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Simultaneous resection of the primary tumour and liver metastases after conversion chemotherapy versus standard therapy in pancreatic cancer with liver oligometastasis: protocol of a multicentre, prospective, randomised phase III control trial (CSPAC-1)

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ABSTRACT

Introduction Approximately 50% of pancreatic ductal adenocarcinoma (PDAC) patients are diagnosed with distant metastasis, especially liver metastasis. The current standard treatment for these stage IV patients is palliative chemotherapy. There is increasing agreement that synchronous PDAC and liver metastasis resection may benefit highly selected patients. Thus, the Chinese Study Group for Pancreatic Cancer (CSPAC)–1 trial is being launched to establish a strategy for selecting PDAC patients with liver oligometastases who may benefit from synchronous resection after conversion chemotherapy.

Methods and analysis In this study, liver oligometastasis is defined as no more than three metastatic lesions irrespective of their distribution within the liver lobes. The trial contains two steps. In the first step, 1000 to 1200 needle biopsy-confirmed PDAC patients with liver oligometastases are eligible for inclusion. Candidates will receive first-line chemotherapy. The RECIST V.1.1 criteria combined with tumour markers will be applied to evaluate the tumour response to chemotherapy every two cycles. Pancreatic cancer and hepatic metastasis resectability will be identified by multidisciplinary teams. Approximately 300 patients who meet our criteria will enter the second step and be randomly assigned at a 1:1 ratio to simultaneous resection of the primary pancreatic cancer lesion and liver oligometastases if no extensive metastatic sites are found during surgery or standard chemotherapy. Postoperative chemotherapy is recommended, and regimen selection should be based on the preoperative chemotherapy regimen. The primary endpoint is real overall survival (from enrolment to death). This study was activated in July 2018 and is expected to complete accrual within 5 years.

Ethics and dissemination This trial has been approved by the Clinical Research Ethics Committee of Fudan University Shanghai Cancer Centre. Written informed consent will be obtained from all participants. Serious adverse events will be reported. Trial results will be submitted for peer-reviewed publication.

Strengths and limitations of this study

- Conversion surgery is becoming increasingly possible with the introduction of intensive chemotherapies; however, the actual clinical benefits of resection in such cases has not yet been sufficiently investigated.
- A multicentre, prospective, randomised phase III control trial is the most appropriate design to demonstrate the efficacy of simultaneous resection and may contribute to updating international recommendations or guidelines.
- The proposed sample size in this study is sufficient to validate the conclusion.
- The study includes some defects, including the fact that simultaneous resection is not a standard treatment so it is performed only in certain selected patients; however, currently, there are no widely accepted inclusion criteria or indicators for conversion surgery.

Trial registration number NCT03398291; Pre-results.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with one of the worst prognoses (the 5 year survival rate is merely 9%)[1 2] among gastrointestinal tumours. It is one of the world's top 10 malignant tumours and ranks 9th in China.[3] Radical surgery is the only opportunity to cure this malignant disease. However, 80% of patients are diagnosed with advanced disease, and over 50% of them have metastatic pancreatic cancer,[4 5] which has a median survival time of 4 to 6 months with a 5 year survival rate of

<5%.[6] Chemotherapy remains the mainstay treatment for this population. It has been reported that 5-fluorouracil (5-FU), leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) and nab-paclitaxel plus gemcitabine (NG) regimens can significantly improve the overall survival (OS) of pancreatic cancer patients with liver metastasis (11.1 months and 8.5 months, respectively).[7 8] These two regimens have gradually become the first-line treatments for this population.[9–11] For Asian population, the median OS of gemcitabine plus S-1 (GS) regimens for metastatic PDAC is 10.1 months.[12] Therefore, it is of critical importance to explore a new strategy to improve the survival of patients with metastatic pancreatic cancer.

