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Title page

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Abstract

Introduction: Upfront surgeries are not beneficial to most patients with pancreatic cancer. Therefore, chemoradiotherapy has been placed more emphasis in locally advanced pancreatic cancer recently. Gemcitabine based regimens or FOLFORINOX has been proven as a standard chemotherapy in pancreatic cancer. However, severe toxicities may prevent the completion of chemotherapy. S-1 has showed better objective response rates and similar overall survival rates and progression free survival rates compared with gemcitabine, revealing that S-1 may be a potential candidate for pancreatic cancer, especially in patients refractory to gemcitabine. Additionally, stereotactic body radiation therapy with cyberknife could provide better efficacy than conventional radiotherapy in pancreatic cancer. Therefore, cyberknife with S-1 simultaneously followed by sequential S-1 as an initial treatment may bring about favorable outcomes but needs further study.

Methods and analysis: The SILAPANC trial is a prospective, single-center, one armed and ongoing study. 190 eligible patients are required to initially receive cyberknife with one cycle of S-1 simultaneously. After the concurrent chemoradiotherapy, two or three cycles of S-1 are sequentially given. Doses and

fractions depend on the location and volume of the tumor and the adjacent organs at risk. S-1 is taken orally, twice daily, at a dose of 80 mg/m^2 for 28 days, followed by a 14-day interval. The primary objectives are overall survival and 1-, 2-, 3-, 4- and 5-year overall survival rates. The secondary objectives are cancer specific survival, progression free survival, time to progression, local control rates, clinical benefit rates, radiation-induced acute and late toxicities, adverse effects of chemotherapy and quality of life of patients. Besides, variables most predictive of prognosis would be identified via multivariate methods.

Ethics and dissemination: Approvals have been granted by the Changhai Hospital Ethics Committee (CHEC-2016-032-01). The results will be disseminated in peer-reviewed journals and at conferences.

Trial registration number: NCT02704143.

Strengths and limitations of this study:

- This is the first study to evaluate the feasibility and efficacy of SBRT with cyberknife combined with S-1 followed by sequential S-1 initially treated in patients with locally advanced pancreatic cancer.
- Due to no optimal treatment in locally advanced pancreatic cancer and high adverse effects of standard chemotherapy, alternative combination therapies with favorable efficacy and low toxicities are urgent. Cyberknife and S-1 have been proved effective and low incidences of adverse effects in pancreatic cancer.
- This is a single-center, one arm study. Comparison with other treatment needs to

be further investigated after the phase II trial.

- Loss of participants at follow-up is inevitable. Hence, recruitment and duration of the study may be extended for availability of data for analysis.

Keywords: stereotactic body radiation therapy, stereotactic body radiotherapy, stereotactic ablative body radiotherapy, locally advanced pancreatic cancer, S-1, initial treatment

Introduction

Although the incidence rate of pancreatic cancer is not as high as that of other gastrointestinal carcinoma in China, cancer mortalities in males and females ranked sixth and seventh, respectively, in 2013, with a surprising low 5-year survival rate (<5%).[1] Among patients first diagnosed with pancreatic cancer, only 15-20% of these patients are suitable for surgery,[2] and the 5-year survival rate of patients with R0 resection remains <20%.[3-5]

Therefore, better efficacy could not be obtained *via* surgery alone, resulting in great emphasis on adjuvant chemoradiotherapy. In 1997, gemcitabine has been confirmed to be the standard chemotherapy for pancreatic cancer.[6] However, it has not been proven whether gemcitabine can significantly improve prognosis in long term follow-ups, and some patients are refractory to gemcitabine. Hence, there is an urgent need for the development of more effective chemotherapy.

S-1 is the prodrug of 5-fluorouracil (5-FU), which comprise of tegafur, gimeracil (dihydropyrimidine dehydrogenase inhibitor) and oteracil (inhibitor of phosphorylation in the gastrointestinal tract), with a ratio of 1:0.4:1. The first phase II clinical trials revealed good clinical efficacy with S-1.[7] In GEST, S-1 had better objective response rates than gemcitabine. In addition, S-1 is not inferior to gemcitabine in terms of overall survival (OS) rates and progression free survival (PFS) rates. Furthermore, the significant improvement of PFS rates can be achieved by the combination of S-1 and gemcitabine.[8] There was no difference between the incidence rates of the adverse effects of S-1 and gemcitabine. Therefore, S-1 is an alternative for

treating locally advanced or metastatic pancreatic cancer, especially for those resistant to gemcitabine. Although there are no phase III studies on S-1, phase II studies have already shown better disease control rates (52-58%), median OS time (4.5-6.3 months) and tolerable adverse effects in gemcitabine-resistant advanced pancreatic cancers treated with S-1.[9-10]

However, few encouraging results are gained with the combination of S-1 and the other drug.[8, 11-13] As a result, S-1 combined with radiotherapy has been gradually applied for the treatment of pancreatic cancer. Besides, 5-FU has been proven to be radiosensitive; thus, improving clinical efficacy.[14]

Compared with conventional radiation, a single-fraction dose and total dose of the target volume can be increased in stereotactic body radiation therapy (SBRT). In addition, doses of organs at risk would be reduced; thus, effectively improving local control rates and reducing radiation-related toxicity.[15-16] Shorter courses of SBRT also enhance patient's compliance and render the initial of other treatments on schedule possible.[16] Nevertheless, few studies have focused on S-1 combined with SBRT for locally advanced pancreatic cancer. Hence, the efficacy of combining S-1 and SBRT needs to be further confirmed. Based on our experience in treating locally advanced pancreatic cancers, SBRT combined with S-1 followed by sequential S-1 as the initial treatment for locally advanced pancreatic cancer has been proposed to evaluate its clinical efficacy.

2. Methods

2.1 Study design

This study is a single-center, prospective, single arm and phase II clinical trial designed and sponsored by the Department of Radiation Oncology of Changhai Hospital, which evaluated the safety and efficacy of combining cyberknife with S-1 as an initial treatment in patients with locally advanced pancreatic cancer. After obtaining the patients' written informed consent, their information on baseline characteristics, individual treatment plans and follow-up would be processed by database administrators responsible for this clinical trial. Although FOLFIRINOX and gemcitabine-based chemotherapy have been proven as a standard chemotherapy, side effects, especially gastrointestinal and hematological toxicities, may hamper the completion of the full treatment with these drugs, and probably even result in reduced quality of life. Therefore, the advantage of S-1 in this case due to its features may display a favorable tolerability and safety profile. Presumably, this yields an innovative therapy, if deemed favorable, compared with conventional chemotherapy; and this could be another alternative, or even a recommended therapy, when patients are vulnerable or resistant to gemcitabine. The main rationale for the active recruitment of the SILAPANC trial was to demonstrate the good tolerability of treatment with SBRT *via* cyberknife in combination with S-1, followed by sequential S-1 and to assess a potential therapeutic benefit based on the prognosis of patients.

2.2 Study objectives

SLIAPANC trial aims to investigate the efficacy and adverse effects of cyberknife with S-1 in patients with locally advanced pancreatic cancer. This study primarily aims to:

1. Evaluate the prognosis of patients with locally advanced pancreatic cancer after radiochemotherapy;

2. Determine adverse effects attributable to cyberknife or S-1;.

The secondary objectives are:

1. To analyze the quality of life of patients with locally advanced pancreatic cancer treated with cyberknife combined with S-1;

2. To demonstrate the potential factors associated with the safety and prognosis of patients with locally advanced pancreatic cancer after radiochemotherapy.

