oral intake on POD6. The abdominal drainage tube routinely stays 2-3 weeks postoperatively according to the amount of

postoperative drainage fluid and amylase level in drainage fluid. Although to a certain extent it may increase the incidence of POPF, especially the grade B POPF, we prefer to retain abdominal drainage tubes in postoperative 1 month. And maybe that's the reason for a low incidence of re-puncture and drainage for pancreatic fistula and a low readmission rate in our center.[26] However, the long fasting time may prolong the length of hospital stay and delay the recovery of postoperative gastrointestinal function. This prospective randomised controlled trial study will compare patients who start enteral nutrition on POD3 with patients who start on POD7 in the length of hospital stay, the incidence of postoperative pancreatic fistula, postoperative complications, and long-term prognosis to further evaluate the feasibility and safety of early enteral nutrition.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Trial status

The Study has been started on 1 December 2021, with 85 subjects having been recruited at the time of the final revision of this manuscript.

Dissemination

The study website (www.chictr.org.cn) contains all up-todate information regarding the trial. Final trial results will be published in a peer-reviewed journal. Furthermore, results will be presented at appropriate national and international conferences.

Acknowledgements
We gratefully acknowledge all the participants enrolled in this trial.

Author contributions
JJY conceived the study, prepared the initial protocol, and drafted the manuscript. DRX participated in designing the trial protocol, polished the language of the manuscript, and helped to develop the study analysis.
The authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent Not applicable

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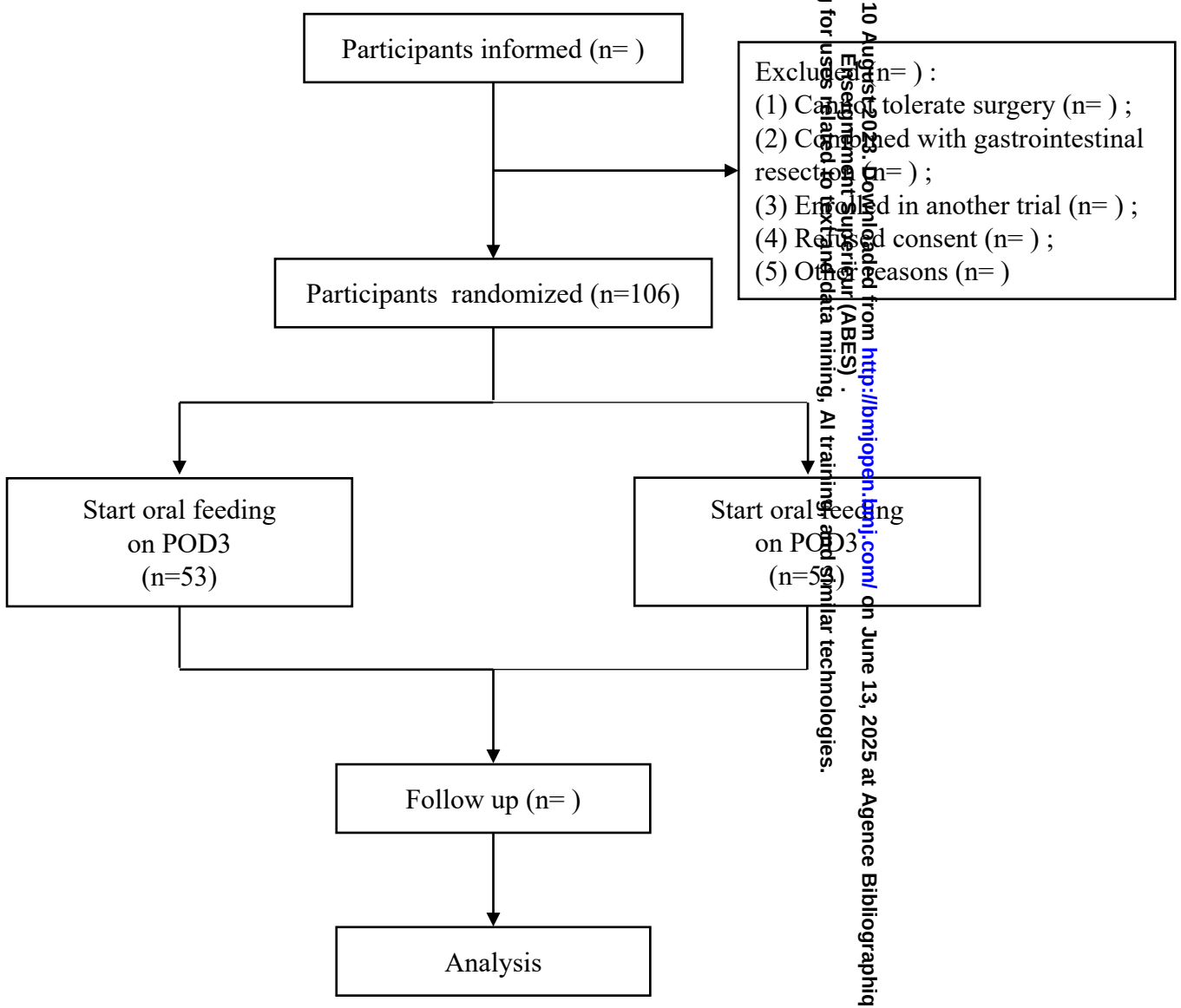
Figure 1 Flow chart of study pathway.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each	5-6

		outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	4

		assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary	6

		and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a There's no auditing trial conduct
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a Protocol has not been modifications
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a This is a single-center trail
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial	6

trial care		care, and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a This trail will not collect, evaluat, and store biological specimens.

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Secondary Subject Heading:	Surgery
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ABSTRACT

Introduction

Postoperative pancreatic fistula (POPF) remains one of the main complications following pancreatic resection. Despite the low postoperative mortality caused by pancreatic fistula, the readmission and intervention rates in patients with pancreatic fistula are still considerable. At present, there have been abundant studies on pancreatic fistula after pancreaticoduodenectomy, but few studies on feeding protocol after distal pancreatectomy or enucleation of pancreatic tumors. We designed this trial to test the hypothesis that early feeding does not increase the incidence of postoperative pancreatic fistula and has a better influence on the long-term prognosis in patients who undergo distal pancreatectomy or enucleation of pancreatic tumors.

Methods and analysis

This is a prospective randomised controlled trial conducted in a single center. A total of 106 patients undergoing distal pancreatectomy or enucleation of pancreatic tumors will be recruited with informed consent. They are randomly assigned to either an early or a late feeding group. In the early feeding group, each included patient begins enteral nutrition on postoperative day (POD) 3, and in the late feeding group, patients begin enteral nutrition on the POD7. The primary outcome is the incidence of POPF. The secondary outcomes include the length of postoperative hospital stay, postoperative complications, and indicators of long-term prognosis.

Ethics and dissemination

The research ethics committee of the Peking University Third Hospital approved the study (M2021395). Findings will be disseminated in a peer-reviewed journal and in national and/or international meetings to guide future practice.

Trial registration number ChiCTR2100053978

Strengths and limitations of this study

1. This study will be the first randomised controlled trial to compare the two feeding regimens after distal pancreatectomy and enucleation of pancreatic tumors since ISGPS redefined and updated the classification of pancreatic fistula in 2016.
2. Due to practical reasons, the patients and the clinicians administering the treatment in the study cannot be blinded to the assignment of the groups, although the principal investigator and clinicians conducting the follow-up evaluation are blinded.
3. The study included patients with different pancreatic tumor diagnoses and prognoses, which may have been too broad a choice.

INTRODUCTION

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. The International Study Group of Pancreatic Surgery (ISGPS) classified POPF into three risk levels in 2005.[1] In 2016, ISGPF revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer included in the pancreatic fistula.[2] The definition of grade C pancreatic fistula is stricter. The occurrence of postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even death.[3-5]

Distal pancreatectomy and enucleation of pancreatic tumors are the standard treatment for pancreatic body and tail tumors. Compared with pancreatoduodenectomy, although distal pancreatectomy and enucleation of pancreatic tumors are less difficult, there're still a considerable number of patients suffering from pancreatic fistula due to the anatomical characteristics of the pancreas and the physiological characteristics of the patient. [6] According to the ISGPS Evidence Map of Pancreatic Surgery, the incidence of pancreatic fistula remains at 5-60%.[7] Despite the low mortality caused by pancreatic fistula, there're still a considerable percentage of patients suffering from readmission and percutaneous drainage.[8-10]

For the prevention of pancreatic fistula after distal pancreatectomy and enucleation of pancreatic tumors, there are still some controversies in intraoperative procedures, early postoperative nutritional support, the timing of drainage tube removal, and the use of somatostatin analogs. Since fasting is an essential condition for inhibiting pancreatic secretion in patients with postoperative pancreatic fistula, the necessity of "nil per os" (NPO) has been emphasized in the past.[1] However, long-term intravenous nutrition can cause dysbiosis and lead to metabolic adverse events.[11] It has been confirmed that enteral nutrition helps maintain gastrointestinal integrity and immune capacity.[12 13] Recently, American Gastroenterological Association (AGA) updated the clinical practice in patients with pancreatic necrosis, this expert review recommended that enteral feeding should be initiated early to decrease the risk of infected necrosis. In patients without nausea, vomiting, and no signs of severe ileus, a trial of oral nutrition should be recommended immediately.[14]

In recent years, with the continuous deepening of the concept of enhanced recovery after surgery (ERAS), an increasing number of researches have reported that ERAS does not increase the incidence of postoperative pancreatic fistula and other complications, but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients.[15 16] However, most of the previous studies focused on pancreaticoduodenectomy[17-21] and only a small number of researches on distal pancreatectomy.[6 22 23] Pecorelli et al. performed an observational case-control study to assess the feasibility and safety of ERAS programs for laparoscopic distal pancreatectomy and to analyze its financial impact compared to traditional management.[16] But the key elements of ERAS programs include not only early enteral nutrition but also other perioperative care. It cannot prove directly whether early enteral nutrition plays significant role in accelerating recovery in these patients. In the study of Fujii et al., patients who developed POPF after distal pancreatectomy were randomly

assigned to the dietary intake group or the no dietary intake group, and each group consisted of 15 patients.[24] Patients in the no dietary intake group fasted until drain removal. In the dietary intake group, food intake was started on postoperative day (POD) 6. The final results showed that no significant differences were found in the length of drain placement, POPF-related intra-abdominal hemorrhage, other complications, or the length of postoperative hospital stay between the two groups.