The most frequent site of metastasis in pancreatic carcinoma is the liver followed by the peritoneum, lungs and pleura, bones and adrenal glands.[13] A substantial body of evidence has gradually recognised the curative potential of liver and pulmonary metastasectomy.[14 15] Radical surgery to treat both primary and metastatic sites has been accepted and conducted in an increasing number of tumour types[16–18]; however, there are few reports of surgical resection in pancreatic cancer with synchronous metastases.[19–22] In addition, these reports included only selected patients, with a median OS of approximately 10 to 14 months.[23 24] Currently, the guidelines for the treatment of PDAC with liver metastasis advocate for systematic chemotherapy as the first-line treatment and do not recommend resection of the primary tumour and synchronous distant metastases without preoperative treatment.[10 25]

In metastatic PDAC, resection of the primary pancreatic cancer lesion may produce some benefits in patients with complete resolution of metastases by chemotherapy.[26] Furthermore, a few patients have shown a remarkable response to their chemotherapy regimen, and shrinkage of liver metastases and significant reductions in tumour markers (eg, cancer antigen 19-9 (CA19-9)) were found,[27] indicating conversion surgery might be a potential option for these patients. Case reports[28–31] and our previous small-sample study showed that conversion surgery might be considered in highly selected patients with favourable imaging and CA19-9 response results following chemotherapy at high-volume centres providing multidisciplinary care.

Synchronous resection of primary tumours and metastatic sites continues to be attempted.[32–34] The usefulness of conversion surgery in metastasised pancreatic cancer patients remains controversial, thus these patients should be enrolled in prospective clinical trials or institutional registries to better quantify the potential benefits. There is no registered clinical trial of simultaneous resection of the primary tumour and liver metastases after conversion chemotherapy in pancreatic cancer with liver oligometastasis at ClinicalTrials.gov. Based on this current status, the Chinese Study Group for Pancreatic Cancer (CSPAC) initiated the first prospective, randomised phase III control trials in this field, aiming to explore the optimal strategy to improve the prognosis and prolong the survival time of these kinds of patients. According to the previous research,[35–38] oligometastasis is defined as ≤3 metastatic liver lesions irrespective of their distribution within the liver lobes in pancreatic cancer patients with liver metastasis in our study.

METHODS AND ANALYSIS

Objectives

The primary objective of this study is to compare the real overall survival (rOS, the time from diagnosis to death due to any cause) achieved by simultaneous resection of the primary tumour and liver metastases after conversion chemotherapy versus that achieved by standard chemotherapy in pancreatic cancer patients with liver oligometastasis. The following are the secondary study objectives: OS, the quality of life (QoL) scores, the procedure-related complications and mortality.

Trial design

In the conversion chemotherapy stage, 1000 to 1200 patients with liver oligometastasis will be enrolled and receive the first-line regimen. Then, approximately 300 patients who successfully complete conversion chemotherapy and are eligible for surgical resection will be randomly assigned (1:1 ratio) to either simultaneous resection of the primary tumour and liver metastases (operation/treatment arm) or standard first-line chemotherapy for metastatic pancreatic cancer (control arm) to investigate the efficacy and safety of this surgery. A study flow chart is shown in figure 1. The complete protocol is attached in online supplementary file.

Site selection

This phase III trial will take place in hepatobiliary-pancreatic units or pancreatic cancer centres that have a high volume of pancreatic cancer cases and that belong to the CSPAC. Sites will be eligible to participate based on current case volume, surgical quality, adequate experience with clinical oncology and the ability to perform needle biopsy and histopathology to the protocol's standards. For volume, we determined that the number of surgical cases of pancreatic cancer mainly composed of pancreaticoduodenectomy should be more than 50 per year. Meanwhile, a multidisciplinary team will collaborate to determine the regimens of the patients.

Patient recruitment

The study population will be identified by the pancreatic cancer multidisciplinary team. The diagnosis of PDAC with liver metastasis will be made with enhanced CT/MRI or positron emission tomography (PET)/CT, and biopsy will be performed to obtain pathological evidence in accordance with the protocol. The inclusion and exclusion criteria prior to or after conversion chemotherapy are listed in the box below (box 1). Written informed consent will be obtained from all participants and the informed consent form is attached in online supplementary file.