2.3 Participants and eligibility

To be eligible for inclusion in the SILAPANC trial, all patients with clinical suspicion for pancreatic cancer, as presented in the imaging studies, were required to receive pathological examinations. If deemed necessary, further high-quality dedicated imaging of the pancreas was performed before enrollment into the study and undergoing any study-related procedures. Biopsies were performed with fine needle aspiration *via* endoscopic ultrasound by experienced gastroenterologists. Specimen sections would be evaluated by two independent pathologists. After confirmed diagnosis of locally advanced pancreatic cancer by pathological examinations, patients should have the willingness and ability to provide an informed consent and

comply with subsequent treatment plans, tests and other study procedures.

The following inclusion and exclusion criteria would be employed to preserve high internal validity and reduce risks of SBRT or S-1-induced adverse effects. In our study, locally advanced pancreatic cancer includes borderline resectable or unresectable tumors without metastatic pancreatic cancer.

Inclusion criteria:

(1) Borderline resectable:[17]

(a) Pancreatic head/uncinate process:

(i) Solid tumor contacts with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for a safe and complete resection and reconstruction;

(ii) Solid tumor contact with the superior mesenteric artery of ≤180°;

(iii) The presence of variant arterial anatomy (such as accessory right hepatic artery, replaced right hepatic artery, replaced common hepatic artery, and the origin of replaced or accessory artery), and the presence and degree of tumor contact should be noted, if present, as it may affect surgical planning.

(b) Pancreatic body/tail:

(i) Solid tumor contact with the celiac axis of ≤180°;

(ii) Solid tumor contact with the celiac axis of ≥180° without the involvement of the aorta, and with intact and uninvolved gastroduodenal artery.

(c) Solid tumor contact with superior mesenteric veins or portal veins of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein,

but with a suitable vessel proximal and distal to the site of involvement, allowing for the safe and complete resection of the tumor and vein reconstruction;

(d) Solid tumor contact with the inferior vena cava.

(2) Unresectable without metastasis:[17]

(a) Pancreatic head/uncinate process:

(i) Solid tumor contact with the superior mesenteric artery >180°;

(ii) Solid tumor contact with the celiac axis >180°;

(iii) Solid tumor contact with the first jejunal superior mesenteric artery branch;

(iv) Unreconstructible superior mesenteric vein/portal vein due to involvement or occlusion (can be due to tumor or bland thrombus);

(v) Contact with most proximal draining jejunal branch into the superior mesenteric vein.

(b) Pancreatic body/tail:

(i) Solid tumor contact of >180° with the superior mesenteric artery branch;

(ii) Solid tumor contact with the celiac axis and aortic involvement;

(iii) Unreconstructible superior mesenteric vein/portal vein to tumor involvement or occlusion (can be due to tumor or bland thrombus).

(3) Age ranging from 18 to 75 years old;

(4) Karnofsky performance score (KPS) ≥70;

(5) Normal renal function (serum creatinine ≤2.0 mg/dl);

(6) Normal liver function (serum total bilirubin ≤3.0 mg/dl, serum AST ≤2.5 of the

upper limit of normal, serum ALT ≤2.5 of the upper limit of normal);

(7) Routine blood test: WBC ≥3.5×10^9/L, neutrophils ≥1.5×10^9/L, hemoglobin ≥80 g/L, and platelet ≥70×10^9/L.

Exclusion criteria:

(1) Ampulla of Vater cancer;

(2) Metastatic pancreatic cancer;

(3) Patients who have received surgeries, chemotherapy or other treatments prior to SBRT;

(4) Patients under the age of 18 or above the age of 75;

(5) KPS <70;

(6) Gastrointestinal inflammation or other diseases (especially active inflammatory bowel disease, non-healing peptic ulcer, gastrointestinal bleeding or perforation within six months);

(7) Impaired organ functions:

(a) Heart failure (NYHA III-IV);

(b) Respiratory failure;

(c) Renal insufficiency (serum creatinine >2.0 mg/dl).

(d) Hepatic insufficiency (serum total bilirubin >3.0 mg/dl, serum AST >2.5 of the upper limit of normal, serum ALT >2.5 of the upper limit of normal or Child-Pugh class B or C);

(e) Routine blood test: WBC <3.5×10^9/L, neutrophils <1.5×10^9/L, hemoglobin <80 g/L, platelet <70×10^9/L or other hematological diseases;

(f) Severe nervous system diseases.

(8) Pregnant women or lactating women;

(9) Patients enrolled in other clinical trials;

(10) Patients who did not provide an informed consent.

Due to better diagnostic yield, safety and the potential lower risk of peritoneal seeding, endoscopic ultrasound-guided fine-needle aspiration was preferred for all patients suspected of pancreatic cancer. However, patients with high risks of bleeding, pancreatitis or pancreatic fistula were not recommended to receive biopsies. Therefore, it is crucial and mandatory to establish the clinical diagnosis of pancreatic cancer with cautiousness by the multidisciplinary team based on medical history and all kinds of tests before the following treatment.

2.4 Pre-treatment assessment

Potential participants with locally advanced pancreatic cancer confirmed by initial screening were required to undergo a detailed pre-treatment assessment, in order to exclude any conditions contradictory to SBRT and S-1. Hence, participants would receive personal interviews with physicians for a detailed explanation of the whole study and related-treatments. In addition, written informed consent must be provided prior to the patients' participation to the study, stating their willingness to be treated according to the study protocol. Furthermore, it is important for these patients to complete the required laboratory tests and other examinations for the evaluation of their medical conditions, including blood routine tests, liver and renal function tests,

coagulation function tests, tumor markers, physical examinations and KPS scores.

After collection of data regarding pre-treatment assessment, this information would be carefully checked and sent to the designers for the final approval of the study enrollment and verification of the diagnosis. After successful enrollment into the study, the baseline quality of life of the participants was evaluated before treatment *via* questionnaires (EORTC QLQ-PAN26 and QLQ-C30).

2.5 Withdrawal of participants

Participants could withdraw from the study any time for any reason without any consequences. In addition, investigators are required to follow-up the whole treatment in case of radiochemotherapy-related severe adverse effects, in which investigators would stop the treatment temporarily or even exclude patients from the study. Patients who were intolerable from the treatment would definitely receive other alternative therapies based on the guidelines and experience of the multidisciplinary team. For every participant who withdraws from the study, the reasons for withdrawal from treatment should be recorded in detail in the database.

2.6 Ethical approval

This study complies with the current Declaration of Helsinki, and the principles of Good Clinical Practice (GCP) guidelines. This clinical trial has been registered and entered in the clinicaltrials.gov database (NCT02704143). This trial will also be carried out in keeping with local legal and regulatory requirements. The study

protocol and informed consents are approved by the independent Ethic Committee of Changhai hospital.

Prior to enrollment, the potential candidates would receive information on the study both verbally and in writing. They would be given one week to decide whether to participate into the study. Thereafter, informed consent, during which a physician will explain the nature, scope and possible consequences of the trial to the patient, is obtained from each patient. The investigators will not assume any demands, including publishing or reporting of individual patient data, especially data required for this clinical trial, until a valid consent has been obtained. Patients' data would be kept strictly confidential within the study, but their pseudonymous medical records and information would be extracted from the database and reviewed for trial purposes by authorized individuals other than their treating physicians.

