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Protocol

Version no.	v 1.0
Version date	2018-12-01

Protocol title:	Effect of laparoscopic versus open pancreaticoduodenectomy on overall survival in patients with resectable pancreatic cancer (TJDBPS07): A study protocol for a multicenter, randomized controlled clinical trial
Protocol number:	TJDBPS07
Investigating institute:	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology
Statistical analysis institute:	Tongji Medical College, Huazhong University of Science and Technology

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the applicable regulation–International Conference on Harmonization Good Clinical Practice (ICH GCP). The principal investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement via documented approval from the institutional review board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in this study have completed the Human Subjects Protection and ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes can be implemented in the study. All changes to the consent form will be approved by IRB; a determination will be made regarding whether new consent needs to be obtained from participants who have already provided consent, using a previously approved consent form.

18 PROTOCOL SYNOPSIS

Protocol title	Effect of laparoscopic versus open pancreaticoduodenectomy on overall survival in patients with resectable pancreatic cancer (TJDBPS07): A study protocol for a multicenter, randomized controlled clinical trial
Study number:	NCT03785743
Principal investigator:	Renyi Qin
Study center(s):	10
Study objective(s):	The broad goal of this trial is to evaluate the safety and efficacy of laparoscopic pancreaticoduodenectomy (LPD) and open pancreaticoduodenectomy (OPD) procedures. The main hypothesis is that LPD is non-inferior to OPD procedures in terms of overall survival in the treatment of pancreatic cancer. The primary outcome variable is the postoperative length of stay. The secondary outcome variables include estimated blood loss, operation time, complication rate, R0 resection rate, comprehensive complication index (CCI), and overall survival.
Study design:	This is a prospective, randomized, controlled, multicenter trial with two treatment arms: LPD versus OPD
Number of subjects:	200 patients
Study population:	All pancreatic cancer patients with an indication for pancreaticoduodenectomy
Surgical methods	Group 1: LPD Group 2: OPD
Study duration	7 years
Outcomes	The primary outcome variable is the 5-year overall survival rate. The secondary outcome variables include the overall survival, 3-year and 5-year disease-free survival rates, 90-day mortality rate, incidence of severe perioperative complications (Clavien–Dindo grade ≥III), length of stay, estimated blood loss, and operation time.
Eligibility	**Inclusion criteria** 1) Age between 18 years and 75 years. 2) Histologically confirmed or clinically diagnosed pancreatic cancer by an MDT without histopathologic evidence. 3) Patients feasible to undergo both LPD and OPD according to MDT evaluations. 4) Patients understanding and willing to comply with this trial.

	5) Provision of written informed consent before patient registration. 6) Patients meeting the curative treatment intent in accordance with clinical guidelines. **Exclusion criteria** 1) Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs. 2) Patients requiring left, central or total pancreatectomy or other palliative surgery. 3) Preoperative American Society of Anesthesiologists score ≥ 4. 4) History of other malignant disease. 5) Pregnant or breast-feeding women. 6) Patients with serious mental disorders. 7) Patients treated with neoadjuvant therapy. 8) Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data. 9) Body mass index > 35 kg/m2. 10) Patients participating in any other clinical trials within 3 months.
Statistical methods:	**Hypothesis:** Let u_1 denote the effect size in the LPD group and u_2 denote the effect size in the OPD group. The statistical hypothesis is H_0 : P1–P2 > - 10% H_1 : P1–P2 ≤ - 10% α = 0.05(two-sided) **General consideration:** (1) All statistical tests will be two-sided, with P<0.05 considered to represent a statistically significant difference and 95% confidence intervals (CIs). All data will be analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). (2) Quantitative data will be described by the number of cases, means, standard deviations, medians, interquartile ranges, and ranges. Qualitative data will be described as frequencies, constituent ratios, or percentages. In the effect research and comparison, we will select appropriate data sets according to specific research goals with the appropriate statistical analysis methods. In the intergroup comparison of qualitative data, we will use the χ^2 test; the independent samples t-test will be used to compare quantitative data between the groups. (3) Before data locking, the data set will be determined by the principal investigators together with the biostatistician. (4) The SPIRIT checklist was referred to when writing this study protocol.

1. INTRODUCTION

Pancreatic cancer is estimated to rank ninth among the most common cancers and fourth among the leading causes of cancer deaths in the United States.[1] Surgery (laparotomy or minimally invasive surgery) is the only potentially curative and preferred treatment for patients with pancreatic malignant tumors.[2] Previously reported studies have indicated that adjuvant chemotherapy after radical surgery could significantly enhance the curative effect and achieve promising improvements in overall survival and disease-free survival for patients with resected pancreatic adenocarcinoma.[3 4] As recommended by the National Comprehensive Cancer Network (NCCN) Guidelines for Pancreatic Adenocarcinoma (version 1.2019) and the Pancreatic Cancer Committee of the Chinese Anti-Cancer Association, radical surgery followed by adjuvant chemotherapy based on gemcitabine is a preferred and effective treatment strategy for patients with pancreatic cancer.[5 6]

Pancreaticoduodenectomy (PD), the standard procedure for resectable masses in the periampullary region, including pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures.[7] Since first performed and introduced by Gagner et al. in 1994, laparoscopic PD (LPD) has rapidly and widely spread owing to its potential technical advantages focusing on the precision of movements and three-dimensional view.[8 9] Recently, an increasing number of studies, including some large-scale multicenter randomized controlled trials have reported the safety and feasibility of LPD for the treatment of periampullary tumors.[10 11] In addition, several reports have focused on the comparison of LPD and open PD (OPD) in the treatment of pancreatic cancer. The results suggest that LPD yielded equivalent 5-year overall survival and superior perioperative clinical outcomes in comparison to OPD.[12] However, these reports were from retrospective studies, which are associated with inherent limitations such as patient selection biases, missing or incomplete data, and variables that were unaccounted for, making the results difficult to interpret definitively.

Accordingly, it is imperative to conduct prospective large-scale multicenter randomized controlled trials to analyze outcomes of interest and obtain high-level evidence. This TJDBPS07 trial aims to compare the long-term oncological outcomes and short-term surgical outcomes of LPD and OPD in the treatment of pancreatic cancer.

2. STUDY OBJECTIVES

The primary objective of this trial is to test the hypothesis that LPD is non-inferior to OPD procedures for the treatment of pancreatic cancer in terms of safety and feasibility, based on a composite primary endpoint of the 5-year overall survival rate. Simultaneously, the secondary endpoints, including the 5-year disease-free survival rate, 90-day mortality rate, incidence of severe perioperative complications (Clavien–Dindo grade ≥III), length of stay, estimated blood loss, and operation time, are set to assess the patient-related benefits of LPD for pancreatic cancer compared with OPD.

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Design

The TJDBPS07 trial is characterized as a prospective, multicenter, randomized controlled, non-inferiority, and open labelled study with two parallel groups and a primary outcome of overall survival.

3.2 Number of subjects

This study is a randomized parallel controlled non-inferiority design clinical trial with a 1:1 ratio between groups. With reference to the results of previously published clinical studies, the 3-year overall survival rates for patients with malignant pancreatic head tumors who underwent OPD and LPD are 31% and 41%, respectively. Assuming a non-inferiority cut-off value of -10%, a one-sided significance level of 0.025, and that a 0.85 degree of power should be obtained, a total of 180 patients are required for the two groups (90 patients in each group). Considering a drop-out rate of 10%, the sample size of the study was finally estimated to be 200 patients, with 100 patients in each group.

3.3 Randomization

We applied a stratified randomized block design for the 10 centers with a block number of four. The

randomization scheme was conceptualized using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Randomization will be centralized through a computer-generated system and performed in a parallel fashion. A data manager who is blinded to the data analysis or patient enrolment will generate the randomization schedule. Allocation will be announced and handled by the study coordinators only after baseline assessment and patient consent to participate in the study have been secured. The randomization schedule will not be available to study recruiters or physicians. Allocation will be conducted by the independent data manager. Specifically, when appropriate patients are enrolled, the researcher will inform the data manager, and then the random number and exact treatment group will be returned simultaneously.