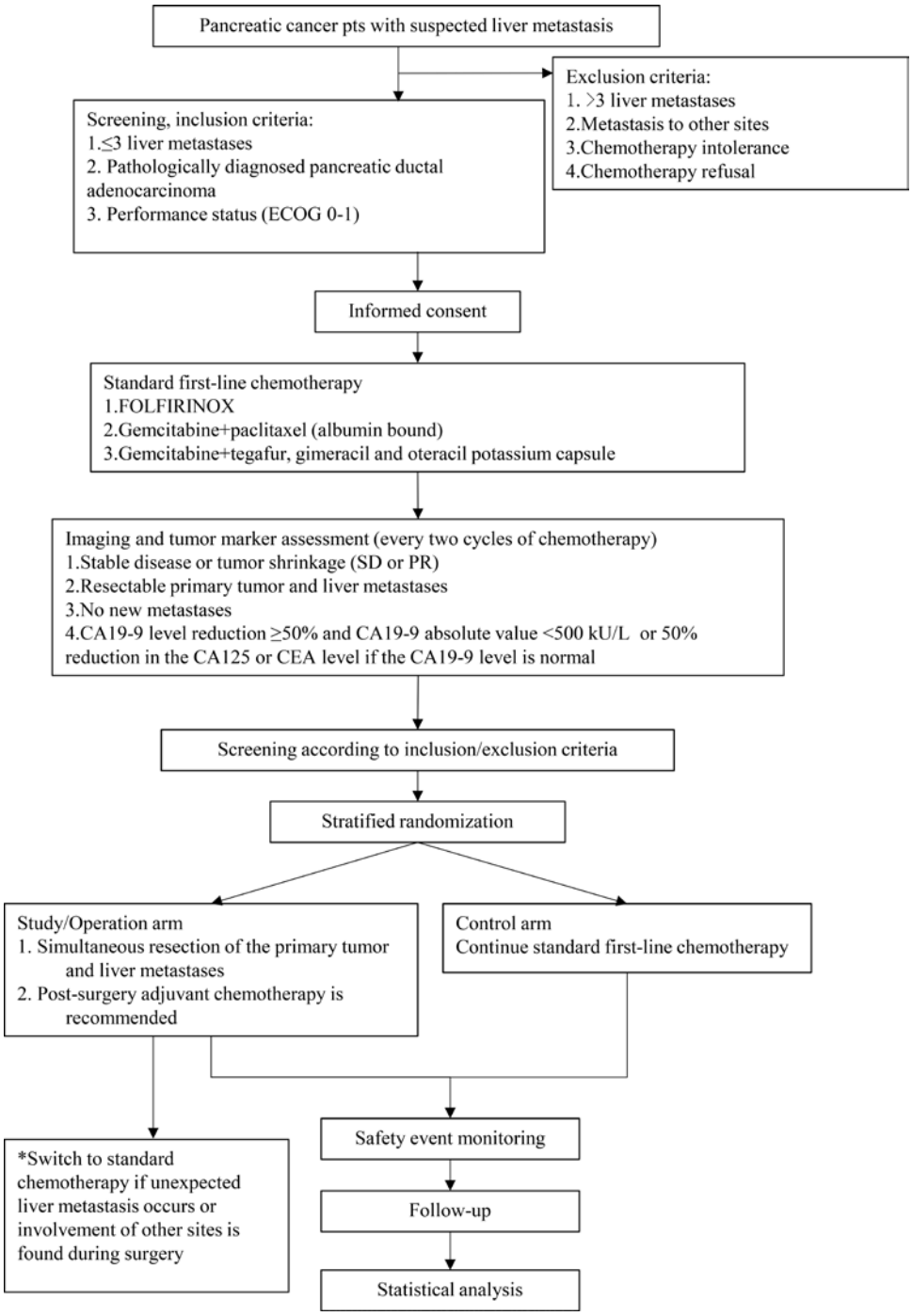

Figure 1 Study flow chart for CSPAC-1 trial. CA 19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CSPAC, ChineseStudy Group for Pancreatic Cancer; ECOG, EasternCooperative Oncology Group; FOLFIRINOX, 5-FU,leucovorin, irinotecan and oxaliplatin; PR,partial response; pts, patients; SD, stable disease; 5-FU, 5-fluorouracil.