2.7 Study procedures

2.7.1 Trial overview

After the successful assessment and obtaining an informed consent, the participants would be assigned into the treatment group. Individualized treatment plans would be made after the simulation, and these would be finally confirmed after a consensus is reached by two radiation oncologists and a medical physicist. The fractions and radiation doses of the cyberknife depend on each patient's medical condition, as well as the spatial location of the tumor and the adjacent organs at risk. Participants were required to receive SBRT with cyberknife and one cycle of S-1 simultaneously. After

the concurrent radiochemotherapy, two or three cycles of S-1 were sequentially given. Optimization of the combination of cyberknife and S-1 focuses on the interval between the cyberknife and the initial S-1. However, due to severe adverse effects or those regarded as grade 3 or 4 toxicity, the doses of radiation or S-1 may be modified or the interval of each radiation and the initial of S-1 may be delayed, or the treatment may even be stopped temporarily. These patients would be treated immediately and properly or, if deemed necessary, under the consultation of the multiple disciplinary team. For some patients, if they are reluctant to participate in the trial or were inappropriate for the treatment, as requested evaluated by investigators, they would withdraw from the study and receive other alternative treatments. Figure 1 illustrates the flow diagram of the study.

2.7.2 Doses of S-1

The doses of S-1 are calculated by the body surface. Hence, patients allocated into the cyberknife combined with S-1 arm received S-1 orally, twice daily, at a dose of 80 mg/m^2 for 28 days, followed by a 14-day interval.

2.7.3 CT simulation for treatment planning

Each patient fasted for at least eight hours before the simulation. Vacuum bags were customized with patients in the supine position, according to the patient's body shape for immobilization during the cyberknife. SBRT was delivered *via* the cyberKnife, an image-guided frameless stereotactic robotic radiosurgery system (Accuray

Corporation, Sunnyvale CA), that consists of a linear accelerator mounted on a robot arm with six degrees of freedom. In this system, the confluence of a large number of non-isocentric pencil beams permited the treatment of irregularly shaped target volumes with rapid dose falloffs. The cyberKnife tracking system automatically compensated for the alignment offset and patient motion by adjusting the treatment isocenter. In addition, a CT based treatment planning system was used at our institution. Then, plain CT and an enhanced pancreatic parenchymal CT were performed for radiation treatment planning and target delineation. CT images were acquired under breath hold (preferably end-expiratory). Pretreatment diagnostic imaging was co-registered to the simulation CT in cases where the patient was unable to tolerate intravenous contrast. The scan range included the whole pancreas, at least 10 cm above and below the tumor. Spiral CT was performed with a slice thickness of 1.5 mm, and images were reconstructed in slices of 1.5 mm at most. Intravenous contrast enhancement was performed with an injection of 80-100 ml of iodixanol, a flow rate of 2.5 ml/sec, and a delay of 45-55 seconds; as acquired for the pancreatic parenchymal phase.

2.7.4 Registration and tracking

The co-registrations of biphasic CT images were based on fiducials and anatomical (spinal) fusion. Before CT simulation, fiducials were implanted using endoscopic ultrasound or CT guidance. This is pivotal for treatment planning and delivery. CT simulation was performed 1-3 weeks after fiducial placement. This time interval was

required to avoid early fiducial marker displacement or migration. In order to improve the accuracy of the treatment planning, the recommended number of implanted fiducials was preferably close to 3-5, but not in the tumor. As a result, given that fiducials could simulate the spatial location and displacement of the tumor, which was attributable to respiration, motion tracking was performed by means of the correlation with these seeds; and fiducial markers rendered the Synchrony system equipped in the cyberknife feasible. This allowed for respiratory motion tracking during irradiation. Nevertheless, patients with high risk of bleeding, abdominal infection, pancreatitis or pancreatic fistula were contradictory to several fiducial implants. Hence, one fiducial plus X-sight spine and Synchrony Tracking technique would be alternatively used. Before treatment, direct digital radiography images of the spine would be applied to detect 6-D errors; and this would be subsequently corrected for X-sight spine tracking on the patient's positioning. This would enable fiducial tracking during treatment.

2.7.5 Treatment planning and target delineation

After CT simulation, CT images were transferred to the workstation where the target volumes were contoured by an attending radiation oncologist. Gross tumor volume (GTV) was delineated as a radiographically evident gross disease by contrast CT acquired from the portal-venous phase. At the discretion of the physician, clinical target volume (CTV) encompassing areas of the potential subclinical disease spread was also designated. In most cases, the CTV equaled GTV. A 2-5 mm expansion margin was included to determine the planning target volume (PTV). When the tumor

was adjacent to critical organs, the expansion of CTV was avoided. Therefore, an individualized treatment plan would be developed based on tumor geometry and location. Ninety percent of PTV should be covered by the prescription dose. The prescription isodose line was limited to 70-75%, which would restrict the tumor D_{max}. If dose level violated the constraint of SBRT, the patient would be considered as ineligible for this trial. The single dose of CTV varied from 6.5-9 Gy. In particular, these doses would be reduced if the tumor was approximately one-third or more of the duodenum or stomach circumference, or if the tumor abutted the bowel in only one area, as determined by the relationship of the tumor to the duodenum in axial, coronal and sagittal planes in CT scans, or the space between the tumor and the bowel wall was <3 mm. Normal tissue constraints were according to the American Association of Physicists in Medicine guidelines in TG-101,[18] as presented in Table 1.

Table 1. Critical structures and threshold doses

Organs	Threshold doses (five fractions)	Minimum critical volume below threshold
Parallel organs		
Liver	21 Gy	700 cc
Kidney	17.5 Gy	200 cc

Organs	Threshold doses (five fractions)	Max point dose	Max critical volume above threshold

Serial organs			
Spinal cord	23 Gy	30 Gy	0.35 cc
Duodenum	18 Gy	32 Gy	5 cc
Bowel	19.5 Gy	35 Gy	5 cc
Stomach	18 Gy	32 Gy	10 cc
Esophagus	19.5 Gy	35 Gy	5 cc
Colon	25 Gy	38 Gy	20 cc

2.7.6 Long-term follow-up

Patients are re-evaluated after cyberknife every one month for the first three months, every 2-3 months for the next two years, and every six months for a total five years. Remissions of symptoms and radiation-related toxicities would be assessed. In addition, they would undergo laboratory tests, physical examinations, analysis of quality of life, KPS scores and imaging studies every month within the first three months. Subsequent examinations in later follow-ups are the same.

2.8 Outcomes

2.8.1 Outcome definitions

Primary outcomes of the study were OS and 1-, 2-, 3-, 4- and 5-year OS rates. OS was defined as the time from the date of enrollment to death from any cause. Patients lost to follow-up, withdrawn, or alive at the end of the follow-up should be kept confidential.