3.4 Random number sequence

Each subject in the study will be uniquely identified by a 7-digit subject number with Arabic numerals. The subject number will start with 07, plus the 2-digit center number of the center where he/she is located, followed by the 3-digit subject number. For example, the number of the first enrolled subject at the first center is 0701001, and so on.

3.5 Randomization table storage

The randomization table will be generated by an independent statistician using the SAS statistical software, and the randomization parameters will be stored in the randomization table to ensure reproducibility of the randomization process. The randomization table and the number of seeds will be stored as randomization files at the ethics office of the group leader.

3.6 Image evaluation

Efficacy evaluation in this study is divided into evaluation by the investigators of the research center and evaluation by an independent reading committee (IRC). During the study period, a researcher authorized by the research center will evaluate and determine the continuous use of drugs among the subjects. Disease progression assessed by the investigator will be reviewed and confirmed by the IRC. Before the IRC confirms disease progression, the subject should be kept in the study as much as possible, unless the investigator believes that continuing the study confers a greater risk than benefit to the subject or that the patient has already experienced obvious tumor progression. For instance, the emergence of obvious new malignant lesions, regardless of the results of target and non-target lesions, will not affect the final results of efficacy evaluation. Among subjects who withdraw halfway without being assessed for the primary efficacy indicators, the primary endpoint still needs to be followed up (unless the subject withdraws informed consent or has begun another form of anti-tumor therapy). For more information on operations related to the IRC evaluation, please refer to the “Central Imaging Operation Manual” provided by the sponsor.

3.7 Study duration

The period of the study begins when the first patient signs the informed consent and ends 3 calendar years after the last enrolled patient has undergone surgery. The end of the study is defined as 3 calendar years after the last patient receives surgical treatment. Before the end of the study, the investigator can remove patients who will not continue to benefit from the study. At the end of the study, patients who the investigator believes can still benefit from the treatment in this study will be provided with the possibility of extending the treatment outside the trial protocol.

3.8 Blinding

Patients and surgeons are unblinded to the treatment, while the data collectors, outcome assessors, and data analysts are blinded. The primary endpoint of this study is the overall survival and cannot be influenced by the data collectors, outcome assessors, and data analysts who are blinded and are also not involved in the preoperative, perioperative, and postoperative management of the patients, and thus have no determination of the overall survival. The surgeons will only perform the surgery and will not be involved in postoperative management. The patients have little influence concerning the length of stay since they will be discharged immediately once the discharge criteria are met. Most of the criteria are objective conditions including a lack of need for any intravenous infusion, a fully healed incision without infection,

well-functioning major organs, and near-normal hematological parameters. These conditions will not be influenced by the patients even in the absence of blinding.

4. SUBJECT SELECTION AND WITHDRAWAL

Subjects must meet the following criteria before they are allowed to participate in this study. All medical or non-medical conditions of each enrolled subject are within the consideration range of whether they meet the test standards or not. The investigator should review, confirm, and record whether the subjects are suitable to participate in this study before they are included.

4.1 Inclusion criteria

1) Age between 18 years and 75 years.

2) Histologically confirmed or clinically diagnosed pancreatic cancer by an MDT without histopathologic evidence.

3) Patients feasible to undergo both LPD and OPD according to MDT evaluations.

4) Patients understanding and willing to comply with this trial.

5) Provision of written informed consent before patient registration.

6) Patients meeting the curative treatment intent in accordance with clinical guidelines.

4.2 Exclusion criteria

1) Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs.

2) Patients requiring left, central or total pancreatectomy or other palliative surgery.

3) Preoperative American Society of Anesthesiologists score ≥ 4.

4) History of other malignant disease.

5) Pregnant or breast-feeding women.

6) Patients with serious mental disorders.

7) Patients treated with neoadjuvant therapy.

8) Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.

9) Body mass index > 35 kg/m2.

10) Patients participating in any other clinical trials within 3 months.

4.3 Loss to visit

If a subject misses one scheduled follow-up and the researcher is unable to establish contact within 7 days, this will be considered a loss to visit.

If the subject is unable to return during the specified visit period, the investigator should take the following measures. Before confirming that the subject is lost to visit, the investigator or authorized researcher shall try his best to contact the subject (if possible, make more than 3 calls or send messages via SMS or WeChat), and record efforts made in the subject's medical history or research files. The researcher should try to contact the subject and reschedule a visit within 7 days. The researcher should emphasize to the subject the importance of the return visit according to the plan, and at the same time determine the subject's willingness to continue participating in the trial. If the subject is still unable to establish contact, this will be considered a withdrawal, and the reason for withdrawal is recorded as loss to visit.

4.4 Withdrawal

The subject has the right to withdraw from the study at any time for any reason, and the researcher can also decide to withdraw the subject from the study at any time. If such withdrawal occurs or if the subject fails to return for follow-up evaluation, the investigator must determine the main reason for the early withdrawal and record this information. Subjects can withdraw from the study for any of the following reasons:

1. The implemented treatment is proven to violate the study protocol
2. Incomplete data leading to effects on the estimation of efficacy or safety
3. Inability to tolerate surgery and subsequent adjuvant therapy
4. Patients voluntarily ask to quit for personal reasons
5. Cases histologically confirmed as not pancreatic cancer
6. Cases intraoperatively/postoperatively confirmed to be locally advanced
7. Patients intraoperatively/postoperatively confirmed to have distant metastases
8. Loss to visit

If the subject withdraws from the study, a complete final clinical evaluation of the patient should be performed. If subjects withdraw from the study due to adverse events (AEs) or abnormal laboratory test results, these specific events need to be recorded in detail.

5. TREATMENT TECHNIQUES

5.1 LPD techniques

The standard operative technique is described as follows. Any small variations according to the surgeon's preference, such as a different order in surgical steps, a variation in approach, or pancreatic anastomosis technique, will be allowed but must be recorded authentically in the case record form.

All procedures are to be performed by two regularly trained pancreatic surgeons. Patients will be under general anesthesia and placed in a supine position; an anti-Trendelenburg position (10–30°) may be used, if necessary. The right arm will be placed along the body and the left arm at 90° abduction for accessing arterial monitoring. A 12-mm trocar (Versaport™; Covidien, Dublin, Ireland) will be placed slightly lower than the umbilicus, and pneumoperitoneum established. Two 12-mm trocars will then be placed, both lateral to the first trocar on the right and left in the midclavicular lines. Another two 5-mm trocars will be placed at the right and left infracostal arches on both sides of the anterior axillary line (3–4 cm subcostally). Diagnostic laparoscopy will be performed to rule out any abnormalities and metastasis. The cystic duct and artery will be transected, and the gallbladder will be moved and set aside. The round ligament will be retracted to the anterior abdominal wall, possibly with a suture, according to the surgeons' experience. The lesser sac will be opened, and a Kocher manoeuvre will be performed, thereby, mobilising the duodenum. The gastro-epiploic artery and vein will be transected. The distal stomach will be transected on the left side of the pylorus with an endostapler (Endo GIA™ Auto Suture, Covidien) after temporarily removing the nasogastric tube. The common hepatic arteries on the inferior border of the pancreas will be suspended with a rubber band. Lymph node station 8a will be dissected. Subsequently, the right gastric artery and gastroduodenal artery will be ligated and transected with at least two Hem-o-lok clips (WECK® Polymer Ligation System; Teleflex Incorporated, PA, USA) and one firm ligation (Ethicon®; Johnson & Johnson, NJ, USA). The portal vein (PV) will be identified at the superior border of the pancreatic neck, and the superior mesenteric vein (SMV) will be identified at the inferior border of the pancreas. A tunnel will be created posterior to the pancreatic neck and anterior to the SMV and PV. The pancreas will be slung with a vascular blocking band and then transected with ultrasonic shears (THUNDERBEAT; Olympus America Inc., PA, USA), while the pancreatic duct will be transected sharply with scissors and intubated to ensure patency. The jejunum will be transected approximately 15 cm from the ligament of Treitz with an endostapler (Endo GIA™ Auto Suture, Covidien). After retracting the duodenum and jejunum to the right side of the mesenteric root, the duodenum will be stretched and the uncinate process mobilized. The branches of the SMA and SMV will be carefully handled until the uncinate process is fully dissected. Retroportal lymph nodes will be resected according to the International Study Group on Pancreatic Surgery guidelines.[18] The common hepatic duct will be tunnelled and transected for anastomosis.