Patient screening

There will be two screening periods in the study. The first one is prior to first-line chemotherapy; the second one is during the first-line chemotherapy regimen while imaging and tumour markers are being assessed. Prior to initiating the first-line chemotherapy regimen, according to the inclusion/exclusion criteria, disease characteristics including the features of the primary tumour (location, number, volume, involvement of large blood vessels, cancer embolus and involvement of the surrounding tissue) and liver metastases (number, volume, location and resectability) will be assessed by imaging examination (abdominal CT/MRI plain plus enhanced scanning; PET/CT is not regularly used), pathological type will be identified by biopsy (primary or metastatic lesion) and levels of tumour markers (CA19-9, cancer antigen 125 (CA125) and carcinoembryonicantigen (CEA)) will be measured. Notably, liver metastases should be re-evaluated by the same imaging used at first assessment at the time of the inclusion into the study to guarantee the

Box 1 Inclusion and exclusion criteria

Inclusion criteria prior to conversion chemotherapy
1. Voluntary participation with informed consent and willing to follow the protocol
2. Aged 18 to 75 years old
3. Performance status (Eastern Cooperative Oncology Group) 0 to 1
4. Phase IV patients with ≤3 hepatic metastatic foci
5. Diagnosis confirmed by pathological examination via biopsy of the primary tumour or metastatic lesion

Exclusion criteria prior to conversion chemotherapy
1. Refuse to receive systemic chemotherapy or potential surgery
2. More than three hepatic metastatic foci or metastasis in other areas (eg, the peritoneum, lungs, bones or brain)
3. Presence of another malignant tumour(s)
4. Prior antitumour treatment (including chemotherapy, radiotherapy and ablation therapy)
5. Presence of central nervous system disorder, mental disease, unstable angina pectoris, congestive heart failure, severe arrhythmia or another severe disease
6. Use of warfarin maintenance treatment

Inclusion criteria after conversion chemotherapy (before randomisation)

Results for imaging (CT or MRI) and tumour markers (cancer antigen 19-9 (CA19-9), cancer antigen 125 (CA125), carcinoembryonicantigen (CEA)), which are assessed following every two cycles of conversion chemotherapy, should meet the criteria below:
1. Stable disease or partial response (RECIST V.1.1)
2. Resectable primary tumour and metastatic lesion(s)
3. No new metastatic lesions
4. Decrease in the CA19-9 level >50% with an absolute value <500 U/mL or at least a 50% reduction in the CA125 or CEA level if the patient had a normal CA19-9 level prior to conversion chemotherapy

Exclusion criteria after conversion chemotherapy (before randomisation)
1. Presence of another malignant tumour(s)
2. Presence of contraindication for surgery
3. Unwillingness or inability to follow the research protocol

homogeneous evaluation. During chemotherapy, the response to chemotherapy, including changes in the primary tumour, liver metastases, the levels of tumour markers, etc, are assessed every two cycles. Through strict secondary inclusion/exclusion criteria, the patients with relatively favourable tumour biology will be selected for randomisation via software and then entered into the corresponding group.

INTERVENTIONS

Definition of conversion surgery and chemotherapy options

In this study, 'conversion surgery' is defined as the 'surgical resection of pancreatic cancer with liver oligometastases after a favourable chemotherapy response'.

Regimen 1: FOLFIRINOX regimen: intravenous injection of 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, 400 mg/m^2 calcium folinate and 400 mg/m^2 5-FU on day 1, followed by intravenous infusion of 2400 mg/m^2 5-FU for 46 hours; 2 weeks per cycle.

Regimen 2: Gemcitabine plus paclitaxel (albumin bound) regimen: 125 mg/m^2 paclitaxel (albumin bound) and 1000 mg/m^2 gemcitabine on days 1, 8 and 15; 4 weeks per cycle.

Regimen 3: Gemcitabine plus tegafur, gimeracil and oteracil potassium capsule regimen: injection of 1000 mg/m^2 gemcitabine on days 1 and 8, and tegafur, gimeracil and oteracil potassium capsule administered on days 1 to 14, 3 weeks per cycle.

