

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Laparoscopic versus open pancreaticoduodenectomy for pancreatic cancer: study protocol for a multicentre randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057128
Article Type:	Protocol
Date Submitted by the Author:	10-Sep-2021
Complete List of Authors:	<p>Pan, Shutao; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Qin, Tingting; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Yin, Taoyuan; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Yu, Xianjun; Fudan University Shanghai Cancer Center, Department of Pancreatic Surgery</p> <p>Li, Jing; The Second Affiliated Hospital, Army Medical University, PLA, Department of Pancreatico-Hepatobiliary Surgery</p> <p>Liu, Jun; Shandong Provincial Hospital, Department of Hepato–Pancreato–Biliary Surgery</p> <p>Zhao, Wenxing; The Affiliated Hospital of Xuzhou Medical College, Department of General Surgery</p> <p>Chen, Xuemin; Department of Hepatopancreatobiliary Surgery, the Third Affiliated Hospital of Soochow University, Department of Hepatopancreatobiliary Surgery, the Third Affiliated Hospital of Soochow University</p> <p>Li, Dewei; Chongqing University Cancer Hospital, Department of Hepatobiliary and Pancreatic Oncology; The First Affiliated Hospital of Chongqing Medical University, Department of Hepatobiliary Surgery</p> <p>Liu, Jianhua; The Second Hospital of Hebei Medical University, Department of Hepato–Pancreato–Biliary Surgery</p> <p>Li, Jingdong; Affiliated Hospital of North Sichuan Medical College, Department of Pancreatico-Hepatobiliary Surgery</p> <p>Liu, Yahui; Jilin University First Hospital, Department of Hepatobiliary and Pancreatic Surgery</p> <p>Zhu, Feng; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Wang, Min; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Zhang, Hang; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Qin, Renyi; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < ONCOLOGY



1
2
3
4 **Laparoscopic versus open pancreaticoduodenectomy for pancreatic cancer:**
5 **study protocol for a multicentre randomised controlled trial**
6
7
8

9 Shutao Pan¹, Tingting Qin¹, Taoyuan Yin¹, Xianjun Yu², Jing Li³, Jun Liu⁴, Wenxing
10 Zhao⁵, Xuemin Chen⁶, Dewei Li⁷, Jianhua Liu⁸, Jingdong Li⁹, Yahui Liu¹⁰, Feng Zhu¹,
11 Min Wang¹✉, Hang Zhang¹✉, Renyi Qin¹✉, Minimally Invasive Treatment Group in
12 the Pancreatic Disease Branch of China's International Exchange and Promotion
13 Association for Medicine and Healthcare (MITG-P-CPAM).
14
15
16
17
18

19 **Author affiliations**

20
21 ¹Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji
22 Medical College, Huazhong University of Science and Technology, Wuhan, Hubei
23 430030, China.
24
25

26 ²Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center,
27 Shanghai, 200032, China
28

29 ³Department of Pancreatico-Hepatobiliary Surgery, The Second Affiliated Hospital,
30 Army Medical University, PLA, Chongqing 404100, China.
31

32 ⁴Department of Hepato–Pancreato–Biliary Surgery, Shandong Provincial Hospital,
33 Shandong 250000, China.
34

35 ⁵Department of General Surgery, The Affiliated Hospital of Xuzhou Medical College,
36 Xuzhou, 221004, China.
37
38

39 ⁶Department of Pancreaticobiliary Surgery, The Third Affiliated Hospital of Soochow
40 University, Jiangsu 213000, China.
41

42 ⁷Department of Hepatobiliary and Pancreatic Oncology, Chongqing University
43 Cancer Hospital, Chongqing, Chongqing Municipality, China; Department of
44 Hepatobiliary Surgery, First Affiliated Hospital of Chongqing Medical University,
45 Chongqing, Chongqing Municipality, China.
46
47

48 ⁸Department of Hepato–Pancreato–Biliary Surgery, The Second Hospital of Hebei
49 Medical University, Shijiazhuang, Hebei 050017, China.
50

51 ⁹Department of Pancreatico-Hepatobiliary Surgery, Affiliated Hospital of North
52 Sichuan Medical College, Sichuan 637000, China.
53

54 ¹⁰Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin
55 University, 71 Xinmin Street, Changchun, Jilin 130021, China.
56
57
58
59

60 Shutao Pan, Tingting Qin and Taoyuan Yin are joint first authors.

1
2
3
4
5
6 ✉Corresponding author

7
8 Min Wang, MD

9 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
10 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
11 Hubei 430030, China.

12 Email: wangmin0013128@aliyun.com.
13
14

15
16 Hang Zhang, MD

17 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
18 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
19 Hubei 430030, China.

20 Email: zhanghang@hust.edu.cn
21
22

23
24 Renyi Qin, MD

25 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
26 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
27 Hubei 430030, China.

28 Tel.: +27-8366-5294; Fax: +27-8366-5294

29 Email: ryqin@tjh.tjmu.edu.cn
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic cancer. Minimally invasive surgery, which initially emerged as hybrid-laparoscopy and recently developed into total laparoscopy surgery, has been widely used for various abdominal surgeries. However, controversy persists regarding whether laparoscopic PD (LPD) is inferior to open PD (OPD) for resectable pancreatic cancer treatment. Further studies, especially randomised clinical trials, are warranted to compare these two surgical techniques.

Methods and analysis: The TJDBPS07 study is designed as a prospective, randomised controlled, parallel-group, open-label, multicentre noninferiority study. All participating pancreatic surgical centres comprise specialists who have performed no less than 104 LPDs and OPDs, respectively. A total of 200 strictly selected PD candidates diagnosed with pancreatic cancer will be randomised to receive LPD or OPD. The primary outcome is the 5-year overall survival rate, whereas the secondary outcomes include overall survival, disease-free survival, 90-day mortality rate, incidence of severe perioperative complications, length of stay, estimated blood loss, and operation time. We hypothesize that LPD is not inferior to OPD for the treatment of resectable pancreatic cancer. The enrolment schedule is estimated to be 2 years and follow-up for each patient will be 5 years.

Ethics and dissemination: This study received approval from the Tongji Hospital Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology and monitor from an independent third-party organization. Results of this trial will be presented in international meetings and published in a peer-reviewed journal.

Trial registration: Clinical Trials Register, NCT03785743. Registered on 10 Mar. 2019.

Strengths and limitations of this study

To the best of our knowledge, this will be the first randomised controlled trial to compare LPD and OPD for resectable pancreatic cancer treatment in a large multicentre setting and will provide convincing evidence on performance of pancreatic cancer resection.

All participating pancreatic surgical centres are qualified with experienced surgeons who have performed no less than 104 LPDs and OPDs, respectively.

Each patient will attend a follow-up of at least 5 years to determine the study primary outcome, the 5-year overall survival rate, which is the most used indicator for describing cancer survival.

This is an open-label trial; accordingly, participants and clinicians will not be blinded to interventions.

The primary outcome of this trial will be derived from data acquired during the long-term follow-up, requiring high levels of follow-up compliance and challenging coordination between surgeons, oncologists, visitors, and patients.

INTRODUCTION

Pancreatic cancer is a highly fatal malignancy having poor responses to therapy and is estimated to be the 4th leading cause of cancer mortality¹. Pancreaticoduodenectomy (PD), the standard procedure for resectable pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures^{2,3}. Compared with traditional open surgery, minimally invasive surgery has many advantages, such as small incision, minimal intraoperative bleeding, fast postoperative recovery, and so on.⁴, which are essential factors in the development of modern surgery. However, the long-term survival benefits of minimally invasive surgery in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival (OS) and disease-free survival (DFS) than open surgery for patients with early-stage cervical cancer⁵.

Since its inception by Gagner et al. in 1994, laparoscopic PD (LPD) has been increasingly performed owing to its potential technical advantages^{6,7}. Recently, an increasing number of studies, including some large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for treatment of periampullary or pancreatic tumours⁸. Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) in highly experienced surgeons who have past the learning curve^{9,10}. However, the application of LPD to pancreatic cancer treatment is concerning. Several studies have focused on the comparison of LPD and OPD in pancreatic cancer treatment and suggested that LPD generated equivalent oncologic outcomes and promising superior long-term survival outcomes compared with OPD¹¹. However, retrospective studies are associated with inherent limitations, including patient selection biases, missing or incomplete data, and unaccounted-for variables, making results difficult to interpret definitively. No RCTs have investigated the effects of LPD and OPD on survival in patients with pancreatic cancer.

To explore the long-term safety and efficacy of LPD in patients with pancreatic cancer using high-level evidence, the Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM) designs and conducts this prospective large-scale multicentre RCT to analyse outcomes of interest, immediately after finishing the TJDBPS01 trial, which interpreted the safety and feasibility of LPD compared with those of OPD. Accordingly, this trial aims to compare the long-term oncological and short-term surgical outcomes of LPD and OPD performed by highly experienced surgeons that have surmounted the learning curve for pancreatic cancer treatment.

METHODS AND ANALYSIS

Trial design

This trial is characterized as a prospective, multicentre, randomised controlled, and open-label study comprising two parallel groups of OPD and LPD. Patients diagnosed with pancreatic malignant tumour requiring PD will be consecutively recruited. This study will be conducted at ten high-volume pancreatic surgery centres in China, with surgeries being conducted by experienced surgeons. After providing written informed consents, 200 patients will be preoperatively allocated in a 1:1 ratio to either the LPD or OPD arm. The recruiting time is estimated to be 2 years and the follow-up time will be 5 years. The primary endpoint of this trial is the 5-year OS rate. The study will be prepared, analysed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines¹², as presented in Figure 1.

Qualifications of participating surgeons and centres

The responsible participating surgeons shall satisfy the following qualifications as previously described in the TJDBPS01 study⁹: (1) having completed no less than 104 cases of LPDs; (2) having completed no less than 104 cases of OPDs¹⁰; and (3) having completed trainings of the Tongji Hospital LPD training program. Moreover, the participating centres shall perform more than 50 PDs annually. Surgeons willing to participate shall offer one recently unedited LPD and OPD surgery video, respectively, to the TJDBPS07 research council for evaluation. If the research council approves the surgical techniques, the surgeon and the centre will be permitted to participate in this study as a collaborator. Eligible patients will be discussed at regularly scheduled multidisciplinary team (MDT) meetings. Randomisation and assignment of a study-specific ID will be performed by the study sponsor.

Population and eligibility criteria

All adult patients indicated for elective PD because of a pancreatic mass will be screened for eligibility. Eligible patients will be assessed by the pancreatic MDTs of the participating centres. The MDTs should confirm that the pancreatic mass is highly suspected to be a pancreatic malignant tumour and of sufficient concern to require resection. Imaging data of contrast enhanced multi-thin sliced computed tomography (CT) scan (1mm) with or without endoluminal ultrasonography (EUS) will be regarded as the standard evaluation for each PD candidate. Histological diagnoses of malignancies are encouraged to be acquired but not a necessity¹³. All patients will sign the informed consent and be allowed to leave the trial at any time. The exact inclusion and exclusion criteria are below.

Inclusion criteria

- 1) Age between 18 years and 75 years.
- 2) Histologically confirmed pancreatic cancer 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 without vascular invasion and not requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.
- 5) Patients without distant metastases, including peritoneal, liver, distant lymph node metastases, or involvement of other organs.
- 6) Preoperative American Society of Anaesthesiologists (ASA) score ≤ 3 .
- 7) Patients understanding and willing to comply with this trial.
- 8) Provision of written informed consent before patient registration.
- 9) Patients meeting the curative treatment intent in accordance with clinical guidelines.

Exclusion criteria

- 1) Pregnant or breast-feeding women.
- 2) Patients with serious mental disorders.
- 3) Patients treated with neoadjuvant therapy.
- 4) Patients requiring left, central or total pancreatectomy or other palliative surgery.
- 5) History of other malignant disease.
- 6) Body mass index $> 35 \text{ kg/m}^2$.
- 7) Patients participating in any other clinical trials within 3 months.

Endpoints

The primary endpoint of this trial is the 5-year overall survival rate, which is defined as the percentage of patients in this trial who are alive 5 years postoperatively [time frame: 5 years postoperatively].

Other crucial indicators are included as secondary endpoints, including (1) overall survival (i.e., the interval between the day of surgery and the day of death for various reasons [time frame: 5 years postoperatively]); (2) disease-free survival (i.e., the interval between the day of surgery and the day of tumour recurrence [time frame: 5 years postoperatively]); (3) 90-day mortality (i.e., the percentage of patients who died within 90 days postoperatively). Mortality will be calculated by dividing the number of patients who died by the number of all patients undergoing surgical treatment; (4) incidence of severe perioperative complications (i.e., the proportion of patients demonstrating severe perioperative complications with Clavien-Dindo score \geq III). Proportions will be calculated by dividing the number of patients with any severe intraoperative/postoperative complication by the number of all patients undergoing surgical treatment; (5) length of stay (i.e., the number of nights spent in the hospital from the end of the surgical procedure until discharge or death); and (6) intraoperative indicators, including estimated blood loss and operation time.

Sample size

The sample size calculation was performed according to the primary endpoint, the 5-year OS rate, and the non-inferiority design of this trial. Assumptions were made based on a previous study by Kuesters et al.¹⁴, which compared LPD with OPD for pancreatic cancer treatment with the 5-year OS rate being 20% in the LPD group and 14% in the OPD group. Based on the 6% decrease in 5-year OS rate in the OPD group compared with the LPD group, the sample size required for each group was estimated to be 86 patients to achieve a non-inferiority limit of 10% at a one-tailed significance level of 2.5% with a power of 80% and a balanced design (1:1 ratio). Moreover, the primary analyses will be based on the modified intention to treat (mITT), per protocol (PP), and as treated (AT) sets. We aimed to reach a statistical power of 80% when analysing the smallest population, namely the PP set.

Patients converted from LPD to open surgery will not be included in the PP set. Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group and 91 patients in the OPD group will be needed to analyse using the one-sided *t* test at a one-sided significance level of 0.025. PASS version 15.0.5 will be used to make calculations. An additional 10% of patients will be needed to be randomised considering the non-resectable patients, patients withdrawing from the study, and patients lost to follow-up. Accordingly, 91 patients in the LPD arm and 100 patients in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1, requiring 100 patients in each arm and 200 patients in total to be included for randomisation.

Patient timeline and description of trial visits

The study duration is estimated to be 7 calendar years, with an enrolment schedule of 2 years and follow-up period of 5 years for each patient. The end of the trial was defined as 5 calendar years since the last enrolled patient received surgery. This protocol is reported in accordance with the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Table 1, supplemental file 1)¹⁵.

Data collection and assessment are recommended to be conducted at the responsible surgical centre. Baseline data will be collected during the screening/baseline visit, and surgical data will be collected intra- and postoperatively.