Preparation of the pancreatic stump and jejunal loop: The pancreatic stump remnant will be dissected

to approximately 0.5 cm (no more than 1.0 cm) in length, and careful hemostasis will be established with ultrasonic shears or absorbable sutures. A size 6–8 Fr plastic catheter will then be inserted as a stent into the pancreatic duct remnant to prevent pancreatic duct stenosis after suture placement. The jejunal limb will be brought up to the right of the middle colic vessels in a retrocolic manner, and the blind end will be placed near the pancreatic remnant. Negative resection margin status on the frozen section of the specimen will be confirmed before intracorporeal reconstruction if malignancy is suspected.

Pancreaticojejunal anastomosis: An embedding end-to-side pancreaticojejunal anastomosis, including four layers of mattress sutures, will be constructed.[19] The first layer of the anastomosis will be created between the posterior wall of the pancreatic stump and the posterior seromuscular layer of the jejunum. Two completely transpancreatic 4-0 prolene (Premilene; B. Braun Medical Ltd., Sheffield, UK) mattress sutures will be placed at a point approximately 0.2 cm from the superior and inferior edges of the main pancreatic duct, respectively. The most critical surgical step in the placement of the first and second mattress sutures will be interlocking them in the posterior wall of the jejunum. Care should be taken to pre-set the sutures to avoid passing them through or injuring the main pancreatic duct. Both mattress sutures will be preplaced approximately 0.5 cm from the cut edge of the pancreatic remnant. The number of these sutures varies depending on the size of the pancreatic duct but typically ranges from two to four sutures. After a small, full-thickness jejunotomy is created in line with the pancreatic duct, the second layer of the anastomosis will be created between the posterior wall of the pancreatic stump and the posterior wall of the small jejunal hole. Two completely transpancreatic 4-0 prolene mattress sutures will be placed following the first two sutures, while a full-thickness mattress suture in the posterior wall of the small hole will be placed in the jejunum approximately 0.2 cm from the edge. The third and fourth mattress sutures will be interlocked in the posterior wall of the jejunal hole. The posterior wall of the jejunal loop will then be tightly anastomosed with the posterior wall of the pancreatic stump without any remaining suture intervals. The third layer of the anastomosis will be created between the anterior wall of the pancreatic stump and the anterior wall of the jejunum. Two incompletely transpancreatic interlocking 4-0 prolene mattress sutures will be placed as described for the second layer of the anastomosis. However, the mattress sutures will not completely penetrate the pancreatic parenchyma but only enter the tissue halfway. The fifth and sixth mattress sutures are supposed to interlock in the anterior wall of the jejunal hole. The fourth layer of the anastomosis will be created between the anterior wall of the pancreatic stump and the anterior wall of the jejunum. Four incompletely transpancreatic interrupting 4-0 prolene mattress sutures will be placed to close the gaps in the superoinferior margin of the anastomosis to strengthen the sutures on its anterior wall, achieving a pancreatico-enteric anastomosis. Approximately 10 cm distally, an end-to-side hepaticojejunostomy will be constructed with running (bile duct dilatation of >5 mm) or interrupted (bile duct dilatation of ≤5 mm) sutures (Novosyn; B. Braun Medical Ltd.). Approximately 40 cm distal to the biliary anastomosis, an antecolic side-to-side gastroenterostomy will be created with the staple technique, and two layers of running 3-0 sutures (Novosyn; B. Braun Medical Ltd.) will be used to close the gastric stump. Two 27 Fr surgical drains will be placed through the foramen of Winslow and the upper region of the pancreaticojejunal stoma. After achieving hemostatic control, the trocars will be removed. The specimen will be extracted through an upper-middle incision, which will be subsequently closed in layers together with the closure of the trocars. A video clip for illustrative purposes of the basic laparoscopic surgical procedure is available upon request.

5.2 OPD techniques

OPD will be performed by the same group of surgeons. A right-sided rectus muscle abdominal incision is preferred for better exposure. The key steps are similar to those taken in the LPD group. Since outcomes of OPD worldwide are promising and convincing, the surgical technique in the OPD arm reflects their usual practice; also, the anastomoses will be performed according to the protocol of each center. Procedural variations according to the surgeon's preferences are allowed but must be recorded on the case record form. Two surgical drains will be placed as described in the LPD procedure.

5.3 Conversion from LPD to OPD

Conversion is defined in any patient in the LPD group for whom a skin incision is used for reasons other than trocar placement or specimen removal. The data of subjects allocated to LPD who undergo intraoperative conversion to OPD will be analyzed in the LPD group according to intention-to-treat (ITT) principles. Reasons for conversion should be carefully recorded in the surgical record.

5.4 Postoperative management

Postoperatively, antibiotics will be administered in addition to either parenteral or enteral nutrition. Somatostatin analogues are not routinely used for preventing postoperative pancreatic fistula (POPF). The abdominal drains will be kept in place for observation and removed if they are not productive and/or the presence of a pancreatic fistula or bile leakage is excluded. Amylase level determination in the drains will be performed on the third postoperative day or when a fistula is suspected following the criteria of the International Study Group of Pancreatic Fistula (ISGPF). Information regarding the management of pancreatic fistula, including antibiotic administration, enteral or parenteral nutrition, administration of therapeutic somatostatin analogues, and percutaneous or endoscopic interventional drainage, will be recorded. Patients will be discharged when the following criteria are met: (1) no need for intravenous infusion, (2) able to ingest solid or semisolid food, (3) no need for analgesics or fully comforted by orally analgesics, (4) incision is fully healed without infection, (5) able to get out of bed without assistance, (6) can walk at least 250 meters on a flat floor, and (7) major organs functioning well and near-normal hematological parameters. The operating surgeons will not be involved in the postoperative management, and hence, cannot influence the discharge of the patients.

5.5 Postoperative adjuvant treatment

5.5.1 Indications for postoperative adjuvant chemotherapy

After completing surgical treatment, subjects pathologically diagnosed with pancreatic ductal adenocarcinoma should receive postoperative adjuvant chemotherapy in accordance with the NCCN recommendation.[5]

5.2.2 Postoperative adjuvant chemotherapy procedures

In this study, gemcitabine-based chemotherapy will be recommended. The adjuvant chemotherapy cycle lasts for six months (six months after surgery). Based on the patient's physical strength and tolerance, the first chemotherapy regimen should be initiated within 8 weeks after surgery, and then administered regularly.

During chemotherapy, the follow-up plan should be used to assess whether there is tumor recurrence. If tumor recurrence occurs during chemotherapy, the adjuvant chemotherapy regimen in this study should be stopped, and each participating research center should determine its own follow-up treatment plan based on clinical practice. Information regarding tumor recurrence and the follow-up treatment plan should be recorded in the case report form (CRF). If there is no tumor recurrence during chemotherapy, adjuvant chemotherapy should be completed within six months. The presence of tumor recurrence should be continuously evaluated according to the follow-up plan.

Written informed consent should be obtained prior to adjuvant chemotherapy. Patients who refuse postoperative adjuvant chemotherapy or have not completed the entire adjuvant chemotherapy cycle will not be considered as discontinued cases in this study; however, details and the reason should be recorded in the CRF.

Adjuvant chemotherapy, toxic reactions, and intolerance dose adjustment principles should follow the published drug toxicity and dose adjustment guidelines for each chemotherapy regimen, which are not explained in detail in this protocol.

5.2.3 Safety evaluation indexes of postoperative adjuvant chemotherapy

Before and after each postoperative adjuvant chemotherapy cycle, the researcher should immediately fill in the safety evaluation indicators for the study participants. The specific contents include:

1. Physical state (Eastern Cooperative Oncology Group [ECOG] score);

2. Subjective and objective state (according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0 abbreviated record);

3. Results of blood tests:

- Peripheral venous blood evaluation: white blood cell count, hemoglobin concentration, and platelet count
- Blood biochemistry parameters: levels of albumin, sodium, potassium, total bilirubin, aspartate transaminase, alanine transaminase, and creatinine
- Serum tumor markers: carbohydrate antigen 19-9, cancer antigen 125, carcinoembryonic antigen levels

4. If necessary, the following safety assessment items should be implemented during chemotherapy (please refer to CTCAE version 3.0):

- Neurotoxicity
- Cardiovascular toxicity (cardiotoxicity, ischemic heart disease, etc.)
- Bone marrow suppression and infection caused by immune dysfunction
- Other(s)

6. ENDPOINTS

6.1 Primary endpoints

The primary outcome is the 5-year overall survival rate.