Evaluation of conversion chemotherapy

The RECIST V.1.1 criteria combined with tumour markers will be applied to evaluate the tumour response to chemotherapy every two cycles. CA19-9 is the most commonly used serum tumour marker for pancreatic cancer, and this marker will be used to improve the selection of PDAC patients with liver metastases who can benefit from resection after conversion chemotherapy. However, approximately 5% to 10% of the population are Lewis-negative individuals; it is known that these individuals exhibit little to no CA19-9 secretion.[39] CA125 and CEA are alternative markers because they are the most common serum tumour markers for PDAC after CA19-9. In addition, the capacity for resection of both the primary tumour and liver metastases will be carefully evaluated before surgical intervention.

Judgement of resectability

Multidisciplinary participation is required for resectability judgement. The resectability of the primary tumour will be judged based on National Comprehensive Cancer Network (NCCN) guidelines. Resectable pancreatic cancer is defined as no tumour-vessel (including the celiac trunk, superior mesenteric artery and common hepatic artery) interface. Borderline resectable pancreatic cancer is defined as pancreas head/uncinate process tumours that have (1) tumour abutment of the common hepatic artery with no extension to the celiac axis or branches of the hepatic artery, allowing complete tumour resection and reconstruction and (2) tumour-smooth muscle actin (SMA) involvement ≤180°; pancreatic body/tail tumours should have tumour-celiac axis involvement ≤180°. The criteria for resectable liver metastases are (1) R0 resection is achievable for the metastatic lesion, (2) at least two adjacent hepatic segments are preserved, (3) the blood vessels and bile ducts of the remnant liver can maintain normal function, (4) the remnant liver volume will be >50% and (5) an A level of liver function is present.

Rational and randomisation for the study

Eligible patients who undergo successful conversion chemotherapy will be randomly assigned (1:1 ratio) to either operation/treatment arm or control arm using randomisation software (supported by Biomedical informatics & Statistics Centre, School of Public Health, Fudan University). Specifically, the location of pancreatic cancer (head vs body and tail), the level of CA19-9 (37 U/mL as a cut-off) before randomisation and the number of

liver metastases (1, 2 and 3) will be used as strata when conducting random allocation.

Treatment procedure and duration

In the operation group, an exploratory laparotomy or a laparoscopy will be performed prior to simultaneous resection of the primary tumour and liver metastases. A simultaneous resection is performed only when both of the following criteria are met: (1) no visible other metastases and (2) both the primary tumour and metastatic lesion(s) are resectable. Simultaneous resection will be abandoned if either of the two criteria is not met. Postoperative chemotherapy based on the initial regimen (the regimen and dosage can be adjusted according to individual performance status, haematological adverse reactions, etc) as well as relevant supportive treatment will be administered for 4 to 6 weeks after simultaneous resection if no serious complications occur. Six cycles of postoperative chemotherapy should be given if no recurrence or new metastasis occurs. An altered chemotherapy regimen will be prescribed if recurrence or new metastasis is found. Postoperative chemotherapy will be delayed if severe complications occur after simultaneous resection. Patients unfit for simultaneous resection will continue first-line chemotherapy at 2 weeks following surgery. Second-line chemotherapy or best supportive care will be given if patients fail to respond to first-line chemotherapy. In the control arm, the patients will continue initial first-line chemotherapy. Second-line chemotherapy or best supportive care will be given if the patients fail to respond to first-line chemotherapy. The study assessment schedules are summarised in table 1.

Study completion

Patients will be considered to have been treated according to protocol if they have received both preoperative chemotherapy and subsequent radical resection or standard chemotherapy in whole course in the absence of disease recurrence or severe adverse effects leading to the discontinuation of the protocol treatment. The completion of the study is equal to the termination of monitoring, which is on patient death. Additional treatments, including chemotherapy after completion of the treatment in protocol, are not defined in the protocol and depend on the oncologist's discretion or the practice in use at the institution.

Quality control and quality guarantee

An expert committee participated in the discussion of the study plan, providing guidance for the study design in regard to scientific and ethical aspects, and will supervise the implementation of the study, urging that quality problems be resolved and participate in the review of the summary report to ensure the study conclusion is correct and reliable. The study will be regularly inspected by the superior competent department and regulatory authority during the study period to ensure compliance with the study plan and Good Clinical Practice (GCP) guidelines. Original data will be used to check the integrity and accuracy of the record in the Case Report Form. The subjects' privacy is of critical importance and will be respected and protected at all times. Unannounced inspections will be performed by the regulatory authority to ensure full compliance with laws and regulations as well as ethical rules.

Patients and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures. Furthermore, patients will not be involved in the recruitment of participants or in decisions regarding the research profiles.

Study design and statistical analysis

Study design and sample size

CSPAC-1 is an open-label, multicentre, prospective, randomised phase III trial evaluating the efficacy and safety of simultaneous resection of the primary tumour and liver metastases after conversion chemotherapy versus standard therapy in pancreatic cancer with liver oligometastasis. The primary endpoint of this study is rOS. Our null hypothesis is that there is no differences in rOS between the operation arm and the control arm. The alternative hypothesis is that there is a difference between the operation arm and the control arm. Based on previous small-sample study results (the expected median survival times are 20.3 months and 14.0 months in the operation arm and the control arm, respectively), the assumption that enrolment will require 60 months and the requirement that the last patient be followed for at least 24 months, a total of 268 patients (134 vs 134) is needed according to PASS 11.0 software (two-sided log-rank test, significance 0.05; power 80%). Considering a 10% drop-out rate, 298 patients are needed. Therefore, we plan to enrol 300 patients (150 per group), which will be sufficient to meet the needs for sample size.

Analysis plan

The study statistical analysis plan will be made by a professional statistician with the principle investigator when the study plan is determined. SPSS 22.0 software will be used for statistical analysis. The efficacy of chemotherapy or response rate will be measured with the RECIST V.1.1 criteria within 4 weeks after the completion of conversion chemotherapy, the resectability of the primary pancreatic lesion will be judged based on NCCN guidelines, the surgical morbidity rate will be measured with CTCAE V.4.0 and the Clavien-Dindo classification and acute and late toxicity rates will be measured with CTCAE V.4.0.

A log-rank test will be performed to compare differences in rOS between the operation arm and the control arm. Patients who are still alive when last monitored will be censored at the date of last follow-up. A Kaplan-Meier curve will be used to plot the difference in rOS. OS will be analysed using the same method as that used to analyse rOS. Descriptive analysis using a covariance

Table 1 Time and events table: flow chart of the study procedure

Required measurement	Preliminary screening	Conversion chemotherapy	Randomisation				Follow-up
			Baseline screening	Study arm	Control arm	Examination after treatment	
Informed consent	✔						
ECOG scoring	✔	✔	✔	✔	✔	✔	✔
Abdominal CT scan (plain + enhanced)	✔		✔				
Abdominal MRI scan (plain + enhanced)	✔		✔				
Chest CT plain scan	✔		✔				✔
Pathological examination	✔						
CA19-9, CA125 and CEA	✔	✔	✔	✔	✔	✔	✔
Demographic data	✔						
History and physical examination	✔		✔				
Routine blood, biochemical and coagulation function	✔	✔	✔	✔	✔	✔	✔
Blood, urine and stool samples for lab tests	✔	✔					
Other tumour markers		✔					
ECG		✔	✔				
QoL scoring		✔	✔	✔	✔	✔	✔
First-line chemotherapy regimen and dosage		✔			✔		
Concomitant treatment		✔		✔	✔		
Adverse events		✔	✔	✔	✔	✔	✔
Inclusion criteria			✔				
Randomisation			✔				
Urine pregnancy test			✔				
Abdominal CT plain scan							✔
Surgical method				✔			
Adjuvant chemotherapy and dosage				✔			
Recurrence/metastasis/progress and survival status						✔	✔

CA125, cancer antigen 125; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; QoL, quality of life.

analysis (ANCOVA) model will be performed for changes in QoL when compared with baseline QoL. The baseline serves as a covariant in the model, and the effects of assessors are considered to be random. The value of difference (D-value) in each group before and after treatment, the LS means of the difference in D-values and the 95% confidential interval of the difference between the two groups will be calculated based on the model. Changes in QoL before and after treatment in each group will be compared using a paired-sample t-test. These analyses will include patient follow-up data and will be performed 2 years after the completion of enrolment.

Safety measures

Serious adverse events including death within 30 days from the end of protocol treatment, procedure-induced severe complications and unexpected grade 4 toxicities must be reported to the safety desk of the trial within 72 hours. Death occurring more than 30 days after the end of protocol treatment, expected non-haematological grade 4 toxicities and unexpected grade 3 toxicities will be reported to the safety desk of the trial within 15 days.

Quality assurance

Chemotherapy

All chemotherapy treatment plans for enrolled patients will be reviewed centrally by an independent committee. To assess regimen compliance, the following parameters will be reviewed: performance status, concomitant diseases, chemotherapy regimen, dosage and cycles, tolerance of toxicity and side effects, overall treatment time and tumour response evaluation by imaging and tumour marker assessments (RECIST V.1.1).

Pathology

For optimal staging, the minimum number of lymph nodes examined will vary from 12 to 15 based on NCCN and International Study Group of Pancreatic Surgery recommendations. Inking pancreatic anterior/posterior margins, superior mesenteric vessel (SMA and SMV) margins, portal vein margins, the bile duct margin, the stomach margin and proximal and distal enteric margins is recommended for accurate analysis of margin positivity.

Withdrawal from study

Patients will be able to withdraw from the study at any point. Data collected up to the point of withdrawal will be retained for use within analyses.

OUTCOMES

Primary outcome：rOS，the last patient be followed for at least 24 months.

Key secondary outcomes include:

- To explore the OS (the time from randomisation to death due to any cause) between operation arm and control arm;
- To assess the QoL scores by Quality of Life Questionnaire Core 30;
- To observe the procedure-related complications and mortality.

ETHICS AND DISSEMINATION

This trial will be performed in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. The Clinical Research Ethics Committee of Fudan University Shanghai Cancer Centre approved this protocol on 25 December 2017. Approval was acquired from the institutional review board of each institution before initiating patient accrual. Patient enrolment began on 1 July 2018. Every investigator must obey the rules and requirements of the International Conference on Harmonisation E6 Guidelines for GCP for Trials on Pharmaceutical Products.

The originals of all central study documents will be archived at the principal study site for at least 5 years after preparation of the final report. The participants, healthcare professionals, the public and other relevant groups will be informed of the study results. We aim to publish results from this study in the form of one or several manuscripts in international medical journals. The principal investigator will review all manuscripts.

TIME SCALE

The date of trial registration was 12 January 2018. The date of enrolment of the first patient was 1 July 2018. Recruitment is scheduled to be terminated by 1 June 2021. This study is ongoing, with an estimated completion date of 1 June 2023. The planned duration of enrolment is 60 months, and the study is expected to last 84 months.

DISCUSSION

For tumours with relatively favourable biology, simultaneous resection of the primary tumour and liver metastases versus conventional palliative (chemo)therapy might confer a survival benefit by reducing the tumour burden, giving the patient an extended time of chemotherapy and potentially maintaining their QoL. A prospective, randomised control study, CSPAC-1, was launched to confirm that conversion surgery can effectively prolong the OS of pancreatic cancer patients with liver oligometastasis.

Current studies, specifically the largest reports from Hackert *et al*,[40] examined prognosis in 128 patients with oligometastases (one to three lesions; liver metastasis in 85 patients and lymph node metastasis in 43 patients) who underwent surgery for primary pancreatic cancer as well as metastatic lesions; they reported a median OS time of 12.3 months in the 128 patients. Although the survival duration was almost the same as that of patients treated by chemotherapy, 5 year survival was achieved in 8.1% of the patients with liver metastases and 10.1% of the patients with lymph node metastases. Furthermore, there were no differences in survival depending on the number

of metastatic lesions, size of the metastatic tumour(s), location of the metastases in the liver or lymph node or serum CA19-9 level. Wright *et al*[30] analysed, retrospectively, 1147 patients with stage IV pancreatic cancer in two major institutes in the USA, and reported a resection rate of only 2.0%. These patients generally received the FOLFIRINOX regimen and the criteria for conversion surgery included the disappearance of liver metastases and normalisation or a marked decrease in the serum CA19-9 level. Twenty-four (4.5%) of the 535 patients in this study with pancreatic cancer and liver metastasis met the above criteria and underwent surgical resection of the primary site and hepatic resection if the metastatic site was still evident. The median OS times from the time of surgery and from the time of diagnosis were 18.2 months and 34.1 months, respectively. The median duration from diagnosis to surgical resection was 10 months, similar to that in Wright's report. Although the authors reported favourable OS for selected patients, early recurrence was detected within 6 months of surgery in seven patients (30.4%). Moreover, they could not identify the best indicators for conversion surgery for metastasised pancreatic cancer.[31]

Therefore, controversies remain based on these limited data. Surgery can be performed safely with low morbidity and mortality in high-volume hepato-pancreato-biliary centres, but conversion surgery is performed in less than 5% of patients with metastasised PDAC, and there are very few long-term survivors.[41] The challenge right now is how to select patients,[42 43] and the optimal duration of preoperative chemotherapy, the optimal timing for surgery and the predictive factors for resection and survival need to be identified. Perhaps the most important factor is the natural course of the disease, which is unique to each patient.[44] Chemosensitivity is another important factor that could influence long-term survival and should therefore also be considered and evaluated. The number of patients who underwent conversion surgery following systemic therapy was limited. A strategy to select which patients are most likely to benefit from conversion surgery is urgently needed.

In summary, the usefulness of conversion surgery for metastasised PDAC remains controversial. CSPAC-1 aims to establish a treatment strategy to select patients who can benefit from simultaneous resection of primary pancreatic cancer and liver metastatic sites. The results of this trial are planned to be released in 2025.

Participating institutions

Ruijin Hospital Affiliated to The Shanghai Jiao Tong University Medical School, Shanghai Changzheng Hospital, Xinhua Hospital Affiliated to Shanghai Jiaotong University School Of Medicine, Huadong Hospital Affiliated To Fudan University, The Affiliated Tumor Hospital of Harbin Medical University, The First Affiliated Hospital of Harbin Medical University, The Second Hospital of Hebei Medical University, Sun Yat-sen University Cancer Center, The Affiliated Hospital of Inner Mongolia Medical University, Zhujiang Hospital of Southern Medical University, The First People's Hospital of Changzhou, Jiangsu Province Hospital, Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine, Cancer Hospital Chinese Academy of Medical Science, Shenzhen Center, Xijing Hospital of Airforce Medical University, Sun Yat-sen Memorial Hospital Affiliated to Sun Yat-sen University, The First Affiliated Hospital Affiliated to Sun Yat-sen University, Beijing Cancer Hospital, Zhejiang Provincial People's Hospital, The First Affiliated Hospital Affiliated to Zhejiang University, The Second Affiliated hospital of Zhejiang University School of Medicine, Union Hospital Tongji Medical College Huazhong University of Science And Technology, Tongji Medical College Huazhong University of Science &Technology, Zhongda Hospital Southeast University, The First Affiliated Hospital of Xi'an Jiaotong University, Shaoxing People's Hospital, Changhai Hospital of Shanghai, Tenth People's Hospital of Tongji University, The First Affiliated Hospital of Soochow University, The First Affiliated Hospital Of USTC (Anhui Provincial Hospital), Chinese PLA General Hospital, Ningbo Medical Center Lihuili Hospital, Nantong Tumor Hospital, The Second Xiangya Hospital of Central South University, Hwa Mei Hospital, University of Chinese Academy of Sciences (Ningbo No.2 Hospital), Shandong Provincial Hospital, Xinqiao Hospital Army Medical University, West China Hospital of Sichuan University, Fourth Hospital of Hebei Medical University Hospital, Henan Cancer Hospital.

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Contributors SS, JX and XJY conceived of and planned the trial. MYW, JH and SS drafted the trial protocol and edited its final version. This trial is under the support of the Chinese Study Group for Pancreatic Cancer (CSPAC). All of the authors read and approved the final version of the protocol and of the manuscript.

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Competing interests XJY has received research funding from BeiGene Pharmaceutical.

Patient consent for publication Not required.

Ethics approval The study protocol has been approved by the Clinical Research Ethics Committee of Fudan University Shanghai Cancer Center (permission number: 1712179-9) (December 2017).

Provenance and peer review Not commissioned; externally peer reviewed.

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