Short-term follow-ups will be conducted 1 day, 1 week, 1 month, and 3 months postoperatively, and follow-up contents will include laboratory inspection indicators, Eastern Cooperative Oncology Group (ECOG) score, Karnofsky Performance Scale (KPS) score, postoperative wound recovery, wound pain level, drainage of each drainage tube postoperatively, postoperative recovery (i.e., time until getting out of

1
2
3 bed, imported food, and so on), weight, adverse events, combined medication, and
4 postoperative complications.
5

6 Long-term follow-ups will be conducted every 3 months in the first postoperative year
7 and every 6 months from the second postoperative year onwards. The following
8 follow-up contents will be traced and recorded: clinical evaluations including internal
9 inspections (such as weight, KPS score, and ECOG score), chemotherapy-related
10 adverse events, imaging items to prove the existence of tumour recurrence or
11 metastasis (record the date of recurrence, location and follow-up treatment), the date
12 of death, and the cause of death (i.e., disease- or treatment-related mortality).
13
14
15
16

17 18 **Randomisation and blinding** 19

20 Eligible patients signed the informed consent form will be screened within one week
21 prior to randomisation. We will employ a 1:1 randomisation pattern for arms A and B,
22 stratified by participating centres. Random numbers will be generated by SAS
23 software version 9.40 (SAS Institute, Inc., Cary, NC) and randomisation will be
24 performed through a centralized computer-generated system by providing random
25 numbers using dynamic blocks. Within each block, randomisation is balanced, and
26 every patient is assigned to a treatment using the randomisation scheme.
27
28
29

30 This is an open-label trial, and randomisation procedure and outcome will not be
31 blinded to patients and surgeons. However, data collectors, outcome assessors, and
32 data analysts will be blinded during statistical analysis. Surgeons will not participate
33 in the data collection process which will be conducted by an independent team.
34 Analysis processes will be blinded, and the statistician will be provided with only
35 group codes instead of group names.
36
37
38
39

40 **Intervention** 41

42 Surgical procedures need to comply with PD technique standards as previously
43 described¹⁶. Any appropriate changes in surgical procedures according to the
44 surgeon's own experience and preference are permitted, including changes in
45 procedure order, surgical approach, and anastomosis method. All Changes will be
46 recorded in the case report form.
47
48
49
50

51 **Experimental intervention-LPD techniques** 52

53 Patients will take a supine position and undergo the general anaesthesia. Five trocars
54 in total will be used. Routine and standard lymph node dissections will be maintained
55 as recommended by guidelines. The pancreatic stump will be sent for quick frozen
56 pathological examination intraoperatively; moreover, it is necessary to confirm that
57 the pancreatic margin specimen is pathologically negative before digestive tract
58 reconstruction. Surgeons will determine reconstruction type according to their
59
60

1
2
3 experiences and preferences. After reconstruction, two drainage tubes are routinely
4 placed, with one near the anastomosis of the pancreaticojejunostomy and the other
5 near the anastomosis of the bile jejunum.
6
7

8 Conversion to open surgery is defined as the use of any skin incision during LPD for
9 other than trocar placement or surgical specimen removal. In cases of conversion, data
10 will be analysed in the LPD group in an intention-to-treat manner. However, reasons
11 for conversion shall be realistically registered and carefully recorded.
12
13

14 15 16 **Control intervention-OPD techniques**

17 Open surgery shall be performed by the same group of surgeons as LPD. Key steps
18 are performed essentially as described in the LPD group. Methods used for
19 reconstruction during OPD must be consistent with those during LPD in the same
20 single centre.
21
22
23

24 25 26 **Concomitant treatment**

27 The TJDBPS07 trial follows TJDBPS01 which compared LPD and OPD; accordingly,
28 the principles of perioperative management are similar to those previously described¹⁶.
29 Whatever medical devices and materials that are most used in daily practice of each
30 participant centre can be used if recorded carefully in surgical records. Antibiotics are
31 given to patients 30 min before skin incision and 2 h after incision. Patient-controlled
32 analgesia will be used to control postoperative pain. Time to remove the nasogastric
33 tube depends on each patients' situation evaluated by doctors of each participating
34 centre; early removal is encouraged. Patients can be discharged if they do not need
35 any intravenous infusion or intravenous analgesics, do not have incision infections or
36 any major organ dysfunction, can tolerate oral semi-liquid food, can get off bed and
37 walk at least 250 m in a plain road without assistance, and have normal
38 haematological parameters.
39
40
41
42

43 After surgical resection, patients pathologically diagnosed with pancreatic cancer will
44 receive adjuvant chemotherapy according to the National Comprehensive Cancer
45 Network (NCCN) guideline¹⁷. Written consent for adjuvant chemotherapy should be
46 obtained. Different regimens recommended in the aforementioned guideline are
47 permitted, and the treatment duration is at the discretion of the responsible treating
48 oncologist. Detailed information on adjuvant chemotherapy will be recorded. Relapse
49 cases will be treated according to the recommendations of NCCN guideline at the
50 corresponding participating centres.
51
52
53
54

55 56 57 **Data collection and management**

58 All data will be collected using an electronic case report form. The datasets generated
59 during the study will be stored in a local database, which is managed by the data
60

1
2
3 collection group of Tongji Hospital. Investigators from each participating institution
4 will have access to the data of their respective patients. All data are pseudonymized,
5 and patient details are encoded.
6

7
8 Data collection will include variables related to patient demographics, intraoperative
9 information, histopathological information, postoperative clinical findings, adjuvant
10 chemotherapy, and follow-up.
11

12 Patient demographics: age, gender, height (cm), weight (kg), smoking, drinking, main
13 complaint, clinical diagnosis, comorbidities, surgical history, underlying malignant
14 disease, ECOG score, ASA score, imaging results, preoperative blood samples (i.e.,
15 haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio),
16 plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA),
17 preoperative biliary drainage, and date of admission.
18

19
20 Intraoperative information: operation date, surgical approach (laparoscopic or open),
21 conversion to open surgery, intraoperative death, texture of pancreas, diameter of the
22 main pancreatic duct, placement of intra-abdominal drain, type of reconstruction,
23 anastomosis approach (intracorporeal or extracorporeal), anastomosis performance
24 (linear stapler, circular stapler, hand-sewn, or combinations), total operative time,
25 each anastomosis time (pancreaticojejunostomy, cholangiohepaticojejunostomy, and
26 gastroenterostomy), intraoperative complications, estimated blood loss, and
27 intraoperative blood transfusion.
28

29
30 Histopathological information: tumour location, tumour size, histological type,
31 surgical margin status (R0 resection rates), number of lymph nodes, number of
32 positive lymph nodes, depth of invasion (T classification), lymph node status (N
33 classification), and American Joint Committee on Cancer staging.
34

35
36 Postoperative clinical findings: length of postoperative stay, postoperative blood
37 transfusion, length of intravenous analgesic use, drain production and amylase,
38 postoperative blood samples (i.e., haemoglobin level, white blood cell count, and
39 granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers
40 (i.e., CA19–9, CA125, and CEA), date of patient mobilization, date of liquid diet,
41 date of drain removal, postoperative complication, reoperation, Clavien-Dindo grade,
42 adverse event, cost of surgery, and cost of hospitalization.
43

44
45 Adjuvant chemotherapy: date of adjuvant chemotherapy, chemotherapy regimens,
46 side effects, imaging results, haemoglobin level, white blood cell count, and related
47 tumour markers (i.e., CA19–9, CA125, and CEA).
48

49
50 Follow-up: date of follow-up visit, patient status (alive, dead or lost to follow-up),
51 ECOG score, KPS score, imaging results, related tumour markers (i.e., CA19–9,
52 CA125, and CEA), DFS, and OS.
53

54 55 56 57 58 **Risk of bias** 59 60

1
2
3 All adult patients with pancreatic masses suitable for PD will be screened in all
4 participating centres. The recruited patients will be expected to be generalizable and
5 representative to the wider population. Standard randomisation will be conducted to
6 ensure comparable baseline characteristics between each group. To minimize
7 confounding, allocations will be stratified by centre.
8
9

10 The primary outcome of this trial is the 5-year OS rate, which is objective and will be
11 obtained from the planned follow-up data. The participants, surgeons, and nursing
12 staff will not be blinded to interventions due to the characteristics of this trial, which
13 compares minimally invasive and conventional open surgery. The responsible
14 surgeons will not be involved in the postoperative management of patients and
15 determination of patients' discharge. Data collectors, outcome assessors, and data
16 analysts will all be blinded to surgical techniques.
17
18
19

20 To minimize missing data bias, data for the primary outcome will be routinely
21 collected and regularly reviewed.
22

23 Results of this trial will be reported in accordance with the CONSORT statement¹² to
24 minimize reporting bias. In addition, the trial protocol is reported according to the
25 SPIRIT statement¹⁵ to assure full transparency throughout this trial and subsequent
26 reporting.
27
28
29

30 31 **Assessment of cross-over patients**

32
33 Conversion from LPD to OPD is closely associated with intraoperative situations,
34 including technical infeasibility and significant bleeding, which is unavoidable even
35 in experienced surgeons who have past the learning curves, making it impossible to
36 completely vanish conversion by modifying inclusion and exclusion criteria. The
37 conversion rate in our previous trial comparing LPD and OPD for pancreatic or
38 periampullary tumours was 4%⁹. Considering the techniques complexity in LPD for
39 pancreatic cancer, the maximum conversion rate within this trial is cautiously
40 estimated to be 10%. Reasons for conversion will be recorded in detail and will be
41 further evaluated in the subgroup analysis.
42
43
44
45
46
47

48 **Statistical analysis**

49 A statistical analysis plan will be developed and agreed upon by the data collection
50 group. All main statistical analyses will be performed by an intention-to-treat
51 principle, and the primary analysis will be based on the mITT, PP, and AT set.
52 Patients deemed unresectable intraoperatively or who did not receive surgery
53 resection will not be considered in any of the analysis sets. The mITT set will
54 comprise all patients in the group to which they were randomised regardless of the
55 actual received surgery. The PP set will include patients without major protocol
56 violations. Patients converted from LPD to OPD will not be included in the PP set.
57 The AT set will be analysed with considering the actual treatment of patients, rather
58
59
60

1
2
3 than their randomisation. For robust interpretation, the results of the three primary
4 analysis sets should lead to similar conclusions; otherwise, possible reasons behind
5 discrepancies must be discussed. OS and DFS will be analysed from the date of
6 pancreatic resection to the date of death (for OS) or date of regional recurrence or
7 systemic spread (for DFS). The OS and DFS curves for the entire follow-up period
8 will be estimated according to Kaplan-Meier method and compared using a log-rank
9 test. Time-specific OS and DFS probabilities at appropriate time points will be
10 derived from the survival curves and the Greenwood estimate was used to construct
11 corresponding a 95% confidence interval (CI). Hazard ratios (HRs) and two-sided
12 95% CIs were estimated using a Cox regression model after confirming the
13 proportional hazards assumptions.
14
15

16
17
18 In summary, continuous data will be presented as mean \pm standard deviation and will
19 be compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables will
20 be compared using the χ^2 test or Fisher's exact test, as appropriate. Statistical analysis
21 will be conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). $P <$
22 0.05 will be considered as statistically significant.
23
24

25 This trial is registered at ClinicalTrials.gov (registration number: NCT03785743).
26
27

28 29 **Monitoring**

30 Throughout the trial, a trained, qualified, and independent monitor will periodically
31 visit each participating centre to randomly check protocol compliance, compliance
32 with the inclusion and exclusion criteria, proper implementation, obtainment of
33 informed consent forms, source data verification, and reporting of serious adverse
34 events. Adverse events are graded using the Common Terminology Criteria for
35 Adverse Events (CTCAE) version 5.0¹⁸. The Hospital Ethical Committee and Chinese
36 Clinical Trial Registry are responsible for collection and management of these data.
37 Moreover, an independent agency will handle the auditing every month.
38
39
40
41
42
43

44 **DISCUSSION**

45 The TJDBPS07 trial is designed as a prospective, multicentre, randomised controlled,
46 and open-label trial to assess the long-term oncological and short-term surgical
47 outcomes of LPD and OPD for pancreatic cancer treatment. The results of our
48 TJDBPS01 trial suggested that LPD is a safe and feasible procedure for treating
49 pancreatic or periampullary tumours, with comparable short-term outcomes to OPD in
50 highly experienced hands^{9 16}. The TJDBPS07 trial follows TJDBPS01 and focuses on
51 the comparison of LPD and OPD for treatment of resectable pancreatic cancer. In
52 consideration of the complexity and difficulty of PD, surgeons participating in this
53 trial are required to complete a structured training program for LPD and pass the
54 learning curve by finishing a minimum of 104 LPDs, as suggested by the results of a
55 retrospective study on the learning curve for LPD in China¹⁰.
56
57
58
59
60

1
2
3 With rapid advances in minimally invasive technology, minimally invasive surgery is
4 favoured by surgeons in more and more fields due to its minimal invasiveness and
5 enhanced patient recovery¹⁹. Few RCTs focusing on the impact of minimally invasive
6 surgery on the long-term survival of cancer patients have been conducted, and
7 different conclusions have emerged from existing studies. A study by Yu et al. found
8 that laparoscopic distal gastrectomy and open surgery had comparable DFS and OS in
9 patients with locally advanced gastric cancer²⁰. Moreover, a study by Kitano et al.
10 concluded that laparoscopic D3 surgery was not non-inferior to open surgery in terms
11 of OS in patients with stage II and III colon cancer²¹. However, research by Pedro et
12 al. suggested that for patients with early cervical cancer, minimally invasive radical
13 hysterectomy resulted in lower rates of DFS and OS than open radical hysterectomy⁵.
14 The current guidelines of NCCN suggest that minimally invasive surgery and open
15 surgery are both suitable for surgical treatment of several tumours^{17 22-26}, resulting in
16 the widespread use of minimally invasive surgery. However, more high-quality RCTs
17 are needed to verify whether minimally invasive surgeries can bring the same
18 long-term benefits for patients with tumours as open surgeries do.

19
20
21
22
23
24
25 With a 5-year survival rate of approximately 10%, the highly fatal pancreatic cancer is
26 becoming an increasingly common cause of cancer related mortality. Surgical
27 resection represents the only chance of cure for patients with resectable pancreatic
28 cancer²⁷. Moreover, application of adjuvant chemotherapy significantly improves
29 long-term survival in these patients²⁸. Although an increasing number of researchers
30 are concerned about therapeutic effects of LPD on patients with pancreatic cancer,
31 current evidence is still based on a few observational studies with limited quality²⁹.
32 The data of 322 patients with pancreatic cancer (108 undergoing LPD and 214
33 undergoing OPD) demonstrated that LPD was technically feasible for pancreatic
34 cancer treatment and had better length of stay, postoperative recovery, and pursuing
35 adjuvant treatment than OPD. This study simultaneously showed comparable OS but
36 longer DFS in LPD than OPD³⁰, while other studies have indicated that the long-term
37 survival and perioperative outcomes were comparable between LPD and OPD for
38 treatment of selected pancreatic cancer patients³¹⁻³³. Considering the controversies
39 among existing publications and limitations of observational studies, doctors and
40 researchers in the field of pancreatic cancer emphasize the necessity and importance
41 of large-scale multicentre RCTs.

42
43
44
45
46
47 In conclusion, the TJDBPS07 trial is a multicentre randomised controlled,
48 non-inferiority trial investigating the long-term survival and the preoperative safety of
49 LPD and OPD for resectable pancreatic cancer. This trial aims to evaluate differences
50 in the 5-year OS rate between LPD and OPD for pancreatic cancer treatment. The
51 results of this trial will provide high-level evidence for guiding the daily practice of
52 pancreatic cancer management.

53 54 55 56 57 **Trial status**

58
59 The TJDBPS07 trial was registered on 10 March 2019 on the ClinicalTrials Registry
60

(registration number: NCT03785743). The protocol of this trial was proposed by the investigator from Tongji Hospital, and the final version was approved by Tongji Institutional Review Board. The first enrolled patient has been given the randomised number in September 2019. All ten centres are actively recruiting patients by the time this protocol is submitted. Recruitment will approximately be completed by December 2021.

Patient and public involvement

This trial will not involve either patients or the public in the design, recruitment, conduct of the study, or measurement of outcomes. The trial results will not be notified to every single patient, while instead, the results will be presented in academic conferences, and disseminated via open-access and peer-reviewed journals. This trial will investigate patient-reported outcomes, such as questionnaires about quality of life.

Ethics and dissemination

Each subject will sign an informed consent document before inclusion; this form is provided by a qualified team member and subsequently sent to and preserved by the data collection team. All participations are voluntary and have the right to withdraw from the study for any reason whenever they want to. If they do withdraw, they will still receive standard treatment according to local hospital procedures. The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and its later amendments³⁴. This trial was registered under the Tongji Hospital (trial ID: NCT03785743) and approved by Tongji Hospital Ethics Committee (approval number: TJ-IRB20190318) in March 2019. Local ethical approval was confirmed from each participating centre before recruiting at other centres. All authors have access to study data and reviewed and approved the final manuscript. The results of this trial will be presented in international meetings, and final trial results will be published in an open access, peer-reviewed journal.

Acknowledgements

We thank team of Prof. Ping Yin from the Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, for the data monitoring and statistical support.