6.2 Secondary outcome measures

The secondary outcomes include the following variables:

1. Long-term outcomes: the 3-year overall survival rate, 5-year disease-free survival rate, and 3-year disease-free survival rate;

2. Intraoperative-related indicators: operation time, intraoperative blood loss, intraoperative blood transfusion, pancreatojejunostomy, gastrointestinal anastomosis, gastrointestinal anastomosis time, and pancreatic duct diameter;

3. Intraoperative complications: bile duct injury and nerve injury;

4. Perioperative indicators: postoperative hospital stay, ICU stay, time to get out of bed, time to resumption of oral feeding, time to removal of the drainage tube, postoperative drainage fluid volume, and amylase level;

5. Postoperative pain and analgesic consumption: visual analogue scale (VAS) pain score and analgesic consumption;

6. Postoperative complications: POPF,[13] postoperative hemorrhage (PPH),[14] delayed gastric emptying (DGE),[15] bile leakage,[16] systemic inflammatory response syndrome, abdominal infection, reoperation, Clavien–Dindo classification,[17] and comprehensive complication index score[18];

7. Short-term outcomes: 30/90-day mortality rate and 90-day unplanned readmission rate;

8. Quality of life: changes in the patient's quality of life before surgery, after discharge, and 6 months after surgery; and

9. Economic indicators: surgical expenses and hospitalization expenses.

7. RESEARCH PROCEDURES AND DATA COLLECTION

7.1 Screening period

The screening period starts with the signing of the informed consent form and ends with the completion of randomization or screening failure. Subjects who exit the study after signing the informed consent form and before the start of randomization will be regarded as cases of screening failure. Subjects must sign an informed consent form before proceeding with any screening procedures specified in the study.

The admission of patients will be discussed and decided by the pancreatic MDT of the participating centers.

All patients who are suspected to be enrolled will be evaluated by the following standard procedures: enhanced computed tomography (CT) scan of the upper abdomen (scanning interval, 1 mm), plain abdominal magnetic resonance scan + diffusion-weighted imaging to assess the extent of the disease and the condition of the pancreas. All patients with preoperative total bilirubin levels greater than 100 μmol/L will undergo percutaneous hepatic puncture drainage, and surgery will be considered when the total bilirubin concentration falls below 100 μmol/L. According to guidelines, pathological evidence does not need to be obtained in all patients before surgery.[19]

7.2 Before surgery (visit 1)

All patients will be subjected to preoperative gastrointestinal decompression, indwelling catheterization, gastrointestinal preparation, and indwelling central venous catheter placement. Postoperatively, patients will be subjected to intensive care, oxygen inhalation, blood glucose monitoring, central venous catheterization, postoperative monitoring of serological indicators, and weekly review of abdominal imaging. The following criteria must be met prior to discharge: no intravenous fluid treatment; eating semi-liquid or solid food; adequate pain relief through oral analgesic administration; adequate incision healing without signs of infection; adequate recovery of organ function; free movement (e.g., walking on a flat floor for at least 250 meters); and the major hematologic parameters are basically back to normal.

The preoperative evaluation and examination would involve: 1) chest X-ray examination, 2) plain CT scan/magnetic resonance imaging/positron emission tomography/abdominal ultrasound examination, and 3) 12-lead electrocardiogram examination. Examination results obtained within 6 weeks before the operation will be deemed valid.

Within 10 days before the operation, the following must be completed:

1. Sign informed consent form;
2. Collect data regarding demographics, medical history, and baseline concomitant diseases;
3. Collect and record information about all concomitant medications (including prescription and non-prescription drugs) used in the current and past 12 weeks;
4. Life quality assessment;
5. ECOG score assessment;
6. Height (in cm) and weight (in kg) measurement;
7. Standard preoperative laboratory examinations; and
8. Screening for admission criteria, completion of randomization, and recording the results of randomization.

7.3 Intraoperative (visit 2)

The following will be completed during this visit:

1. Operation according to the results of randomization: LPD or OPD;

2. Record detailed information during and after the operation (including details of the operation, intraoperative complications, blood transfusion, and other special information related to the operation); and

3. Record histopathological information including surgical margin status (R0 resection rates), number of retrieved lymph nodes, number of positive lymph nodes, tumor location, size of the tumor, depth of invasion (T classification), lymph node status (N classification), American Joint Committee on Cancer pathological stage (eighth edition), and histological type.

7.4 Short-term postoperative follow-up (visits 3–7)

The following will be assessed at 1 day, 1 week, 1 month, 3 months, and 6 months after surgery:

1. Laboratory inspection indicators;

2. ECOG score;

3. Postoperative wound recovery and wound pain level (VAS pain score);

4. Drainage of each drainage tube after operation;

5. Postoperative recovery (getting out of bed, imported food, etc.);

6. Weight;

7. AEs;

8. Concomitant medications; and

9. Postoperative complications.

7.5 Long-term postoperative follow-up (visit 8)

Each participant will be followed up every 3 months in the first year after surgery, and every 6 months from the second year onwards. Starting from the 6th month after surgery, follow-up will be carried out as follows:

1. Clinical evaluation including physical assessments (such as weight);

2. Assessment of AEs related to chemotherapy;

3. Histological confirmation of disease recurrence or metastasis to prove the existence of tumor recurrence or metastasis. Here, we will record the date of recurrence, location, and follow-up treatment; and

4. The date of death will be recorded and every effort will be made to determine the cause of death (which may be related to disease or treatment).

8. ADVERSE EVENTS

8.1 Definitions of AEs

An AE is defined as any adverse sign, symptom, or medical condition that occurs after a patient provides informed consent (or the deterioration of any pre-existing condition), regardless of its relation to treatment.

A treatment-related AE is defined as an AE that occurs after surgical treatment, but not before, or any aggravated AE that occurs after surgical treatment.

Information on the occurrence of AEs should be obtained through non-directed questioning of patients during the screening process after signing the informed consent form and at each visit in the study. AEs can also be detected voluntarily by patients during follow-up, or through physical examination, laboratory tests, or other evaluations. Each AE will be evaluated as much as possible to determine:

1. Severity classification (CTCAE grade 1–5);

2. Starting and ending dates;

3. Interrelationship with research and treatment;

4. Measurements taken for research or the study treatment (none, temporary interruption, drug treatment, surgical intervention, unknown, or not applicable);

5. Outcome (unrecovered/unrelieved, recovery/remission, recovery/remission, recovery/remission but with sequelae, lethal, or unknown); and

6. Whether it is a serious AE (SAE), as defined in section 8.4.

Once detected, any AE should be followed up until it is resolved or is adjudged to be permanent. At each follow-up or visit, any change in severity, the relationship with the study treatment, interventional measures, and the outcomes of its treatment should be evaluated.

During the treatment, the natural progression or recurrence of malignant tumors will be recorded as part of the efficacy evaluation and should not be reported as AEs/SAEs.

The severity of AEs will be graded in accordance with CTCAE version 4.0. If there is no certain AE in the CTCAE grading system, the severity of the event shall be graded according to grades 1–5: mild, moderate, severe, life-threatening, and death, respectively:

1. Mild: Slightly uncomfortable, but does not interfere with normal daily activities;
2. Moderate: Severe enough to reduce or affect the comfort of daily activities;
3. Severe: Unable to work or carry out normal daily activities;
4. Life-threatening: Indicates a direct threat to life; and
5. Death.

8.2 Definitions of intraoperative AEs

(1) Intraoperative bleeding: Any occurrence of relevant blood loss that resulted in an action by the surgeon, which was described in the surgeon's or anesthesiologist's report, or for which there is evidence of urgent transfusion therapy during surgery.

(2) Injury of visceral organs or vessels: Any injuries to abdominal organs described in the surgical report, requiring additional surgical procedures that were unrelated to the predefined procedures.