Secondary outcomes included cancer specific survival (CSS), PFS, time to progression (TTP), local control rates (LCR), clinical benefit rates (CBR), radiation-induced acute and late toxicities, adverse effects of chemotherapy and quality of life of the patient. Cancer specific survival was the time from inclusion to death caused by the tumor. Progression-free survival was the time from the date of enrollment to the confirmation of disease progression at any site or death from any cause, if this occurred before disease progression. Local control was considered as a lack of enlargement of the tumor volume radiographically or stable/declining standardized uptake values on PET-CT scans. The definition of time to progression was the time from inclusion to the recurrence of the tumor, including local recurrence or metastasis. Clinical benefit rate was the ratio of the number of patients with complete response, partial response, or stable disease to the total number of enrolled patients.

2.8.2 Evaluation of outcomes

PFS, TTP, LCR and CBR were all associated with treatment response, as determined by the RECIST criteria (version 1.1). Quality of life would be measured through European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and QLQ-PAN26). Radiation-induced acute toxicities were adverse effects that occur within 90 days after treatment, and determined by the Radiation Therapy Oncology Group, “Acute radiation morbidity scoring criteria”. Late toxicities occurring three months after SBRT were evaluated by

the Radiation Therapy Oncology Group/European Organization for Research on the Treatment of Cancer, “Late radiation morbidity scoring schema”.

2.9 Sample size determination

It was assumed that 1-year OS rate was 70% of locally advanced pancreatic cancers treated with cyberknife combined with S-1. The potential benefit of the regimen was approximately 20% increase in 1-year OS rate. In order to have 90% power to reject the null hypothesis if the alternative was true at level alpha = 0.05, the required sample size for our study was 138. Additionally, a loss of 20% of patients due to lost to follow-up or withdrawn due to adverse effects or other reasons was estimated. Hence, a total of 190 patients would be enrolled into this study.

2.10 Data analysis

Statistical testing was performed using SPSS version 20.0 (IBM Corp, Armonk, NY, USA). All outcomes would be analyzed based on intention-to-treat principle. PFS, OS and LC were calculated *via* the Kaplan-Meier method compared by the log-rank (Mantel-Cox) test. Response rates would be compared by a test of proportions. Further analysis would be performed in subgroups stratified by different factors.

2.11 Data management and quality assurance

Data regarding the patient’s characteristics, medical history and results of clinical and laboratory tests or examinations will be kept in a password-protected database at the

Department of Radiation Oncology in Changhai hospital, which will only be disclosed to authorized individuals. The Ethic Committee of Changhai Hospital will be responsible for data monitoring. In addition, trial conducts will be audited by the committee every six months after the recruitment of participants. The accuracy of the data entry into the database will be confirmed by two administrators. The interim results will be accessed to authorized individuals and reported to the Ethic Committee of Changhai Hospital, which would make the final decision to terminate the trial if severe adverse effects frequently occur.

3. Discussion

S-1 has been considered as an important chemotherapeutic drug in pancreatic cancer. In addition to convenient oral medication, many studies have verified that S-1 was not inferior to gemcitabine regarding OS and PFS. In adjuvant therapy, S-1 may be a candidate drug for a patient refractory to gemcitabine, but without phase III clinical trials. In addition, radiotherapy combined with S-1 probably contributed to the lower staging of the tumor, as well as the complication rates of surgeries.[18, 19] It was elucidated that neoadjuvant radiotherapy with S-1 was beneficial to potential candidates for radical surgeries, because OS could be improved significantly.[19]

SBRT with cyberknife has been proven with lower radiation-toxicities, higher accuracy and better efficacy compared with conventional radiotherapy. Therefore, it is pivotal to evaluate the efficacy of SBRT with S-1 as the initial or even neoadjuvant

treatment in locally advanced pancreatic cancer, which may be no inferior to or even more beneficial to patients than standard chemotherapy with conventional radiotherapy. However, no prospective clinical trials have provided such investigation. Hence, the goal of the SILAPANC trial is to assess whether better prognosis could be achieved with cyberknife in combination with S-1 followed by sequential S-1 as an initial treatment, which may provide new insights into the treatment of locally advanced pancreatic cancer.

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Authors' contributions:

Huojun Zhang was the primary investigator of the study. Xiaofei Zhu and Xiaoping Ju designed the protocol and Huojun Zhang amended it. Xiaofei Zhu, Fei Cao and Fang Fang, were responsible for recruitment of participants. Shuiwang Qing and Yuxin Shen were responsible for data entry. Zhen Jia and Yangsen Cao were responsible for data analysis.

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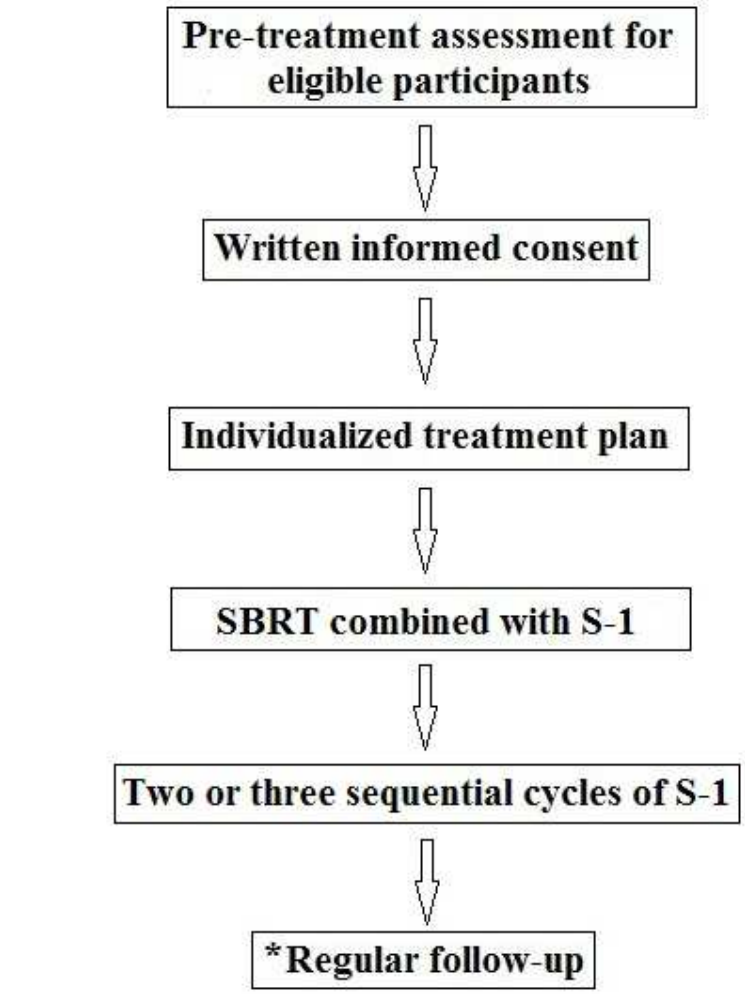

Figure 1 Study flow chart

BMJ Open

Safety and efficacy of stereotactic body radiation therapy combined with S-1 simultaneously followed by sequential S-1 as an initial treatment for locally advanced pancreatic cancer (SILAPANC trial): Study design and rationale of a phase II clinical trial

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Safety and efficacy of stereotactic body radiation therapy combined with S-1 simultaneously followed by sequential S-1 as an initial treatment for locally advanced pancreatic cancer (SILAPANC trial): Study design and rationale of a phase II clinical trial

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Abstract

Introduction: Upfront surgeries are not beneficial to most patients with pancreatic cancer. Therefore, chemoradiotherapy has been placed more emphasis in locally advanced pancreatic cancer recently. Gemcitabine based regimens or FOLFORINOX has been proven as a standard chemotherapy in pancreatic cancer. However, severe toxicities may prevent the completion of chemotherapy. S-1 has showed better objective response rates, similar overall survival rates and progression free survival rates compared with gemcitabine, revealing that S-1 may be a potential candidate in treating pancreatic cancer, especially for patients refractory to gemcitabine. Additionally, stereotactic body radiation therapy with Cyberknife could provide better efficacy than conventional radiotherapy in pancreatic cancer. Therefore, Cyberknife with S-1 simultaneously followed by sequential S-1 as an initial treatment may bring about favorable outcomes but needs further studies.

