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# Preoperative pancreatic stent placement before the enucleation of insulinoma located in the head and neck of the pancreas in proximity to the main pancreatic duct: study protocol for a multicentre randomised clinical trial in Chinese tertiary medical centres

Ruichen Gao ,[1,2] Bohui Yin ,[1,2] Jiabin Jin,[3,4,5] Xiaodong Tian ,[6] Yuhua Zhang ,[7] Jishu Wei,[8] Feng Cao ,[9] Zheng Wang,[10] Zhijun Ma,[11] Min Wang,[12] Shanmiao Gou ,[13] Lin Cong,[2] Qiang Xu ,[2] Wenming Wu ,[2] Yupei Zhao[2]

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For numbered affiliations see end of article.

**Correspondence to**
Dr Qiang Xu; xuqiang@pumch.cn,
Dr Yupei Zhao; zhao8028@263.net and
Dr Wenming Wu; doctorwuu@126.com

## ABSTRACT

**Introduction** The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stent placement before the EN have been demonstrated. Thus, a multicentre open-label study is being conducted to evaluate the efficacy and safety of stent placement in improving the outcome of EN of insulinomas in proximity to the main pancreatic duct.

**Methods and analysis** This is a prospective, randomised, open-label, superiority clinical trial conducted at multiple tertiary centres in China. The major eligibility criterion is the presence of insulinoma located in the head and neck of the pancreas in proximity (≤2 mm) to the main pancreatic duct. Blocked randomisation will be performed to allocate patients into the stent EN group and the direct EN group. Patients in the stent EN group will go through stent placement by the endoscopist within 24 hours before the EN surgery, whereas other patients will receive EN surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate measured by the International Study Group of Pancreatic Surgery standard. Both interventions will be performed in an inpatient setting and regular follow-up will be performed. The primary outcome (POPF rate) will be tested for superiority with the $X^2$ test. The difference in secondary outcomes between the two groups will be analysed using appropriate tests.

**Ethics and dissemination** The study has been approved by the Peking Union Medical College Hospital Institutional Review Board (K23C0195), Ruijin Hospital Ethics Committee (2023-314), Peking University First Hospital Ethics Committee (2024033-001), Institutional Review Board of Xuanwu Hospital of Capital Medical University (2023223-002), Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2023LSK-473), Institutional Review Board of Tongji Medical College Tongji Hospital (TJ-IRB202402059), Ethics Committee of Tongji Medical College Union Hospital (2023-0929) and Shanghai Cancer Center Institutional Review Board (2309282-16). The results of the study will be published in an international peer-reviewed journal.

**Trial registration number** NCT05523778.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A prospective multicentre clinical design to assess the efficacy and safety of a preventive intervention in improving the outcome of enucleation surgery.
⇒ Recruiting patients from multiple tertiary medical centres across China.
⇒ A local online communication tool will be exploited to promote interactions between investigators and patients.
⇒ The lack of blinding of the patients, surgeons, data collectors and data analysts is the limitation of the study.

## INTRODUCTION

Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with an estimated incidence of 1–4 per million per year.[1 2] They are insulin-secreting tumours that cause common clinical features including neuroglycopenia and autonomic nervous system disorders caused

by dysregulated secretion of insulin.[3–5] Surgical management remains the only curative modality for 90% of benign, localised insulinomas.[4 6]

According to several guidelines including the National Comprehensive Cancer Network and the European Neuroendocrine Tumor Society,[7 8] enucleation (EN), a parenchymal-preserving modality that could reduce the risk of late exocrine/endocrine insufficiency, should be considered as the first-line surgical approach for exophytic and peripheral insulinomas.[9]