(3) Anesthesia complications: Any complications occurring during surgery related to anesthesia that induced the interruption of the surgery or changed the normal course of the procedures.

(4) Conversion: Any reasons for conversion surgery should be carefully reported.

(5) Other complications: Other events leading to a deviation from the normal operation course, reported by the surgeons or anesthesiologist.

8.3 Definitions of postoperative AEs

The following postoperative events will be detected and recorded:

(1) Hemorrhage: Any evidence of PPH, including intraluminal and intra-abdominal bleeding. Descriptions of clinical signs and symptoms or the need for transfusion should be recorded. Reports of radiological (digital subtraction angiography) or endoscopic examinations or any surgical procedures should be included (if needed).

(2) POPF: Drain amylase levels will be monitored after surgery; the detection and severity of pancreatic fistula will be classified according to the criteria of the ISGPF.

(3) DGE: DGE will be defined according to the guidelines put forward by the International Study Group of Pancreatic Surgery.

(4) Bile leakage: Bilirubin drainage will be monitored after surgery, and any elevation in bilirubin levels or bile present in the diagnostic puncture of the abdominal cavity will be recorded.

(5) Wound infection: Superficial or deep surgical site infections are both considered and should be reported in the medical records. Superficial infections are considered when the skin or subcutaneous tissue is involved, whereas deep infection is considered when extending into the fascial layer.

(6) Intra-abdominal fluid collection/abscess: Evidence of collection of fluid material, with or without the characteristics of an abscess, confirmed via ultrasound, CT scan, or contrast-enhanced CT scan.

(7) Intestinal obstruction and ileus: Reported diagnosis based on clinical examination and signs of intestinal dilatation on abdominal X-ray.

(8) Wound hernia or dehiscence: Hernia or separation that occurred through a surgical incision in the abdominal wall deriving either from laparotomy or trocar incisions. All available data will be considered from medical records.

(9) Other complications: These include surgery-related complications, not classified by any of the above, and deriving from all available patient records.

8.4 Abnormal laboratory test results

Abnormal laboratory test results that constitute AEs (considered to be clinically significant, leading to clinical symptoms or signs, requiring combined treatment, or adjustments of treatment) should be recorded. Diagnoses are to be reported instead of symptoms or signs. These events are to be followed up until they return to normal, or the reason for the abnormality is identified in sufficient detail. If a certain laboratory abnormality can correspond to the symptoms/signs of a known or reported AE, it is not necessary to separately record the abnormal laboratory test result as another event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. As per CTCAE version 4.03, an event of grade 3 or worse will not automatically be indicated as an SAE unless it meets the following criteria for SAEs and/or is deemed to be one based on the researcher's judgment. According to the provisions of the research protocol, this laboratory abnormality may require suspension of treatment or special intervention; however, it may still constitute an AE by definition.

8.5 Serious AEs

An SAE is defined by at least one of the following characteristics:

1. Causes death or threatens life at any time;

2. Causes permanent or severe disability, deformity, or dysfunction; and

3. Requires hospitalization or prolonged hospitalization, unless the hospitalization is for social reasons and training without any deterioration in the overall condition of the patient; routine treatment or monitoring of the indications studied, without occurrence of any deterioration; or treatment for patients that do not meet any of the above SAE definitions and does not lead to hospitalization.

8.6 Report of serious AEs

To ensure the safety of patients, any SAE occurring after the patient has given written consent until at least 30 days after the patient has stopped treatment, regardless of whether it is suspected to be causally related to the trial, must be reported to the Ethics Committee of the Affiliated Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology within 48 hours of being informed. Any SAE that occurs during the 30-day period or after a confirmed and reported SAE will only be reported again if the investigator suspects a causal relationship with the study treatment. SAEs that occur at different time periods, or SAEs that are considered completely unrelated to previously reported events should be reported separately as new events.

All SAE information will be collected and recorded in the SAE report form. The investigator must evaluate and record the correlations between SAEs and the treatments.

When filling in the follow-up information, the follow-up information should be sent to the same contact person as the SAE report.

8.7 Acquisition of AE information

At each follow-up, the patient will be asked a standard unguided question to understand the patient's health status and medical-related changes. Patients will also be asked if they are hospitalized, if there have been any accidents, if they have taken any new drugs, or if they have changed their current treatment regimens. In addition to observations by patients or investigators, AEs should also be recorded from any data that can be collected (such as laboratory test values and physical examination findings) or safety documents related to the patient.

8.8 Causality assessment of AEs

The researcher's assessment of the causal relationship between AEs and surgical treatment is an important aspect of the AE record. The correlation analysis between surgery and AEs has the following four situational outcomes:

1. Definitely unrelated: There is no connection between the operation and the reported AE;

2. Possibly related: The treatment caused or promoted the occurrence of the AE; that is, the occurrence of the AE follows a reasonable time sequence starting from the operation and/or follows known operation-related reactions, but may also be caused by other factors;

3. Probably related: There is a clear sequence in the occurrence of the operation and the AE, and may be related to the operation. This will be based on known or previously reported surgical complications, or based on the judgment of the investigator's clinical experience; or

4. Definitely related: There is a clear causal relationship between the operation and the AE, and other conditions (complications, progression of the disease state, or reaction after medication) cannot explain the AE.

8.9 Severity assessment of AEs

The severity of the AE will be scored by the investigator as mild, moderate, or severe according to CTCAE version 4.0.

Changes in the severity of the AE should be recorded so that the duration of the event can be assessed at each intensity level. AEs characterized by intermittent occurrence need to be recorded in terms of the occurrence and duration of each AE.

8.10 Management of AEs

When any subject has an AE/SAE, besides the detailed records, it will be managed in accordance with the standard treatment measures and requirements of each center.

8.11 Research management committee

The research management committee includes clinical experts in pancreatic surgery, including the investigators participating in this trial and members of the hospital ethics committee.

9. DATA MANAGEMENT

9.1 Case report form

The CRF is a mode of recording clinical data in clinical trials. The researcher should record all relevant data of each subject in the trial in a timely and truthful manner. The researcher should not change the CRF data unless the change is really needed. The researcher should sign and indicate the date and reason for the change. The CRF will be kept by the main investigator after the completion of the trial. The completed CRF will be reviewed by the clinical monitor, and the content will no longer be modified. To ensure privacy, each subject's name on the CRF must be abbreviated in Pinyin.

9.2 Missing data

Bias due to missing data will be investigated by comparing the baseline characteristics of participants with and without missing values. Depending on the extent of missing levels, the predictors of missing values will be identified. The primary outcome analysis will be conducted according to the ITT approach and will be adjusted for the predictors of missing values as part of the sensitivity analysis. In addition, multiple imputation will be used to impute missing data, and the imputed data will also be analyzed as part of the sensitivity analyzes.

9.3 Data monitoring

The efficacy and safety data will be acquired 90 days after the patient signs the informed consent form and the initial visit. The secure data will be used to evaluate the severity of AEs based on the CTCAE 4.0 standard. All AEs will be recorded on the CRF, from the signing of the informed consent form to the end of the study. LinkDoc Technology (Beijing, China) will act as the independent third party and will conduct

data monitoring throughout the entire trial.

9.4 Database construction

Proofreading of records and establishment of the database will be performed by a specific statistician. Questionable data should be forwarded to the investigator for verification by a clinical research assistant. The investigator should verify it as soon as possible and return the verified data in time, and record the data a second time. After the database has been audited, the data will be locked by the main researchers and statisticians. To ensure data security, irrelevant personnel cannot access and modify the data, and the data must be backed up. Any data can only be changed after the principal investigator and the data administrator have signed a consent form.

9.5 Data preservation

The various raw data in this trial should be recorded in a timely, true, accurate, and complete manner. All materials of this clinical trial belong to the Affiliated Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. Other investigators can apply for the use of relevant data from the main investigators. The investigators are not allowed to provide the data to a third party in any form.

10. STATISTICAL ANALYSIS

10.1 General considerations

The data from this study will be analyzed and reported following the CONSORT guidelines.[20] Before locking the database, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyzes pertaining to this research. Any deviations from the planned analyzes will be described and justified in the final integrated clinical study report.