Methods and analysis: The SILAPANC trial is a prospective, single-center, one

armed and ongoing study. One hundred and ninety eligible patients are required to initially receive Cyberknife with one cycle of S-1 simultaneously. After the concurrent chemoradiotherapy, two or three cycles of S-1 are sequentially given. Doses and fractions depend on the locations and volumes of tumors and the adjacent organs at risk. S-1 is taken orally, twice daily, at a dose of 80 mg/m^2 for 28 days, followed by a 14-day interval. The primary objectives are overall survival and 1-, 2-, 3-, 4- and 5-year overall survival rates. The secondary objectives are cancer specific survival, progression free survival, time to progression, local control rates, clinical benefit rates, radiation-induced acute and late toxicities, adverse effects of chemotherapy and quality of life of patients. Besides, variables most predictive of prognosis would be identified via multivariate methods.

Ethics and dissemination: Approvals have been granted by the Changhai Hospital Ethics Committee (CHEC-2016-032-01). The results will be disseminated in peer-reviewed journals and at conferences.

Trial registration number: NCT02704143.

Strengths and limitations of this study:

- This is the first study to evaluate the feasibility and efficacy of SBRT with Cyberknife combined with S-1 followed by sequential S-1 initially treated in patients with locally advanced pancreatic cancer.
- Due to no optimal treatment in locally advanced pancreatic cancer and high adverse effects of the standard chemotherapy, alternative combination therapies

with favorable efficacy and low toxicities are urgent. Cyberknife and S-1 have been proved effective in pancreatic cancer with low incidences of adverse effects.

- This is a single-center, one arm study. Comparison with other treatment needs to be further investigated after the phase II trial.
- Loss of participants at follow-up is inevitable. Hence, recruitment and duration of the study may be extended for availability of data for analysis.

Keywords: stereotactic body radiation therapy, stereotactic body radiotherapy, stereotactic ablative body radiotherapy, locally advanced pancreatic cancer, S-1, initial treatment

1. Introduction

Although the incidence rate of pancreatic cancer was not as high as that of other gastrointestinal cancer in China, cancer mortalities in males and females ranked the sixth and seventh, respectively, in 2013, with surprising low 5-year survival rates (<5%).[1] Among patients first diagnosed with pancreatic cancer, only 15-20% of these patients were suitable for surgery,[2] and the 5-year survival rate of patients with R0 resection remained <20%.[3-5]

Therefore, better efficacy could not be obtained *via* surgeries alone, resulting in great emphasis on adjuvant chemoradiotherapy. In 1997, gemcitabine has been confirmed to be the standard chemotherapy for pancreatic cancer.[6] However, it has not been proven whether gemcitabine can significantly improve prognosis in long term follow-ups, especially when some patients were refractory to gemcitabine. Hence, there was an urgent need for the development of more effective chemotherapy.

S-1 is the prodrug of 5-fluorouracil (5-FU), which comprises of tegafur, gimeracil (dihydropyrimidine dehydrogenase inhibitor) and oteracil (inhibitor of phosphorylation in the gastrointestinal tract), with a ratio of 1:0.4:1. The first phase II clinical trials revealed good clinical efficacy with S-1.[7] In GEST, S-1 had better objective response rates than gemcitabine. In addition, S-1 was not inferior to gemcitabine in terms of overall survival (OS) rates and progression free survival (PFS) rates. Furthermore, the significant improvement of PFS rates could be achieved by the combination of S-1 and gemcitabine.[8] There was no difference between the incidence rates of the adverse effects of S-1 and gemcitabine. Therefore, S-1 was an alternative

for treating locally advanced or metastatic pancreatic cancer, especially for those resistant to gemcitabine. Although there are no phase III studies on S-1, phase II studies have already shown better disease control rates (52-58%), median OS time (4.5-6.3 months) and tolerable adverse effects in gemcitabine-resistant advanced pancreatic cancers treated with S-1.[9-10]

However, few encouraging results were gained with the combination of S-1 and the other medication.[8, 11-13] As a result, S-1 combined with radiotherapy has been gradually applied for the treatment of pancreatic cancer. Besides, 5-FU has been proven to be radiosensitive; thus, improving clinical efficacy.[14]

Compared with conventional radiation, a single-fraction dose and the total dose of the target volume can be increased in stereotactic body radiation therapy (SBRT). In addition, doses of organs at risk would be reduced; thus, effectively improving local control rates and reducing radiation-related toxicities.[15-16] Shorter courses of SBRT also enhance patient's compliance and render the initial of other treatments on schedule possible.[16] Previous studies on SBRT combined with other chemotherapy regimens were presented in Table 1. Nevertheless, few studies have focused on S-1 combined with SBRT for locally advanced pancreatic cancer. Hence, the feasibility of combining S-1 and SBRT needs to be further confirmed. Based on our experience in treating locally advanced pancreatic cancer, SBRT combined with S-1 followed by sequential S-1 as the initial treatment for locally advanced pancreatic cancer has been proposed to evaluate its clinical efficacy.

Table 1. Recent studies evaluating SBRT in pancreatic cancer

Study	Patients	Dose	Median OS (mo)	1 year OS rate	Toxicity	Chemotherapy
Chuong et al[17] (2013)	73 BR or LA	5-10Gy×5f	16.4 BR; 15 LA	72.2% BR; 68.1% LA	5% Grade 3 (late)	3 cycles GTX
Herman et al[18] (2014)	49 LA	6.6Gy×5f	13.9	59%	2% Acute Grade≥2 11% Late Grade≥2	GEM followed by SBRT
Mahadevan et al[19] (2010)	36 LA	8-12Gy×3f	20	-----	33% Grade 1–2 8% Grade 3	Post-SBRT GEM
Koong et al[20] (2004)	15 LA	15-25Gy×1f	11	-----	33% Grade 1–2 0% Grade 3	None
Koong et al[5] (2005)	16 LA	25Gy×1f (boost)	8.3	15%	69% Grade 1–2 12.5% Grade 3	5-FU with EBRT prior to boost
Hoyer et al[21] (2005)	22 LA	15Gy×3f	5.4	5%	79% Grade 2 4.5% Grade 4	None
Schellenberg et al[22] (2008)	16 LA	25Gy×1f	11.4	50%	19% acute toxicity 47% late toxicity	1 cycle of induction GEM + post-SBRT GEM