Authors' contributions

RYQ, MW and FZ obtained funding for the study. RYQ, HZ and MW designed the study. XJY, JiL, JuL, WXZ, XMC, DWL, JHL, JDL, YHL and RYQ performed the

1
2
3 operations. STP TTQ and TYY drafted the manuscript. RYQ, HZ and MW
4 contributed to critical revision of the manuscript for important intellectual content and
5 approved the final version of the manuscript. All authors have read and approved the
6 final manuscript.
7
8
9

10 11 **Funding statement**

12
13 The study was supported by grants from The National Natural Science Foundation of
14 China (82073249, 81874205, 81773160), Tongji Hospital Clinical Research Flagship
15 Program (2019CR203).
16
17

18 19 **Disclaimer**

20
21 The funder had no role in the design of the study, data collection, or writing this
22 manuscript.
23
24

25 26 **Competing interests**

27
28 The authors and each study site declare no conflicts of interest.
29
30

31 32 **Patient consent for publication**

33
34 Not required.
35
36

37 38 **Provenance and peer review**

39
40 Not commissioned; externally peer reviewed.
41
42

43 44 **REFERENCE**

- 45
46 1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: a cancer journal for clinicians*
47 2020;70(1):7-30. doi: 10.3322/caac.21590 [published Online First: 2020/01/09]
48
49 2. Mizrahi JD, Surana R, Valle JW, et al. Pancreatic cancer. *Lancet (London, England)*
50 2020;395(10242):2008-20. doi: 10.1016/s0140-6736(20)30974-0 [published Online First:
51 2020/07/01]
52
53 3. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial
54 milestones and the pioneers. *HPB : the official journal of the International Hepato Pancreato*
55 *Biliary Association* 2011;13(6):377-84. doi: 10.1111/j.1477-2574.2011.00305.x [published
56 Online First: 2011/05/26]
57
58 4. Zhang YH, Zhang CW, Hu ZM, et al. Pancreatic cancer: Open or minimally invasive surgery? *World*
59 *J Gastroenterol* 2016;22(32):7301-10. doi: 10.3748/wjg.v22.i32.7301 [published Online First:
60

- 2016/09/14]
5. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *The New England journal of medicine* 2018;379(20):1895-904. doi: 10.1056/NEJMoa1806395 [published Online First: 2018/11/01]
 6. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. *Surgical endoscopy* 1994;8(5):408-10. doi: 10.1007/bf00642443 [published Online First: 1994/05/01]
 7. Liu M, Ji S, Xu W, et al. Laparoscopic pancreaticoduodenectomy: are the best times coming? *World journal of surgical oncology* 2019;17(1):81. doi: 10.1186/s12957-019-1624-6 [published Online First: 2019/05/12]
 8. Nickel F, Haney CM, Kowalewski KF, et al. Laparoscopic Versus Open Pancreaticoduodenectomy: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Annals of surgery* 2020;271(1):54-66. doi: 10.1097/sla.0000000000003309 [published Online First: 2019/04/12]
 9. Wang M, Li D, Chen R, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours: a multicentre, open-label, randomised controlled trial. *The lancet Gastroenterology & hepatology* 2021;6(6):438-47. doi: 10.1016/s2468-1253(21)00054-6 [published Online First: 2021/04/30]
 10. Wang M, Peng B, Liu J, et al. Practice Patterns and Perioperative Outcomes of Laparoscopic Pancreaticoduodenectomy in China: A Retrospective Multicenter Analysis of 1029 Patients. *Annals of surgery* 2021;273(1):145-53. doi: 10.1097/sla.0000000000003190 [published Online First: 2019/01/24]
 11. Chen K, Zhou Y, Jin W, et al. Laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic outcomes and long-term survival. *Surgical endoscopy* 2020;34(5):1948-58. doi: 10.1007/s00464-019-06968-8 [published Online First: 2019/07/19]
 12. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)* 2010;340:c869. doi: 10.1136/bmj.c869 [published Online First: 2010/03/25]
 13. Asbun HJ, Conlon K, Fernandez-Cruz L, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. *Surgery* 2014;155(5):887-92. doi: 10.1016/j.surg.2013.12.032 [published Online First: 2014/03/26]
 14. Kuesters S, Chikhladze S, Makowiec F, et al. Oncological outcome of laparoscopically assisted pancreatoduodenectomy for ductal adenocarcinoma in a retrospective cohort study. *International journal of surgery (London, England)* 2018;55:162-66. doi: 10.1016/j.ijsu.2018.05.026 [published Online First: 2018/05/29]
 15. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed)* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
 16. Zhang H, Feng Y, Zhao J, et al. Total laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy (TJDBPS01): study protocol for a multicentre, randomised controlled clinical trial. *BMJ open* 2020;10(2):e033490. doi: 10.1136/bmjopen-2019-033490 [published Online First: 2020/02/13]
 17. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive*

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- Cancer Network : JNCCN* 2021;19(4):439-57. doi: 10.6004/jnccn.2021.0017 [published Online First: 2021/04/13]
18. Common terminology criteria for adverse events (CTCAE) v5.0. [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf accessed June 20, 2020.
19. Gandaglia G, Ghani KR, Sood A, et al. Effect of minimally invasive surgery on the risk for surgical site infections: results from the National Surgical Quality Improvement Program (NSQIP) Database. *JAMA surgery* 2014;149(10):1039-44. doi: 10.1001/jamasurg.2014.292 [published Online First: 2014/08/22]
20. Yu J, Huang C, Sun Y, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *Jama* 2019;321(20):1983-92. doi: 10.1001/jama.2019.5359 [published Online First: 2019/05/29]
21. Kitano S, Inomata M, Mizusawa J, et al. Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. *The lancet Gastroenterology & hepatology* 2017;2(4):261-68. doi: 10.1016/s2468-1253(16)30207-2 [published Online First: 2017/04/14]
22. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2018;16(7):874-901. doi: 10.6004/jnccn.2018.0061 [published Online First: 2018/07/15]
23. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2019;17(1):64-84. doi: 10.6004/jnccn.2019.0001 [published Online First: 2019/01/20]
24. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(2):191-226. doi: 10.6004/jnccn.2021.0007 [published Online First: 2021/02/06]
25. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(5):541-65. doi: 10.6004/jnccn.2021.0022 [published Online First: 2021/05/25]
26. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(3):329-59. doi: 10.6004/jnccn.2021.0012 [published Online First: 2021/03/17]
27. Neoptolemos JP, Kleeff J, Michl P, et al. Therapeutic developments in pancreatic cancer: current and future perspectives. *Nature reviews Gastroenterology & hepatology* 2018;15(6):333-48. doi: 10.1038/s41575-018-0005-x [published Online First: 2018/05/03]
28. Strobel O, Neoptolemos J, Jäger D, et al. Optimizing the outcomes of pancreatic cancer surgery. *Nature reviews Clinical oncology* 2019;16(1):11-26. doi: 10.1038/s41571-018-0112-1 [published Online First: 2018/10/21]
29. Peng L, Zhou Z, Cao Z, et al. Long-Term Oncological Outcomes in Laparoscopic Versus Open Pancreaticoduodenectomy for Pancreatic Cancer: A Systematic Review and Meta-Analysis.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- Journal of laparoscopic & advanced surgical techniques Part A* 2019;29(6):759-69. doi: 10.1089/lap.2018.0683 [published Online First: 2019/03/06]
30. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Annals of surgery* 2014;260(4):633-8; discussion 38-40. doi: 10.1097/sla.0000000000000937 [published Online First: 2014/09/10]
31. Stauffer JA, Coppola A, Villacreses D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic adenocarcinoma: long-term results at a single institution. *Surgical endoscopy* 2017;31(5):2233-41. doi: 10.1007/s00464-016-5222-1 [published Online First: 2016/09/09]
32. Zhou W, Jin W, Wang D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a propensity score matching analysis. *Cancer communications (London, England)* 2019;39(1):66. doi: 10.1186/s40880-019-0410-8 [published Online First: 2019/10/30]
33. Kwon J, Song KB, Park SY, et al. Comparison of Minimally Invasive Versus Open Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Propensity Score Matching Analysis. *Cancers* 2020;12(4) doi: 10.3390/cancers12040982 [published Online First: 2020/04/25]
34. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053 [published Online First: 2013/10/22]

Table 1: Schedule of study enrolment, interventions, and assessments

	Study Period																
	Enrollment	Allocation	Treatment	Discharge	Post-allocation												Close-out
Time point	Outpatient clinic /Admission	Before Surgery	Surgery	After Surgery	Month 1 (T1)	Month 3 (T2)	Month 6 (T3)	Month 9 (T4)	Month 12 (T5)	Month 18 (T6)	Month 24 (T7)	Month 30 (T8)	Month 36 (T9)	Month 42 (T10)	Month 48 (T11)	Month 54 (T12)	Month 60 (T13)
Enrollment																	
Eligibility screen	×																
Informed consent	×																
Allocation		×															
Interventions																	
LPD			×														
OPD			×														
Assessments																	
Baseline characteristics	×																
Blood routine	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Blood biochemistry	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Tumor marker	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Abdominal CT scan	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Surgical record			×														
Postoperative record				×													
Pathological findings				×													
Adjuvant therapy					×	×	×	×	×	×	×	×	×	×	×	×	×
Survival status						×	×	×	×	×	×	×	×	×	×	×	×

LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

1
2
3
4 **Figure legend.**
5

6 Figure 1: Flow diagram for TJDBPS07. CONSORT, Consolidated Standards of
7 Reporting Trials; LPD, laparoscopic pancreaticoduodenectomy; OPD, open
8 pancreaticoduodenectomy.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



CONSORT

TRANSPARENT REPORTING of TRIALS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Assessed for eligibility (n=)

Excluded

- Not meeting inclusion criteria (n=)
- Declined to participate (n=)
- Other reasons (n=)

Randomised (n=200)

Enrollment

Allocation

Allocated to intervention LPD (n=)

- Received allocated intervention (n=)
- Did not receive allocated intervention (record reasons) (n=)
-

Allocated to intervention OPD (n=)

- Received allocated intervention (n=)
- Did not receive allocated intervention (record reasons) (n=)
-

Follow-up

Short-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Short-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Long-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Long-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Analysis

Analysed (n=)

- Excluded from analysis (record reasons) (n=)

Analysed (n=)

- Excluded from analysis (record reasons) (n=)

Per Protocol (n=)

Modified Intention to Treat (n=)

As Treated (n=)

Per Protocol (n=)

Modified Intention to Treat (n=)

As Treated (n=)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3;14
Protocol version	3	Date and version identifier	14-15
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5

1 2 3 4 5 6 7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
8 9	Methods: Participants, interventions, and outcomes			
10 11 12 13 14	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
15 16 17 18 19 20	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
21 22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
26 27 28 29 30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
31 32 33 34 35		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
36 37 38		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
39 40 41 42 43 44 45 46 47 48	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
49 50 51 52 53 54	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
55 56 57 58 59 60	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6;15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	annex
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057128.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Dec-2021
Complete List of Authors:	<p>Pan, Shutao; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Qin, Tingting; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Yin, Taoyuan; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Yu, Xianjun; Fudan University Shanghai Cancer Center, Department of Pancreatic Surgery</p> <p>Li, Jing; The Second Affiliated Hospital, Army Medical University, PLA, Department of Pancreatico-Hepatobiliary Surgery</p> <p>Liu, Jun; Shandong Provincial Hospital, Department of Hepato–Pancreato–Biliary Surgery</p> <p>Zhao, Wenxing; The Affiliated Hospital of Xuzhou Medical College, Department of General Surgery</p> <p>Chen, Xuemin; Department of Hepatopancreatobiliary Surgery, the Third Affiliated Hospital of Soochow University, Department of Hepatopancreatobiliary Surgery, the Third Affiliated Hospital of Soochow University</p> <p>Li, Dewei; Chongqing University Cancer Hospital, Department of Hepatobiliary and Pancreatic Oncology; The First Affiliated Hospital of Chongqing Medical University, Department of Hepatobiliary Surgery</p> <p>Liu, Jianhua; The Second Hospital of Hebei Medical University, Department of Hepato–Pancreato–Biliary Surgery</p> <p>Li, Jingdong; Affiliated Hospital of North Sichuan Medical College, Department of Pancreatico-Hepatobiliary Surgery</p> <p>Liu, Yahui; Jilin University First Hospital, Department of Hepatobiliary and Pancreatic Surgery</p> <p>Zhu, Feng; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Wang, Min; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Zhang, Hang; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p>

	Qin, Renyi; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery
Primary Subject Heading :	Gastroenterology and hepatology
Secondary Subject Heading:	Oncology, Surgery
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < ONCOLOGY

SCHOLARONE™
Manuscripts

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

1
2
3
4 **Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal**
5 **adenocarcinoma: study protocol for a multicentre randomised controlled trial**
6
7
8

9 Shutao Pan¹, Tingting Qin¹, Taoyuan Yin¹, Xianjun Yu², Jing Li³, Jun Liu⁴, Wenxing
10 Zhao⁵, Xuemin Chen⁶, Dewei Li⁷, Jianhua Liu⁸, Jingdong Li⁹, Yahui Liu¹⁰, Feng Zhu¹,
11 Min Wang¹✉, Hang Zhang¹✉, Renyi Qin¹✉, Minimally Invasive Treatment Group in
12 the Pancreatic Disease Branch of China's International Exchange and Promotion
13 Association for Medicine and Healthcare (MITG-P-CPAM).
14
15
16
17
18

19 **Author affiliations**

20
21 ¹Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji
22 Medical College, Huazhong University of Science and Technology, Wuhan, Hubei
23 430030, China.
24
25

26 ²Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center,
27 Shanghai, 200032, China
28

29 ³Department of Pancreatico-Hepatobiliary Surgery, The Second Affiliated Hospital,
30 Army Medical University, PLA, Chongqing 404100, China.
31

32 ⁴Department of Hepato–Pancreato–Biliary Surgery, Shandong Provincial Hospital,
33 Shandong 250000, China.
34

35 ⁵Department of General Surgery, The Affiliated Hospital of Xuzhou Medical College,
36 Xuzhou, 221004, China.
37
38

39 ⁶Department of Pancreaticobiliary Surgery, The Third Affiliated Hospital of Soochow
40 University, Jiangsu 213000, China.
41

42 ⁷Department of Hepatobiliary and Pancreatic Oncology, Chongqing University
43 Cancer Hospital, Chongqing, Chongqing Municipality, China; Department of
44 Hepatobiliary Surgery, First Affiliated Hospital of Chongqing Medical University,
45 Chongqing, Chongqing Municipality, China.
46
47

48 ⁸Department of Hepato–Pancreato–Biliary Surgery, The Second Hospital of Hebei
49 Medical University, Shijiazhuang, Hebei 050017, China.
50

51 ⁹Department of Pancreatico-Hepatobiliary Surgery, Affiliated Hospital of North
52 Sichuan Medical College, Sichuan 637000, China.
53

54 ¹⁰Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin
55 University, 71 Xinmin Street, Changchun, Jilin 130021, China.
56
57
58
59

60 Shutao Pan, Tingting Qin and Taoyuan Yin are joint first authors.

1
2
3
4
5
6 ✉Corresponding author

7
8 Min Wang, MD

9 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
10 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
11 Hubei 430030, China.

12 Email: wangmin0013128@aliyun.com.
13
14

15
16 Hang Zhang, MD

17 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
18 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
19 Hubei 430030, China.

20 Email: zhanghang@hust.edu.cn
21
22

23
24 Renyi Qin, MD

25 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
26 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
27 Hubei 430030, China.

28 Tel.: +27-8366-5294; Fax: +27-8366-5294

29 Email: ryqin@tjh.tjmu.edu.cn
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic head cancer. Minimally invasive surgery, which initially emerged as hybrid-laparoscopy and recently developed into total laparoscopy surgery, has been widely used for various abdominal surgeries. However, controversy persists regarding whether laparoscopic PD (LPD) is inferior to open PD (OPD) for resectable pancreatic ductal adenocarcinoma (PDAC) treatment. Further studies, especially randomised clinical trials, are warranted to compare these two surgical techniques.

Methods and analysis: The TJDBPS07 study is designed as a prospective, randomised controlled, parallel-group, open-label, multicentre noninferiority study. All participating pancreatic surgical centres comprise specialists who have performed no less than 104 LPDs and OPDs, respectively. A total of 200 strictly selected PD candidates diagnosed with PDAC will be randomised to receive LPD or OPD. The primary outcome is the 5-year overall survival rate, whereas the secondary outcomes include overall survival, disease-free survival, 90-day mortality, complication rate, comprehensive complication index, length of stay, and intraoperative indicators. We hypothesize that LPD is not inferior to OPD for the treatment of resectable PDAC. The enrolment schedule is estimated to be 2 years and follow-up for each patient will be 5 years.

Ethics and dissemination: This study received approval from the Tongji Hospital Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, and monitor from an independent third-party organization. Results of this trial will be presented in international meetings and published in a peer-reviewed journal.

Trial registration: Clinical Trials Register, NCT03785743. Registered on 10 Mar. 2019.

Strengths and limitations of this study

This trial aims to compare long-term safety of LPD and OPD for resectable PDAC treatment in a large multicentre setting and will provide evidence on performance of PDAC resection.

All participating pancreatic surgical centres are qualified with experienced surgeons who have performed no less than 104 LPDs and OPDs, respectively.

Each patient will attend a follow-up of at least 5 years to determine the study primary outcome, the 5-year overall survival rate, which is the most used indicator for describing cancer survival.

This is an open-label trial; accordingly, participants and clinicians will not be blinded to interventions.

The primary outcome of this trial will be derived from data acquired during the long-term follow-up, requiring high levels of follow-up compliance and challenging coordination between surgeons, oncologists, visitors, and patients.

INTRODUCTION

Pancreatic cancer is a highly fatal malignancy with poor responses to therapy and is estimated to be the fourth leading cause of cancer mortality¹. Among all types of pancreatic cancer, the vast majority are pancreatic ductal adenocarcinoma (PDAC)². Pancreaticoduodenectomy (PD), the standard procedure for resectable pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures^{2,3}. Compared with traditional open surgery, minimally invasive surgery has several advantages, such as small incision, minimal intraoperative bleeding, and fast postoperative recovery, among others⁴, which are essential factors promoting the development of surgical treatments. However, the long-term survival benefits of minimally invasive surgery in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival (OS) and disease-free survival (DFS) than open surgery for patients with early-stage cervical cancer⁵.

Since its inception by Gagner et al. in 1994, laparoscopic PD (LPD) has been increasingly performed owing to its potential technical advantages^{6,7}. As shown by the ISGPS Evidence Map of Pancreatic Surgery⁸, an increasing number of studies, including 4 large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for treatment of periampullary or pancreatic tumours⁹⁻¹³. Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) by highly experienced surgeons who have passed the learning curve^{12,14}. However, the application of LPD to PDAC treatment is concerning. Several studies have focused on the comparison of LPD and OPD for PDAC treatment and suggested that LPD was associated with equivalent oncologic outcomes and promising superior long-term survival outcomes compared with OPD¹⁵. However, retrospective studies are associated with inherent limitations, including patient selection biases, missing or incomplete data, and unaccounted-for variables, making results difficult to interpret definitively. No RCTs have investigated the effects of LPD and OPD on survival in patients with PDAC.