10.2 Statistical analysis data sets

The full analysis set (FAS), the per-protocol analysis set (PPS), and the safety analysis set (SS) will be established. The efficacy analysis will be carried out based on the FAS and PPS. Demographics and baseline characteristics will be analyzed based on the FAS. Safety assessments will be performed using the SS.

(1) FAS: Based on the ITT principle, this refers to all patients who will undergo surgical treatment and who will have the primary outcome evaluation data after treatment.

(2) PPS: This is a subset of the FAS, and refers to patients who meet the following conditions in the FAS: (i) the primary outcome evaluation data are complete and (ii) no major protocol violations exist that will affect the primary outcome evaluation.

10.3 Statistical hypothesis

The primary outcome of this study is the 3-year overall survival rate. Assuming that the 3-year overall survival rate of the LPD group is P1, and the 3-year overall survival rate of the OPD group is P2, the null hypothesis (H_0) is H_0: P1–P2 > -10% and the alternative hypothesis (H_1) is: H_1: P1–P2 ≤ -10%, with an alpha level of 0.05 (two-sided) and a non-inferiority threshold of -10%.

The secondary outcome index and the test level of safety analysis will be performed using a two-sided α = 0.05. Differences with two-sided P<0.05 are considered to be statistically significant.

10.4 General analysis principles

(1) All statistical tests will be performed with a two-sided P<0.05 considered to represent a statistically significant difference with a 95% level of significance. All data will be analyzed using SAS version 9.4 (SAS Institute Inc.).

(2) Quantitative data will be described as the number of cases, means, standard deviations, medians, interquartile ranges, and ranges. Qualitative data will be described as frequencies, constituent ratios, or percentages. In the comparison of effects, we will select the appropriate data set according to the specific research goal using the appropriate statistical analysis method. Intergroup comparison of qualitative data will be performed using the χ^2 test, and the independent samples *t*-test will be used to compare quantitative data between the groups.

(3) The FAS will be used to evaluate the intergroup equivalence of baseline indicators, including demographic characteristics. Outcomes will be analyzed using the FAS and PPS.

(4) Prior to data locking, the data set will be determined together by the principal investigators and the biostatistician.

(5) The SPIRIT checklist was referred to when writing this study protocol.

10.5 Safety analysis

As mentioned above, the safety analysis will be mainly based on the frequency of AEs, the number of patients whose laboratory test values fall outside the predetermined range, and the number of patients with data worthy of clinical attention. Simultaneously, other safety data (such as vital signs and special examinations) will be considered appropriate.

The χ^2 test (including the Cochran–Mantel–Haenszel χ^2 test) or the Fisher's exact probability method will be used in the safety data analysis to compare the incidence of AEs/adverse reactions in each group, and AEs/adverse reactions that occurred in this analysis will be listed. Normal or abnormal changes in laboratory inspection results before or after the test and the relationship with the test drug will be statistically described.

10.6 Exploratory analysis

According to the actual data collected in this study, the log-rank test will be used to analyze the overall survival rate according to the pathological stage and other tumor-specific indicators of interest to compare the survival of patients among different subgroups or characteristics. Other exploratory analyzes will be further defined according to the research objectives.

10.7 Special value processing

Subjects who withdraw early or fail to provide sufficient data for any reason will be considered as cases of early suspension or non-evaluable, and will not be included in the final analysis.

For each missing data that cannot be traced back in the analysis, the degree of missingness will first be determined. For variables with a missingness rate exceeding 5%, the multiple imputation method will be used to fill in the missing data.

11. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1 Ethics approval and consent to participate

Approval from the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20180512) was received in May 2018. All patients will sign an informed consent document before entering the study. Consent will be obtained by the consultant or designated team member and preserved by the data collection group. This study has gained ethical approval at both the central and local levels for each participating center, and central ethical approval has been confirmed by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Recruitment will not start at other centers in the trial until local ethical approval has been obtained. Participating in both groups does not imply any additional risk for the subjects included, since the groups will not be deprived of the application of the most up-to-date recommendations. Any results from this trial (publications and conference presentations) will be published in peer-reviewed journals and conference proceedings.

11.2 Quality assurance

All aspects of the study will be carefully monitored with respect to Good Clinical Practice and standard operating procedures for compliance with applicable government regulations. The study monitor will have access to all records necessary to ensure the integrity of the data and will periodically review the progress of the study with the principal investigator.

11.3 Confidentiality

All study-related information and participant information will be stored securely at the study site in locked cabinets in areas with limited access. All local databases will be secured with a password-protected access system.

11.4 Archiving study documents

According to the International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of two years. These documents may be retained for a longer period according to applicable legal requirements.

11.5 Good clinical practice

The procedures set out in this clinical study protocol are designed to ensure that the investigator abides by the principles of the ICH guidelines on Good Clinical Practice, and the Declaration of Helsinki (version 1989). The clinical study will also be carried out in keeping with national and local legal requirements.

11.6 Informed consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from him/her according to the regulatory and legal requirements of the country in which the study is being conducted. As part of this procedure, the principal investigator or designee must explain orally and in writing the nature, duration, and purpose of the study, and the procedures to be performed in such a manner that the study subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she is free to withdraw from the study at any time. The principal investigator or designee will provide the Independent Ethics Committee (IEC)-approved informed consent form prior to the start of the study. The patient will have time to ask questions before signing the informed consent form. The information sheet and informed consent document must be signed and dated. One copy will be handed to the patient and the investigator will retain a copy as part of the clinical study records. The investigator will not undertake any investigation specifically required only for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF. If a protocol amendment is required, the subject information sheet and informed consent document may need to be revised to reflect the changes to the protocol. If the subject information sheet and informed consent document are revised, it must be reviewed and approved by the responsible IEC, and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled.

11.7 Protocol approval and amendment(s)

Prior to trial initiation, the clinical study protocol and other relevant documents will be approved by the IEC, in accordance with local legal requirements. This protocol is to be followed exactly. Any modifications of the protocol that may impact the conduct of the study, potentially benefitting the patients or that may affect patient safety, including changes in study design, sample size, and study procedures, will require a formal protocol amendment. In addition, this would need to be submitted to the IEC, and health authorities must be notified in accordance with local regulations.

11.8 Publication policy

Each participating investigator, with equal rights, will be able to access the data of the registry, perform

statistical analyzes, discuss the results, and freely write scientific manuscripts. The manuscript would be approved by all the authors before publication.

11.9 Consent for publication

Written informed consent will be obtained from the patients for publication of their individual details and accompanying images in this paper. The consent form is held by the authors' institution and is available for review by the Editor-in-Chief.

12. PROTOCOL COMPLIANCE

The researcher will make all due efforts to avoid deviation from the protocol. Under no circumstances should the investigator contact Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology or the agent who supervises the study to request approval of a plan deviation, because unauthorized deviations will not be allowed.

13. PROTOCOL REVISION

Any changes or additions to the protocol can only take place in the form of a written amendment, which must be approved by Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, IRB/IEC/REB, and government health departments. Only amendments adopted for patient safety can be implemented before IRB/IEC/REB approval. Although formal protocol amendments need to be approved, it is expected that investigators will immediately take necessary measures for the safety of patients enrolled in this study, even if such measures are a deviation from the protocol. In this case, the researcher should notify the Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology and the IRB/IEC/REB of this measure within 14 workdays.

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Statistical analysis plan

Version no.	V3.0
Version date	2018-03-20

Protocol title:	Effect of laparoscopic versus open pancreaticoduodenectomy on overall survival in patients with resectable pancreatic cancer (TJDBPS07): A study protocol for a multicenter, randomized controlled clinical trial
Protocol number:	TJDBPS07
Investigating institute:	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology
Statistical analysis institute:	Tongji Medical College, Huazhong University of Science and Technology

Statistical analysis plan
Signature page of investigating institute

I, hereby, sign here to declare that I have read the statistical analysis plan (version 3.0) in detail and agree to analyze and summarize the safety and efficacy data of the laparoscopic and open pancreaticoduodenectomy study in accordance with the statistical analysis plan.

Investigating institute: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Principal investigator (Sign) _____ Date _____

1. Overview

1.1 Objective

The broad goal of this trial is to evaluate the long-term and short-term safety and efficacy of laparoscopic pancreaticoduodenectomy (LPD) and open pancreaticoduodenectomy (OPD) procedures for the treatment of pancreatic cancer.