Schellenberg et al[23] (2011)	20 LA	25Gy×1f	11.8	50%	15% Grades 1–2 5%≥Grade 3	1 cycle of induction GEM + post-SBRT GEM
Mahadevan et al[24] (2011)	39 LA	8-12Gy×3f	20	-----	41% Grade 1–2 0% Acute Grade 3 9% Late Grade 3	2 cycles induction GEM
Polistina et al[25] (2010)	23 LA	10Gy×3f	10.6	39.1%	20% Grade 1 0% Grade 2	6 weeks of induction GEM
Rwigema et al[26] (2011)	71 (LA, LR, RPM, MD)	24Gy×1f	10.3	41%	39.5% Grade 1–2 4.2% Grade 3	90% received chemotherapy (various regimens)
Gurka et al[27] (2013)	10 LA	5Gy×5f	12.2	-----	0% Grade 3	1 cycle GEM prior to SBRT, 6 cycles GEM total
Didolkar et al[28] (2010)	85 LA or LR	5-10Gy×3f	18.6	50%	22.3%≥Grade 3	Post-SBRT GEM
Goyal et al[29]	19 LA or LR	20-25Gy×1f	14.4	56%	11% Grade 1–2	68% 5-FU or

(2012)	8-10Gy×3f	16% Grade 3	GEM based

Abbreviation: BR, borderline resectable; GEM, gemcitibine; GTX, gemcitibine, taxotere, and xeloda; LA, locally advanced; LR, locally recurrent; MD, metastatic disease; RPM, resected positive margins; 5-FU, 5-flourouracil.

2. Methods

2.1 Study design

This study is a single-center, prospective, single arm and phase II clinical trial designed and sponsored by the Department of Radiation Oncology of Changhai Hospital, which evaluated the safety and efficacy of combining Cyberknife with S-1 followed by sequential S-1 as an initial treatment in patients with locally advanced pancreatic cancer. After obtaining the patients' written informed consents, their information about baseline characteristics, individual treatment plans and follow-ups would be processed by database administrators responsible for this clinical trial. Although FOLFIRINOX and gemcitabine-based chemotherapy have been proven as a standard chemotherapy, side effects, especially gastrointestinal and hematological toxicities, may hamper the completion of the full treatment with these drugs, and probably even result in reduced quality of life. Therefore, the advantage of S-1 in this case due to its features may display a favorable tolerability and safety profile. Presumably, this yields an innovative therapy, if deemed favorable, compared with conventional chemotherapy; and this could be another alternative, or even a recommended therapy, when patients are vulnerable or resistant to gemcitabine. The main rationale for the active recruitment of the SILAPANC trial is to demonstrate the good tolerability of treatment with SBRT *via* Cyberknife combined with S-1, followed by sequential S-1 and to assess a potential therapeutic benefit based on the prognosis of patients.

2.2 Study objectives

SLIAPANC trial aims to investigate the efficacy and adverse effects of Cyberknife with S-1 in patients with locally advanced pancreatic cancer. The primarily objectives are:

1. To evaluate the prognosis of patients with locally advanced pancreatic cancer after radiochemotherapy;

2. To determine adverse effects attributable to Cyberknife or S-1;.

The secondary objectives are:

1. To analyze the quality of life of patients with locally advanced pancreatic cancer treated with Cyberknife combined with S-1;

2. To demonstrate the potential factors associated with the safety and prognosis of patients with locally advanced pancreatic cancer after radiochemotherapy.

2.3 Participants and eligibility

To be eligible for inclusion in the SILAPANC trial, all patients with clinical suspicion for pancreatic cancer, as presented in the imaging studies, were required to receive pathological examinations. If deemed necessary, further high-quality dedicated imaging of the pancreas should be performed before patients are enrolled into the study and undergo any study-related procedures. Biopsies were performed with fine needle aspiration *via* endoscopic ultrasound by experienced gastroenterologists. Specimen sections would be evaluated by two independent pathologists. After confirmed diagnosis of locally advanced pancreatic cancer by pathological

examinations, patients should have the willingness and ability to provide an informed consent and comply with subsequent treatment plans, tests and other study procedures.

The following inclusion and exclusion criteria would be employed to preserve high internal validity and reduce risks of SBRT or S-1-induced adverse effects. In our study, locally advanced pancreatic cancer included borderline resectable or unresectable tumors without metastatic pancreatic cancer.

Inclusion criteria:

(1) Borderline resectable:[30]

(a) Pancreatic head/uncinate process:

(i) Solid tumor contacts with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for a safe and complete resection and reconstruction;

(ii) Solid tumor contact with the superior mesenteric artery of ≤180°;

(iii) The presence of variant arterial anatomy (such as accessory right hepatic artery, replaced right hepatic artery, replaced common hepatic artery, and the origin of replaced or accessory artery), and the presence and degree of tumor contact should be noted, if present, as it may affect surgical planning.

(b) Pancreatic body/tail:

(i) Solid tumor contact with the celiac axis of ≤180°;

(ii) Solid tumor contact with the celiac axis of ≥180° without the involvement of the aorta, and with intact and uninvolved gastroduodenal artery.

(c) Solid tumor contact with superior mesenteric veins or portal veins of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein, but with a suitable vessel proximal and distal to the site of involvement, allowing for the safe and complete resection of the tumor and vein reconstruction;

(d) Solid tumor contact with the inferior vena cava.

(2) Unresectable without metastasis:[30]

(a) Pancreatic head/uncinate process:

(i) Solid tumor contact with the superior mesenteric artery >180°;

(ii) Solid tumor contact with the celiac axis >180°;

(iii) Solid tumor contact with the first jejunal superior mesenteric artery branch;

(iv) Unreconstructible superior mesenteric vein/portal vein due to involvement or occlusion (can be due to tumor or bland thrombus);

(v) Contact with most proximal draining jejunal branch into the superior mesenteric vein.

(b) Pancreatic body/tail:

(i) Solid tumor contact of >180° with the superior mesenteric artery branch;

(ii) Solid tumor contact with the celiac axis and aortic involvement;

(iii) Unreconstructible superior mesenteric vein/portal vein to tumor involvement or occlusion (can be due to tumor or bland thrombus).

(3) Age ranging from 18 to 75 years old;

(4) Karnofsky performance score (KPS) ≥70;

(5) Normal renal function (serum creatinine ≤2.0 mg/dl);

(6) Normal liver function (serum total bilirubin ≤3.0 mg/dl, serum AST ≤2.5 of the upper limit of normal, serum ALT ≤2.5 of the upper limit of normal);

(7) Routine blood test: WBC $\geq 3.5\times10^9$/L, neutrophils $\geq 1.5\times10^9$/L, hemoglobin ≥80 g/L, and platelet $\geq 70\times10^9$/L.

Exclusion criteria:

(1) Ampulla of Vater cancer;

(2) Metastatic pancreatic cancer;

(3) Patients who have received surgeries, chemotherapy or other treatments prior to SBRT;

(4) Patients under the age of 18 or above the age of 75;

(5) KPS <70;

(6) Gastrointestinal inflammation or other diseases (especially active inflammatory bowel disease, non-healing peptic ulcer, gastrointestinal bleeding or perforation within six months);

(7) Impaired organ functions:

(a) Heart failure (NYHA III-IV);

(b) Respiratory failure;

(c) Renal insufficiency (serum creatinine >2.0 mg/dl).

(d) Hepatic insufficiency (serum total bilirubin >3.0 mg/dl, serum AST >2.5 of the upper limit of normal, serum ALT >2.5 of the upper limit of normal or Child-Pugh class B or C);

(e) Routine blood test: WBC $<3.5\times10^9$/L, neutrophils $<1.5\times10^9$/L, hemoglobin <80 g/L, platelet $<70\times10^9$/L or other hematological diseases;

(f) Severe nervous system diseases.