Therefore, evidence regarding whether early enteral nutrition can be tolerated in patients undergoing distal pancreatectomy or enucleation of pancreatic tumors remains to be further explored from large randomised controlled trials.

MATERIALS AND METHODS

Study design and setting

This prospective randomised controlled trial is conducted at the Department of General Surgery, Peking University Third Hospital, Beijing, China. The Department of General Surgery offers conventional treatment and care to adult patients with liver, pancreas, biliary tract, gastrointestinal, thyroid, and breast diseases. Annually, the number of pancreatectomy can amount to 150.

Sample size estimation

In this study, the occurrence of postoperative pancreatic fistula (POPF) is the main observation index. Considering that this is a superiority trial, we assume that the incidence of postoperative pancreatic fistula in the early feeding group is lower than in the late feeding group according to the previous literature.[6] The sample size is calculated by PASS software. The incidence of postoperative pancreatic fistula in the early feeding group and the late feeding group was 6.8% and 26.3%, respectively. With a type I error (α=0.05) and type II error (β=0.2), taking into account a dropout of 20%, 53 patients will be included in each group. Taken together, we will recruit a total of 106 patients for this trial.

Randomisation

Randomisation is performed by the principal investigator after distal pancreatectomy and enucleation of pancreatic tumor. The principal investigator uses a random number generator to generate a randomisation scheme. After randomisation, the resident in charge of the patient, who does not participate in data collection and analysis, will be informed about the allocation results by email. According to the predetermined randomisation scheme, eligible patients are immediately allocated to either the early feeding group or the late feeding group after surgery in a ratio of 1:1.

Blinding

Blinding of study contributors is an effective measure to reduce bias.[25] Because of the nature of the intervention, neither patients nor surgeon in charge of the patient can be blinded to the allocation. The principal investigator and outcome assessors conducting the follow-up evaluation are not involved in the treatment of the patients and are blinded to the allocation. Data collectors and analysts are also blinded to the allocation.

Selection of subjects

Inclusion criteria include (1) Patients who undergo open or minimally invasive distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, and enucleation of pancreatic tumor between December 2021 and June 2023; (2) The

preoperative diagnosis is clear and surgical treatment is feasible; (3) No absolute surgical contraindications; (4) All patients and authorized surrogates should be informed about the risks and benefits of surgery, and sign the informed consent.

Exclusion criteria include (1) Patients cannot tolerate surgery, such as with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency; (2) Poor compliance of patients and their authorized surrogates; (3) Patients with combined gastrointestinal resection; (4) Enrolled in another trial.

Patient and public involvement

Patients were not directly involved in the design and conduct of this research. Once the trial is published, results will be shared with involved patients in the form of a newsletter through email. Reports will be made available to interested participants via a seminar day where researchers will describe individual findings.

Treatment procedures

After obtaining written informed consent (model consent form provided in online supplemental file), randomisation is carried out as described above. For each included patient, the following baseline characteristics will be collected: age, gender, height, weight, complication, preoperative laboratory or imaging examinations, and American Society of Anesthesiologists (ASA) classification (I-IV). Type of surgery (distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, and enucleation of pancreatic tumors), type of surgical intervention (robot-assisted, laparoscopic, open), operative time, intraoperative blood loss, tumor localization, tumor size, pancreas texture, pancreatic thickness, and diameter of the pancreatic duct, tumor type, and pathological staging will be collected. All patients included in the study will receive routine treatment regimens perioperatively, including inhibition of pancreatic secretion, acid inhibition, perioperative antibiotic, fluid therapy, and nutritional support during water deprivation and fasting. Patients in the early feeding group start enteral nutrition, which includes oral feeding and nasogastric (NG) or nasojejunal (NJ) feeding, on POD3, and patients in the late feeding group begin enteral nutrition on POD7. The patient's body temperature, visual analogue scale (VAS), ambulation, flatus and defecation, and dietary status will be recorded daily. The patient's nutritional status (BMI/PNI) is regularly monitored. The routine postoperative examination is arranged as follows: hemoglobin (Hb) concentration, white blood cell counts, serum amylase levels, amylase levels in drainage fluid, etc., and other laboratory or imaging examinations may be performed according to the needs of disease to assist in evaluating the position of the drainage tube.

Discharge criteria: no fever, abdominal pain, and distension; no need for surgery-related perioperative treatment; the patient has tolerated the solid food and can move normally; no signs of infection; independently mobile at the preoperative level. The wound is not suppurative, infected, or dehisced. Patients may discharge with or without the abdominal drainage tube.

Follow-up on complications, survival, and quality of life will be performed through outpatient visit, telephone, and other means every 3 months for the first year and then every 6 months. All patients are followed up for 3 years or until recurrence, metastasis,

or death. The study pathway is illustrated in Figure 1.

Outcome measures

The primary outcome measures:

The primary endpoint is POPF. According to the definition proposed by ISGPS in 2017,[1] POPF is defined as 3 times higher than the upper limit of serum amylase in the drainage fluid on or after POD3 and associated with a clinically relevant development or condition related directly to it. The triple value of the upper limit is 330 U/L. POPF is including grade B and grade C POPF. Grade B: Continuous drainage for more than 3 weeks, positive findings of abdominal ultrasonography or CT, complicated with therapeutic agents and less-invasive treatment including percutaneous, endoscopic, or angiographic interventional procedures; Grade C: Reoperation is needed or organ failure occurs, sepsis or death associated with pancreatic fistula.

The secondary outcome measures:

The secondary outcomes include length of postoperative hospital stay, length of drainage, hospitalization cost, disease-free survival (DFS), overall survival (OS), nutritional risk index, body mass index, the rate of pancreatic pseudocyst, peripancreatic effusion, and other perioperative complications, such as abdominal abscess and post-pancreatectomy hemorrhage.

Data collection and management

The investigators will study the instructions for data collection before the trial starts. All data collected will be stored in an electronic case report form (eCRF). Original medical records are collected and cannot be changed by anyone. The original records should not show any correction and can only be accompanied by an explanation, date, and physician signature.

Data analysis

IBM SPSS Statistics 24.0 (IBM, Chicago, IL, USA) will be used as statistical software. Participants with missing primary or secondary outcome data are excluded. Continuous variables will be expressed as mean ± standard deviation, and comparison between groups will be performed by Students' t-test or Mann-Whitney U test. Categorical variables will be expressed as rate and percentage, and χ^2 test will be used for comparison between groups. Multivariate logistic regression analysis was applied to identify independent risk factors of POPF. Kaplan-Meier survival curve will be adopted to analyze the distribution of DFS and OS, and a log-rank test is used to compare the significance of survival between subgroups. Multivariate Cox regression analysis was adopted to select independent prognostic factors. Linear correlation analysis will be used to test the correlation between variables. It will be considered statistically significant when P values of less than 0.05.

Discussion

Pancreatic fistula is a common complication after pancreatic surgery, which can increase the risk of other postoperative complications and even lead to death. Previous studies have shown that early enteral nutrition does not aggravate POPF and prolong drain placement or hospital stay in patients with POPF after pancreatectomy.[21 24 26] Our center is relatively conservative in terms of diet and drainage tube removal time. In our center, all patients usually start enteral nutrition on POD6. The abdominal

drainage tube routinely stays 2-3 weeks postoperatively in the light of the amount of postoperative drainage fluid and amylase level in drainage fluid. Although to a certain extent it may increase the incidence of POPF, especially the grade B POPF, we prefer to retain abdominal drainage tubes in postoperative 1 month. And maybe that's the reason for a low incidence of re-puncture and drainage for pancreatic fistula and a low readmission rate in our center.[27] However, the long fasting time may prolong the length of hospital stay and delay the recovery of postoperative gastrointestinal function.

This prospective randomised controlled trial study will compare patients who start enteral nutrition on POD3 with patients who start on POD7 in the length of hospital stay, the incidence of postoperative pancreatic fistula, postoperative complications, and long-term prognosis to further evaluate the feasibility and safety of early enteral nutrition. Considering the different ways of enteral nutrition and surgical intervention may have an impact on POPF. If possible, stratified analysis will be adopted. Of course, since there are only 53 patients in each group, we speculate that the results may have insufficient power for detecting a significant difference in the incidence of POPF between the groups. However, if the length of postoperative hospital stay in this group is shorter, or the hospitalization cost is relatively lower without increasing the incidence of POPF, it will also be a meaningful discovery.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Trial status

The Study has started on 1 December 2021, with 85 subjects having been recruited at the time of the final revision of this manuscript.

Ethics and Dissemination

Since the two enteral nutrition methods in this project are routinely performed in clinical practice, participation in this project will not increase a risk to patient safety. Patients need to attend the outpatient clinic to follow up and undergo some necessary examinations after hospital discharge. All patients' data will be kept confidential and not disclosed. The patient's information will be represented by a unique number, and the coded information will be properly stored in the center. When the research information and data obtained from this study are published in scientific conferences or scientific journals, the identity of patients will not be disclosed. It is essential to obtain the signature of the informed consent, which must be signed by both the researcher and the participant, who will receive a copy. The study promoter is responsible for obtaining the approval of the Institutional Ethics Committee involved in the study.

The study website (www.chictr.org.cn) contains all up-to-date information regarding the trial. Final trial results, whether positive, negative, or inconclusive, will be published in a peer-reviewed journal. Furthermore, results will be presented at appropriate national and international conferences.

Acknowledgements
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Author contributions
JYY conceived the study, prepared the initial protocol, and drafted the manuscript. DRX participated in designing the trial protocol, polished the language of the manuscript, and provided comments on the study statistic analysis. The authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent Not applicable.