1.2 Design

The TJDBPS07 trial is characterized as a prospective, multicenter, randomized controlled, non-inferiority, and open labelled study with two parallel groups and overall survival as the primary outcome.

1.3 Study details

Screening and identification of eligible patients will take place within the pancreatic multidisciplinary team (MDT) of each participating center.

All adult patients with histologically proven pancreatic cancer or a preoperative clinical diagnosis of pancreatic cancer without histopathologic proof, and for whom the indication for pancreaticoduodenectomy (PD) will be evaluated, will be informed of their eligibility to take part in the study.

After the consent form is signed, participants will be randomized into the LPD or OPD group in a 1:1 allocation.

Postoperative short-term follow-up will be carried out at 1 day, 1 week, 1 month, 3 months, and 6 months after surgery. Long-term follow-up will be carried out every 3 months in the first year after surgery and every 6 months from the second year onwards. All patients will be followed up for a period of five years. All the patients will be free to participate in this study and can decide to withdraw at any time.

2. Outcome measures

2.1 Primary outcome

The primary outcome is the 5-year overall survival rate.

2.2 Secondary outcomes

The secondary outcomes include the following variables:

1. Long-term outcomes: the 3-year overall survival rate, 5-year disease-free survival rate, and 3-year disease-free survival rate;

2. Intraoperative-related indicators: operation time, intraoperative blood loss, intraoperative blood transfusion, pancreatojejunostomy, gastrointestinal anastomosis, gastrointestinal anastomosis time, and pancreatic duct diameter;

3. Intraoperative complications: bile duct injury and nerve injury;

4. Perioperative indicators: postoperative hospital stay, intensive care unit stay, time to get out of bed, time to resumption of oral feeding, time to removal of drainage tube, postoperative drainage fluid volume, and amylase level;

5. Postoperative pain and analgesic consumption: visual analogue scale pain score and analgesic consumption;

6. Postoperative complications: postoperative pancreatic fistula, postoperative hemorrhage, delayed gastric emptying, systemic inflammatory response syndrome, abdominal infection, reoperation, Clavien–Dindo classification, and comprehensive complication index score;

7. Short-term outcomes: 30/90-day mortality rate and 90-day unplanned readmission rate;

8. Quality of life: changes in the patient's quality of life before surgery, after discharge, and 6 months after surgery; and

9. Economic indicators: surgical expenses and hospitalization expenses.

3. Statistical analysis data sets

The modified intention-to-treat set (mITT), per-protocol analysis set (PPS), and safety analysis set (SS) will be established. The efficacy analysis will be carried out based on the mITT and PPS. Demographic and baseline characteristics will be analyzed based on the full analysis set (FAS). Safety assessments will be performed on the SS.

(1) mITT: Based on the intention-to-treat principle, all patients who received surgical treatment and have the primary outcome evaluation data after treatment.

(2) PPS: This is a subset of the FAS, which includes patients who meet the following conditions: (i) the primary outcome evaluation data are complete and (ii) no major protocol violations exist that will affect the primary outcome evaluation.

(3) SS: All patients subjected to surgery will be included.

4. Missing data

The primary outcome analysis will be performed according to the intention-to-treat principle and will be adjusted for the predictors of missing values as part of the sensitivity analysis. In addition, multiple imputation will be applied to variables with missing data. The imputed data will also be analyzed as part of the sensitivity analyzes.

5. Statistical plan

5.1 Sample size

This study is a randomized parallel controlled non-inferiority design clinical trial with a 1:1 ratio between groups. With reference to the results of previously published clinical studies, the 3-year overall survival rates for patients with malignant pancreatic head tumors who underwent OPD and LPD are 31% and 41%, respectively. Assuming a non-inferiority cut-off value of -10%, a one-sided significance level of 0.025, and that a 0.85 degree of power should be obtained, a total of 180 patients are required for the two groups (90 patients in each group). Considering a drop-out rate of 10%, the sample size of the study was finally estimated to be 200 patients, with 100 patients in each group.

5.2 General analysis principles

(1) All statistical tests will be performed with a two-sided $P<0.05$ considered to represent a statistically significant difference, with a 95% level of significance. All data will be analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

(2) All analyzes will be performed separately for the LPD and OPD groups.

(3) The mITT set will be used to evaluate the intergroup equivalence of baseline indicators including demographic characteristics. The outcomes will be analyzed using the mITT and PPS sets.

(4) Descriptive quantitative variables will be described as the mean, standard deviation, 95% confidence intervals of means, ranges, interquartile ranges, median, and number of observations. For categorical variables frequencies and percentages will be given for all values or categories. Exact 95% Clopper–Pearson confidence intervals will be provided for key categorical variables.

(5) Kaplan–Meier analysis of time to event variables.

(6) Multivariable analysis of time to event variables by means of Cox proportional hazards models. The

independent variables to be used will be specified in the final statistical analysis plan.

(7) All analyzes are regarded as exploratory; therefore, no significance level is fixed.

(8) Prior to data locking, the data set will be determined together by the principal investigators and the biostatistician.

(9) The SPIRIT checklist was referred to when writing this study protocol.

5.3 Efficacy analysis

The statistical analysis of efficacy will consist of:

(1) Kaplan–Meier analysis of disease-free survival and overall survival

(2) Multivariable analysis of progression-free survival and overall survival by means of Cox proportional hazards models

(3) Estimation with exact 95% confidence intervals of year-specific survival rates and year-specific disease-free survival rates

(4) Descriptive analysis of the other perioperative-related indicators

(5) Determination of rate differences and corresponding 95% confidence intervals between the two groups calculated using the Newcombe method

(6) Comparison of surgical and disease-related characteristics, as well as outcomes, between the two groups using the *t*-test for continuous data, the Mann–Whitney *U* test for variables with non-parametric distributions, and the chi-squared or Fisher's exact tests for categorical data, as appropriate.

Informed consent

Information page

Dear Mrs/Mr,

First of all, thank you for your interest in our clinical research! We invite you to participate in a randomized controlled clinical trial of laparoscopic versus open pancreaticoduodenectomy for resectable pancreatic cancer. Before you decide whether to participate in this study, please read the following as much as possible to help you understand the research, its purpose, the research process and deadlines, and what may occur after you participate in this study, which may be benefits, risks or discomfort. If you prefer, you can also discuss it with your family, friends, or ask your doctor for an explanation.

Research introduction

I. Research background and purposes

1. Research background

Pancreatic cancer is estimated to rank ninth among the most common cancers and fourth among the leading causes of cancer deaths in the United States. Surgery (laparotomy or minimally invasive surgery) is the only potentially curative and preferred treatment for patients with pancreatic malignant tumors. Previously reported studies have indicated that adjuvant chemotherapy after radical surgery could significantly enhance the curative effect and achieve promising improvements in overall survival and disease-free survival for patients with resected pancreatic adenocarcinoma. As recommended by the National Comprehensive Cancer Network (NCCN) Guidelines for Pancreatic Adenocarcinoma (version 1.2019) and the Pancreatic Cancer Committee of the Chinese Anti-Cancer Association, radical surgery followed by adjuvant chemotherapy based on gemcitabine is a preferred and effective treatment strategy for patients with pancreatic cancer.

Pancreaticoduodenectomy (PD), the standard procedure for resectable masses in the periampullary region, including pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures. Since first performed and introduced by Gagner et al. in 1994, laparoscopic PD (LPD) has rapidly and widely spread owing to its potential technical advantages focusing on the precision of movements and three-dimensional view. Recently, an increasing number of studies, including some large-scale multicenter randomized controlled trials have reported the safety and feasibility of LPD for the treatment of periampullary tumors. In addition, several reports have focused on the comparison of LPD and open PD (OPD) in the treatment of pancreatic cancer. The results suggest that LPD yielded equivalent 5-year overall survival and superior perioperative clinical outcomes in comparison to OPD. However, these reports were from retrospective studies, which are associated with inherent limitations such as patient selection biases, missing or incomplete data, and variables that were unaccounted for, making the results difficult to interpret definitively.

Accordingly, it is imperative to conduct prospective large-scale multicenter randomized controlled trials to analyze outcomes of interest and obtain high-level evidence. This TJDBPS07 trial aims to compare the long-term oncological outcomes and short-term surgical outcomes of LPD and OPD in the treatment of pancreatic cancer.