However, in cases of endophytic insulinomas or tumours in proximity to the main pancreatic duct (MPD), the optimal choice of surgical intervention is controversial. Standard pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy, is indicated in guidelines as they aggressively eliminate normal pancreatic tissue, which can lead to long-term consequences including exocrine and endocrine pancreatic insufficiency.[10 11] Recently, duodenum-preserving pancreatic head resection (DPPHR) was alternatively recommended for the resection of large pancreatic neuroendocrine tumours.[12] In contrast, performing EN in cases with endophytic insulinomas and tumours in proximity to the MPD still baffles many surgeons as several retrospective researches suggested a significantly elevated rate of postoperative morbidity, especially postoperative pancreatic fistula (POPF). Lu *et al* compared postoperative morbidity between PD and EN, indicating a significant difference in POPF (18.1% vs 61.1%) between the two approaches,[13] and Heeger *et al* reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumours located ≤3 mm from the MPD.[14] Another study involving 52 patients who underwent EN also demonstrated a high POPF rate of 60% in the group of tumours located at less than or equal to 2 mm from the MPD.[15] Recently, Aussilhou *et al* suggested the proximity to MPD (<3 mm) as an independent risk factor of POPF in EN.[16] Therefore, preventive measures in EN that decrease the POPF rate would encourage the implementation of EN thus improving the long-term benefits for patients with insulinomas in proximity to the MPD.

POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative stenting is believed to prevent the MPD injury in that it not only helps to identify the location of MPD in the surgical field to prevent intraoperative damage but also decompresses pancreatic duct by reducing pancreatic juice leakage from the resection plane and providing support to the duct when stricture develops. Pertinent clinical evidence involving stenting and EN is still lacking. Some researchers reported the usage of preoperative stenting as a prophylaxis for EN,[17–21] and despite the fact that they all revealed the feasibility and safety of the technique, most of these researches involved a limited number of patients and were single-arm studies.

Based on the knowledge and shortcomings of this topic, our team has collected 18 patients undergoing preoperative stenting in our centre for 5 years. We retrospectively analysed the risk factor of postoperative complications, especially POPF, and discovered that the distance from insulinoma to MPD (≤2 mm) was an independent risk factor for POPF (OR=6.011, p=0.003). In addition, the preoperative pancreatic stent substantially reduced the incidence of POPF in patients with tumours located in proximity to the MPD (37.5% vs 71.4%, p=0.028).[22] Therefore, we launched the current clinical trial to assess the efficacy and safety of preoperative stenting before EN of insulinoma in the head and neck of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic Surgery (https://www.evidencemap.surgery/), this is the first trial of its kind.[23]

## METHODS AND ANALYSIS

### Study setting

This is a multicentre, double-arm, prospective, randomised trial in eight high-volume medical centres in China. Experienced surgeons will determine the eligibility of their patients and obtain informed consent forms (see online supplemental materials). Eligible patients with insulinoma in proximity to the MPD (≤2 mm) will be allocated randomly into two groups: stent EN group, where the pancreatic duct stents will be placed in patients by an endoscopist within 24 hours before the EN surgery, and direct EN group, where patients will receive direct EN surgery. An overview of the protocol is shown in figure 1. The study started in February 2023 and is planned to finish patient recruitment in December 2025.

### Endpoints

Primary endpoint: rate of POPF within 3 months after EN.

Secondary endpoints:

1. Rate of post-stent placement acute pancreatitis in stent EN group within 3 weeks after EN
2. Operation time
3. Intraoperative blood loss
4. Rate of postoperative abdominal infection within 3 weeks after EN
5. Rate of post-pancreatectomy haemorrhage (PPH) within 3 weeks after EN
6. Rate of postoperative lung infection within 3 weeks after EN
7. Rate of postoperative delayed gastric emptying within 3 weeks after EN
8. Rate of postoperative dyspepsia within 6 months after EN
9. Rate of postoperative hyperglycaemia within 6 months after EN
10. Total cost of hospitalisation

### Definition

In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by the International Study Group of Pancreatic Surgery.[24–26] Pancreatitis, abdominal infection, dyspepsia, lung infection and

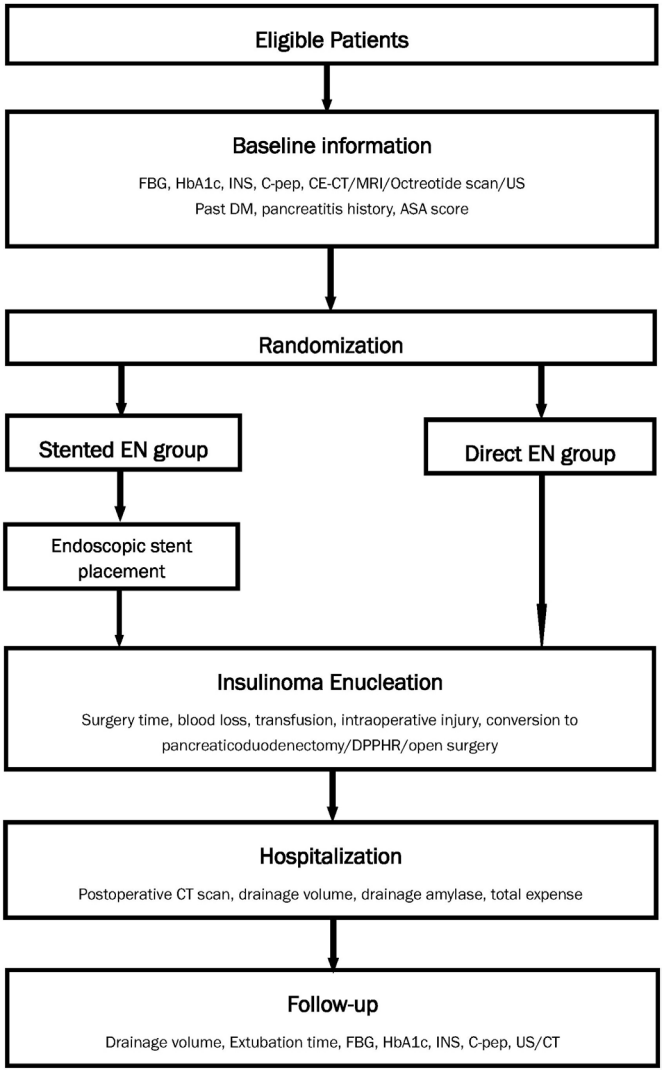


**Figure 1** Flow chart of the study. ASA, American Society of Anesthesiologists; CE-CT, contrast-enhanced CT; C-pep, C peptide; DM, diabetes mellitus; DPPHR, duodenum-preserving pancreatic head resection; EN, enucleation; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; INS, insulin; US, ultrasound.

hyperglycaemia will be evaluated based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe adverse events are defined as grade 3 or higher in CTCAE.

### Patients' eligibility

Inclusion and exclusion criteria are shown in box 1.

### Randomisation

Randomisation will be initiated by authorised investigators of the trial after checking the informed consent and the inclusion and exclusion criteria. Each eligible patient will be allocated an individual code/randomisation number, which has to be recorded in a case report form (CRF). Blocked randomisation (blocked number=4) for each centre will be performed using SAS OnDemand for Academics by the study assistant prior to the start of the enrolment.

**Box 1 Inclusion and exclusion criteria**

Inclusion criteria:
- ⇒ Age 18–75 years.
- ⇒ The clinical qualitative diagnosis of insulinoma is clear.
- ⇒ The localisation diagnosis is clear, and it was determined that the tumour is single, located in the head and neck.
- ⇒ The distance between the tumour and the main pancreatic duct is determined to be ≤2 mm by preoperative imaging (enhanced CT, MRI, etc).
- ⇒ Truly informed and voluntarily participate in this study, with written informed consent.

Exclusion criteria:
- ⇒ Maximum diameter of the tumour >2 cm proven pathologically.
- ⇒ Severe cardiopulmonary complications.
- ⇒ Combined with other known tumour diseases.
- ⇒ Invasive insulinoma or insulinoma with suspicious metastasis.
- ⇒ Previous upper abdominal surgery history.
- ⇒ Refusal or inability to cooperate in the study.

After randomisation, surgeons in all centres who enrol the patient will be informed of the intervention assignment.

### Blinding

Following recent academic recommendations on the implementation of blinding in surgical trials,[27] meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which comprise of patients, surgeons, data collectors, data analysts and outcome assessors. Patients participating in this study cannot be blinded due to the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records that are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts unviable. Recognising the critical importance of blinding in assessing primary and secondary endpoints, especially those related to complications, outcome assessors are kept blinded to participant group allocation. Based on our protocol, the assessment of endpoints is directly linked with objective clinical data which can be provided to independent assessors with blindness of allocation. This strategy plays a pivotal role in reducing potential bias in the assessment of primary and secondary outcomes while concurrently insulating the operating surgeon from

subjective judgement regarding clinical endpoints. Emergency unblinding is not deemed necessary.

### Study interventions

After baseline visit and admission, eligible participants will be randomised to the stent EN group or the direct EN group, as shown in figure 1.

### Preoperative MPD stenting

The preoperative pancreatic duct stent was regarded as a possible effective method to prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours before the EN endoscopically. The stent length should span the site of the tumour. The length and the diameter of the stent used will be recorded in the CRF. The stent will be removed by duodenoscopy about 3 months after surgery. Endoscopic stent placement and removal represent a common procedure at the Endoscopic Center of Peking Union Medical College Hospital and other centres and will be carried out by experienced endoscopists (minimum of 50 procedures) for the study. Any adverse events will be recorded in the CRF including stent-related pancreatitis. Blood amylase will be tested 2–4 hours after stenting before EN to discover potential stenting-related acute pancreatitis.

### Enucleation

During the surgery, intraoperative ultrasound will be performed to evaluate the location of the tumour and the distance between the tumour and MPD. The peripheral pancreatic lobule covering the tumour will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon will suture the lesion and suspend it, and then the insulinoma will be dissected from the normal pancreatic tissue. Dissection will be performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens will be regularly investigated to identify benign insulinomas. The operative field will be carefully examined and MPD disruption will be repaired immediately once detected. The prophylactic abdominal drainage tube will be applied. Intraoperative conversion (to open procedure, DPPHR or PD), surgery time, blood loss and transfusion volume will be recorded in the CRF.

### Postoperative management

General clinical treatment and pancreatic fistula prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume will be recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood will be routinely measured on the first, third, fifth and seventh postoperative days. Extubation would be considered if the drainage volume is less than 10 mL for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the drainage tube has not been removed at the time of discharge, the patient will be instructed to record the daily drainage until extubation in the outpatient setting.

### Follow-up

For the first 3 months after discharge, patients should maintain a regular follow-up session every 2 weeks through outpatient or telephone. The following information will be collected during each follow-up: basic information and the general condition of the patient, whether the patient has been extubated (if not extubated, record the recent drainage condition), recent medical interventions, and possible manifestations of dyspepsia or hyperglycaemia. Laboratory tests and imaging examinations will be done at the surgeon's discretion. Normally, CT or MRI scans will be performed routinely at 3 months postoperatively, just before stent removal, and then again 3 months after the stent removal.

### Statistical methods

#### Hypothesis

##### *Null hypothesis*

The rate of POPF in patients who undergo MPD stent placement before EN is not less than that of patients who undergo EN directly.

##### *Alternative hypothesis*

The rate of POPF in patients who undergo MPD stent placement before EN is less than that of patients who undergo EN directly.

#### Sample size calculation

In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the MPD who underwent EN were included, of which 16 had stent placement and 28 had no stent placement, and the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the above-mentioned POPF rate in two conditions, 38 evaluable patients per group will provide 85% power to reject the null hypothesis in a Z test (unpooled) for superiority at a one-sided significance level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically relevant difference. Therefore, 78 patients in total are to be recruited in the study considering possible dropout.

#### Statistical analysis

The primary outcome (rate of POPF) will be tested for superiority with a $X^2$ test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: first, after about 50% of the patients have been discharged and second, after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% CIs. Differences in secondary outcomes between two groups will be analysed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, $X^2$ tests, Fisher's exact tests, etc).

## Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by the Peking Union Medical College Hospital Institutional Review Board (approval number K23C0195), Ruijin Hospital Ethics Committee (2023-314), Peking University First Hospital Ethics Committee (2024033-001), Institutional Review Board of Xuanwu Hospital of Capital Medical University (2023223-002), Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2023LSK-473), Institutional Review Board of Tongji Medical College Tongji Hospital (TJ-IRB202402059), Ethics Committee of Tongji Medical College Union Hospital (2023-0929) and Shanghai Cancer Center Institutional Review Board (2309282-16), and registered in ClinicalTrials.gov (NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki.[28] Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits and inspections. Results will be published in an international peer-reviewed journal.

In response to the submission and approval of our protocol, several modifications have been incorporated into the study design, all of which have undergone thorough scrutiny and received approval from our ethics committee. First, a new time point at postoperative day 7 has been added for the measurement of amylase levels, leveraging the existing practice of routinely measuring amylase levels for all patients at this time point. Second, we have introduced an exclusion criterion based on the maximum diameter of the tumour (>2 cm), a feasible addition given that no enrolled patients before this change met the exclusion criteria. Third, a significant refinement involves blinding outcome assessors, a practicable adjustment as assessors can re-evaluate outcomes solely based on the information recorded in the CRF. Lastly, we have clarified that the primary outcome measurement will occur at 90 days postoperatively, enhancing precision in reporting the study's findings. These modifications aim to strengthen the study's scientific integrity, participant safety and overall methodological rigour.

## Patient and public involvement

Throughout the study, a study account based on a local online communication tool (WeChat) will be established to receive any suggestions and consultations from patients involved, and information about the study will be updated for all patients who subscribed to the study account.

## DISCUSSION

Generally, EN is preferred to other operation approaches in treating insulinomas, as it circumvents complicated reconstructions and possible subsequent complications. However, POPF is common in the EN of insulinomas that are proximal to MPD, which limits its clinical application. In this clinical trial, we aim to demonstrate the safety and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies have shown promising effects of MPD stent in the prevention of POPF but with limited evidence. In this study, we aim to include patients who are prone to suffer from POPF to validate the efficacy of MPD stent. In our previous research, we demonstrated the distance from insulinoma to MPD (≤2 mm) was an independent risk factor for POPF. Therefore, it is a reasonable and feasible choice to confine patients whose tumours are 'deep' in our ongoing trial. Preoperative MPD stent placement, as an extra intervention procedure for treating insulinoma, is still a vague yet practical technique in the prevention of POPF. Thus, the conduction of this clinical trial in a randomised controlled way is under the general ethical principle of clinical equipoise according to our present knowledge. In this way, the result of this multicentre, prospective, randomised control clinical trial can offer substantial information on the feasibility of this approach, and thus hopefully widen the indication of EN and partially alter the treatment pathway of insulinoma.

**Author affiliations**
[1]Peking Union Medical College, Beijing, People's Republic of China
[2]Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, People's Republic of China
[3]Department of General Surgery, Pancreatic Disease Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
[4]Research Institute of Pancreatic Diseases, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
[5]Department of General Surgery, Ruijin-Hainan Hospital, Shanghai Jiao Tong University School of Medicine, Hainan, People's Republic of China
[6]Department of Hapatobiliary and Pancreatic Surgery, Peking University First Hospital, Beijing, People's Republic of China
[7]Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, People's Republic of China
[8]Pancreas Center, The First Affiliated Hospital With Nanjing Medical University, Nanjing, Jiangsu, People's Republic of China
[9]Xuanwu Hospital, Beijing, People's Republic of China
[10]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, People's Republic of China
[11]Panjin People's Hospital, Panjin, Liaoning, People's Republic of China
[12]Department of Biliary-Pancreatic Surgery, Huazhong University of Science and Technology Tongji Medical College Tongji Hospital, Wuhan, Hubei, People's Republic of China
[13]Department of Pancreatic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China

**Contributors** RG, BY, LC, QX, WW and YZhao participated in creating the study design. RG drafted the manuscript. JJ, XT, YZhang, JW, FC, ZW, ZM, MW and SG provided a critical revision of the manuscript. QX obtained the funding for this study. All the authors read and approved the final manuscript.

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**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** Consent obtained directly from patient(s).

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**ORCID iDs**
Ruichen Gao http://orcid.org/0000-0001-9244-2428
Bohui Yin http://orcid.org/0000-0003-4553-2943
Xiaodong Tian http://orcid.org/0000-0002-3129-2662
Yuhua Zhang http://orcid.org/0000-0002-1308-1992
Feng Cao http://orcid.org/0000-0001-7412-2455
Shanmiao Gou http://orcid.org/0000-0003-1988-0901
Qiang Xu http://orcid.org/0000-0002-6785-7178
Wenming Wu http://orcid.org/0000-0003-0691-8333

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