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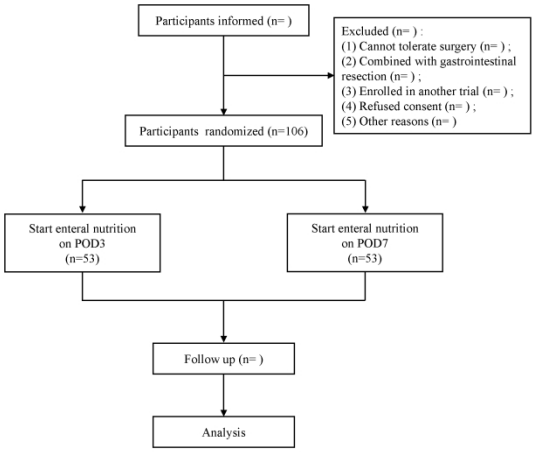
Figure 1 Flow chart of study pathway.



Flow chart of study pathway.

338x190mm (300 x 300 DPI)

Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors

INFORMED CONSENT DOCUMENT（V2.0　2021-9-9）

Please understand the possible risks and benefits of the research before you make an informed decision to participate in the study. This process is called informed consent. The Ethics Committee (EC) has approved the information in this consent form and approved the research physician to conduct this research. An Ethics committee (EC) is an independent group of experts and nonspecialists designed to help protect the rights of research subjects. It does not mean that the EC has approved your participation in the research or that the study is risk-free. This consent form may contain words that you do not understand. Ask the research physician or researcher to explain anything you do not clearly understand. You may take home an unsigned copy of this consent form to think about or consult with family, friends, or anyone you choose before making a decision. If you decide to participate in this research, you will be asked to read and sign this consent form to confirm that you have understood the study instructions and agreed to participate. You will receive a copy of the signed consent form. As you read this consent form, please note: "you" and "your" in the text refer to the person participating in the research and not to the parent/guardian or legally authorized representative who may have signed this consent form on behalf of the research participant.

Dear Sir/Madam:

We invite you to participate in clinical research entitled “Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors”. Before deciding to participate in this research, please read the following as carefully as possible to understand the research objectives, procedures, durations, and the benefits, risks, and discomfort associated with participating in the research. You can also discuss it with your kinsfolk or friends to help you decide whether to participate in the study. If you have any questions, please address them to the doctor or investigator responsible for the research. You are free to decide whether to take part in this research trial. If you choose not to participate, this will not affect the care you get from your doctors.

This informed consent form contains three parts. The first part is the introduction of this research and some problems that may encounter in the study, and the second part is the consent statement of the subjects. Please sign your name in the corresponding position in the second part after reading the first part carefully. The doctor or researcher will declare and sign in the last section.

PART1

1. Background of this subject

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. In 2016, the International Study Group of Pancreatic Surgery (ISGPS) revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer included in the pancreatic fistula. The definition of grade C pancreatic fistula is more strict. The postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even deaths.

Distal pancreatectomy and enucleation are the standard treatment for pancreatic body and tail tumors. The reported incidence of clinically relevant pancreatic fistula remains at 6%-34% due to the anatomical characteristics of the pancreas and the physiological characteristics of the patients. Despite the low mortality caused by pancreatic fistula, there's still a considerable percentage of patients suffering from readmission and percutaneous drainage.

In recent years, with the continuous deepening of the enhanced recovery after surgery (ERAS), an increasing number of studies have reported that ERAS does not increase the incidence of postoperative pancreatic fistula and other complications but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients. However, most previous studies focused on pancreaticoduodenectomy and only a small number of researches on distal pancreatectomy.

Therefore, evidence regarding whether early oral intake can be tolerated in patients undergoing distal pancreatectomy or enucleation remains to be further explored in large randomized controlled trials.

2. The main contents of this subject

A total of 106 patients who underwent laparoscopic or open distal pancreatectomy or enucleation of pancreatic tumors at the Department of General Surgery of Peking University Third Hospital from December 2021 to June 2023 were enrolled in this study.

All patients were evaluated by detailed medical history collection, physical examination, imaging examination, and/or pathological biopsy. Researchers use a random number generator to generate a randomization scheme. According to the predetermined randomization scheme, eligible patients are randomized at 1:1 to either the early feeding group or the late feeding group. The patients in the early feeding group began enteral nutrition on the third day after surgery, and the patients in the late feeding group began enteral nutrition on the 7th day after surgery. According to the differences in postoperative conditions and long-term survival effects, the relevant data on perioperative characteristics and long-term survival were obtained. The subsequent radiotherapy, chemotherapy, and other comprehensive treatment for pancreatic cancer were provided according to the postoperative pathology and condition changes. This study was approved by the Ethics Committee of Peking University Third Hospital. The Ethics committee of Peking University Third Hospital has considered that the study complies with the principles of the Declaration of Helsinki and complies with medical ethics.

3. Process and deadline of this subject

This study requires your cooperation to complete the relevant examinations and treatment. Patients were followed up after hospital discharge by telephone, letter, or e-mail regarding long-term complications, survival, and quality of life.

4. Exclusion criteria (You will be considered unfit to participate in the study if one of the following occurs)

4.1. Patients cannot tolerate surgery, such as those with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency;

4.2. Poor compliance of patients and their authorized surrogates;

4.3. Patients with combined gastrointestinal resection;

4.4. Enrolled in another trial.

5. Possible risks, discomfort, and inconvenience of participating in the study

The two enteral nutrition methods in this program are the current clinical practice, so participating in the program itself will not increase your treatment risk. This study does not involve the collection and use of blood, tissue, and other biological samples.

During the study period, you need to go to the hospital on time for follow-up and do some necessary

examinations, which will take up some time and may cause trouble or inconvenience.

After clinical treatment, including during the study period, if you suffered from any discomfort, new changes in your condition, or any unexpected situation, whether related to the study, you should promptly notify your doctor, who will make a judgment and give appropriate medical treatment.

6. The benefit of participating in the study

If you participate in the study, the findings will have important implications for clinical decision-making in all patients with this condition.

The benefit of participating in the study include specialized follow-up, reexamination clinic, and consultation. This project will set up a follow-up, reexamination, and consultation clinic so that you can get timely and comprehensive postoperative condition consultation and monitoring.

7. The costs of participating in the study

In this study, there are no tests outside your current routine diagnosis and treatment, which will not increase your treatment costs. At present, the examination items, surgery, and postoperative follow-up of this study are routine medical procedures, and do not require additional examinations or costs.

8. Treatment of study-related injuries

If you are injured as a result of participating in the study, Peking University Third Hospital will provide the necessary medical care immediately, and bear the cost of the treatment and the corresponding financial compensation by the relevant laws and regulations. Please contact Professor Xiu at ******.

If you experience any discomfort or any unexpected situation, whether related to new medical technology research, you should notify your doctor in time, he/she will make a judgment and provide medical treatment. Doctors will do their best to prevent and treat possible harm.

If an adverse event occurs during a clinical trial, the committee of medical experts will determine whether it is related to the clinical study. The hospital will provide treatment costs and corresponding financial compensation for study-related injuries.

9. Confidentiality of Personal Information

Your medical records (medical records, physical and chemical examination reports, etc.) will be kept completely in the hospital. Doctors (researchers), professional academic committees, ethics committees, and health supervision and management departments will be allowed to access your medical records. Your

identity will not be disclosed in any public report of the results of this study. We will make every effort to protect the privacy of your medical data within the scope of the law.

10. About refusal to participate or withdrawal

You may choose not to participate in this study, or withdraw at any time after informing the investigators without discrimination or retaliation. You will begin to take food 7 days after surgery, and your medical treatment and rights will not be affected.

If you do not comply with the study protocol, or have any other reason, you may be asked to withdraw from the study without your consent.

Your participation in this study is voluntary. If you have questions related to the study, research-related injury, or rights of participants, you can contact Professor Xiu at ******.

If you have any questions related to your rights and interests, or if you would like to express your dissatisfaction and concerns about participating in this study, please contact the Office of Research Ethics, Peking University Third Hospital, at ******.

PART2

The patient (subject) consented to the statement.

I have read the above description of the study and had the opportunity to discuss it with physicians and ask questions. All my questions were satisfactorily answered.

I am aware of the risks and benefits that may arise from participation in this study. I have known that participation in the study was voluntary. I confirm that I have had ample time to consider this and understand that:

- I can always ask my doctor for more information.
- I may withdraw from this study at any time without discrimination or retaliation, and medical treatment and benefits will not be affected.

I also know that if I withdrew from the study, especially for treatment reasons, it would be in my best interests and the best interests of the study if I informed my doctor of the changes in my condition and

completed the corresponding physical and physical examinations.

If I need to take any other medication as a result of a change in my condition, I will seek advice from my doctor beforehand or tell my doctor so afterward.

I consent to the health management supervision department, ethics committee, or professional academic committee to access my research data.

I will be provided with a signed and dated copy of the informed consent form.

Finally, I decided to participate in the study and follow my doctor's advice as much as possible. Participant:

Name_____ Date_____ Signature _____ Tel.：_____

The legal representative of the participant:

Name_____ Date_____ Signature _____ Tel.：_____

PART3

I have informed the subject of the background, purpose, procedures, risks, and benefits of " Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors ". I have given him/her enough time to read the informed consent, discuss it with others, and answer his/her questions about the study. I have told the subject to contact Professor Xiu at any time when he or she has problems related to the research, and to contact the General Office of Research Ethics of Peking University Third Hospital at any time when he or she has problems related to his or her rights and interests, and provided accurate contact information. I have informed the subject that he may withdraw from the study at any time without any reason; I have informed that the subject will be given a copy of this informed consent form containing my signature and his/her signature.

Doctor (Researcher):

Name_____ Date_____ Signature _____ Tel.：_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each	5-6

		outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	4

		assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary	6

		and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a There's no auditing trial conduct
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a Protocol has not been modifications
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a This is a single-center trail
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial	6

trial care		care, and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a This trail will not collect, evaluat, and store biological specimens.

BMJ Open

Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors in a major academic university hospital in China: protocol for a single-center randomised controlled trial

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Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors in a major academic university hospital in China: protocol for a single-center randomised controlled trial

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Keywords: enteral nutrition; pancreatic fistula; distal pancreatectomy; enucleation; pancreatic tumor

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ABSTRACT

Introduction

Postoperative pancreatic fistula (POPF) remains one of the main complications following pancreatic resection. Despite pancreatic fistula having a low postoperative mortality rate, the readmission and intervention rates in patients with pancreatic fistula are still considerable. Although there are several studies on pancreatic fistula development after pancreaticoduodenectomy, there are only a few studies on the feeding protocols applied after distal pancreatectomy or enucleation of pancreatic tumors. We designed this trial to test the hypothesis that early feeding does not increase the incidence of postoperative pancreatic fistula and positively influences the long-term prognosis in patients who undergo distal pancreatectomy or enucleation of pancreatic tumors.

Methods and analysis

This is a prospective randomised controlled trial that will be conducted in a single center. A total of 106 patients undergoing distal pancreatectomy or enucleation of pancreatic tumors will be recruited after providing informed consent. They will be randomly assigned to either an early or late feeding group. The early feeding group will begin enteral nutrition on postoperative day (POD) 3, and the late feeding group will begin enteral nutrition on POD7. The primary outcome is the incidence of POPF. The secondary outcomes include the length of postoperative hospital stay, postoperative complications, and indicators of long-term prognosis.

Ethics and dissemination

Peking University Third Hospital Medical Science Research Ethics Committee approved the study (M2021395). Findings will be disseminated in a peer-reviewed journal and in national and/or international meetings to guide future practice.

Trial registration number ChiCTR2100053978

Strengths and limitations of this study

1. This study will be the first randomised controlled trial to compare the two feeding regimens after distal pancreatectomy and enucleation of pancreatic tumors since ISGPS redefined and updated the classification of pancreatic fistula in 2016.
2. Due to practical reasons, the patients and the clinicians administering the treatment in the study cannot be blinded to the assignment of the groups, although the principal investigator and clinicians conducting the follow-up evaluation are blinded.
3. The study includes patients with different pancreatic tumor diagnoses and prognoses, which may be too broad a choice.

INTRODUCTION

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. The International Study Group of Pancreatic Surgery (ISGPS) classified POPF into three risk levels in 2005.[1] In 2016, ISGPF revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer including it in the pancreatic fistula definition.[2] The definition of grade C pancreatic fistula is stricter. Postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even death.[3-5]

Distal pancreatectomy and enucleation of pancreatic tumors are the standard treatment for pancreatic body and tail tumors. Compared with pancreatoduodenectomy, distal pancreatectomy and enucleation of pancreatic tumors are less difficult, but a considerable number of patients still experience pancreatic fistula due to their physiological characteristics and the anatomical characteristics of the pancreas.[6] According to the ISGPS Evidence Map of Pancreatic Surgery, the incidence of pancreatic fistula remains at 5-60%.[7] Despite the low mortality caused by pancreatic fistula, there're still a considerable percentage of patients require readmission and percutaneous drainage.[8-10]

The prevention of pancreatic fistula after distal pancreatectomy and enucleation of pancreatic tumors is still being debated with respect to intraoperative procedures, early postoperative nutritional support, the timing of drainage tube removal, and the use of somatostatin analogs. Since fasting is an essential condition for inhibiting pancreatic secretion in patients with postoperative pancreatic fistula, the necessity of "nil per os" (NPO) has been emphasized in the past.[1] However, long-term intravenous nutrition can cause dysbiosis and lead to metabolic adverse events.[11] It has been confirmed that enteral nutrition helps maintain gastrointestinal integrity and immune capacity.[12 13] Recently, the American Gastroenterological Association (AGA) updated clinical practice guidelines for patients with pancreatic necrosis, and this expert review recommended that enteral feeding should be initiated early to decrease the risk of infected necrosis. In patients without nausea, vomiting, and no signs of severe ileus, a trial of oral nutrition should be recommended immediately.[14]

In recent years, the increased application of enhanced recovery after surgery (ERAS) has led to an increasing number of studies reporting that ERAS does not increase the incidence of postoperative pancreatic fistula or other complications but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients.[15 16] However, most previous studies have focused on pancreaticoduodenectomy[17-21] and only a small number of researches studies have focused on distal pancreatectomy.[6 22 23] Pecorelli et al. performed an observational case-control study to assess the feasibility and safety of ERAS programs for laparoscopic distal pancreatectomy and to compare its financial impact compared with that of traditional management.[16] However, the key elements of ERAS programs include early enteral nutrition and other perioperative care. It is impossible to directly prove whether early enteral nutrition plays a significant role in accelerating recovery in these patients. In the study by Fujii et al., patients who developed POPF after distal

pancreatectomy were randomly assigned to the dietary intake group or the no dietary intake group, and each group consisted of 15 patients.[24] Patients in the no dietary intake group fasted until drain removal. In the dietary intake group, food intake was started on postoperative day (POD) 6. The final results showed that no significant differences were found in the length of drain placement, incidence of POPF-related intra-abdominal hemorrhage, other complications, or the length of postoperative hospital stay between the two groups.

Therefore, evidence regarding whether early enteral nutrition can be tolerated in patients undergoing distal pancreatectomy or enucleation of pancreatic tumors remains to be further explored in large randomised controlled trials.

MATERIALS AND METHODS

Study design and setting

This prospective randomised controlled trial is conducted at the Department of General Surgery, Peking University Third Hospital, Beijing, China. The Department of General Surgery offers conventional treatment and care to adult patients with liver, pancreas, biliary tract, gastrointestinal, thyroid, and breast diseases. One hundred and fifty pancreatectomies are performed in the department each year. This study starts on 1 December 2021, and 106 patients are expected to be enrolled by 1 June 2023.

Sample size estimation

In this study, postoperative pancreatic fistula (POPF) is the main observation index. Considering that this is a superiority trial, we can assume that the incidence of postoperative pancreatic fistula in the early feeding group will belower than that in the late feeding group according to the previous literature.[6] The sample size was calculated by PASS software. The incidence of postoperative pancreatic fistula in the early feeding group and the late feeding group was 6.8% and 26.3%, respectively. With a type I error (α=0.05) and type II error (β=0.2), considering a dropout of 20%, 53 patients will be included in each group. Taken together, we will recruit a total of 106 patients for this trial.

Randomisation

Randomisation will be performed by the principal investigator after distal pancreatectomy and enucleation of pancreatic tumor. The principal investigator uses a random number generator to generate a randomisation scheme. After randomisation, the resident in charge of the patient, who does not participate in data collection or analysis, will be informed about the allocation results by email. According to the predetermined randomisation scheme, eligible patients are immediately allocated to either the early feeding group or the late feeding group after surgery at a ratio of 1:1.

Blinding

Blinding of study contributors is an effective measure to reduce bias.[25] Because of the nature of the intervention, neither patients nor the surgeon in charge of the patient can be blinded to the allocation. The principal investigator and outcome assessors conducting the follow-up evaluation are not involved in the treatment of the patients and are blinded to the allocation. Data collectors and analysts will also be blinded to the allocation.

Selection of subjects

Inclusion criteria:(1) patients undergoing open or minimally invasive distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, or enucleation of pancreatic tumor between 1 December 2021 and 1 June 2023; (2) patients with a clear preoperative diagnosis and undergoing a feasible surgical treatment; (3) patients with no absolute surgical contraindications; and (4) patients who are informed about the risks and benefits of surgery and sign the informed consent form.

Exclusion criteria: (1) patients who cannot tolerate surgery, such as those with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency; (2) patients or their authorized surrogates who exhibit poor compliance; (3) patients undergoing combined gastrointestinal resection; and (4) patients being enrolled in another trial.

Patient and public involvement

Patients were not directly involved in the design or implementation of this research. Once the trial is published, the results will be shared with the involved patients in the form of a newsletter through email. Reports will be made available to interested participants in a seminar in which researchers will describe individual findings.

Treatment procedures

After obtaining written informed consent (model consent form provided in online supplemental file), randomisation will be carried out as described above. For each included patient, the following baseline characteristics will be collected: age, sex, height, weight, complications, preoperative laboratory or imaging examinations, and American Society of Anesthesiologists (ASA) classification (I-IV). Type of surgery (distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, and enucleation of pancreatic tumors), type of surgical intervention (robot-assisted, laparoscopic, open), operative time, intraoperative blood loss, tumor localization, tumor size, pancreas texture, pancreatic thickness, and diameter of the pancreatic duct, tumor type, and pathological staging will also be recorded. All patients included in the study will receive routine treatment regimens perioperatively, including inhibition of pancreatic secretion, acid inhibition, perioperative antibiotics, fluid therapy, and nutritional support during water deprivation and fasting. Patients in the early feeding group will start enteral nutrition, which includes oral feeding and nasogastric (NG) or nasojejunal (NJ) feeding, on POD3, and patients in the late feeding group will begin enteral nutrition on POD7. The patient's body temperature, visual analogue scale (VAS) score, ambulation, flatus and defecation, and dietary status will be recorded daily. The patient's nutritional status (BMI/PNI) is regularly monitored. The routine postoperative examination is arranged as follows: hemoglobin (Hb) concentration, white blood cell counts, serum amylase levels, amylase levels in drainage fluid, etc., and other laboratory or imaging examinations may be performed according to the needs of the disease to assist in evaluating the position of the drainage tube.

Discharge criteria: no fever, abdominal pain, and distension; no need for surgery-related perioperative treatment; the patient cantolerate the solid food and move normally; no signs of infection; and independently mobile in the preoperative setting. The wound is not suppurative, infected, or dehisced. Patients may be discharged with or without the abdominal drainage tube.

Follow-up on complications, survival, and quality of life will be performed through outpatient visits, telephone calls, and other means every 3 months for the first year and then every 6 months. All patients will be followed up for 3 years or until recurrence, metastasis, or death. The study pathway is illustrated in Figure 1.

Outcome measures

The primary outcome measures:

The primary endpoint is POPF. According to the definition proposed by ISGPS in 2017,[1] POPF is defined as 3 times higher than the upper limit of serum amylase in the drainage fluid on or after POD3, indicating a clinically relevant development or condition directly related to it. The triple value of the upper limit is 330 U/L. POPF is including grade B and grade C POPF. Grade B: Continuous drainage for more than 3 weeks, positive findings on abdominal ultrasonography or CT, complicated by therapeutic agents and needing less-invasive treatment including percutaneous, endoscopic, or angiographic interventional procedures; Grade C: Reoperation is needed or organ failure, sepsis or death occurs.

The secondary outcome measures:

The secondary outcomes include peripancreatic effusion, pancreatic pseudocyst, postpancreatectomy hemorrhage, abdominal abscess, disease-free survival (DFS), progression-free survival (PFS), hospitalization cost, and length of postoperative hospital stay.

Data collection and management

The investigators will study the instructions for data collection before the trial starts. All data collected will be stored in an electronic case report form (eCRF). Original medical records are collected and cannot be changed by anyone. The original records should not show any correction and can only be accompanied by an explanation, date, and physician signature.

Data analysis

Analyses were performed according to intention to treat, meaning that there were no crossovers between groups. IBM SPSS Statistics 24.0 (IBM, Chicago, IL, USA) will be used as statistical software. Participants with missing primary or secondary outcome data are excluded. Continuous variables will be expressed as the mean ± standard deviation, and comparisons between groups will be performed by Student's t-test or Mann-Whitney U test. Categorical variables will be expressed as rates and percentages, and χ^2 test will be used for comparisons between groups. Multivariate logistic regression analysis was applied to identify independent risk factors for POPF. Kaplan-Meier survival curve will be adopted to analyze the distribution of DFS and OS, and a log-rank test will be used to compare the significance of survival between subgroups. Multivariate Cox regression analysis was adopted to select independent prognostic factors. Linear correlation analysis will be used to test the correlation between variables. P values less than 0.05 will be considered statistically significant.

Discussion

Pancreatic fistula is a common complication developing after pancreatic surgery, that can increase the risk of other postoperative complications and even lead to death. Previous studies have shown that early enteral nutrition does not aggravate POPF or

prolong drain placement or hospital stay in patients with POPF after pancreatectomy.[21 24 26] Our center is relatively conservative in terms of return to diet and drainage tube removal time. In our center, all patients usually start enteral nutrition on POD6. The abdominal drainage tube is typically placed for 2-3 weeks postoperatively based on the amount of postoperative drainage fluid and amylase level in the drainage fluid. Although prolonged placement of an abdominal drainage tube may increase the incidence of POPF, especially the grade B POPF, we prefer to retain abdominal drainage tubes for 1 month postoperatively. This may be the reason for the low incidence of re-puncture and drainage for a pancreatic fistula and the low readmission rate in our center.[27] However, the long fasting time may prolong the length of hospital stay and delay the recovery of postoperative gastrointestinal function.

This prospective randomised controlled trial will compare patients who start enteral nutrition on POD3 with patients who start on POD7 in terms of length of hospital stay, incidences of postoperative pancreatic fistula and postoperative complications, and long-term prognosis to further evaluate the feasibility and safety of early enteral nutrition. Different methods of enteral nutrition and surgical intervention may have an impact on POPF. If possible, stratified analysis will be adopted. Of course, since there are only 53 patients in each group, we speculate that the results may have insufficient power for detecting a significant difference in the incidence of POPF between the groups. However, if the length of postoperative hospital stay in this group is shorter, or the hospitalization cost is relatively lower without increasing the incidence of POPF, it will also be a meaningful discovery.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Trial status

The first patient was enrolled in this study on 7 December 2021, with 85 subjects having been recruited at the time of the final revision of this manuscript.

Ethics and Dissemination

Since the two enteral nutrition methods in this project are routinely performed in clinical practice, participation in this project will not increase the risk to patient safety. Patients need to attend the outpatient clinic for follow-up and undergo some necessary examinations after hospital discharge. All patients' data will be kept confidential and not disclosed. The patient's information will be represented by a unique number, and the coded information will be properly stored in the center. When the research information and data obtained from this study are published in scientific conferences or scientific journals, the identity of patients will not be disclosed. It is essential to obtain the signature of the informed consent, which must be signed by both the researcher and the participant, who will receive a copy. This study has been approved by Peking University Third Hospital Medical Science Research Ethics Committee (M2021395).

The study website (www.chictr.org.cn) contains all up-to-date information regarding the trial. Final trial results, whether positive, negative, or inconclusive, will be published in a peer-reviewed journal. Furthermore, the results will be presented at appropriate national and international conferences.

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We gratefully acknowledge all the participants enrolled in this trial.

Author contributions
JYY conceived the study, prepared the initial protocol, and drafted the manuscript. DRX participated in designing the trial protocol, polished the language of the manuscript, and provided comments on the study statistical analysis. The authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent Not applicable.

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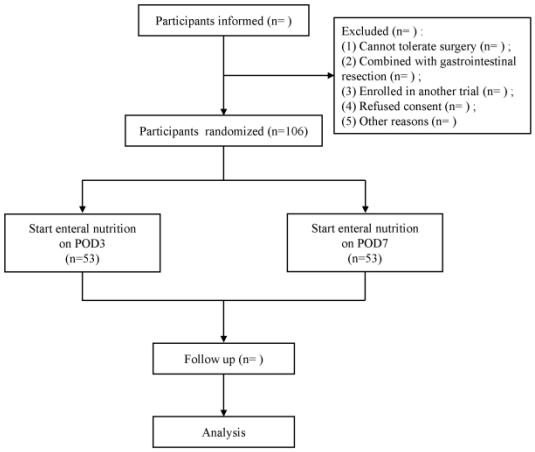
27 Wang H, Xiu D, Jiang B, et al. Postoperative pancreatic fistula in distal pancreatectomy: experience from 1 institution. Pancreas. 2014;43(4):588-591.

Figure 1 Flow chart of study pathway.



Flow chart of study pathway.

338x190mm (300 x 300 DPI)

Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors

INFORMED CONSENT DOCUMENT（V2.0　2021-9-9）

Please understand the possible risks and benefits of the research before you make an informed decision to participate in the study. This process is called informed consent. The Ethics Committee (EC) has approved the information in this consent form and approved the research physician to conduct this research. An Ethics committee (EC) is an independent group of experts and nonspecialists designed to help protect the rights of research subjects. It does not mean that the EC has approved your participation in the research or that the study is risk-free. This consent form may contain words that you do not understand. Ask the research physician or researcher to explain anything you do not clearly understand. You may take home an unsigned copy of this consent form to think about or consult with family, friends, or anyone you choose before making a decision. If you decide to participate in this research, you will be asked to read and sign this consent form to confirm that you have understood the study instructions and agreed to participate. You will receive a copy of the signed consent form. As you read this consent form, please note: "you" and "your" in the text refer to the person participating in the research and not to the parent/guardian or legally authorized representative who may have signed this consent form on behalf of the research participant.

Dear Sir/Madam:

We invite you to participate in clinical research entitled “Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors”. Before deciding to participate in this research, please read the following as carefully as possible to understand the research objectives, procedures, durations, and the benefits, risks, and discomfort associated with participating in the research. You can also discuss it with your kinsfolk or friends to help you decide whether to participate in the study. If you have any questions, please address them to the doctor or investigator responsible for the research. You are free to decide whether to take part in this research trial. If you choose not to participate, this will not affect the care you get from your doctors.

This informed consent form contains three parts. The first part is the introduction of this research and some problems that may encounter in the study, and the second part is the consent statement of the subjects. Please sign your name in the corresponding position in the second part after reading the first part carefully. The doctor or researcher will declare and sign in the last section.

PART1

1. Background of this subject

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. In 2016, the International Study Group of Pancreatic Surgery (ISGPS) revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer included in the pancreatic fistula. The definition of grade C pancreatic fistula is more strict. The postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even deaths.

Distal pancreatectomy and enucleation are the standard treatment for pancreatic body and tail tumors. The reported incidence of clinically relevant pancreatic fistula remains at 6%-34% due to the anatomical characteristics of the pancreas and the physiological characteristics of the patients. Despite the low mortality caused by pancreatic fistula, there's still a considerable percentage of patients suffering from readmission and percutaneous drainage.

In recent years, with the continuous deepening of the enhanced recovery after surgery (ERAS), an increasing number of studies have reported that ERAS does not increase the incidence of postoperative pancreatic fistula and other complications but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients. However, most previous studies focused on pancreaticoduodenectomy and only a small number of researches on distal pancreatectomy.

Therefore, evidence regarding whether early oral intake can be tolerated in patients undergoing distal pancreatectomy or enucleation remains to be further explored in large randomized controlled trials.

2. The main contents of this subject

A total of 106 patients who underwent laparoscopic or open distal pancreatectomy or enucleation of pancreatic tumors at the Department of General Surgery of Peking University Third Hospital from December 2021 to June 2023 were enrolled in this study.

All patients were evaluated by detailed medical history collection, physical examination, imaging examination, and/or pathological biopsy. Researchers use a random number generator to generate a randomization scheme. According to the predetermined randomization scheme, eligible patients are randomized at 1:1 to either the early feeding group or the late feeding group. The patients in the early feeding group began enteral nutrition on the third day after surgery, and the patients in the late feeding group began enteral nutrition on the 7th day after surgery. According to the differences in postoperative conditions and long-term survival effects, the relevant data on perioperative characteristics and long-term survival were obtained. The subsequent radiotherapy, chemotherapy, and other comprehensive treatment for pancreatic cancer were provided according to the postoperative pathology and condition changes. This study was approved by the Ethics Committee of Peking University Third Hospital. The Ethics committee of Peking University Third Hospital has considered that the study complies with the principles of the Declaration of Helsinki and complies with medical ethics.

3. Process and deadline of this subject

This study requires your cooperation to complete the relevant examinations and treatment. Patients were followed up after hospital discharge by telephone, letter, or e-mail regarding long-term complications, survival, and quality of life.

4. Exclusion criteria (You will be considered unfit to participate in the study if one of the following occurs)

4.1. Patients cannot tolerate surgery, such as those with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency;

4.2. Poor compliance of patients and their authorized surrogates;

4.3. Patients with combined gastrointestinal resection;

4.4. Enrolled in another trial.

5. Possible risks, discomfort, and inconvenience of participating in the study

The two enteral nutrition methods in this program are the current clinical practice, so participating in the program itself will not increase your treatment risk. This study does not involve the collection and use of blood, tissue, and other biological samples.

During the study period, you need to go to the hospital on time for follow-up and do some necessary

examinations, which will take up some time and may cause trouble or inconvenience.

After clinical treatment, including during the study period, if you suffered from any discomfort, new changes in your condition, or any unexpected situation, whether related to the study, you should promptly notify your doctor, who will make a judgment and give appropriate medical treatment.

6. The benefit of participating in the study

If you participate in the study, the findings will have important implications for clinical decision-making in all patients with this condition.

The benefit of participating in the study include specialized follow-up, reexamination clinic, and consultation. This project will set up a follow-up, reexamination, and consultation clinic so that you can get timely and comprehensive postoperative condition consultation and monitoring.

7. The costs of participating in the study

In this study, there are no tests outside your current routine diagnosis and treatment, which will not increase your treatment costs. At present, the examination items, surgery, and postoperative follow-up of this study are routine medical procedures, and do not require additional examinations or costs.

8. Treatment of study-related injuries

If you are injured as a result of participating in the study, Peking University Third Hospital will provide the necessary medical care immediately, and bear the cost of the treatment and the corresponding financial compensation by the relevant laws and regulations. Please contact Professor Xiu at ******.

If you experience any discomfort or any unexpected situation, whether related to new medical technology research, you should notify your doctor in time, he/she will make a judgment and provide medical treatment. Doctors will do their best to prevent and treat possible harm.

If an adverse event occurs during a clinical trial, the committee of medical experts will determine whether it is related to the clinical study. The hospital will provide treatment costs and corresponding financial compensation for study-related injuries.

9. Confidentiality of Personal Information

Your medical records (medical records, physical and chemical examination reports, etc.) will be kept completely in the hospital. Doctors (researchers), professional academic committees, ethics committees, and health supervision and management departments will be allowed to access your medical records. Your

identity will not be disclosed in any public report of the results of this study. We will make every effort to protect the privacy of your medical data within the scope of the law.

10. About refusal to participate or withdrawal

You may choose not to participate in this study, or withdraw at any time after informing the investigators without discrimination or retaliation. You will begin to take food 7 days after surgery, and your medical treatment and rights will not be affected.

If you do not comply with the study protocol, or have any other reason, you may be asked to withdraw from the study without your consent.

Your participation in this study is voluntary. If you have questions related to the study, research-related injury, or rights of participants, you can contact Professor Xiu at ******.

If you have any questions related to your rights and interests, or if you would like to express your dissatisfaction and concerns about participating in this study, please contact the Office of Research Ethics, Peking University Third Hospital, at ******.

PART2

The patient (subject) consented to the statement.

I have read the above description of the study and had the opportunity to discuss it with physicians and ask questions. All my questions were satisfactorily answered.

I am aware of the risks and benefits that may arise from participation in this study. I have known that participation in the study was voluntary. I confirm that I have had ample time to consider this and understand that:

- I can always ask my doctor for more information.
- I may withdraw from this study at any time without discrimination or retaliation, and medical treatment and benefits will not be affected.

I also know that if I withdrew from the study, especially for treatment reasons, it would be in my best interests and the best interests of the study if I informed my doctor of the changes in my condition and

completed the corresponding physical and physical examinations.

If I need to take any other medication as a result of a change in my condition, I will seek advice from my doctor beforehand or tell my doctor so afterward.

I consent to the health management supervision department, ethics committee, or professional academic committee to access my research data.

I will be provided with a signed and dated copy of the informed consent form.

Finally, I decided to participate in the study and follow my doctor's advice as much as possible. Participant:

Name_____ Date_____ Signature _____ Tel.：_____

The legal representative of the participant:

Name_____ Date_____ Signature _____ Tel.：_____

PART3

I have informed the subject of the background, purpose, procedures, risks, and benefits of " Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors ". I have given him/her enough time to read the informed consent, discuss it with others, and answer his/her questions about the study. I have told the subject to contact Professor Xiu at any time when he or she has problems related to the research, and to contact the General Office of Research Ethics of Peking University Third Hospital at any time when he or she has problems related to his or her rights and interests, and provided accurate contact information. I have informed the subject that he may withdraw from the study at any time without any reason; I have informed that the subject will be given a copy of this informed consent form containing my signature and his/her signature.

Doctor (Researcher):

Name_____ Date_____ Signature _____ Tel.：_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each	5-6

		outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	4

		assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary	6

		and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a There's no auditing trial conduct
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a Protocol has not been modifications
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a This is a single-center trail
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial	6

trial care		care, and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a This trail will not collect, evaluat, and store biological specimens.

BMJ Open

Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors in a major academic university hospital in China: protocol for a single-center randomised controlled trial

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Keywords:	Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Nutritional support < ONCOLOGY, NUTRITION & DIETETICS

Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors in a major academic university hospital in China: protocol for a single-center randomised controlled trial

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Keywords: enteral nutrition; pancreatic fistula; distal pancreatectomy; enucleation; pancreatic tumor

Word count: 2411

ABSTRACT

Introduction

Postoperative pancreatic fistula (POPF) remains one of the main complications following pancreatic resection. Despite pancreatic fistula having a low postoperative mortality rate, the readmission and intervention rates in patients with pancreatic fistula are still considerable. Although there are several studies on pancreatic fistula development after pancreaticoduodenectomy, there are only a few studies on the feeding protocols applied after distal pancreatectomy or enucleation of pancreatic tumors. We designed this trial to test the hypothesis that early feeding does not increase the incidence of postoperative pancreatic fistula and positively influences the long-term prognosis in patients who undergo distal pancreatectomy or enucleation of pancreatic tumors.

Methods and analysis

This is a prospective randomised controlled trial that will be conducted in a single center. A total of 106 patients undergoing distal pancreatectomy or enucleation of pancreatic tumors will be recruited after providing informed consent. They will be randomly assigned to either an early or late feeding group. The early feeding group will begin enteral nutrition on postoperative day (POD) 3, and the late feeding group will begin enteral nutrition on POD7. The primary outcome is the incidence of POPF. The secondary outcomes include the length of postoperative hospital stay, postoperative complications, and indicators of long-term prognosis.

Ethics and dissemination

Peking University Third Hospital Medical Science Research Ethics Committee approved the study (M2021395). Findings will be disseminated in a peer-reviewed journal and in national and/or international meetings to guide future practice.

Trial registration number ChiCTR2100053978

Strengths and limitations of this study

1. This study will be the first randomised controlled trial to compare the two feeding regimens after distal pancreatectomy and enucleation of pancreatic tumors since ISGPS redefined and updated the classification of pancreatic fistula in 2016.
2. Due to practical reasons, the patients and the clinicians administering the treatment in the study cannot be blinded to the assignment of the groups, although the principal investigator and clinicians conducting the follow-up evaluation are blinded.
3. The study includes patients with different pancreatic tumor diagnoses and prognoses, which may be too broad a choice.

INTRODUCTION

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. The International Study Group of Pancreatic Surgery (ISGPS) classified POPF into three risk levels in 2005.[1] In 2016, ISGPF revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer including it in the pancreatic fistula definition.[2] The definition of grade C pancreatic fistula is stricter. Postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even death.[3-5]

Distal pancreatectomy and enucleation of pancreatic tumors are the standard treatment for pancreatic body and tail tumors. Compared with pancreatoduodenectomy, distal pancreatectomy and enucleation of pancreatic tumors are less difficult, but a considerable number of patients still experience pancreatic fistula due to their physiological characteristics and the anatomical characteristics of the pancreas.[6] According to the ISGPS Evidence Map of Pancreatic Surgery, the incidence of pancreatic fistula remains at 5-60%.[7] Despite the low mortality caused by pancreatic fistula, there're still a considerable percentage of patients require readmission and percutaneous drainage.[8-10]

The prevention of pancreatic fistula after distal pancreatectomy and enucleation of pancreatic tumors is still being debated with respect to intraoperative procedures, early postoperative nutritional support, the timing of drainage tube removal, and the use of somatostatin analogs. Since fasting is an essential condition for inhibiting pancreatic secretion in patients with postoperative pancreatic fistula, the necessity of "nil per os" (NPO) has been emphasized in the past.[1] However, long-term intravenous nutrition can cause dysbiosis and lead to metabolic adverse events.[11] It has been confirmed that enteral nutrition helps maintain gastrointestinal integrity and immune capacity.[12 13] Recently, the American Gastroenterological Association (AGA) updated clinical practice guidelines for patients with pancreatic necrosis, and this expert review recommended that enteral feeding should be initiated early to decrease the risk of infected necrosis. In patients without nausea, vomiting, and no signs of severe ileus, a trial of oral nutrition should be recommended immediately.[14]

In recent years, the increased application of enhanced recovery after surgery (ERAS) has led to an increasing number of studies reporting that ERAS does not increase the incidence of postoperative pancreatic fistula or other complications but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients.[15 16] However, most previous studies have focused on pancreaticoduodenectomy[17-21] and only a small number of researches studies have focused on distal pancreatectomy.[6 22 23] Pecorelli et al. performed an observational case-control study to assess the feasibility and safety of ERAS programs for laparoscopic distal pancreatectomy and to compare its financial impact compared with that of traditional management.[16] However, the key elements of ERAS programs include early enteral nutrition and other perioperative care. It is impossible to directly prove whether early enteral nutrition plays a significant role in accelerating recovery in these patients. In the study by Fujii et al., patients who developed POPF after distal

pancreatectomy were randomly assigned to the dietary intake group or the no dietary intake group, and each group consisted of 15 patients.[24] Patients in the no dietary intake group fasted until drain removal. In the dietary intake group, food intake was started on postoperative day (POD) 6. The final results showed that no significant differences were found in the length of drain placement, incidence of POPF-related intra-abdominal hemorrhage, other complications, or the length of postoperative hospital stay between the two groups.

Therefore, evidence regarding whether early enteral nutrition can be tolerated in patients undergoing distal pancreatectomy or enucleation of pancreatic tumors remains to be further explored in large randomised controlled trials.

MATERIALS AND METHODS

Study design and setting

This prospective randomised controlled trial is conducted at the Department of General Surgery, Peking University Third Hospital, Beijing, China. The Department of General Surgery offers conventional treatment and care to adult patients with liver, pancreas, biliary tract, gastrointestinal, thyroid, and breast diseases. One hundred and fifty pancreatectomies are performed in the department each year. This study starts on 1 December 2021, and 106 patients are expected to be enrolled by 1 June 2023.

Sample size estimation

In this study, postoperative pancreatic fistula (POPF) is the main observation index. Considering that this is a superiority trial, we can assume that the incidence of postoperative pancreatic fistula in the early feeding group will belower than that in the late feeding group according to the previous literature.[6] The sample size was calculated by PASS software. The incidence of postoperative pancreatic fistula in the early feeding group and the late feeding group was 6.8% and 26.3%, respectively. With a type I error (α=0.05) and type II error (β=0.2), considering a dropout of 20%, 53 patients will be included in each group. Taken together, we will recruit a total of 106 patients for this trial.

Randomisation

Randomisation will be performed by the principal investigator after distal pancreatectomy and enucleation of pancreatic tumor. The principal investigator uses a random number generator to generate a randomisation scheme. After randomisation, the resident in charge of the patient, who does not participate in data collection or analysis, will be informed about the allocation results by email. According to the predetermined randomisation scheme, eligible patients are immediately allocated to either the early feeding group or the late feeding group after surgery at a ratio of 1:1.

Blinding

Blinding of study contributors is an effective measure to reduce bias.[25] Because of the nature of the intervention, neither patients nor the surgeon in charge of the patient can be blinded to the allocation. The principal investigator and outcome assessors conducting the follow-up evaluation are not involved in the treatment of the patients and are blinded to the allocation. Data collectors and analysts will also be blinded to the allocation.

Selection of subjects

Inclusion criteria:(1) patients undergoing open or minimally invasive distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, or enucleation of pancreatic tumor between 1 December 2021 and 1 June 2023; (2) patients with a clear preoperative diagnosis and undergoing a feasible surgical treatment; (3) patients with no absolute surgical contraindications; and (4) patients who are informed about the risks and benefits of surgery and sign the informed consent form.

Exclusion criteria: (1) patients who cannot tolerate surgery, such as those with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency; (2) patients or their authorized surrogates who exhibit poor compliance; (3) patients undergoing combined gastrointestinal resection; and (4) patients being enrolled in another trial.

Patient and public involvement

Patients were not directly involved in the design or implementation of this research. Once the trial is published, the results will be shared with the involved patients in the form of a newsletter through email. Reports will be made available to interested participants in a seminar in which researchers will describe individual findings.

Treatment procedures

After obtaining written informed consent (model consent form provided in online supplemental file), randomisation will be carried out as described above. For each included patient, the following baseline characteristics will be collected: age, sex, height, weight, complications, preoperative laboratory or imaging examinations, and American Society of Anesthesiologists (ASA) classification (I-IV). Type of surgery (distal pancreatectomy and splenectomy, spleen-preserving distal pancreatectomy, and enucleation of pancreatic tumors), type of surgical intervention (robot-assisted, laparoscopic, open), operative time, intraoperative blood loss, tumor localization, tumor size, pancreas texture, pancreatic thickness, and diameter of the pancreatic duct, tumor type, and pathological staging will also be recorded. All patients included in the study will receive routine treatment regimens perioperatively, including inhibition of pancreatic secretion, acid inhibition, perioperative antibiotics, fluid therapy, and nutritional support during water deprivation and fasting. Patients in the early feeding group will start enteral nutrition, which includes oral feeding and nasogastric (NG) or nasojejunal (NJ) feeding, on POD3, and patients in the late feeding group will begin enteral nutrition on POD7. The patient's body temperature, visual analogue scale (VAS) score, ambulation, flatus and defecation, and dietary status will be recorded daily. The patient's nutritional status (BMI/PNI) is regularly monitored. The routine postoperative examination is arranged as follows: hemoglobin (Hb) concentration, white blood cell counts, serum amylase levels, amylase levels in drainage fluid, etc., and other laboratory or imaging examinations may be performed according to the needs of the disease to assist in evaluating the position of the drainage tube.

Discharge criteria: no fever, abdominal pain, and distension; no need for surgery-related perioperative treatment; the patient cantolerate the solid food and move normally; no signs of infection; and independently mobile in the preoperative setting. The wound is not suppurative, infected, or dehisced. Patients may be discharged with or without the abdominal drainage tube.

Follow-up on complications, survival, and quality of life will be performed through outpatient visits, telephone calls, and other means every 3 months for the first year and then every 6 months. All patients will be followed up for 3 years or until recurrence, metastasis, or death. The study pathway is illustrated in Figure 1.

Outcome measures

The primary outcome measures:

The primary endpoint is POPF. According to the definition proposed by ISGPS in 2017,[1] POPF is defined as 3 times higher than the upper limit of serum amylase in the drainage fluid on or after POD3, indicating a clinically relevant development or condition directly related to it. The triple value of the upper limit is 330 U/L. POPF is including grade B and grade C POPF. Grade B: Continuous drainage for more than 3 weeks, positive findings on abdominal ultrasonography or CT, complicated by therapeutic agents and needing less-invasive treatment including percutaneous, endoscopic, or angiographic interventional procedures; Grade C: Reoperation is needed or organ failure, sepsis or death occurs.

The secondary outcome measures:

The secondary outcomes include peripancreatic effusion, pancreatic pseudocyst, postpancreatectomy hemorrhage, abdominal abscess, disease-free survival (DFS), progression-free survival (PFS), hospitalization cost, and length of postoperative hospital stay.

Data collection and management

The investigators will study the instructions for data collection before the trial starts. All data collected will be stored in an electronic case report form (eCRF). Original medical records are collected and cannot be changed by anyone. The original records should not show any correction and can only be accompanied by an explanation, date, and physician signature.

Data analysis

Analyses were performed according to intention to treat, meaning that there were no crossovers between groups. IBM SPSS Statistics 24.0 (IBM, Chicago, IL, USA) will be used as statistical software. Participants with missing primary or secondary outcome data are excluded. Continuous variables will be expressed as the mean ± standard deviation, and comparisons between groups will be performed by Student's t-test or Mann-Whitney U test. Categorical variables will be expressed as rates and percentages, and χ^2 test will be used for comparisons between groups. Multivariate logistic regression analysis was applied to identify independent risk factors for POPF. Kaplan-Meier survival curve will be adopted to analyze the distribution of DFS and OS, and a log-rank test will be used to compare the significance of survival between subgroups. Multivariate Cox regression analysis was adopted to select independent prognostic factors. Linear correlation analysis will be used to test the correlation between variables. P values less than 0.05 will be considered statistically significant.

Discussion

Pancreatic fistula is a common complication developing after pancreatic surgery, that can increase the risk of other postoperative complications and even lead to death. Previous studies have shown that early enteral nutrition does not aggravate POPF or

prolong drain placement or hospital stay in patients with POPF after pancreatectomy.[21 24 26] Our center is relatively conservative in terms of return to diet and drainage tube removal time. In our center, all patients usually start enteral nutrition on POD6. The abdominal drainage tube is typically placed for 2-3 weeks postoperatively based on the amount of postoperative drainage fluid and amylase level in the drainage fluid. Although prolonged placement of an abdominal drainage tube may increase the incidence of POPF, especially the grade B POPF, we prefer to retain abdominal drainage tubes for 1 month postoperatively. This may be the reason for the low incidence of re-puncture and drainage for a pancreatic fistula and the low readmission rate in our center.[27] However, the long fasting time may prolong the length of hospital stay and delay the recovery of postoperative gastrointestinal function.

This prospective randomised controlled trial will compare patients who start enteral nutrition on POD3 with patients who start on POD7 in terms of length of hospital stay, incidences of postoperative pancreatic fistula and postoperative complications, and long-term prognosis to further evaluate the feasibility and safety of early enteral nutrition. Different methods of enteral nutrition and surgical intervention may have an impact on POPF. If possible, stratified analysis will be adopted. Of course, since there are only 53 patients in each group, we speculate that the results may have insufficient power for detecting a significant difference in the incidence of POPF between the groups. However, if the length of postoperative hospital stay in this group is shorter, or the hospitalization cost is relatively lower without increasing the incidence of POPF, it will also be a meaningful discovery.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Trial status

The first patient was enrolled in this study on 7 December 2021, with 85 subjects having been recruited at the time of the final revision of this manuscript.

Ethics and Dissemination

Since the two enteral nutrition methods in this project are routinely performed in clinical practice, participation in this project will not increase the risk to patient safety. Patients need to attend the outpatient clinic for follow-up and undergo some necessary examinations after hospital discharge. All patients' data will be kept confidential and not disclosed. The patient's information will be represented by a unique number, and the coded information will be properly stored in the center. When the research information and data obtained from this study are published in scientific conferences or scientific journals, the identity of patients will not be disclosed. It is essential to obtain the signature of the informed consent, which must be signed by both the researcher and the participant, who will receive a copy. This study has been approved by Peking University Third Hospital Medical Science Research Ethics Committee (M2021395).

The study website (www.chictr.org.cn) contains all up-to-date information regarding the trial. Final trial results, whether positive, negative, or inconclusive, will be published in a peer-reviewed journal. Furthermore, the results will be presented at appropriate national and international conferences.

Acknowledgements
We gratefully acknowledge all the participants enrolled in this trial.

Author contributions
JYY conceived the study, prepared the initial protocol, and drafted the manuscript. DRX participated in designing the trial protocol, polished the language of the manuscript, and provided comments on the study statistical analysis. The authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Consent Not applicable.

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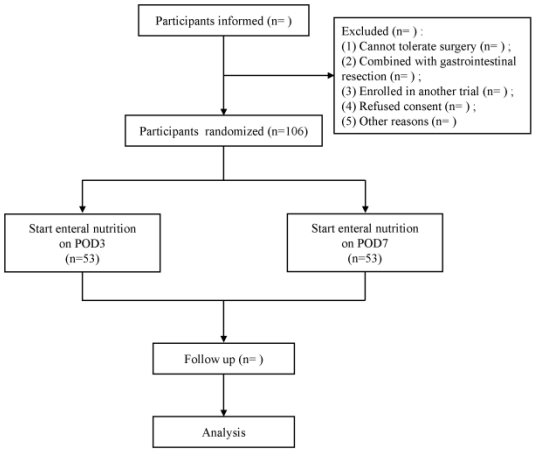
Figure 1 Flow chart of study pathway.