2. Research purposes

The purpose of this study is to evaluate the efficacy and safety of LPD for resectable pancreatic cancer compared with OPD.

3. Study participants and expected number of participants

This study will be conducted at 10 medical centers all over China. The number of participants in this study is expected to be 200.

II. Who can participate in this study?

Patients with the following characteristics can participate in the study:

1) Age between 18 years and 75 years.

2) Histologically confirmed or clinically diagnosed pancreatic cancer by an MDT without histopathologic evidence.

3) Patients feasible to undergo both LPD and OPD according to MDT evaluations.

4) Patients understanding and willing to comply with this trial.

5) Provision of written informed consent before patient registration.

6) Patients meeting the curative treatment intent in accordance with clinical guidelines.

III. Who is not suitable for research?

Patients with any of the following characteristics are not suitable for this study:

1) Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs.

2) Patients requiring left, central or total pancreatectomy or other palliative surgery.

3) Preoperative American Society of Anesthesiologists score ≥ 4.

4) History of other malignant disease.

5) Pregnant or breast-feeding women.

6) Patients with serious mental disorders.

7) Patients treated with neoadjuvant therapy.

8) Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.

9) Body mass index > 35 kg/m2.

10) Patients participating in any other clinical trials within 3 months.

IV. What will be done if you participate in the research?

If you meet the inclusion criteria and agree to participate, you will be evaluated according to the following steps. You will be allocated to one of two groups according to the study plan to undergo either laparoscopic and open surgery. Both groups will undergo pancreaticoduodenectomy and you may be assigned to either group. During enrolment or surgical operation, your interests will be the first consideration. All patients will undergo routine nursing typical for patients undergoing biliary and pancreatic surgery. Various study parameters will be collected before, during, and after surgery, including but not limited to routine blood parameters, blood biochemistry parameters, tumor marker estimation, estimated blood loss, anastomosis characteristics, and complications. The researchers will conduct safety and efficacy assessments and judgments. Patients histologically diagnosed with pancreatic cancer will undergo six cycles of adjuvant chemotherapy recommended in the NCCN guideline within six months postoperatively, and will be subjected to follow-up for 60 months. The time points of follow-up are 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after discharge. Follow-up will be conducted on the ward and via telephone follow-up. The follow-up will include assessments of each patient's condition, treatment, medications being received, and any adverse events.

V. Possible benefits of participating in the study

Although there is already evidence that pancreaticoduodenectomy is satisfactory for treatment, this does not guarantee that it will work for you. The open and laparoscopic methods used in this study are not the only existing treatments. If your condition is not improving, you can ask your doctor about alternative treatments that are possible.

VI. Adverse reactions, risks, and protective measures for participating in the study

During the trial, if there is any discomfort in the study, or your condition changes, or any unexpected situation, regardless of whether it is related to treatment, you should promptly notify your doctor, who will make an accurate judgment regarding medical treatment. The main adverse reactions and risks are as follows:

1. In the operation, the surgical method is determined according to medical conditions;

2. Due to differences in the patient's condition (critical, complicated, or poor systemic conditions) and individual differences, sudden situations may occur during and after surgery, including multiple organ failure (such as heart failure, respiratory failure, liver failure, renal failure, or disseminated intravascular coagulation) and unpredictable changes in the condition that may be life-threatening;

3. Major bleeding and hemorrhagic shock may occur during surgery, and is life-threatening;

4. Operations due to anatomical variations and severe adhesions for therapeutic purposes. Damage to surrounding and nearby tissues and organs may be inevitable, and the corresponding organs need to be repaired or reconstructed;

5. Special medical supplies such as chemotherapy pumps and anastomotic devices may be used during surgery, and special treatments such as radiofrequency therapy and cryotherapy may be administered during surgery;

6. Patients with tumors may not be able to undergo surgical resection due to the condition, or recurrence and metastasis after resection, requiring further treatment;

7. Recurrent bleeding after surgery, local/systemic infection, bile leakage, pancreatic leakage, intestinal leakage, anastomotic leakage, and other changes in the condition may be life-threatening and require reoperation;

8. Other unforeseen or unpredictable adverse consequences and medical risks;

9. Admission to the intensive care unit, if necessary, after surgery;

10. Postoperative examination findings may be inconsistent with preoperative diagnosis and intraoperative diagnosis. The final diagnosis is based on the findings of postoperative examination;

11. Determine the risk of biopsy of the lesion under the endoscope under the conditions of the operation;

12. During the operation, malignant tumor metastasis is found, and it is difficult to cure radically. The risk of radical resection is high. Only palliative anastomosis is possible;

13. During the operation, the abdominal cavity is widely invaded, and it is not possible to perform resection or palliative anastomosis;

14. Postoperative abdominal adhesions, intestinal adhesions, and intestinal obstruction may require relevant treatment;

15. Long-term bed rest, pulmonary infection, and deep vein thrombosis may occur;

16. Incision healing may occur after surgery, with infection of the incision, incision splitting, incisional hernia, etc.;

17. Exocrine pancreatic insufficiency;

18. LPD may result in tissue adhesion, intraoperative bleeding, etc.; and

19. Pneumoperitoneum.

Protective measures: If patients participating in the trial have the above complications, they will be contacted by a professional medical team to deal with and treat them for the first time.

VII. Relevant costs

The costs of patient's follow-up examination, including abdominal color Doppler ultrasound, abdominal computed tomography and adjuvant therapy, chemotherapy, and other costs will be

subsidized or even waived on a situational basis. If an adverse event occurs in the clinical trial, the Medical Expert Committee will determine if it is related to the surgery or trial. The costs of treatments and examinations required for other co-existing diseases will not be covered.

VIII. Confidentiality of clinical data

Your medical records (research medical records, case report forms, test results, etc.) will be kept entirely at the hospital where you are attending. The doctor will record the results of all tests on your medical record. Researchers, ethics committees, and higher-level medical administrations will be allowed to access your medical records. Any public report about the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law.

According to medical research ethics, in addition to personal privacy information, experimental data will be available for public inquiry and sharing. Query and sharing will be limited to web-based electronic databases, ensuring that no personal private information will be disclosed.

IX. How can I get more information?

You can ask any questions about this research at any time and get answers.

If there is any important new information during the study that may affect your willingness to continue participating, your doctor will notify you in a timely manner.

X. You can voluntarily choose to participate in the research or withdraw from the study

The decision regarding whether or not to participate in the research is entirely up to you. You may decline to participate in the study or withdraw at any time. This will not affect your relationship with the doctor and will not affect your medical or other benefits.

For your best interest, your doctor or researcher may discontinue your participation in this study at any time during the course of your research.

XI. What should I do now?

Participation in this clinical study is based on a completely voluntary principle and needs to be carried out with your consent and signed informed consent. The decision regarding whether or not you participate in this clinical study is entirely based on your own wishes. You have the right to suspend participation and withdraw from the study treatment at any time. Exiting this study will not affect your medical treatment.

Your physician may suspend your participation in this study in advance if your health condition makes you not suitable for continued participation or you do not comply with the research program requirements.

The doctor will promptly notify you or your legal representative if there is medical information that may affect your willingness to continue participating during the course of the study. Before you make a decision to participate in this study, please ask as many questions as possible until you fully understand the study treatments

Informed consent

Signature page

Clinical research project: **Effect of laparoscopic versus open pancreaticoduodenectomy on overall survival in patients with resectable pancreatic cancer (TJDBPS07): A multicenter, randomized controlled clinical trial**

Research center name:_____

I have carefully read the contents of the informed consent form, and the researchers have answered my questions.

I fully participated in the study and fully cooperated with the researcher after fully understanding the purpose, methods, possible therapeutic benefits and possible risks, and other provisions mentioned in the informed consent form.

I understand that I can withdraw from the study at any time and I do not need to provide any reason. The medical services I receive and the legal rights I enjoy are not affected at all.

Finally, I decided to agree to participate in this study and to ensure compliance with my doctor's advice.

Subject's signature: Date:

Contact Number:

I have explained fully detail to the participant, including the potential risks.

Doctor's signature: Date:

Contact number: