BMJ Open

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

Jingya Yuan , Dianrong Xiu

**To cite:** Yuan J, Xiu D. Effects of early enteral nutrition on pancreatic fistula and long-term prognosis after distal pancreatectomy or enucleation of pancreatic tumours in a major academic university hospital in China: protocol for a single-centre randomised controlled trial. *BMJ Open* 2023;**13**:e068469. doi:10.1136/bmjopen-2022-068469

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068469).

Received 19 September 2022
Accepted 07 July 2023



Department of General Surgery, Peking University Third Hospital, Beijing, Beijing, China

**Correspondence to**
Dianrong Xiu;
xiudianrong@163.com

## 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 tumours. We designed this trial to test the hypothesis that early feeding does not increase the incidence of POPF and positively influences the long-term prognosis in patients who undergo distal pancreatectomy or enucleation of pancreatic tumours.

**Methods and analysis** This is a prospective randomised controlled trial that will be conducted in a single centre. A total of 106 patients undergoing distal pancreatectomy or enucleation of pancreatic tumours 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

⇒ This study will be the first randomised controlled trial to compare the two feeding regimens after distal pancreatectomy and enucleation of pancreatic tumours since International Study Group of Pancreatic Surgery redefined and updated the classification of pancreatic fistula in 2016.
⇒ 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.
⇒ The study includes patients with different pancreatic tumour 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, International Study Group of Pancreatic Fistula (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. POPF increases the risk of other postoperative complications, such as bleeding, multiple organ failure and even death.[3–5]

Distal pancreatectomy and enucleation of pancreatic tumours are the standard treatment for pancreatic body and tail tumours. Compared with pancreatoduodenectomy, distal pancreatectomy and enucleation of pancreatic tumours 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

are still a considerable percentage of patients who require readmission and percutaneous drainage.[8–10]

The prevention of pancreatic fistula after distal pancreatectomy and enucleation of pancreatic tumours is still being debated with respect to intraoperative procedures, early postoperative nutritional support, the timing of drainage tube removal and the use of somatostatin analogues. Since fasting is an essential condition for inhibiting pancreatic secretion in patients with POPF, the necessity of 'nil per os' has been emphasised 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 POPF 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 programmes for laparoscopic distal pancreatectomy and to compare its financial impact compared with that of traditional management.[16] However, the key elements of ERAS programmes 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 haemorrhage, 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 tumours 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, POPF is the main observation index. Considering that this is a superiority trial, we can assume that the incidence of POPF in the early feeding group will be lower than that in the late feeding group according to the previous literature.[6] The sample size was calculated by PASS software. The incidence of POPF in the early feeding group and the late feeding group was 6.8% and 26.3%, respectively. With a type I error ($\alpha$=0.05) and type II error ($\beta$=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 tumour. 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 tumour 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 6 months, cerebral infarction, severe liver, kidney or cardiopulmonary insufficiency; (2) patients or their authorised 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 tumours), type of surgical intervention (robot-assisted, laparoscopic and open), operative time, intraoperative blood loss, tumour localisation, tumour size, pancreas texture, pancreatic thickness and diameter of the pancreatic duct, tumour 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 or nasojejunal feeding, on POD3 and patients in the late feeding group will begin enteral nutrition on POD7. The patient's body temperature, visual analogue scale score, ambulation, flatus and defecation and dietary status will be recorded daily. The patient's nutritional status (Body Mass Index/Prognostic Nutritional Index) is regularly monitored. The routine postoperative examination is arranged as follows: haemoglobin concentration, white 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 can tolerate 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 three 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 haemorrhage, abdominal abscess, disease-free survival (DFS), progression-free survival, hospitalisation 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. 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 V.24.0 (IBM, Chicago, Illinois, 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±SD, 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 $\chi^2$ 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 analyse the distribution of DFS and overall survival, 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.

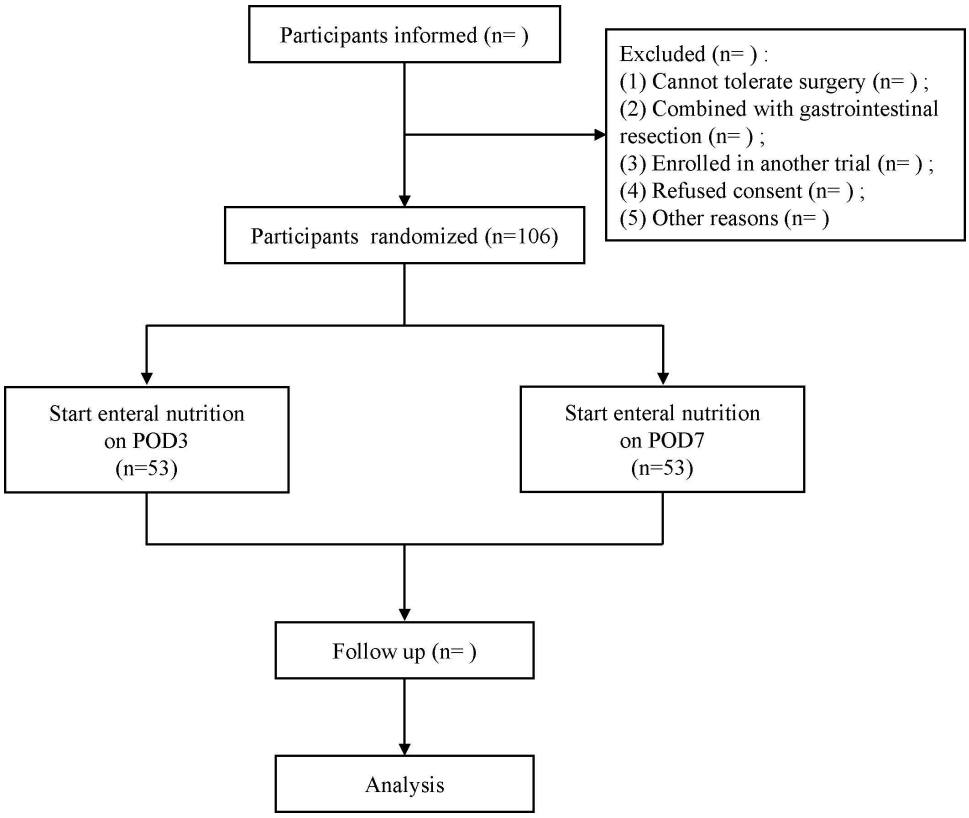


**Figure 1** Flow chart of study pathway. POD, postoperative day.

P values less than 0.05 will be considered statistically significant.

## DISCUSSION

Pancreatic fistula is a common complication developing 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 or prolong drain placement or hospital stay in patients with POPF after pancreatectomy.[21 24 26] Our centre is relatively conservative in terms of return to diet and drainage tube removal time. In our centre, 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 repuncture and drainage for a pancreatic fistula and the low readmission rate in our centre.[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 POPF 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 hospitalisation 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 centre. 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.

**Contributors** JY conceived the study, prepared the initial protocol and drafted the manuscript. DX 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.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**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.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.



**ORCID iD**

Jingya Yuan http://orcid.org/0000-0001-8697-0611

## REFERENCES

1 Bassi C, Dervenis C, Butturini G, *et al*. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;138:8–13.
2 Bassi C, Marchegiani G, Dervenis C, *et al*. The 2016 update of the international study group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017;161:584–91.
3 Ke ZX, Xiong JX, Hu J, *et al*. Risk factors and management of postoperative pancreatic fistula following pancreaticoduodenectomy: single-center experience. *Curr Med Sci* 2019;39:1009–18.
4 McMillan MT, Vollmer CM Jr, Asbun HJ, *et al*. The characterization and prediction of ISGPF grade C fistulas following pancreatoduodenectomy. *J Gastrointest Surg* 2016;20:262–76.
5 Smits FJ, van Santvoort HC, Besselink MG, *et al*. Management of severe pancreatic fistula after pancreatoduodenectomy. *JAMA Surg* 2017;152:540–8.
6 Wang Y, Li J, Weng Y, *et al*. A new enhanced recovery after surgery pathway for left-sided pancreatic cancer patients after distal pancreatectomy. *Transl Cancer Res* 2019;8:2613–20.
7 Probst P, Hüttner FJ, Meydan Ö, *et al*. Evidence map of pancreatic surgery-a living systematic review with meta-analyses by the international study group of pancreatic surgery (ISGPS). *Surgery* 2021;170:1517–24.
8 Van Buren G 2nd, Bloomston M, Schmidt CR, *et al*. A prospective randomized multicenter trial of distal pancreatectomy with and without routine intraperitoneal drainage. *Ann Surg* 2017;266:421–31.
9 Keung EZ, Asare EA, Chiang Y-J, *et al*. Postoperative pancreatic fistula after distal pancreatectomy for non-pancreas retroperitoneal tumor resection. *Am J Surg* 2020;220:140–6.
10 Maggino L, Malleo G, Bassi C, *et al*. Decoding grade B pancreatic fistula: a clinical and economical analysis and subclassification proposal. *Ann Surg* 2019;269:1146–53.
11 Fan BG. Effects of parenteral nutrition on the exocrine pancreas in response to cholecystokinin. *JPEN J Parenter Enteral Nutr* 2008;32:57–62.
12 Gilliland TM, Villafane-Ferriol N, Shah KP, *et al*. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. *Nutrients* 2017;9:243.
13 Karagianni VT, Papalois AE, Triantafillidis JK. Nutritional status and nutritional support before and after pancreatectomy for pancreatic cancer and chronic pancreatitis. *Indian J Surg Oncol* 2012;3:348–59.
14 Baron TH, DiMaio CJ, Wang AY, *et al*. American gastroenterological association clinical practice update: management of pancreatic necrosis. *Gastroenterology* 2020;158:67–75.
15 Richardson J, Di Fabio F, Clarke H, *et al*. Implementation of enhanced recovery programme for laparoscopic distal pancreatectomy: feasibility, safety and cost analysis. *Pancreatology* 2015;15:185–90.
16 Pecorelli N, Capretti G, Balzano G, *et al*. Enhanced recovery pathway in patients undergoing distal pancreatectomy: a case-matched study. *HPB (Oxford)* 2017;19:270–8.
17 Joliat G-R, Labgaa I, Petermann D, *et al*. Cost-benefit analysis of an enhanced recovery protocol for pancreaticoduodenectomy. *Br J Surg* 2015;102:1676–83.
18 Liu X, Chen Q, Fu Y, *et al*. Early Nasojejunal nutrition versus early oral feeding in patients after pancreaticoduodenectomy: a randomized controlled trial. *Front Oncol* 2021;11:656332.
19 Sun YM, Wang Y, Mao YX, *et al*. The safety and feasibility of enhanced recovery after surgery in patients undergoing pancreaticoduodenectomy: an updated meta-analysis. *Biomed Res Int* 2020;2020:7401276.
20 Hwang SE, Jung MJ, Cho BH, *et al*. Clinical feasibility and nutritional effects of early oral feeding after pancreaticoduodenectomy. *Korean J Hepatobiliary Pancreat Surg* 2014;18:84.
21 Klek S, Sierzega M, Turczynowski L, *et al*. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. *Gastroenterology* 2011;141:157–63,
22 Aoyama T, Kazama K, Murakawa M, *et al*. Safety and feasibility of enhanced recovery after surgery in the patients underwent distal pancreatectomy for pancreatic cancer. *J Cancer Res Ther* 2018;14:S724–9.
23 Nussbaum DP, Penne K, Speicher PJ, *et al*. The role of clinical care pathways: an experience with distal pancreatectomy. *J Surg Res* 2014;190:64–71.
24 Fujii T, Yamada S, Murotani K, *et al*. Oral food intake versus fasting on postoperative pancreatic fistula after distal pancreatectomy: a multi-institutional randomized controlled trial. *Medicine (Baltimore)* 2015;94:e2398.
25 Probst P, Zaschke S, Heger P, *et al*. Evidence-based recommendations for blinding in surgical trials. *Langenbecks Arch Surg* 2019;404:273–84.
26 Fujii T, Nakao A, Murotani K, *et al*. Influence of food intake on the healing process of postoperative pancreatic fistula after pancreatoduodenectomy: a multi-institutional randomized controlled trial. *Ann Surg Oncol* 2015;22:3905–12.
27 Wang H, Xiu D, Jiang B, *et al*. Postoperative pancreatic fistula in distal pancreatectomy: experience from 1 institution. *Pancreas* 2014;43:588–91.