To explore the long-term safety and efficacy of LPD in patients with PDAC using high-level evidence, the Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM) designs and conducts this prospective large-scale multicentre RCT to analyse outcomes of interest, immediately after the TJDBPS01 trial, which interpreted the safety and feasibility of LPD compared with those of OPD. Accordingly, this trial aims to compare the long-term oncological and short-term surgical outcomes of LPD and OPD performed by highly experienced surgeons that have surmounted the learning curve for PDAC treatment.

METHODS AND ANALYSIS

Trial design

This trial is characterized as a prospective, multicentre, randomised controlled, and open-label study comprising two parallel groups of patients undergoing OPD and LPD. Patients diagnosed with pancreatic malignant tumours requiring PD will be consecutively recruited. This study will be conducted at ten high-volume pancreatic surgery centres in China, with surgeries being conducted by experienced surgeons. After providing written informed consents, 200 patients will be preoperatively allocated in a 1:1 ratio to either the LPD or OPD arm. The recruitment duration is estimated to be 2 years and the follow-up duration will be 5 years. The primary endpoint of this trial is the 5-year OS rate. The study will be prepared, analysed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines¹⁶, as presented in Figure 1.

Qualifications of participating surgeons and centres

The responsible participating surgeons shall satisfy the following qualifications as previously described in the TJDBPS01 study¹²: (1) having completed no less than 104 cases of LPDs; (2) having completed no less than 104 cases of OPDs¹⁴; and (3) having completed trainings of the Tongji Hospital LPD training program. Moreover, the participating centres shall perform more than 50 PDs annually. Surgeons willing to participate shall offer one recently unedited LPD and OPD surgery video, respectively, to the TJDBPS07 research council for evaluation. If the research council approves the surgical techniques, the surgeon and the centre will be permitted to participate in this study as a collaborator. Eligible patients will be discussed at regularly scheduled multidisciplinary team (MDT) meetings. Randomisation and assignment of a study-specific ID will be performed by the study sponsor.

Population and eligibility criteria

All adult patients indicated for elective PD because of a pancreatic mass will be screened for eligibility. Eligible patients will be assessed by the pancreatic MDTs of the participating centres. The MDTs should confirm that the pancreatic mass is highly suspected to be a pancreatic malignant tumour and of sufficient concern to require resection. Imaging data of contrast enhanced multi-thin sliced computed tomography (CT) scan (1mm) with or without endoluminal ultrasonography (EUS) will be regarded as the standard evaluation for each PD candidate. The last CT imaging should be performed within 4 weeks before the surgery. Histological diagnoses of malignancies are encouraged to be acquired but not a necessity¹⁷. All patients will sign the informed consent and be allowed to leave the trial at any time. The exact inclusion and exclusion criteria are below.

Inclusion criteria

- 1) Age between 18 years and 75 years.
- 2) Histologically confirmed PDAC or clinically diagnosed PDAC 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) Pregnant or breast-feeding women.
- 2) Patients with serious mental disorders.
- 3) Patients treated with neoadjuvant therapy.
- 4) Patients requiring left, central or total pancreatectomy or other palliative surgery.
- 5) Patients with vascular invasion and requiring vascular resection as evaluated by the MDT team according to abdominal imaging data.
- 6) Patients with distant metastases, including peritoneal, liver, distant lymph node metastases, and involvement of other organs.
- 7) Preoperative American Society of Anaesthesiologists (ASA) score ≥ 4 .
- 8) History of other malignant disease.
- 9) Body mass index $> 35 \text{ kg/m}^2$.
- 10) Patients participating in any other clinical trials within 3 months.

Endpoints

The primary endpoint of this trial is the 5-year overall survival rate, which is defined as the percentage of patients in this trial who are alive 5 years postoperatively [time frame: 5 years postoperatively].

Other crucial indicators are included as secondary endpoints, including (1) overall survival (i.e., the interval between the day of surgery and the day of death for various reasons [time frame: 5 years postoperatively]); (2) disease-free survival (i.e., the interval between the day of surgery and the day of tumour recurrence [time frame: 5 years postoperatively]); (3) 90-day mortality (i.e., the percentage of patients who died within 90 days postoperatively). Mortality will be calculated by dividing the number of patients who died by the number of all patients undergoing surgical treatment; (4) complication rate (complications related to PD are defined according to the

1
2
3 International Study Group of Pancreatic Surgery; complication grades are defined
4 according to the Clavien-Dindo classification system) (5) comprehensive
5 complication index¹⁸ (CCI, calculated as the sum of all complications that are
6 weighted for their severity, available at www.assessurgery.com); (6) length of stay
7 (i.e., the number of nights spent in the hospital from the end of the surgical procedure
8 until discharge or death); and (7) intraoperative indicators, including estimated blood
9 loss and operation time.
10
11
12
13
14

15 **Sample size**

16
17 The sample size calculation was performed according to the primary endpoint, the 5-
18 year OS rate, and the non-inferiority design of this trial. Assumptions were made
19 based on a previous study by Kuesters et al.¹⁹, which compared LPD with OPD for
20 PDAC treatment with the 5-year OS rate being 20% in the LPD group and 14% in the
21 OPD group. Based on the 6% decrease in 5-year OS rate in the OPD group compared
22 with the LPD group, the sample size required for each group was estimated to be 86
23 patients to achieve a non-inferiority limit of 10% at a one-tailed significance level of
24 2.5% with a power of 80% and a balanced design (1:1 ratio). Moreover, the primary
25 analyses will be based on the modified intention to treat (mITT), per protocol (PP),
26 and as treated (AT) sets. We aimed to reach a statistical power of 80% when
27 analysing the smallest population, namely the PP set.
28
29
30
31

32 Patients converted from LPD to open surgery will not be included in the PP set.
33 Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the
34 maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio
35 of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group
36 and 91 patients in the OPD group will be needed for analysis using the one-sided *t* test
37 at a one-sided significance level of 0.025. PASS version 15.0.5 will be used for the
38 calculations. An additional 10% of patients will be needed to be randomised
39 considering the non-resectable patients, patients withdrawing from the study, and
40 patients lost to follow-up. Accordingly, 100 patients in the LPD arm and 91 patients
41 in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1,
42 requiring 100 patients in each arm and 200 patients in total to be included for
43 randomisation.
44
45
46
47
48
49

50 **Patient timeline and description of trial visits**

51
52 The study duration is estimated to be 7 calendar years, with an enrolment schedule of
53 2 years and a follow-up period of 5 years for each patient. The end of the trial was
54 defined as 5 calendar years since the last enrolled patient received surgery. This
55 protocol is reported in accordance with the guidelines of the Standard Protocol Items:
56 Recommendations for Interventional Trials (SPIRIT; Table 1, supplemental file 1)²⁰.
57
58

59 Data collection and assessment are recommended to be conducted at the responsible
60

1
2
3 surgical centre. Baseline data will be collected during the screening/baseline visit, and
4 surgical data will be collected intra- and postoperatively.
5

6 Short-term follow-ups will be conducted 1 day, 1 week, 1 month, and 3 months
7 postoperatively, and follow-up contents will include laboratory inspection indicators,
8 Eastern Cooperative Oncology Group (ECOG) score, Karnofsky Performance Scale
9 (KPS) score, postoperative wound recovery, wound pain level, drainage of each
10 drainage tube postoperatively, postoperative recovery (i.e., time until getting out of
11 bed, imported food, and so on), weight, adverse events, combined medication, and
12 postoperative complications.
13
14
15

16 Long-term follow-ups will be conducted every 3 months within the first postoperative
17 year and every 6 months from the second postoperative year onwards. The following
18 follow-up contents will be tracked and recorded: clinical evaluations including
19 internal inspections (such as weight, KPS score, and ECOG score), chemotherapy-
20 related adverse events, imaging items to prove the existence of tumour recurrence or
21 metastasis (record the date of recurrence, location and follow-up treatment), the date
22 of death, and the cause of death (i.e., disease- or treatment-related mortality).
23
24
25
26
27

28 **Randomisation and blinding**

29
30 Eligible patients signed the informed consent form will be screened within one week
31 prior to randomisation. Randomisation will be assigned on the day the preoperative
32 evaluation is finished and the patient is diagnosed with PDAC, eligible for PD. We
33 will employ a 1:1 randomisation pattern for arms A and B, stratified by participating
34 centres. Random numbers will be generated by SAS software version 9.40 (SAS
35 Institute, Inc., Cary, NC) and randomisation will be performed through a centralized
36 computer-generated system by providing random numbers using dynamic blocks.
37 Within each block, randomisation is balanced, and every patient is assigned to a
38 treatment using the randomisation scheme.
39
40
41

42 This is an open-label trial, and randomisation procedure and outcome will not be
43 blinded to patients and surgeons. However, data collectors, outcome assessors, and
44 data analysts will be blinded during statistical analysis. Surgeons will not participate
45 in the data collection process which will be conducted by an independent team.
46 Analysis processes will be blinded, and the statistician will be provided with only
47 group codes instead of group names.
48
49
50
51

52 **Intervention**

53
54 Surgical procedures need to comply with PD technique standards as previously
55 described²¹. Any appropriate changes in surgical procedures according to the
56 surgeon's own experience and preference are permitted, including changes in
57 procedure order, surgical approach, and anastomosis method. All changes will be
58 recorded in the case report form.
59
60

Experimental intervention-LPD techniques

Patients will take a supine position and undergo general anaesthesia. Five trocars in total will be used. Routine and standard lymph node dissections will be maintained as recommended by guidelines. The pancreatic stump will be sent for quick frozen pathological examination intraoperatively; moreover, it is necessary to confirm that the pancreatic margin specimen is pathologically negative before digestive tract reconstruction. Surgeons will determine the reconstruction type according to their experiences and preferences. After reconstruction, two drainage tubes are routinely placed, with one near the anastomosis of the pancreaticojejunostomy and the other near the anastomosis of the bile jejunum.

Conversion to open surgery is defined as the use of any skin incision during LPD for other than trocar placement or surgical specimen removal. For cases of conversion, data will be analysed in the LPD group in an intention-to-treat manner. However, reasons for conversion shall be realistically registered and carefully recorded.

Control intervention-OPD techniques

Open surgery shall be performed by the same group of surgeons as LPD. Key steps are performed essentially as described in the LPD group. Methods used for reconstruction during OPD must be consistent with those during LPD in the same single centre.

Concomitant treatment

The TJDBPS07 trial follows TJDBPS01 which compared LPD and OPD; accordingly, the principles of perioperative management are similar to those previously described²¹. Whatever medical devices and materials that are most used in daily practice of each participant centre can be used if recorded carefully in surgical records. Antibiotics are given to patients 30 min before skin incision and 2 h after incision. Patient-controlled analgesia will be used to control postoperative pain. Time to remove the nasogastric tube depends on each patients' situation evaluated by doctors of each participating centre; early removal is encouraged. The abdominal drains will be placed routinely for patients. The timepoint of drain removal depends on every patient's manifestation, laboratory examination results (the concentration of drain fluid amylase (DFA) on postoperative days (PODs) 1 and 3), and imaging findings. In patients with a DFA concentration of less than 5000 U/L on POD 1, early drain removal at 72 h is recommended. In patients with a DFA concentration of more than 5000 U/L on POD 1, drain removal will be decided by the corresponding surgeon according to the patient's situation. Patients can be discharged if they meet the following discharge criteria: no need for intravenous infusion, well tolerance of oral solid or semisolid food, no need for intravenous analgesics, well wound healing, well tolerance of

1
2
3 independent walking at least 250 m in a plain road, well major organ function with
4 near-normal haematological parameters.
5

6 After surgical resection, patients pathologically diagnosed with PDAC will receive
7 adjuvant chemotherapy according to the National Comprehensive Cancer Network
8 (NCCN) guideline²². Written informed consent for adjuvant chemotherapy should be
9 obtained. Different regimens recommended in the aforementioned guideline are
10 permitted, and the treatment duration is at the discretion of the responsible treating
11 oncologist. Detailed information on adjuvant chemotherapy will be recorded. Relapse
12 cases will be treated according to the recommendations of the NCCN guideline at the
13 corresponding participating centres.
14
15
16
17
18

19 **Data collection and management**

20 All data will be collected using an electronic case report form. The datasets generated
21 during the study will be stored in a local database, which is managed by the data
22 collection group of Tongji Hospital. Investigators from each participating institution
23 will have access to the data of their respective patients. All data are pseudonymized,
24 and patient details are encoded.
25
26
27

28 Data collection will include variables related to patient demographics, intraoperative
29 information, histopathological information, postoperative clinical findings, adjuvant
30 chemotherapy, and follow-up.
31
32

33 Patient demographics: age, gender, height (cm), weight (kg), smoking, drinking, main
34 complaint, clinical diagnosis, comorbidities, surgical history, underlying malignant
35 disease, ECOG score, ASA score, imaging results, preoperative blood samples (i.e.,
36 haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio),
37 plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and
38 carcinoembryonic antigen (CEA)), preoperative biliary drainage, and date of
39 admission.
40
41
42

43 Intraoperative information: operation date, surgical approach (laparoscopic or open),
44 conversion to open surgery, intraoperative death, texture of pancreas, diameter of the
45 main pancreatic duct, placement of intra-abdominal drain, type of reconstruction,
46 anastomosis approach (intracorporeal or extracorporeal), anastomosis performance
47 (linear stapler, circular stapler, hand-sewn, or combinations), total operative time,
48 each anastomosis time (pancreaticojejunostomy, cholangiohepaticojejunostomy, and
49 gastroenterostomy), intraoperative complications, estimated blood loss, and
50 intraoperative blood transfusion.
51
52
53

54 Histopathological information: tumour location, tumour size, histological type,
55 surgical margin status (R0 resection rates), number of lymph nodes, number of
56 positive lymph nodes, depth of invasion (T classification), lymph node status (N
57 classification), and American Joint Committee on Cancer staging.
58
59

60 Postoperative clinical findings: length of postoperative stay, postoperative blood

transfusion, length of intravenous analgesic use, drain production and amylase, postoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA), date of patient mobilization, date of liquid diet, date of drain removal, postoperative complication, reoperation, Clavien-Dindo grade, adverse event, cost of surgery, and cost of hospitalization.

Adjuvant chemotherapy: date of adjuvant chemotherapy, chemotherapy regimens, side effects, imaging results, haemoglobin level, white blood cell count, and related tumour markers (i.e., CA19–9, CA125, and CEA).

Follow-up: date of follow-up visit, patient status (alive, dead or lost to follow-up), ECOG score, KPS score, imaging results, related tumour markers (i.e., CA19–9, CA125, and CEA), DFS, and OS.

Data Availability Statement

The final datasets will not be available to the public. However, researchers will have access to the study data in de-identified form from the corresponding author after reasonable request when the study is completed.

Risk of bias

All adult patients with pancreatic masses eligible for PD will be screened in all participating centres. The recruited patients will be expected to be generalizable and representative to the wider population. Standard randomisation will be conducted to ensure comparable baseline characteristics between each group. To minimize confounding, allocations will be stratified by centre.

The primary outcome of this trial is the 5-year OS rate, which is objective and will be obtained from the planned follow-up data. The participants, surgeons, and nursing staff will not be blinded to interventions due to the characteristics of this trial, which compares minimally invasive surgery and conventional open surgery. The responsible surgeons will not be involved in the postoperative management of patients and determination of patients' discharge. Data collectors, outcome assessors, and data analysts will all be blinded to surgical techniques.

To minimize missing data bias, data for the primary outcome will be routinely collected and regularly reviewed.

Results of this trial will be reported in accordance with the CONSORT statement¹⁶ to minimize reporting bias. In addition, the trial protocol is reported according to the SPIRIT statement²⁰ to assure full transparency throughout this trial and subsequent reporting.

Assessment of cross-over patients

Conversion from LPD to OPD is closely associated with intraoperative situations, including technical infeasibility and significant bleeding, which is unavoidable even for experienced surgeons who have passed the learning curves, making it impossible to eliminate conversion by modifying inclusion and exclusion criteria. The conversion rate in our previous trial comparing LPD and OPD for pancreatic or periampullary tumours was 4%¹². Considering the techniques complexity in LPD for PDAC, the maximum conversion rate within this trial is cautiously estimated to be 10%. Reasons for conversion will be recorded in detail and further evaluated in the subgroup analysis.

Statistical analysis

A statistical analysis plan will be developed and agreed upon by the data collection group. All main statistical analyses will be performed according to an intention-to-treat principle, and the primary analysis will be based on the mITT, PP, and AT set. Patients deemed unresectable intraoperatively or who do not receive surgical resection will not be considered in any of the analysis sets. The mITT set will comprise all patients in the group to which they were randomised regardless of the actual received surgery. The PP set will include patients without major protocol violations. Patients converted from LPD to OPD will not be included in the PP set. The AT set will be analysed with considerations of the actual treatment of patients, rather than their randomisation. For robust interpretation, the results of the three primary analysis sets should lead to similar conclusions; otherwise, possible reasons behind discrepancies must be discussed. OS and DFS will be analysed from the date of pancreatic resection to the date of death (for OS) or date of regional recurrence or systemic spread (for DFS). The OS and DFS curves for the entire follow-up period will be estimated according to Kaplan-Meier method and compared using a log-rank test. Time-specific OS and DFS probabilities at appropriate time points will be derived from the survival curves and the Greenwood estimate will be used to construct corresponding a 95% confidence interval (CI). Hazard ratios (HRs) and two-sided 95% CIs will be estimated using a Cox regression model after confirming the proportional hazards assumptions.

In summary, continuous data will be presented as mean \pm standard deviation and will be compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables will be compared using the χ^2 test or Fisher's exact test, as appropriate. Statistical analyses will be conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). *P* < 0.05 will denote statistical significance.

This trial is registered at ClinicalTrials.gov (registration number: NCT03785743).

Monitoring

1
2
3 Throughout the trial, a trained, qualified, and independent monitor will periodically
4 visit each participating centre to randomly check protocol compliance, compliance
5 with the inclusion and exclusion criteria, proper implementation, obtainment of
6 informed consent forms, source data verification, and reporting of serious adverse
7 events. Adverse events will be graded using the Common Terminology Criteria for
8 Adverse Events (CTCAE) version 5.0²³. The Hospital Ethical Committee and Chinese
9 Clinical Trial Registry are responsible for collection and management of these data.
10 Moreover, an independent agency will handle the auditing every month.
11
12
13
14
15

16 DISCUSSION

17
18 The TJDBPS07 trial is designed as a prospective, multicentre, randomised controlled,
19 and open-label trial to assess the long-term oncological and short-term surgical
20 outcomes of LPD and OPD for PDAC treatment. The results of our TJDBPS01 trial
21 suggested that LPD is a safe and feasible procedure for treating pancreatic or
22 periampullary tumours, with comparable short-term outcomes to OPD in highly
23 experienced hands^{12 21}. The TJDBPS07 trial follows TJDBPS01 and focuses on the
24 comparison of LPD and OPD for treatment of resectable PDAC. In consideration of
25 the complexity and difficulty of PD, surgeons participating in this trial are required to
26 complete a structured training program for LPD and pass the learning curve by
27 finishing a minimum of 104 LPDs, as suggested by the results of a retrospective study
28 on the learning curve for LPD in China¹⁴.
29
30
31
32

33 With rapid advances in minimally invasive technology, minimally invasive surgery is
34 favoured by surgeons in more and more fields due to its minimal invasiveness and
35 enhanced patient recovery²⁴. Few RCTs focusing on the impact of minimally invasive
36 surgery on the long-term survival of cancer patients have been conducted, and
37 different conclusions have emerged from existing studies. A study by Yu et al. found
38 that laparoscopic distal gastrectomy and open surgery had comparable DFS and OS in
39 patients with locally advanced gastric cancer²⁵. Moreover, a study by Kitano et al.
40 concluded that laparoscopic D3 surgery was not inferior to open surgery in terms of
41 OS in patients with stage II and III colon cancer²⁶. However, research by Pedro et al.
42 suggested that for patients with early cervical cancer, minimally invasive radical
43 hysterectomy resulted in lower rates of DFS and OS than open radical hysterectomy⁵.
44 The current guidelines of NCCN suggest that minimally invasive surgery and open
45 surgery are both suitable for surgical treatment of several tumours^{22 27-31}, resulting in
46 the widespread use of minimally invasive surgery. However, more high-quality RCTs
47 are needed to verify whether minimally invasive surgeries can bring the same long-
48 term benefits for patients with tumours as open surgeries do.
49
50
51
52
53

54 With a 5-year survival rate of approximately 10%, the highly fatal pancreatic cancer is
55 becoming an increasingly common cause of cancer-related mortality. Surgical
56 resection represents the only chance of cure for patients with resectable pancreatic
57 cancer³². Moreover, the application of adjuvant chemotherapy significantly improves
58 long-term survival in these patients³³. Although an increasing number of researchers
59
60

1
2
3 are concerned about the therapeutic effects of LPD on patients with PDAC, current
4 evidence is still based on a few observational studies with limited quality³⁴. The data
5 of 322 patients with PDAC (108 undergoing LPD and 214 undergoing OPD)
6 demonstrated that LPD was technically feasible for PDAC treatment and was
7 associated with better length of stay, postoperative recovery, and pursuing adjuvant
8 treatment than OPD. This study simultaneously showed comparable OS but longer
9 DFS in LPD than OPD³⁵, while other studies have indicated that the long-term
10 survival and perioperative outcomes were comparable between LPD and OPD for
11 treatment of selected PDAC patients³⁶⁻³⁸. Considering the controversies among
12 existing publications and limitations of observational studies, doctors and researchers
13 in the field of PDAC emphasize the necessity and importance of large-scale
14 multicentre RCTs.
15
16
17
18

19 In conclusion, the TJDBPS07 trial is a multicentre randomised controlled, non-
20 inferiority trial investigating the long-term survival and the preoperative safety of
21 LPD and OPD for resectable PDAC. This trial aims to evaluate differences in the 5-
22 year OS rate between LPD and OPD for PDAC treatment. The results of this trial will
23 provide high-level evidence for guiding the daily practice of PDAC management.
24
25
26
27
28

29 **Trial status**

30 The TJDBPS07 trial was registered on 10 March 2019 at the ClinicalTrials Registry
31 (registration number: NCT03785743). The protocol of this trial was proposed by the
32 investigator from Tongji Hospital, and the final version was approved by Tongji
33 Institutional Review Board. The first enrolled patient has been given the randomised
34 number in August 2019. All ten centres are actively recruiting patients by the time
35 this protocol is submitted. Recruitment will approximately be completed by
36 December 2021.
37
38
39
40
41

42 **Patient and public involvement**

43 This trial will not involve either patients or the public in the design, recruitment,
44 conduct of the study, or measurement of outcomes. The trial results will not be
45 notified to every single patient, while instead, the results will be presented in
46 academic conferences, and disseminated via open-access and peer-reviewed journals.
47 This trial will investigate patient-reported outcomes, using tools such as
48 questionnaires about quality of life.
49
50
51
52
53

54 **Ethics and dissemination**

55 Each participant will sign an informed consent document before inclusion; this form
56 is provided by a qualified team member and subsequently sent to and preserved by the
57 data collection team. All participations are voluntary and have the right to withdraw
58
59
60

1
2
3 from the study for any reason whenever they want to. If they do withdraw, they will
4 still receive standard treatment according to local hospital procedures. The study will
5 be conducted in accordance with the principles outlined in the Declaration of Helsinki
6 and its later amendments³⁹. This trial was registered under the Tongji Hospital (trial
7 ID: NCT03785743) and approved by Tongji Hospital Ethics Committee (approval
8 number: TJ-IRB20190318) in March 2019. Local ethical approval was confirmed
9 from each participating centre before recruiting at other centres. All authors have
10 access to study data and reviewed and approved the final manuscript. The results of
11 this trial will be presented in international meetings, and final trial results will be
12 published in an open access, peer-reviewed journal.
13
14
15
16
17
18

19 **Acknowledgements**

20
21 We thank the team of Prof. Ping Yin from the Department of Epidemiology and
22 Biostatistics, School of Public Health, Tongji Medical College, Huazhong University
23 of Science and Technology, for the data monitoring and statistical support.
24
25
26

27 **Authors' contributions**

28
29 RYQ, MW, and FZ obtained funding for the study. RYQ, HZ, and MW designed the
30 study. XJY, JiL, JuL, WXZ, XMC, DWL, JHL, JDL, YHL, and RYQ performed the
31 operations. STP, TTQ, and TYY drafted the manuscript. RYQ, HZ, and MW
32 contributed to the critical revision of the manuscript for important intellectual content
33 and approved the final version of the manuscript. All authors have read and approved
34 the final manuscript.
35
36
37
38
39

40 **Funding statement**

41
42 The study was supported by grants from The National Natural Science Foundation of
43 China (82073249, 81874205, 81773160), Tongji Hospital Clinical Research Flagship
44 Program (2019CR203).
45
46
47

48 **Disclaimer**

49
50 The funder had no role in the design of the study, data collection, or writing this
51 manuscript.
52
53
54

55 **Competing interests**

56
57 The authors and each study site declare no conflicts of interest.
58
59
60

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer-reviewed.

REFERENCE

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: a cancer journal for clinicians* 2020;70(1):7-30. doi: 10.3322/caac.21590 [published Online First: 2020/01/09]
2. Mizrahi JD, Surana R, Valle JW, et al. Pancreatic cancer. *Lancet (London, England)* 2020;395(10242):2008-20. doi: 10.1016/s0140-6736(20)30974-0 [published Online First: 2020/07/01]
3. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2011;13(6):377-84. doi: 10.1111/j.1477-2574.2011.00305.x [published Online First: 2011/05/26]
4. Zhang YH, Zhang CW, Hu ZM, et al. Pancreatic cancer: Open or minimally invasive surgery? *World J Gastroenterol* 2016;22(32):7301-10. doi: 10.3748/wjg.v22.i32.7301 [published Online First: 2016/09/14]
5. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *The New England journal of medicine* 2018;379(20):1895-904. doi: 10.1056/NEJMoa1806395 [published Online First: 2018/11/01]
6. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. *Surgical endoscopy* 1994;8(5):408-10. doi: 10.1007/bf00642443 [published Online First: 1994/05/01]
7. Liu M, Ji S, Xu W, et al. Laparoscopic pancreaticoduodenectomy: are the best times coming? *World journal of surgical oncology* 2019;17(1):81. doi: 10.1186/s12957-019-1624-6 [published Online First: 2019/05/12]
8. Probst P, Hüttner FJ, Meydan Ö, et al. Evidence Map of Pancreatic Surgery-A living systematic review with meta-analyses by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2021;170(5):1517-24. doi: 10.1016/j.surg.2021.04.023 [published Online First: 2021/07/01]
9. Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. *The British journal of surgery* 2017;104(11):1443-50. doi: 10.1002/bjs.10662 [published Online First: 2017/09/13]
10. Poves I, Burdío F, Morató O, et al. Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreatoduodenectomy: The PADULAP Randomized Controlled Trial. *Annals of surgery* 2018;268(5):731-39. doi: 10.1097/sla.0000000000002893 [published Online First: 2018/08/24]
11. van Hilst J, de Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *The lancet Gastroenterology & hepatology*

- 2019;4(3):199-207. doi: 10.1016/s2468-1253(19)30004-4 [published Online First: 2019/01/28]
12. Wang M, Li D, Chen R, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours: a multicentre, open-label, randomised controlled trial. *The lancet Gastroenterology & hepatology* 2021;6(6):438-47. doi: 10.1016/s2468-1253(21)00054-6 [published Online First: 2021/04/30]
13. Nickel F, Haney CM, Kowalewski KF, et al. Laparoscopic Versus Open Pancreaticoduodenectomy: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Annals of surgery* 2020;271(1):54-66. doi: 10.1097/sla.0000000000003309 [published Online First: 2019/04/12]
14. Wang M, Peng B, Liu J, et al. Practice Patterns and Perioperative Outcomes of Laparoscopic Pancreaticoduodenectomy in China: A Retrospective Multicenter Analysis of 1029 Patients. *Annals of surgery* 2021;273(1):145-53. doi: 10.1097/sla.0000000000003190 [published Online First: 2019/01/24]
15. Chen K, Zhou Y, Jin W, et al. Laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic outcomes and long-term survival. *Surgical endoscopy* 2020;34(5):1948-58. doi: 10.1007/s00464-019-06968-8 [published Online First: 2019/07/19]
16. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)* 2010;340:c869. doi: 10.1136/bmj.c869 [published Online First: 2010/03/25]
17. Asbun HJ, Conlon K, Fernandez-Cruz L, et al. When to perform a pancreatoduodenectomy in the absence of positive histology? A consensus statement by the International Study Group of Pancreatic Surgery. *Surgery* 2014;155(5):887-92. doi: 10.1016/j.surg.2013.12.032 [published Online First: 2014/03/26]
18. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Annals of surgery* 2013;258(1):1-7. doi: 10.1097/SLA.0b013e318296c732 [published Online First: 2013/06/04]
19. Kuesters S, Chikhladze S, Makowiec F, et al. Oncological outcome of laparoscopically assisted pancreatoduodenectomy for ductal adenocarcinoma in a retrospective cohort study. *International journal of surgery (London, England)* 2018;55:162-66. doi: 10.1016/j.ijso.2018.05.026 [published Online First: 2018/05/29]
20. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed)* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
21. Zhang H, Feng Y, Zhao J, et al. Total laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy (TJDBPS01): study protocol for a multicentre, randomised controlled clinical trial. *BMJ open* 2020;10(2):e033490. doi: 10.1136/bmjopen-2019-033490 [published Online First: 2020/02/13]
22. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(4):439-57. doi: 10.6004/jnccn.2021.0017 [published Online First: 2021/04/13]
23. Common terminology criteria for adverse events (CTCAE) v5.0. [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf accessed June 20, 2020.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
24. Gandaglia G, Ghani KR, Sood A, et al. Effect of minimally invasive surgery on the risk for surgical site infections: results from the National Surgical Quality Improvement Program (NSQIP) Database. *JAMA surgery* 2014;149(10):1039-44. doi: 10.1001/jamasurg.2014.292 [published Online First: 2014/08/22]
 25. Yu J, Huang C, Sun Y, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *Jama* 2019;321(20):1983-92. doi: 10.1001/jama.2019.5359 [published Online First: 2019/05/29]
 26. Kitano S, Inomata M, Mizusawa J, et al. Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. *The lancet Gastroenterology & hepatology* 2017;2(4):261-68. doi: 10.1016/s2468-1253(16)30207-2 [published Online First: 2017/04/14]
 27. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2018;16(7):874-901. doi: 10.6004/jnccn.2018.0061 [published Online First: 2018/07/15]
 28. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2019;17(1):64-84. doi: 10.6004/jnccn.2019.0001 [published Online First: 2019/01/20]
 29. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(2):191-226. doi: 10.6004/jnccn.2021.0007 [published Online First: 2021/02/06]
 30. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(5):541-65. doi: 10.6004/jnccn.2021.0022 [published Online First: 2021/05/25]
 31. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(3):329-59. doi: 10.6004/jnccn.2021.0012 [published Online First: 2021/03/17]
 32. Neoptolemos JP, Kleeff J, Michl P, et al. Therapeutic developments in pancreatic cancer: current and future perspectives. *Nature reviews Gastroenterology & hepatology* 2018;15(6):333-48. doi: 10.1038/s41575-018-0005-x [published Online First: 2018/05/03]
 33. Strobel O, Neoptolemos J, Jäger D, et al. Optimizing the outcomes of pancreatic cancer surgery. *Nature reviews Clinical oncology* 2019;16(1):11-26. doi: 10.1038/s41571-018-0112-1 [published Online First: 2018/10/21]
 34. Peng L, Zhou Z, Cao Z, et al. Long-Term Oncological Outcomes in Laparoscopic Versus Open Pancreaticoduodenectomy for Pancreatic Cancer: A Systematic Review and Meta-Analysis. *Journal of laparoendoscopic & advanced surgical techniques Part A* 2019;29(6):759-69. doi: 10.1089/lap.2018.0683 [published Online First: 2019/03/06]
 35. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Annals of surgery* 2014;260(4):633-8; discussion 38-40. doi: 10.1097/sla.0000000000000937 [published Online First: 2014/09/10]
 36. Stauffer JA, Coppola A, Villacreses D, et al. Laparoscopic versus open pancreaticoduodenectomy

- 1
2
3 for pancreatic adenocarcinoma: long-term results at a single institution. *Surgical endoscopy*
4 2017;31(5):2233-41. doi: 10.1007/s00464-016-5222-1 [published Online First: 2016/09/09]
5
6 37. Zhou W, Jin W, Wang D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic
7 ductal adenocarcinoma: a propensity score matching analysis. *Cancer communications*
8 *(London, England)* 2019;39(1):66. doi: 10.1186/s40880-019-0410-8 [published Online First:
9 2019/10/30]
10
11 38. Kwon J, Song KB, Park SY, et al. Comparison of Minimally Invasive Versus Open
12 Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Propensity Score
13 Matching Analysis. *Cancers* 2020;12(4) doi: 10.3390/cancers12040982 [published Online First:
14 2020/04/25]
15
16 39. World Medical Association Declaration of Helsinki: ethical principles for medical research involving
17 human subjects. *Jama* 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053 [published
18 Online First: 2013/10/22]
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1: Schedule of study enrolment, interventions, and assessments

Time point	Study Period																	
	Enrollment	Allocation	Treatment	Discharge	Post-allocation												Close-out	
	Outpatient clinic /Admission	Before Surgery	Surgery	After Surgery	Month 1 (T1)	Month 3 (T2)	Month 6 (T3)	Month 9 (T4)	Month 12 (T5)	Month 18 (T6)	Month 24 (T7)	Month 30 (T8)	Month 36 (T9)	Month 42 (T10)	Month 48 (T11)	Month 54 (T12)	Month 60 (T13)	
Enrollment																		
Eligibility screen																		
Informed consent	×																	
Allocation	×																	
		×																
Interventions																		
LPD																		
OPD			×															
			×															
Assessments																		
Baseline characteristics	×																	
Blood routine	×			×		×	×	×	×	×	×	×	×	×	×	×	×	×
Blood biochemistry	×			×		×	×	×	×	×	×	×	×	×	×	×	×	×
Tumor marker	×			×		×	×	×	×	×	×	×	×	×	×	×	×	×
Abdominal CT scan	×			×		×	×	×	×	×	×	×	×	×	×	×	×	×
Surgical record			×															
Postoperative record				×														
Pathological findings				×														
Adjuvant therapy				×														
Survival status					×	×	×	×	×	×	×	×	×	×	×	×	×	×
						×	×	×	×	×	×	×	×	×	×	×	×	×

LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

1
2
3
4 **Figure legend.**
5

6 Figure 1: Flow diagram for TJDBPS07. CONSORT, Consolidated Standards of
7 Reporting Trials; LPD, laparoscopic pancreaticoduodenectomy; OPD, open
8 pancreaticoduodenectomy.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



CONSORT

TRANSPARENT REPORTING of TRIALS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Assessed for eligibility (n=)

Excluded

- Not meeting inclusion criteria (n=)
- Declined to participate (n=)
- Other reasons (n=)

Randomised (n=200)

Enrollment

Allocation

Follow-up

Analysis

Allocated to intervention LPD (n=)

- Received allocated intervention (n=)
- Did not receive allocated intervention (record reasons) (n=)
-

Allocated to intervention OPD (n=)

- Received allocated intervention (n=)
- Did not receive allocated intervention (record reasons) (n=)
-

Short-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Short-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Long-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Long-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Analysed (n=)

- Excluded from analysis (record reasons) (n=)

Analysed (n=)

- Excluded from analysis (record reasons) (n=)

Per Protocol (n=)

Modified Intention to Treat (n=)

As Treated (n=)

Per Protocol (n=)

Modified Intention to Treat (n=)

As Treated (n=)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3;15
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5

1 2 3 4 5 6 7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
8 9	Methods: Participants, interventions, and outcomes			
10 11 12 13 14	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
15 16 17 18 19 20	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
21 22 23 24 25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
26 27 28 29 30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
31 32 33 34 35		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
36 37 38		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
39 40 41 42 43 44 45 46 47 48	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
49 50 51 52 53 54	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
55 56 57 58 59 60	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12

1 2 3 4 5 6 7 8	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
9 10 11 12 13 14 15 16 17 18 19 20	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
20b		Methods for any additional analyses (eg, subgroup and adjusted analyses)	13	
20c		Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13	
21 22	Methods: Monitoring			
23 24 25 26 27 28 29 30 31 32 33 34 35	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
21b		Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13	
36 37 38 39 40 41	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
42 43 44 45	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
46 47	Ethics and dissemination			
48 49 50 51 52	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
53 54 55 56 57 58 59 60	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6;10;15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11;15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	annex
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: study protocol for a multicentre randomised controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057128.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Feb-2022
Complete List of Authors:	<p>Pan, Shutao; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Qin, Tingting; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Yin, Taoyuan; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Yu, Xianjun; Fudan University Shanghai Cancer Center, Department of Pancreatic Surgery</p> <p>Li, Jing; The Second Affiliated Hospital, Army Medical University, PLA, Department of Pancreatico-Hepatobiliary Surgery</p> <p>Liu, Jun; Shandong Provincial Hospital, Department of Hepato–Pancreato–Biliary Surgery</p> <p>Zhao, Wenxing; The Affiliated Hospital of Xuzhou Medical College, Department of General Surgery</p> <p>Chen, Xuemin; Department of Hepatopancreatobiliary Surgery, the Third Affiliated Hospital of Soochow University, Department of Hepatopancreatobiliary Surgery, the Third Affiliated Hospital of Soochow University</p> <p>Li, Dewei; Chongqing University Cancer Hospital, Department of Hepatobiliary and Pancreatic Oncology; The First Affiliated Hospital of Chongqing Medical University, Department of Hepatobiliary Surgery</p> <p>Liu, Jianhua; The Second Hospital of Hebei Medical University, Department of Hepato–Pancreato–Biliary Surgery</p> <p>Li, Jingdong; Affiliated Hospital of North Sichuan Medical College, Department of Pancreatico-Hepatobiliary Surgery</p> <p>Liu, Yahui; Jilin University First Hospital, Department of Hepatobiliary and Pancreatic Surgery</p> <p>Zhu, Feng; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Wang, Min; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p> <p>Zhang, Hang; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Qin, Renyi; Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Biliary–Pancreatic Surgery
Primary Subject Heading :	Gastroenterology and hepatology
Secondary Subject Heading:	Oncology, Surgery
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < ONCOLOGY



1
2
3
4 **Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal**
5 **adenocarcinoma: study protocol for a multicentre randomised controlled trial**
6
7
8

9 Shutao Pan¹, Tingting Qin¹, Taoyuan Yin¹, Xianjun Yu², Jing Li³, Jun Liu⁴, Wenxing
10 Zhao⁵, Xuemin Chen⁶, Dewei Li⁷, Jianhua Liu⁸, Jingdong Li⁹, Yahui Liu¹⁰, Feng Zhu¹,
11 Min Wang¹✉, Hang Zhang¹✉, Renyi Qin¹✉, Minimally Invasive Treatment Group in
12 the Pancreatic Disease Branch of China's International Exchange and Promotion
13 Association for Medicine and Healthcare (MITG-P-CPAM).
14
15
16
17
18

19 **Author affiliations**

20
21 ¹Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji
22 Medical College, Huazhong University of Science and Technology, Wuhan, Hubei
23 430030, China.
24
25

26 ²Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center,
27 Shanghai, 200032, China
28

29 ³Department of Pancreatico-Hepatobiliary Surgery, The Second Affiliated Hospital,
30 Army Medical University, PLA, Chongqing 404100, China.
31

32 ⁴Department of Hepato–Pancreato–Biliary Surgery, Shandong Provincial Hospital,
33 Shandong 250000, China.
34

35 ⁵Department of General Surgery, The Affiliated Hospital of Xuzhou Medical College,
36 Xuzhou, 221004, China.
37
38

39 ⁶Department of Pancreaticobiliary Surgery, The Third Affiliated Hospital of Soochow
40 University, Jiangsu 213000, China.
41

42 ⁷Department of Hepatobiliary and Pancreatic Oncology, Chongqing University
43 Cancer Hospital, Chongqing, Chongqing Municipality, China; Department of
44 Hepatobiliary Surgery, First Affiliated Hospital of Chongqing Medical University,
45 Chongqing, Chongqing Municipality, China.
46
47

48 ⁸Department of Hepato–Pancreato–Biliary Surgery, The Second Hospital of Hebei
49 Medical University, Shijiazhuang, Hebei 050017, China.
50

51 ⁹Department of Pancreatico-Hepatobiliary Surgery, Affiliated Hospital of North
52 Sichuan Medical College, Sichuan 637000, China.
53

54 ¹⁰Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jilin
55 University, 71 Xinmin Street, Changchun, Jilin 130021, China.
56
57
58
59

60 Shutao Pan, Tingting Qin and Taoyuan Yin are joint first authors.

1
2
3
4
5
6 ✉Corresponding author

7
8 Min Wang, MD

9 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
10 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
11 Hubei 430030, China.

12 Email: wangmin0013128@aliyun.com.
13
14

15
16 Hang Zhang, MD

17 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
18 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
19 Hubei 430030, China.

20 Email: zhanghang@hust.edu.cn
21
22

23
24 Renyi Qin, MD

25 Department of Biliary–Pancreatic Surgery, Affiliated Tongji Hospital, Tongji Medical
26 College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Wuhan,
27 Hubei 430030, China.

28 Tel.: +27-8366-5294; Fax: +27-8366-5294

29 Email: ryqin@tjh.tjmu.edu.cn
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Pancreatic cancer is one of the deadliest cancers and pancreaticoduodenectomy (PD) is recommended as the optimal operation for resectable pancreatic head cancer. Minimally invasive surgery, which initially emerged as hybrid-laparoscopy and recently developed into total laparoscopy surgery, has been widely used for various abdominal surgeries. However, controversy persists regarding whether laparoscopic PD (LPD) is inferior to open PD (OPD) for resectable pancreatic ductal adenocarcinoma (PDAC) treatment. Further studies, especially randomised clinical trials, are warranted to compare these two surgical techniques.

Methods and analysis: The TJDBPS07 study is designed as a prospective, randomised controlled, parallel-group, open-label, multicentre noninferiority study. All participating pancreatic surgical centres comprise specialists who have performed no less than 104 LPDs and OPDs, respectively. A total of 200 strictly selected PD candidates diagnosed with PDAC will be randomised to receive LPD or OPD. The primary outcome is the 5-year overall survival rate, whereas the secondary outcomes include overall survival, disease-free survival, 90-day mortality, complication rate, comprehensive complication index, length of stay, and intraoperative indicators. We hypothesize that LPD is not inferior to OPD for the treatment of resectable PDAC. The enrolment schedule is estimated to be 2 years and follow-up for each patient will be 5 years.

Ethics and dissemination: This study received approval from the Tongji Hospital Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, and monitor from an independent third-party organization. Results of this trial will be presented in international meetings and published in a peer-reviewed journal.

Trial registration: Clinical Trials Register, NCT03785743. Registered on 10 Mar. 2019.

Strengths and limitations of this study

This trial aims to compare long-term safety of LPD and OPD for resectable PDAC treatment in a large multicentre setting and will provide evidence on performance of PDAC resection.

All participating pancreatic surgical centres are qualified with experienced surgeons who have performed no less than 104 LPDs and OPDs, respectively.

Each patient will attend a follow-up of at least 5 years to determine the study primary outcome, the 5-year overall survival rate, which is the most used indicator for describing cancer survival.

This is an open-label trial; accordingly, participants and clinicians will not be blinded to interventions.

The primary outcome of this trial will be derived from data acquired during the long-term follow-up, requiring high levels of follow-up compliance and challenging coordination between surgeons, oncologists, visitors, and patients.

INTRODUCTION

Pancreatic cancer is a highly fatal malignancy with poor responses to therapy and is estimated to be the fourth leading cause of cancer mortality¹. Among all types of pancreatic cancer, the vast majority are pancreatic ductal adenocarcinoma (PDAC)². Pancreaticoduodenectomy (PD), the standard procedure for resectable pancreatic head cancer, is considered one of the subtlest abdominal surgical procedures, involving both difficult resection and complex reconstruction procedures^{2,3}. Compared with traditional open surgery, minimally invasive surgery (MIS) has several advantages, such as small incision, minimal intraoperative bleeding, and fast postoperative recovery, among others⁴, which are essential factors promoting the development of surgical treatments. However, the long-term survival benefits of MIS in patients with cancer remains controversial. For example, minimally invasive radical hysterectomy showed poorer overall survival (OS) and disease-free survival (DFS) than open surgery for patients with early-stage cervical cancer⁵.

Since its inception by Gagner et al. in 1994, laparoscopic PD (LPD) has been increasingly performed owing to its potential technical advantages^{6,7}. As shown by the ISGPS Evidence Map of Pancreatic Surgery⁸, an increasing number of studies, including 4 large-scale randomised controlled trials (RCTs), have reported the safety and feasibility of LPD for treatment of periampullary or pancreatic tumours⁹⁻¹³. Our previous studies, including a multicentre RCT, indicated that LPD is a safe and feasible procedure associated with a shorter length of stay and comparable short-term outcomes to open PD (OPD) by highly experienced surgeons who have passed the learning curve^{12,14}. However, the application of LPD to PDAC treatment is concerning. Several studies have focused on the comparison of LPD and OPD for PDAC treatment and suggested that LPD was associated with equivalent oncologic outcomes and promising superior long-term survival outcomes compared with OPD¹⁵. However, retrospective studies are associated with inherent limitations, including patient selection biases, missing or incomplete data, and unaccounted-for variables, making results difficult to interpret definitively. No RCTs have investigated the effects of LPD and OPD on survival in patients with PDAC.

To explore the long-term safety and efficacy of LPD in patients with PDAC using high-level evidence, the Minimally Invasive Treatment Group in the Pancreatic Disease Branch of China's International Exchange and Promotion Association for Medicine and Healthcare (MITG-P-CPAM) designs and conducts this prospective large-scale multicentre RCT to analyse outcomes of interest, immediately after the TJDBPS01 trial, which interpreted the safety and feasibility of LPD compared with those of OPD. Accordingly, this trial aims to compare the long-term oncological and short-term surgical outcomes of LPD and OPD performed by highly experienced surgeons that have surmounted the learning curve for PDAC treatment.

METHODS AND ANALYSIS

Trial design

This trial is characterized as a prospective, multicentre, randomised controlled, and open-label study comprising two parallel groups of patients undergoing OPD and LPD. Patients diagnosed with pancreatic malignant tumours requiring PD will be consecutively recruited. This study will be conducted at ten high-volume pancreatic surgery centres in China, with surgeries being conducted by experienced surgeons. After providing written informed consents, 200 patients will be preoperatively allocated in a 1:1 ratio to either the LPD or OPD arm. The recruitment duration is estimated to be 2 years and the follow-up duration will be 5 years. The primary endpoint of this trial is the 5-year OS rate. The study will be prepared, analysed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines¹⁶, as presented in Figure 1.

Qualifications of participating surgeons and centres

The responsible participating surgeons shall satisfy the following qualifications as previously described in the TJDBPS01 study¹²: (1) having completed no less than 104 cases of LPDs; (2) having completed no less than 104 cases of OPDs¹⁴; and (3) having completed trainings of the Tongji Hospital LPD training program. Moreover, the participating centres shall perform more than 50 PDs annually. Surgeons willing to participate shall offer one recently unedited LPD and OPD surgery video, respectively, to the TJDBPS07 research council for evaluation. If the research council approves the surgical techniques, the surgeon and the centre will be permitted to participate in this study as a collaborator. Eligible patients will be discussed at regularly scheduled multidisciplinary team (MDT) meetings. Randomisation and assignment of a study-specific ID will be performed by the study sponsor.

Population and eligibility criteria

All adult patients indicated for elective PD because of a pancreatic mass will be screened for eligibility. Eligible patients will be assessed by the pancreatic MDTs of the participating centres. The MDTs should confirm that the pancreatic mass is highly suspected to be a pancreatic malignant tumour and of sufficient concern to require resection. Imaging data of contrast enhanced multi-thin sliced computed tomography (CT) scan (1mm) with or without endoluminal ultrasonography (EUS) will be regarded as the standard evaluation for each PD candidate. The last CT imaging should be performed within 4 weeks before the surgery. Histological diagnoses of malignancies are encouraged to be acquired but not a necessity¹⁷. All patients will sign the informed consent and be allowed to leave the trial at any time. The exact inclusion and exclusion criteria are below.

Inclusion criteria

- 1) Age between 18 years and 75 years.
- 2) Histologically confirmed PDAC or clinically diagnosed PDAC 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 Anaesthesiologists (ASA) 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 $> 35 \text{ kg/m}^2$.
- 10) Patients participating in any other clinical trials within 3 months.

Endpoints

The primary endpoint of this trial is the 5-year overall survival rate, which is defined as the percentage of patients in this trial who are alive 5 years postoperatively [time frame: 5 years postoperatively].

Other crucial indicators are included as secondary endpoints, including (1) overall survival (i.e., the interval between the day of surgery and the day of death for various reasons [time frame: 5 years postoperatively]); (2) disease-free survival (i.e., the interval between the day of surgery and the day of tumour recurrence [time frame: 5 years postoperatively]); (3) 90-day mortality (i.e., the percentage of patients who died within 90 days postoperatively). Mortality will be calculated by dividing the number of patients who died by the number of all patients undergoing surgical treatment; (4) complication rate (complications related to PD, including major complications with

1
2
3 Clavien-Dindo ≥ 3 ¹⁸, postoperative pancreatic fistula¹⁹, postoperative bile leak²⁰,
4 postpancreatectomy haemorrhage²¹, delayed gastric emptying²², and chyle leak²³, are
5 defined according to the International Study Group of Pancreatic Surgery) (5)
6 comprehensive complication index²⁴ (CCI, calculated as the sum of all complications
7 that are weighted for their severity, available at www.assesssurgery.com); (6) length of
8 stay (i.e., the number of nights spent in the hospital from the end of the surgical
9 procedure until discharge or death); and (7) intraoperative indicators, including
10 estimated blood loss and operation time.
11
12
13
14
15

16 **Sample size**

17
18 The sample size calculation was performed according to the primary endpoint, the 5-
19 year OS rate, and the non-inferiority design of this trial. Assumptions were made
20 based on a previous study by Kuesters et al.²⁵, which compared LPD with OPD for
21 PDAC treatment with the 5-year OS rate being 20% in the LPD group and 14% in the
22 OPD group. Based on the 6% decrease in 5-year OS rate in the OPD group compared
23 with the LPD group, the sample size required for each group was estimated to be 86
24 patients to achieve a non-inferiority limit of 10% at a one-tailed significance level of
25 2.5% with a power of 80% and a balanced design (1:1 ratio). Moreover, the primary
26 analyses will be based on the modified intention to treat (mITT), per protocol (PP),
27 and as treated (AT) sets. We aimed to reach a statistical power of 80% when
28 analysing the smallest population, namely the PP set.
29
30
31
32

33 Patients converted from LPD to open surgery will not be included in the PP set.
34 Patients will be randomised in a 1:1 manner to either the LPD or OPD arm, with the
35 maximum conversion rate from LPD to OPD assumed to be 10%, resulting in a ratio
36 of up to 9:10 in the PP set. To meet these assumptions, 83 patients in the LPD group
37 and 91 patients in the OPD group will be needed for analysis using the one-sided *t* test
38 at a one-sided significance level of 0.025. PASS version 15.0.5 will be used for the
39 calculations. An additional 10% of patients will be needed to be randomised
40 considering the non-resectable patients, patients withdrawing from the study, and
41 patients lost to follow-up. Accordingly, 100 patients in the LPD arm and 91 patients
42 in the OPD arm will be randomised. The randomisation ratio of this trial is 1:1,
43 requiring 100 patients in each arm and 200 patients in total to be included for
44 randomisation.
45
46
47
48
49
50

51 **Patient timeline and description of trial visits**

52
53 The study duration is estimated to be 7 calendar years, with an enrolment schedule of
54 2 years and a follow-up period of 5 years for each patient. The end of the trial was
55 defined as 5 calendar years since the last enrolled patient received surgery. This
56 protocol is reported in accordance with the guidelines of the Standard Protocol Items:
57 Recommendations for Interventional Trials (SPIRIT; Table 1, supplemental file 1)²⁶.
58
59
60

1
2
3 Data collection and assessment are recommended to be conducted at the responsible
4 surgical centre. Baseline data will be collected during the screening/baseline visit, and
5 surgical data will be collected intra- and postoperatively.
6
7

8 Short-term follow-ups will be conducted 1 day, 1 week, 1 month, and 3 months
9 postoperatively, and follow-up contents will include laboratory inspection indicators,
10 Eastern Cooperative Oncology Group (ECOG) score, Karnofsky Performance Scale
11 (KPS) score, postoperative wound recovery, wound pain level, drainage of each
12 drainage tube postoperatively, postoperative recovery (i.e., time until getting out of
13 bed, imported food, and so on), weight, adverse events, combined medication, and
14 postoperative complications.
15
16

17 Long-term follow-ups will be conducted every 3 months within the first postoperative
18 year and every 6 months from the second postoperative year onwards. The following
19 follow-up contents will be tracked and recorded: clinical evaluations including
20 internal inspections (such as weight, KPS score, and ECOG score), chemotherapy-
21 related adverse events, imaging items to prove the existence of tumour recurrence or
22 metastasis (record the date of recurrence, location and follow-up treatment), the date
23 of death, and the cause of death (i.e., disease- or treatment-related mortality).
24
25
26
27
28

29 **Randomisation and blinding**

30
31 Eligible patients signed the informed consent form will be screened within one week
32 prior to randomisation. Randomisation will be assigned on the day the preoperative
33 evaluation is finished and the patient is diagnosed with PDAC, eligible for PD. We
34 will employ a 1:1 randomisation pattern for arms A and B, stratified by participating
35 centres. Random numbers will be generated by SAS software version 9.40 (SAS
36 Institute, Inc., Cary, NC) and randomisation will be performed through a centralized
37 computer-generated system by providing random numbers using dynamic blocks.
38 Within each block, randomisation is balanced, and every patient is assigned to a
39 treatment using the randomisation scheme.
40
41
42

43 This is an open-label trial, and randomisation procedure and outcome will not be
44 blinded to patients and surgeons. However, data collectors, outcome assessors, and
45 data analysts will be blinded during statistical analysis. Surgeons will not participate
46 in the data collection process which will be conducted by an independent team.
47 Analysis processes will be blinded, and the statistician will be provided with only
48 group codes instead of group names.
49
50
51
52
53

54 **Intervention**

55
56 Surgical procedures need to comply with PD technique standards as previously
57 described²⁷. Any appropriate changes in surgical procedures according to the
58 surgeon's own experience and preference are permitted, including changes in
59 procedure order, surgical approach, and anastomosis method. All changes will be
60

1
2
3 recorded in the case report form.
4
5
6

7 **Experimental intervention-LPD techniques**

8
9 Patients will take a supine position and undergo general anaesthesia. Five trocars in
10 total will be used. Routine and standard lymph node dissections will be maintained as
11 recommended by guidelines. The pancreatic stump will be sent for quick frozen
12 pathological examination intraoperatively; moreover, it is necessary to confirm that
13 the pancreatic margin specimen is pathologically negative before digestive tract
14 reconstruction. Surgeons will determine the reconstruction type according to their
15 experiences and preferences. After reconstruction, two drainage tubes are routinely
16 placed, with one near the anastomosis of the pancreaticojejunostomy and the other
17 near the anastomosis of the bile jejunum.
18
19

20
21 Conversion to open surgery is defined as the use of any skin incision during LPD for
22 other than trocar placement or surgical specimen removal. For cases of conversion,
23 data will be analysed in the LPD group in an intention-to-treat manner. However,
24 reasons for conversion shall be realistically registered and carefully recorded.
25
26
27

28 **Control intervention-OPD techniques**

29
30 Open surgery shall be performed by the same group of surgeons as LPD. Key steps
31 are performed essentially as described in the LPD group. Methods used for
32 reconstruction during OPD must be consistent with those during LPD in the same
33 single centre.
34
35
36
37

38 **Concomitant treatment**

39
40 The TJDBPS07 trial follows TJDBPS01 which compared LPD and OPD; accordingly,
41 the principles of perioperative management are similar to those previously described²⁷.
42 Whatever medical devices and materials that are most used in daily practice of each
43 participant centre can be used if recorded carefully in surgical records. Antibiotics are
44 given to patients 30 min before skin incision and 2 h after incision. Patient-controlled
45 analgesia will be used to control postoperative pain. Time to remove the nasogastric
46 tube depends on each patients' situation evaluated by doctors of each participating
47 centre; early removal is encouraged. The abdominal drains will be placed routinely
48 for patients. The timepoint of drain removal depends on every patient's manifestation,
49 laboratory examination results (the concentration of drain fluid amylase (DFA) on
50 postoperative days (PODs) 1 and 3), and imaging findings. In patients with a DFA
51 concentration of less than 5000 U/L on POD 1, early drain removal at 72 h is
52 recommended. In patients with a DFA concentration of more than 5000 U/L on POD
53 1, drain removal will be decided by the corresponding surgeon according to the
54 patient's situation. Patients can be discharged if they meet the following discharge
55
56
57
58
59
60

1
2
3 criteria: no need for intravenous infusion, well tolerance of oral solid or semisolid
4 food, no need for intravenous analgesics, well wound healing, well tolerance of
5 independent walking at least 250 m in a plain road, well major organ function with
6 near-normal haematological parameters.
7
8

9 After surgical resection, patients pathologically diagnosed with PDAC will receive
10 adjuvant chemotherapy according to the National Comprehensive Cancer Network
11 (NCCN) guideline²⁸. Written informed consent for adjuvant chemotherapy should be
12 obtained. Different regimens recommended in the aforementioned guideline are
13 permitted, and the treatment duration is at the discretion of the responsible treating
14 oncologist. Detailed information on adjuvant chemotherapy will be recorded. Relapse
15 cases will be treated according to the recommendations of the NCCN guideline at the
16 corresponding participating centres.
17
18
19

20 21 22 **Data collection and management**

23 All data will be collected using an electronic case report form. The datasets generated
24 during the study will be stored in a local database, which is managed by the data
25 collection group of Tongji Hospital. Investigators from each participating institution
26 will have access to the data of their respective patients. All data are pseudonymized,
27 and patient details are encoded.
28
29

30 Data collection will include variables related to patient demographics, intraoperative
31 information, histopathological information, postoperative clinical findings, adjuvant
32 chemotherapy, and follow-up.
33
34

35 Patient demographics: age, gender, height (cm), weight (kg), smoking, drinking, main
36 complaint, clinical diagnosis, comorbidities, surgical history, underlying malignant
37 disease, ECOG score, ASA score, imaging results, preoperative blood samples (i.e.,
38 haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio),
39 plasma total bilirubin level, related tumour markers (i.e., CA19-9, CA125, and
40 carcinoembryonic antigen (CEA)), preoperative biliary drainage, and date of
41 admission.
42
43
44

45 Intraoperative information: operation date, surgical approach (laparoscopic or open),
46 conversion to open surgery, intraoperative death, texture of pancreas, diameter of the
47 main pancreatic duct, placement of intra-abdominal drain, type of reconstruction,
48 anastomosis approach (intracorporeal or extracorporeal), anastomosis performance
49 (linear stapler, circular stapler, hand-sewn, or combinations), total operative time,
50 each anastomosis time (pancreaticojejunostomy, cholangiohepaticojejunostomy, and
51 gastroenterostomy), intraoperative complications, estimated blood loss, and
52 intraoperative blood transfusion.
53
54
55

56 Histopathological information: tumour location, tumour size, histological type,
57 surgical margin status (R0 resection rates), number of lymph nodes, number of
58 positive lymph nodes, depth of invasion (T classification), lymph node status (N
59
60

classification), and American Joint Committee on Cancer staging.

Postoperative clinical findings: length of postoperative stay, postoperative blood transfusion, length of intravenous analgesic use, drain production and amylase, postoperative blood samples (i.e., haemoglobin level, white blood cell count, and granulocyte: lymphocyte ratio), plasma total bilirubin level, related tumour markers (i.e., CA19–9, CA125, and CEA), date of patient mobilization, date of liquid diet, date of drain removal, postoperative complication, reoperation, Clavien-Dindo grade, adverse event, cost of surgery, and cost of hospitalization.

Adjuvant chemotherapy: date of adjuvant chemotherapy, chemotherapy regimens, side effects, imaging results, haemoglobin level, white blood cell count, and related tumour markers (i.e., CA19–9, CA125, and CEA).

Follow-up: date of follow-up visit, patient status (alive, dead or lost to follow-up), ECOG score, KPS score, imaging results, related tumour markers (i.e., CA19–9, CA125, and CEA), DFS, and OS.

Data Availability Statement

The final datasets will not be available to the public. However, researchers will have access to the study data in de-identified form from the corresponding author after reasonable request when the study is completed.

Risk of bias

All adult patients with pancreatic masses eligible for PD will be screened in all participating centres. The recruited patients will be expected to be generalizable and representative to the wider population. Standard randomisation will be conducted to ensure comparable baseline characteristics between each group. To minimize confounding, allocations will be stratified by centre.

The primary outcome of this trial is the 5-year OS rate, which is objective and will be obtained from the planned follow-up data. The participants, surgeons, and nursing staff will not be blinded to interventions due to the characteristics of this trial, which compares MIS and conventional open surgery. The responsible surgeons will not be involved in the postoperative management of patients and determination of patients' discharge. Data collectors, outcome assessors, and data analysts will all be blinded to surgical techniques.

To minimize missing data bias, data for the primary outcome will be routinely collected and regularly reviewed.

Results of this trial will be reported in accordance with the CONSORT statement¹⁶ to minimize reporting bias. In addition, the trial protocol is reported according to the SPIRIT statement²⁶ to assure full transparency throughout this trial and subsequent

1
2
3 reporting.

4 5 6 7 **Assessment of cross-over patients**

8
9 Conversion from LPD to OPD is closely associated with intraoperative situations,
10 including technical infeasibility and significant bleeding, which is unavoidable even
11 for experienced surgeons who have passed the learning curves, making it impossible
12 to eliminate conversion by modifying inclusion and exclusion criteria. The conversion
13 rate in our previous trial comparing LPD and OPD for pancreatic or periampullary
14 tumours was 4%¹². Considering the techniques complexity in LPD for PDAC, the
15 maximum conversion rate within this trial is cautiously estimated to be 10%. Reasons
16 for conversion will be recorded in detail and further evaluated in the subgroup
17 analysis.
18
19
20
21
22

23 **Statistical analysis**

24
25 A statistical analysis plan will be developed and agreed upon by the data collection
26 group. All main statistical analyses will be performed according to an intention-to-
27 treat principle, and the primary analysis will be based on the mITT, PP, and AT set.
28 Patients deemed unresectable intraoperatively or who do not receive surgical resection
29 will not be considered in any of the analysis sets. The mITT set will comprise all
30 patients in the group to which they were randomised regardless of the actual received
31 surgery. The PP set will include patients without major protocol violations. Patients
32 converted from LPD to OPD will not be included in the PP set. The AT set will be
33 analysed with considerations of the actual treatment of patients, rather than their
34 randomisation. For robust interpretation, the results of the three primary analysis sets
35 should lead to similar conclusions; otherwise, possible reasons behind discrepancies
36 must be discussed. OS and DFS will be analysed from the date of pancreatic resection
37 to the date of death (for OS) or date of regional recurrence or systemic spread (for
38 DFS). The OS and DFS curves for the entire follow-up period will be estimated
39 according to Kaplan-Meier method and compared using a log-rank test. Time-specific
40 OS and DFS probabilities at appropriate time points will be derived from the survival
41 curves and the Greenwood estimate will be used to construct corresponding a 95%
42 confidence interval (CI). Hazard ratios (HRs) and two-sided 95% CIs will be
43 estimated using a Cox regression model after confirming the proportional hazards
44 assumptions.
45
46
47
48
49
50
51

52 In summary, continuous data will be presented as mean \pm standard deviation and will
53 be compared using Student's *t* test or Mann-Whitney *U* test. Categorical variables will
54 be compared using the χ^2 test or Fisher's exact test, as appropriate. Statistical analyses
55 will be conducted using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). *P* <
56 0.05 will denote statistical significance.
57
58

59 This trial is registered at ClinicalTrials.gov (registration number: NCT03785743).
60

Monitoring

Throughout the trial, a trained, qualified, and independent monitor will periodically visit each participating centre to randomly check protocol compliance, compliance with the inclusion and exclusion criteria, proper implementation, obtainment of informed consent forms, source data verification, and reporting of serious adverse events. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0²⁹. The Hospital Ethical Committee and Chinese Clinical Trial Registry are responsible for collection and management of these data. Moreover, an independent agency will handle the auditing every month.

DISCUSSION

The TJDBPS07 trial is designed as a prospective, multicentre, randomised controlled, and open-label trial to assess the long-term oncological and short-term surgical outcomes of LPD and OPD for PDAC treatment. The results of our TJDBPS01 trial suggested that LPD is a safe and feasible procedure for treating pancreatic or periampullary tumours, with comparable short-term outcomes to OPD in highly experienced hands^{12 27}. The TJDBPS07 trial follows TJDBPS01 and focuses on the comparison of LPD and OPD for treatment of resectable PDAC. In consideration of the complexity and difficulty of PD, surgeons participating in this trial are required to complete a structured training program for LPD and pass the learning curve by finishing a minimum of 104 LPDs, as suggested by the results of a retrospective study on the learning curve for LPD in China¹⁴.

Minimally invasive surgeries have gained increasing popularity in recent years because they have shown some promise in improving perioperative outcomes³⁰. Nevertheless, their long-term effects on patients with malignant diseases require further exploration. Several RCTs focused on this topic and reported different conclusions. A study by Yu et al. found that laparoscopic distal gastrectomy and open surgery had comparable DFS and OS in patients with locally advanced gastric cancer³¹. Moreover, a study by Kitano et al. concluded that laparoscopic D3 surgery was not inferior to open surgery in terms of OS in patients with stage II and III colon cancer³². However, research by Pedro et al. suggested that for patients with early cervical cancer, minimally invasive radical hysterectomy resulted in lower rates of DFS and OS than open radical hysterectomy⁵. The current guidelines of NCCN suggest that minimally invasive surgeries are feasible and safe for patients with hepatobiliary cancer³³, colon cancer³⁴, rectal cancer³⁵, ovarian cancer³⁶, cervical cancer³⁷, and pancreatic cancer²⁸, among others. Meanwhile, many of these guidelines state that their long-term safety needed to be further evaluated in more high-quality researches.

With a 5-year survival rate of approximately 10%, the highly fatal pancreatic cancer is becoming an increasingly common cause of cancer-related mortality. Surgical

1
2
3 resection represents the only chance of cure for patients with resectable pancreatic
4 cancer³⁸. An increasing number of researchers are interested in the therapeutic effects
5 of LPD on patients with PDAC in recent years³⁹, but there is still a lack of prospective
6 research supporting its long-term safety in these patients. Available evidence is based
7 on a few retrospective studies with limited quality⁴⁰. The data of 322 patients with
8 PDAC (108 undergoing LPD and 214 undergoing OPD) demonstrated that LPD was
9 technically feasible for PDAC treatment and was associated with better length of stay,
10 postoperative recovery, and pursuing adjuvant treatment than OPD. This study
11 simultaneously showed comparable OS but longer DFS in LPD than OPD⁴¹, while
12 other studies have indicated that the long-term survival and perioperative outcomes
13 were comparable between LPD and OPD for treatment of selected PDAC patients⁴²⁻⁴⁴.
14 Considering the controversies among existing publications and limitations of
15 observational studies, doctors and researchers in the field of PDAC emphasize the
16 necessity and importance of large-scale multicentre RCTs.
17
18
19
20
21

22 In conclusion, the TJDBPS07 trial is a multicentre randomised controlled, non-
23 inferiority trial investigating the long-term survival and the preoperative safety of
24 LPD and OPD for resectable PDAC. This trial aims to evaluate differences in the 5-
25 year OS rate between LPD and OPD for PDAC treatment. The results of this trial will
26 provide high-level evidence for guiding the daily practice of PDAC management.
27
28
29
30

31 **Trial status**

32
33 The TJDBPS07 trial was registered on 10 March 2019 at the ClinicalTrials Registry
34 (registration number: NCT03785743). The protocol of this trial was proposed by the
35 investigator from Tongji Hospital, and the final version was approved by Tongji
36 Institutional Review Board. The first enrolled patient has been given the randomised
37 number in August 2019. All ten centres are actively recruiting patients by the time
38 this protocol is submitted. Recruitment will approximately be completed by
39 December 2021.
40
41
42
43
44

45 **Patient and public involvement**

46
47 This trial will not involve either patients or the public in the design, recruitment,
48 conduct of the study, or measurement of outcomes. The trial results will not be
49 notified to every single patient, while instead, the results will be presented in
50 academic conferences, and disseminated via open-access and peer-reviewed journals.
51 This trial will investigate patient-reported outcomes, using tools such as
52 questionnaires about quality of life.
53
54
55
56

57 **Ethics and dissemination**

58
59 Each participant will sign an informed consent document before inclusion; this form
60

1
2
3 is provided by a qualified team member and subsequently sent to and preserved by the
4 data collection team. All participations are voluntary and have the right to withdraw
5 from the study for any reason whenever they want to. If they do withdraw, they will
6 still receive standard treatment according to local hospital procedures. The study will
7 be conducted in accordance with the principles outlined in the Declaration of Helsinki
8 and its later amendments⁴⁵. This trial was registered under the Tongji Hospital (trial
9 ID: NCT03785743) and approved by Tongji Hospital Ethics Committee (approval
10 number: TJ-IRB20190318) in March 2019. Local ethical approval was confirmed
11 from each participating centre before recruiting at other centres. All authors have
12 access to study data and reviewed and approved the final manuscript. The results of
13 this trial will be presented in international meetings, and final trial results will be
14 published in an open access, peer-reviewed journal.
15
16
17
18
19
20

21 **Acknowledgements**

22 We thank the team of Prof. Ping Yin from the Department of Epidemiology and
23 Biostatistics, School of Public Health, Tongji Medical College, Huazhong University
24 of Science and Technology, for the data monitoring and statistical support.
25
26
27
28
29

30 **Authors' contributions**

31 RYQ, MW, and FZ obtained funding for the study. RYQ, HZ, and MW designed the
32 study. XJY, JiL, JuL, WXZ, XMC, DWL, JHL, JDL, YHL, and RYQ performed the
33 operations. STP, TTQ, and TYY drafted the manuscript. RYQ, HZ, and MW
34 contributed to the critical revision of the manuscript for important intellectual content
35 and approved the final version of the manuscript. All authors have read and approved
36 the final manuscript.
37
38
39
40
41

42 **Funding statement**

43 The study was supported by grants from The National Natural Science Foundation of
44 China (82073249, 81874205, 81773160), Tongji Hospital Clinical Research Flagship
45 Program (2019CR203).
46
47
48
49
50

51 **Disclaimer**

52 The funder had no role in the design of the study, data collection, or writing this
53 manuscript.
54
55
56
57

58 **Competing interests**

59 The authors and each study site declare no conflicts of interest.
60

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer-reviewed.

REFERENCE

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA: a cancer journal for clinicians* 2020;70(1):7-30. doi: 10.3322/caac.21590 [published Online First: 2020/01/09]
2. Mizrahi JD, Surana R, Valle JW, et al. Pancreatic cancer. *Lancet (London, England)* 2020;395(10242):2008-20. doi: 10.1016/s0140-6736(20)30974-0 [published Online First: 2020/07/01]
3. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 2011;13(6):377-84. doi: 10.1111/j.1477-2574.2011.00305.x [published Online First: 2011/05/26]
4. Zhang YH, Zhang CW, Hu ZM, et al. Pancreatic cancer: Open or minimally invasive surgery? *World J Gastroenterol* 2016;22(32):7301-10. doi: 10.3748/wjg.v22.i32.7301 [published Online First: 2016/09/14]
5. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *The New England journal of medicine* 2018;379(20):1895-904. doi: 10.1056/NEJMoa1806395 [published Online First: 2018/11/01]
6. Gagner M, Pomp A. Laparoscopic pylorus-preserving pancreatoduodenectomy. *Surgical endoscopy* 1994;8(5):408-10. doi: 10.1007/bf00642443 [published Online First: 1994/05/01]
7. Liu M, Ji S, Xu W, et al. Laparoscopic pancreaticoduodenectomy: are the best times coming? *World journal of surgical oncology* 2019;17(1):81. doi: 10.1186/s12957-019-1624-6 [published Online First: 2019/05/12]
8. Probst P, Hüttner FJ, Meydan Ö, et al. Evidence Map of Pancreatic Surgery-A living systematic review with meta-analyses by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2021;170(5):1517-24. doi: 10.1016/j.surg.2021.04.023 [published Online First: 2021/07/01]
9. Palanivelu C, Senthilnathan P, Sabnis SC, et al. Randomized clinical trial of laparoscopic versus open pancreatoduodenectomy for periampullary tumours. *The British journal of surgery* 2017;104(11):1443-50. doi: 10.1002/bjs.10662 [published Online First: 2017/09/13]
10. Poves I, Burdío F, Morató O, et al. Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreatoduodenectomy: The PADULAP Randomized Controlled Trial. *Annals of surgery* 2018;268(5):731-39. doi: 10.1097/sla.0000000000002893 [published Online First: 2018/08/24]
11. van Hilst J, de Rooij T, Bosscha K, et al. Laparoscopic versus open pancreatoduodenectomy for

- 1
2
3 pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded,
4 randomised controlled phase 2/3 trial. *The lancet Gastroenterology & hepatology*
5 2019;4(3):199-207. doi: 10.1016/s2468-1253(19)30004-4 [published Online First: 2019/01/28]
6
7 12. Wang M, Li D, Chen R, et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or
8 periampullary tumours: a multicentre, open-label, randomised controlled trial. *The lancet*
9 *Gastroenterology & hepatology* 2021;6(6):438-47. doi: 10.1016/s2468-1253(21)00054-6
10 [published Online First: 2021/04/30]
11
12 13. Nickel F, Haney CM, Kowalewski KF, et al. Laparoscopic Versus Open Pancreaticoduodenectomy:
13 A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Annals of surgery*
14 2020;271(1):54-66. doi: 10.1097/sla.0000000000003309 [published Online First: 2019/04/12]
15
16 14. Wang M, Peng B, Liu J, et al. Practice Patterns and Perioperative Outcomes of Laparoscopic
17 Pancreaticoduodenectomy in China: A Retrospective Multicenter Analysis of 1029 Patients.
18 *Annals of surgery* 2021;273(1):145-53. doi: 10.1097/sla.0000000000003190 [published
19 Online First: 2019/01/24]
20
21 15. Chen K, Zhou Y, Jin W, et al. Laparoscopic pancreaticoduodenectomy versus open
22 pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic outcomes and
23 long-term survival. *Surgical endoscopy* 2020;34(5):1948-58. doi: 10.1007/s00464-019-06968-
24 8 [published Online First: 2019/07/19]
25
26 16. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated
27 guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)*
28 2010;340:c869. doi: 10.1136/bmj.c869 [published Online First: 2010/03/25]
29
30 17. Asbun HJ, Conlon K, Fernandez-Cruz L, et al. When to perform a pancreatoduodenectomy in the
31 absence of positive histology? A consensus statement by the International Study Group of
32 Pancreatic Surgery. *Surgery* 2014;155(5):887-92. doi: 10.1016/j.surg.2013.12.032 [published
33 Online First: 2014/03/26]
34
35 18. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical
36 complications: five-year experience. *Annals of surgery* 2009;250(2):187-96. doi:
37 10.1097/SLA.0b013e3181b13ca2 [published Online First: 2009/07/30]
38
39 19. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group
40 (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*
41 2017;161(3):584-91. doi: 10.1016/j.surg.2016.11.014 [published Online First: 2017/01/04]
42
43 20. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a
44 definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*
45 2011;149(5):680-8. doi: 10.1016/j.surg.2010.12.002 [published Online First: 2011/02/15]
46
47 21. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study
48 Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007;142(1):20-5. doi:
49 10.1016/j.surg.2007.02.001 [published Online First: 2007/07/17]
50
51 22. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a
52 suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*
53 2007;142(5):761-8. doi: 10.1016/j.surg.2007.05.005 [published Online First: 2007/11/06]
54
55 23. Besselink MG, van Rijssen LB, Bassi C, et al. Definition and classification of chyle leak after
56 pancreatic operation: A consensus statement by the International Study Group on Pancreatic
57 Surgery. *Surgery* 2017;161(2):365-72. doi: 10.1016/j.surg.2016.06.058 [published Online
58 First: 2016/10/04]
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
24. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Annals of surgery* 2013;258(1):1-7. doi: 10.1097/SLA.0b013e318296c732 [published Online First: 2013/06/04]
 25. Kuesters S, Chikhladze S, Makowiec F, et al. Oncological outcome of laparoscopically assisted pancreatoduodenectomy for ductal adenocarcinoma in a retrospective cohort study. *International journal of surgery (London, England)* 2018;55:162-66. doi: 10.1016/j.ijssu.2018.05.026 [published Online First: 2018/05/29]
 26. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed)* 2013;346:e7586. doi: 10.1136/bmj.e7586 [published Online First: 2013/01/11]
 27. Zhang H, Feng Y, Zhao J, et al. Total laparoscopic pancreaticoduodenectomy versus open pancreaticoduodenectomy (TJDBPS01): study protocol for a multicentre, randomised controlled clinical trial. *BMJ open* 2020;10(2):e033490. doi: 10.1136/bmjopen-2019-033490 [published Online First: 2020/02/13]
 28. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(4):439-57. doi: 10.6004/jnccn.2021.0017 [published Online First: 2021/04/13]
 29. Common terminology criteria for adverse events (CTCAE) v5.0. [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf accessed June 20, 2020.
 30. Gandaglia G, Ghani KR, Sood A, et al. Effect of minimally invasive surgery on the risk for surgical site infections: results from the National Surgical Quality Improvement Program (NSQIP) Database. *JAMA surgery* 2014;149(10):1039-44. doi: 10.1001/jamasurg.2014.292 [published Online First: 2014/08/22]
 31. Yu J, Huang C, Sun Y, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *Jama* 2019;321(20):1983-92. doi: 10.1001/jama.2019.5359 [published Online First: 2019/05/29]
 32. Kitano S, Inomata M, Mizusawa J, et al. Survival outcomes following laparoscopic versus open D3 dissection for stage II or III colon cancer (JCOG0404): a phase 3, randomised controlled trial. *The lancet Gastroenterology & hepatology* 2017;2(4):261-68. doi: 10.1016/s2468-1253(16)30207-2 [published Online First: 2017/04/14]
 33. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(5):541-65. doi: 10.6004/jnccn.2021.0022 [published Online First: 2021/05/25]
 34. Benson AB, Venook AP, Al-Hawary MM, et al. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(3):329-59. doi: 10.6004/jnccn.2021.0012 [published Online First: 2021/03/17]
 35. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2018;16(7):874-901. doi: 10.6004/jnccn.2018.0061 [published Online First:

- 2018/07/15]
36. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2021;19(2):191-226. doi: 10.6004/jnccn.2021.0007 [published Online First: 2021/02/06]
37. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2019;17(1):64-84. doi: 10.6004/jnccn.2019.0001 [published Online First: 2019/01/20]
38. Neoptolemos JP, Kleeff J, Michl P, et al. Therapeutic developments in pancreatic cancer: current and future perspectives. *Nature reviews Gastroenterology & hepatology* 2018;15(6):333-48. doi: 10.1038/s41575-018-0005-x [published Online First: 2018/05/03]
39. Kang CM, Lee WJ. Is Laparoscopic Pancreaticoduodenectomy Feasible for Pancreatic Ductal Adenocarcinoma? *Cancers* 2020;12(11) doi: 10.3390/cancers12113430 [published Online First: 2020/11/22]
40. Peng L, Zhou Z, Cao Z, et al. Long-Term Oncological Outcomes in Laparoscopic Versus Open Pancreaticoduodenectomy for Pancreatic Cancer: A Systematic Review and Meta-Analysis. *Journal of laparoendoscopic & advanced surgical techniques Part A* 2019;29(6):759-69. doi: 10.1089/lap.2018.0683 [published Online First: 2019/03/06]
41. Croome KP, Farnell MB, Que FG, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Annals of surgery* 2014;260(4):633-8; discussion 38-40. doi: 10.1097/sla.0000000000000937 [published Online First: 2014/09/10]
42. Stauffer JA, Coppola A, Villacreses D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic adenocarcinoma: long-term results at a single institution. *Surgical endoscopy* 2017;31(5):2233-41. doi: 10.1007/s00464-016-5222-1 [published Online First: 2016/09/09]
43. Zhou W, Jin W, Wang D, et al. Laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a propensity score matching analysis. *Cancer communications (London, England)* 2019;39(1):66. doi: 10.1186/s40880-019-0410-8 [published Online First: 2019/10/30]
44. Kwon J, Song KB, Park SY, et al. Comparison of Minimally Invasive Versus Open Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma: A Propensity Score Matching Analysis. *Cancers* 2020;12(4) doi: 10.3390/cancers12040982 [published Online First: 2020/04/25]
45. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053 [published Online First: 2013/10/22]

Table 1: Schedule of study enrolment, interventions, and assessments

Time point	Study Period																
	Enrollment	Allocation	Treatment	Discharge	Post-allocation												Close-out
	Outpatient clinic /Admission	Before Surgery	Surgery	After Surgery	Month 1 (T1)	Month 3 (T2)	Month 6 (T3)	Month 9 (T4)	Month 12 (T5)	Month 18 (T6)	Month 24 (T7)	Month 30 (T8)	Month 36 (T9)	Month 42 (T10)	Month 48 (T11)	Month 54 (T12)	Month 60 (T13)
Enrollment																	
Eligibility screen																	
Informed consent	×																
Allocation	×																
		×															
Interventions																	
LPD																	
OPD			×														
			×														
Assessments																	
	×																
Baseline characteristics	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Blood routine	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Blood biochemistry	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Tumor marker	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Abdominal CT scan	×			×		×	×	×	×	×	×	×	×	×	×	×	×
Surgical record			×														
Postoperative record				×													
Pathological findings				×													
Adjuvant therapy				×													
Survival status					×	×	×	×	×	×	×	×	×	×	×	×	×
						×	×	×	×	×	×	×	×	×	×	×	×

LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

1
2
3
4 **Figure legend.**

5
6 Figure 1: Flow diagram for TJDBPS07. CONSORT, Consolidated Standards of
7 Reporting Trials; LPD, laparoscopic pancreaticoduodenectomy; OPD, open
8 pancreaticoduodenectomy.
9

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



CONSORT

TRANSPARENT REPORTING of TRIALS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Assessed for eligibility (n=)

Excluded

- Not meeting inclusion criteria (n=)
- Declined to participate (n=)
- Other reasons (n=)

Randomised (n=200)

Enrollment

Allocation

Follow-up

Analysis

Allocated to intervention LPD (n=)

- Received allocated intervention (n=)
- Did not receive allocated intervention (record reasons) (n=)
-

Allocated to intervention OPD (n=)

- Received allocated intervention (n=)
- Did not receive allocated intervention (record reasons) (n=)
-

Short-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Short-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Long-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Long-term follow-up (n=)

- Lost to follow-up (record reasons) (n=)
-

Analysed (n=)

- Excluded from analysis (record reasons) (n=)

Analysed (n=)

- Excluded from analysis (record reasons) (n=)

Per Protocol (n=)

Modified Intention to Treat (n=)

As Treated (n=)

Per Protocol (n=)

Modified Intention to Treat (n=)

As Treated (n=)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3;15
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8

1	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
2				
3				
4				
5	Methods: Assignment of interventions (for controlled trials)			
6				
7	Allocation:			
8				
9	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
10				
11				
12				
13				
14				
15				
16				
17				
18				
19	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
20				
21				
22				
23				
24				
25				
26	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
27				
28				
29				
30	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
31				
32				
33				
34				
35		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
36				
37				
38				
39	Methods: Data collection, management, and analysis			
40				
41	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
42				
43				
44				
45				
46				
47				
48				
49				
50				
51		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
52				
53				
54				
55				
56				
57				
58				
59				
60				

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6;10;15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11;15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	annex
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.