Flow chart of study pathway.

338x190mm (300 x 300 DPI)

Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors

INFORMED CONSENT DOCUMENT（V2.0　2021-9-9）

Please understand the possible risks and benefits of the research before you make an informed decision to participate in the study. This process is called informed consent. The Ethics Committee (EC) has approved the information in this consent form and approved the research physician to conduct this research. An Ethics committee (EC) is an independent group of experts and nonspecialists designed to help protect the rights of research subjects. It does not mean that the EC has approved your participation in the research or that the study is risk-free. This consent form may contain words that you do not understand. Ask the research physician or researcher to explain anything you do not clearly understand. You may take home an unsigned copy of this consent form to think about or consult with family, friends, or anyone you choose before making a decision. If you decide to participate in this research, you will be asked to read and sign this consent form to confirm that you have understood the study instructions and agreed to participate. You will receive a copy of the signed consent form. As you read this consent form, please note: "you" and "your" in the text refer to the person participating in the research and not to the parent/guardian or legally authorized representative who may have signed this consent form on behalf of the research participant.

Dear Sir/Madam:

We invite you to participate in clinical research entitled “Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors”. Before deciding to participate in this research, please read the following as carefully as possible to understand the research objectives, procedures, durations, and the benefits, risks, and discomfort associated with participating in the research. You can also discuss it with your kinsfolk or friends to help you decide whether to participate in the study. If you have any questions, please address them to the doctor or investigator responsible for the research. You are free to decide whether to take part in this research trial. If you choose not to participate, this will not affect the care you get from your doctors.

This informed consent form contains three parts. The first part is the introduction of this research and some problems that may encounter in the study, and the second part is the consent statement of the subjects. Please sign your name in the corresponding position in the second part after reading the first part carefully. The doctor or researcher will declare and sign in the last section.

PART1

1. Background of this subject

Postoperative pancreatic fistula (POPF) is one of the most common complications after pancreatic surgery. In 2016, the International Study Group of Pancreatic Surgery (ISGPS) revised the original classification definition of pancreatic fistula, renamed grade A pancreatic fistula as biochemical fistula, and no longer included in the pancreatic fistula. The definition of grade C pancreatic fistula is more strict. The postoperative pancreatic fistula increases the risk of other postoperative complications, such as bleeding, multiple organ failure, and even deaths.

Distal pancreatectomy and enucleation are the standard treatment for pancreatic body and tail tumors. The reported incidence of clinically relevant pancreatic fistula remains at 6%-34% due to the anatomical characteristics of the pancreas and the physiological characteristics of the patients. Despite the low mortality caused by pancreatic fistula, there's still a considerable percentage of patients suffering from readmission and percutaneous drainage.

In recent years, with the continuous deepening of the enhanced recovery after surgery (ERAS), an increasing number of studies have reported that ERAS does not increase the incidence of postoperative pancreatic fistula and other complications but can significantly shorten the length of postoperative hospital stay and accelerate the recovery of patients. However, most previous studies focused on pancreaticoduodenectomy and only a small number of researches on distal pancreatectomy.

Therefore, evidence regarding whether early oral intake can be tolerated in patients undergoing distal pancreatectomy or enucleation remains to be further explored in large randomized controlled trials.

2. The main contents of this subject

A total of 106 patients who underwent laparoscopic or open distal pancreatectomy or enucleation of pancreatic tumors at the Department of General Surgery of Peking University Third Hospital from December 2021 to June 2023 were enrolled in this study.

All patients were evaluated by detailed medical history collection, physical examination, imaging examination, and/or pathological biopsy. Researchers use a random number generator to generate a randomization scheme. According to the predetermined randomization scheme, eligible patients are randomized at 1:1 to either the early feeding group or the late feeding group. The patients in the early feeding group began enteral nutrition on the third day after surgery, and the patients in the late feeding group began enteral nutrition on the 7th day after surgery. According to the differences in postoperative conditions and long-term survival effects, the relevant data on perioperative characteristics and long-term survival were obtained. The subsequent radiotherapy, chemotherapy, and other comprehensive treatment for pancreatic cancer were provided according to the postoperative pathology and condition changes. This study was approved by the Ethics Committee of Peking University Third Hospital. The Ethics committee of Peking University Third Hospital has considered that the study complies with the principles of the Declaration of Helsinki and complies with medical ethics.

3. Process and deadline of this subject

This study requires your cooperation to complete the relevant examinations and treatment. Patients were followed up after hospital discharge by telephone, letter, or e-mail regarding long-term complications, survival, and quality of life.

4. Exclusion criteria (You will be considered unfit to participate in the study if one of the following occurs)

4.1. Patients cannot tolerate surgery, such as those with a history of cardiac infarction in the past six months, cerebral infarction, severe liver, kidney, or cardiopulmonary insufficiency;

4.2. Poor compliance of patients and their authorized surrogates;

4.3. Patients with combined gastrointestinal resection;

4.4. Enrolled in another trial.

5. Possible risks, discomfort, and inconvenience of participating in the study

The two enteral nutrition methods in this program are the current clinical practice, so participating in the program itself will not increase your treatment risk. This study does not involve the collection and use of blood, tissue, and other biological samples.

During the study period, you need to go to the hospital on time for follow-up and do some necessary

examinations, which will take up some time and may cause trouble or inconvenience.

After clinical treatment, including during the study period, if you suffered from any discomfort, new changes in your condition, or any unexpected situation, whether related to the study, you should promptly notify your doctor, who will make a judgment and give appropriate medical treatment.

6. The benefit of participating in the study

If you participate in the study, the findings will have important implications for clinical decision-making in all patients with this condition.

The benefit of participating in the study include specialized follow-up, reexamination clinic, and consultation. This project will set up a follow-up, reexamination, and consultation clinic so that you can get timely and comprehensive postoperative condition consultation and monitoring.

7. The costs of participating in the study

In this study, there are no tests outside your current routine diagnosis and treatment, which will not increase your treatment costs. At present, the examination items, surgery, and postoperative follow-up of this study are routine medical procedures, and do not require additional examinations or costs.

8. Treatment of study-related injuries

If you are injured as a result of participating in the study, Peking University Third Hospital will provide the necessary medical care immediately, and bear the cost of the treatment and the corresponding financial compensation by the relevant laws and regulations. Please contact Professor Xiu at ******.

If you experience any discomfort or any unexpected situation, whether related to new medical technology research, you should notify your doctor in time, he/she will make a judgment and provide medical treatment. Doctors will do their best to prevent and treat possible harm.

If an adverse event occurs during a clinical trial, the committee of medical experts will determine whether it is related to the clinical study. The hospital will provide treatment costs and corresponding financial compensation for study-related injuries.

9. Confidentiality of Personal Information

Your medical records (medical records, physical and chemical examination reports, etc.) will be kept completely in the hospital. Doctors (researchers), professional academic committees, ethics committees, and health supervision and management departments will be allowed to access your medical records. Your

identity will not be disclosed in any public report of the results of this study. We will make every effort to protect the privacy of your medical data within the scope of the law.

10. About refusal to participate or withdrawal

You may choose not to participate in this study, or withdraw at any time after informing the investigators without discrimination or retaliation. You will begin to take food 7 days after surgery, and your medical treatment and rights will not be affected.

If you do not comply with the study protocol, or have any other reason, you may be asked to withdraw from the study without your consent.

Your participation in this study is voluntary. If you have questions related to the study, research-related injury, or rights of participants, you can contact Professor Xiu at ******.

If you have any questions related to your rights and interests, or if you would like to express your dissatisfaction and concerns about participating in this study, please contact the Office of Research Ethics, Peking University Third Hospital, at ******.

PART2

The patient (subject) consented to the statement.

I have read the above description of the study and had the opportunity to discuss it with physicians and ask questions. All my questions were satisfactorily answered.

I am aware of the risks and benefits that may arise from participation in this study. I have known that participation in the study was voluntary. I confirm that I have had ample time to consider this and understand that:

- I can always ask my doctor for more information.
- I may withdraw from this study at any time without discrimination or retaliation, and medical treatment and benefits will not be affected.

I also know that if I withdrew from the study, especially for treatment reasons, it would be in my best interests and the best interests of the study if I informed my doctor of the changes in my condition and

completed the corresponding physical and physical examinations.

If I need to take any other medication as a result of a change in my condition, I will seek advice from my doctor beforehand or tell my doctor so afterward.

I consent to the health management supervision department, ethics committee, or professional academic committee to access my research data.

I will be provided with a signed and dated copy of the informed consent form.

Finally, I decided to participate in the study and follow my doctor's advice as much as possible. Participant:

Name_____ Date_____ Signature _____ Tel.：_____

The legal representative of the participant:

Name_____ Date_____ Signature _____ Tel.：_____

PART3

I have informed the subject of the background, purpose, procedures, risks, and benefits of " Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumors ". I have given him/her enough time to read the informed consent, discuss it with others, and answer his/her questions about the study. I have told the subject to contact Professor Xiu at any time when he or she has problems related to the research, and to contact the General Office of Research Ethics of Peking University Third Hospital at any time when he or she has problems related to his or her rights and interests, and provided accurate contact information. I have informed the subject that he may withdraw from the study at any time without any reason; I have informed that the subject will be given a copy of this informed consent form containing my signature and his/her signature.

Doctor (Researcher):

Name_____ Date_____ Signature _____ Tel.：_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	9
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	9
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each	5-6

		outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will	4

		assign participants to interventions	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary	6

		and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a Since the two enteral nutrition methods in this project are currently routinely performed in clinical practice, participation in this project will not increase the risk to patients.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a There's no auditing trial conduct
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a Protocol has not been modifications
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a This is a single-center trail
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial	6

trial care		care, and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a This trail will not collect, evaluat, and store biological specimens.