(8) Pregnant women or lactating women;

(9) Patients enrolled in other clinical trials;

(10) Patients who did not provide an informed consent.

Due to better diagnostic yield, safety and the potential lower risk of peritoneal seeding, endoscopic ultrasound-guided fine-needle aspiration is preferred for all patients suspected of pancreatic cancer. However, patients with high risks of bleeding, pancreatitis or pancreatic fistula were not recommended to receive biopsies. Therefore, it is crucial and mandatory to establish the clinical diagnosis of pancreatic cancer with cautiousness by the multidisciplinary team based on medical histories and all kinds of tests before the following treatment.

2.4 Pre-treatment assessment

Potential participants with locally advanced pancreatic cancer confirmed by initial screening were required to undergo a detailed pre-treatment assessment, in order to exclude any conditions contradictory to SBRT and S-1. Hence, participants would receive personal interviews with physicians for a detailed explanation of the whole study and related-treatments. In addition, written informed consents must be provided prior to the patients' participation to the study, stating their willingness to be treated according to the study protocol. Furthermore, it is important for these patients to

complete the required laboratory tests and other examinations for the evaluation of their medical conditions, including blood routine tests, liver and renal function tests, coagulation function tests, tumor markers, physical examinations and KPS scores.

After collection of data regarding pre-treatment assessment, this information would be carefully checked and sent to the designers for the final approval of the study enrollment and verification of the diagnosis. After successful enrollment into the study, the baseline quality of life of the participants will be evaluated before treatment *via* questionnaires (EORTC QLQ-PAN26 and QLQ-C30).

2.5 Withdrawal of participants

Participants could withdraw from the study any time for any reasons without any consequences. In addition, investigators are required to follow-up the whole treatment in case of radiochemotherapy-related severe adverse effects, in which investigators would stop the treatment temporarily or even exclude patients from the study. Patients who are intolerable from the treatment would definitely receive other alternative therapies based on the guidelines and experience of the multidisciplinary team. For every participant who withdraws from the study, the reasons for withdrawal from treatment should be recorded in details in the database.

2.6 Ethical approval

This study complies with the current Declaration of Helsinki, and the principles of Good Clinical Practice (GCP) guidelines. This clinical trial has been registered and

entered in the clinicaltrials.gov database (NCT02704143). This trial will also be carried out in keeping with local legal and regulatory requirements. The study protocol and informed consents are approved by the independent Ethic Committee of Changhai hospital.

Prior to enrollment, the potential candidates would receive information on the study both verbally and in writing. They would be given one week to decide whether to participate into the study. Thereafter, informed consents, during which a physician will explain the nature, scope and possible consequences of the trial to the patient, is obtained from each patient. The investigators will not assume any demands, including publishing or reporting of individual patient's data, especially data required for this clinical trial, until a valid consent has been obtained. Patients' data would be kept strictly confidential within the study, but their pseudonymous medical records and information would be extracted from the database and reviewed for trial purposes by authorized individuals other than their treating physicians.

2.7 Study procedures

2.7.1 Trial overview

After the successful assessment, the participants would be assigned into the treatment group. Individualized treatment plans would be made after the simulation, and these would be finally confirmed after a consensus is reached by two radiation oncologists and a medical physicist. The fractions and radiation doses of Cyberknife depend on each patient's medical condition, as well as the spatial location of the tumor and the

adjacent organs at risk. Participants are required to receive SBRT with Cyberknife and one cycle of S-1 simultaneously. After the concurrent radiochemotherapy, two or three cycles of S-1 will be sequentially given. Optimization of the combination of Cyberknife and S-1 focuses on the interval between Cyberknife and the initial of S-1. However, due to severe adverse effects or those regarded as grade 3 or 4 toxicities, the doses of radiation or S-1 may be modified or the interval of each radiation and the initial of S-1 may be delayed, or the treatment may even be stopped temporarily. These patients would be treated immediately and properly or, if deemed necessary, under the consultation of the multiple disciplinary team. For some patients, if they are reluctant to participate in the trial or are inappropriate for the treatment, as requested evaluated by investigators, they would withdraw from the study and receive other alternative treatments. Figure 1 illustrates the flow diagram of the study.

2.7.2 Doses of S-1

The doses of S-1 are calculated by the body surface. Hence, patients allocated into Cyberknife combined with S-1 arm will receive S-1 orally, twice daily, at a dose of 80 mg/m^2 for 28 days, followed by a 14-day interval.

2.7.3 CT simulation for treatment planning

Each patient should fast for at least eight hours before the simulation. Vacuum bags are customized with patients in the supine position, according to the patient's body shape for immobilization during Cyberknife. SBRT is delivered *via* Cyberknife, an

image-guided frameless stereotactic robotic radiosurgery system (Accuray Corporation, Sunnyvale CA), that consists of a linear accelerator mounted on a robot arm with six degrees of freedom. In this system, the confluence of a large number of non-isocentric pencil beams permits the treatment of irregularly shaped target volumes with rapid dose falloffs. Cyberknife tracking system automatically compensates for the alignment offset and patient motions by adjusting the treatment isocenter. In addition, a CT based treatment planning system is used at our institution. Then, plain CT and an enhanced pancreatic parenchymal CT are performed for radiation treatment planning and target delineations. CT images are acquired under breath hold (preferably end-expiratory). Pretreatment diagnostic imaging would be co-registered to the simulation CT in cases where the patient is unable to tolerate intravenous contrast. The scan range includes the whole pancreas, at least 10 cm above and below the tumor. Spiral CT is performed with a slice thickness of 1.5 mm, and images are reconstructed in slices of 1.5 mm at most. Intravenous contrast enhancement is performed with an injection of 80-100 ml of iodixanol, a flow rate of 2.5 ml/sec, and a delay of 45-55 seconds; as acquired for the pancreatic parenchymal phase.

2.7.4 Registration and tracking

The co-registrations of biphasic CT images are based on fiducials and anatomical (spinal) fusion. Before CT simulation, fiducials should be implanted using endoscopic ultrasound or CT guidance. This is pivotal for treatment planning and delivery. CT

simulation will be performed 7-10 days after fiducial placement. This time interval is required to avoid early fiducial marker displacement or migration. In order to improve the accuracy of the treatment planning, the recommended number of implanted fiducials is preferably close to 3-5, but not in the tumor. As a result, given that fiducials could simulate the spatial location and displacement of the tumor, which is attributable to respiration, motion tracking should be performed by means of the correlation with these seeds; and fiducial markers render the Synchrony system equipped in Cyberknife feasible. This allows for respiratory motion tracking during irradiation. Nevertheless, patients with high risk of bleeding, abdominal infection, pancreatitis or pancreatic fistula are contradictory to several fiducial implants. Hence, one fiducial plus X-sight spine and Synchrony Tracking technique would be alternatively used. Before treatment, direct digital radiography images of the spine would be applied to detect 6-D errors; and this would be subsequently corrected for X-sight spine tracking on the patient's positioning. This would enable fiducial tracking during treatment.

2.7.5 Treatment planning and target delineation

After CT simulation, CT images are transferred to the workstation where the target volumes are contoured by an attending radiation oncologist. Gross tumor volume (GTV) is delineated as a radiographically evident gross disease by contrast CT acquired from the portal-venous phase. At the discretion of the physician, clinical target volume (CTV) encompassing areas of the potential subclinical disease spread is

also designated. In most cases, the CTV equals GTV. A 2-5 mm expansion margin is included to determine the planning target volume (PTV). When the tumor is adjacent to critical organs, the expansion of CTV should be avoided. Therefore, an individualized treatment plan would be developed based on tumor geometries and locations. Ninety percent of PTV should be covered by the prescription dose. The prescription isodose line is limited to 70-75%, which would restrict the tumor D_{max}. If dose level violates the constraint of SBRT, the patient would be considered as ineligible for this trial. The single dose of PTV varies from 6.5-9 Gy. In particular, these doses would be reduced if the tumor is approximately one-third or more of the duodenum or stomach circumference, or if the tumor abuts the bowel in only one area, as determined by the relationship of the tumor to the duodenum in axial, coronal and sagittal planes in CT scans, or the space between the tumor and the bowel wall is <3 mm. Normal tissue constraints are according to the American Association of Physicists in Medicine guidelines in TG-101,[31] as presented in Table 2.

Table 2. Critical structures and threshold doses

Organs	Threshold doses (five fractions)	Minimum critical volume below threshold
Parallel organs		
Liver	21 Gy	700 cc
Kidney	17.5 Gy	200 cc

Organs	Threshold doses (five fractions)	Max point dose	Max critical volume above threshold
Serial organs			
Spinal cord	23 Gy	30 Gy	0.35 cc
Duodenum	18 Gy	32 Gy	5 cc
Bowel	19.5 Gy	35 Gy	5 cc
Stomach	18 Gy	32 Gy	10 cc
Esophagus	19.5 Gy	35 Gy	5 cc
Colon	25 Gy	38 Gy	20 cc

2.7.6 Long-term follow-up

Patients are re-evaluated after Cyberknife every one month for the first three months, every 2-3 months for the next two years, and every six months for a total five years. Remissions of symptoms and radiation-related toxicities would be assessed. In addition, they would undergo laboratory tests, physical examinations, analysis of quality of life, KPS scores and imaging studies every month within the first three months. Subsequent examinations in later follow-ups are the same.

2.8 Outcomes

2.8.1 Outcome definitions

Primary outcomes of the study were OS and 1-, 2-, 3-, 4- and 5-year OS rates. OS is defined as the time from the date of enrollment to death from any cause. Patients lost

to follow-up, withdrawn, or alive at the end of the follow-up should be kept confidential.

Secondary outcomes include cancer specific survival (CSS), PFS, time to progression (TTP), local control rates (LCR), clinical benefit rates (CBR), radiation-induced acute and late toxicities, adverse effects of chemotherapy and quality of life of the patient. Cancer specific survival is the time from inclusion to death caused by the tumor. Progression-free survival is the time from the date of enrollment to the confirmation of disease progression at any sites or death from any causes, if this occurred before disease progression. Local control is considered as a lack of enlargement of the tumor volume radiographically or stable/declining standardized uptake values on PET-CT scans. The definition of time to progression is the time from inclusion to the recurrence of the tumor, including local recurrence or metastasis. Clinical benefit rate is the ratio of the number of patients with complete response, partial response, or stable disease to the total number of enrolled patients.

2.8.2 Evaluation of outcomes

PFS, TTP, LCR and CBR are all associated with treatment response, as determined by the RECIST criteria (version 1.1). Quality of life would be measured through European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30 and QLQ-PAN26). Radiation-induced acute toxicities are adverse effects that occur within 90 days after treatment, and determined by the Radiation Therapy Oncology Group, “Acute radiation morbidity scoring

criteria". Late toxicities occurring three months after SBRT are evaluated by the Radiation Therapy Oncology Group/European Organization for Research on the Treatment of Cancer, "Late radiation morbidity scoring schema".

2.9 Sample size determination

It was assumed that 1-year OS rate was 70% of locally advanced pancreatic cancers treated with Cyberknife combined with S-1. The potential benefit of the regimen was approximately 20% increase in 1-year OS rate. In order to have 90% power to reject the null hypothesis if the alternative was true at level alpha = 0.05, the required sample size for our study was 138. Additionally, a loss of 20% of patients due to lost to follow-up or withdrawn due to adverse effects or other reasons was estimated. Hence, a total of 190 patients would be enrolled into this study.

2.10 Data analysis

Statistical testing will be performed using SPSS version 20.0 (IBM Corp, Armonk, NY, USA). All outcomes would be analyzed based on intention-to-treat principle. PFS, OS and LC are calculated *via* the Kaplan-Meier method compared by the log-rank (Mantel-Cox) test. Response rates would be compared by a test of proportions. Further analysis would be performed in subgroups stratified by different factors.

2.11 Data management and quality assurance

Data regarding the patient's characteristics, medical histories and results of clinical

and laboratory tests or examinations will be kept in a password-protected database at the Department of Radiation Oncology in Changhai hospital, which will only be disclosed to authorized individuals. The Ethic Committee of Changhai Hospital will be responsible for data monitoring. In addition, trial conducts will be audited by the committee every six months after the recruitment of participants. The accuracy of the data entry into the database will be confirmed by two administrators. The interim results will be accessed to authorized individuals and reported to the Ethic Committee of Changhai Hospital, which would make the final decision to terminate the trial if severe adverse effects frequently occur.

3. Discussion

S-1 has been considered as an important chemotherapeutic drug in pancreatic cancer. In addition to convenient oral medication, many studies have verified that S-1 was not inferior to gemcitabine regarding OS and PFS. In adjuvant therapy, S-1 may be a candidate drug for a patient refractory to gemcitabine, but without phase III clinical trials. In addition, radiotherapy combined with S-1 probably contributed to the down staging of the tumor, as well as the lower complication rates of surgeries as the neoadjuvant therapy.[31, 32] It was elucidated that neoadjuvant radiotherapy with S-1 was beneficial to potential candidates for radical surgeries, because OS could be improved significantly.[32]

SBRT with Cyberknife has been proven with lower radiation-toxicities, higher

accuracy and better efficacy compared with conventional radiotherapy. Therefore, it is pivotal to evaluate the efficacy of SBRT with S-1 as the initial or even neoadjuvant treatment in locally advanced pancreatic cancer, which may be not inferior to previous conventional treatment or even more beneficial to patients than standard chemotherapy with conventional radiotherapy. However, no prospective clinical trials have provided such investigation. Hence, the goal of the SILAPANC trial is to assess whether better prognosis could be achieved with Cyberknife combined with S-1 followed by sequential S-1 as an initial treatment, which may provide new insights into the treatment of locally advanced pancreatic cancer.

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Authors' contributions:

Huojun Zhang was the primary investigator of the study. Xiaofei Zhu and Xiaoping Ju designed the protocol and Huojun Zhang amended it. Xiaofei Zhu, Fei Cao and Fang Fang, were responsible for recruitment of participants. Shuiwang Qing and Yuxin Shen were responsible for data entry. Zhen Jia and Yangsen Cao were responsible for data analysis.

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Competing interests statement:

The Authors declare that there is no conflict of interest.

Data sharing statement:

No additional unpublished data are available.

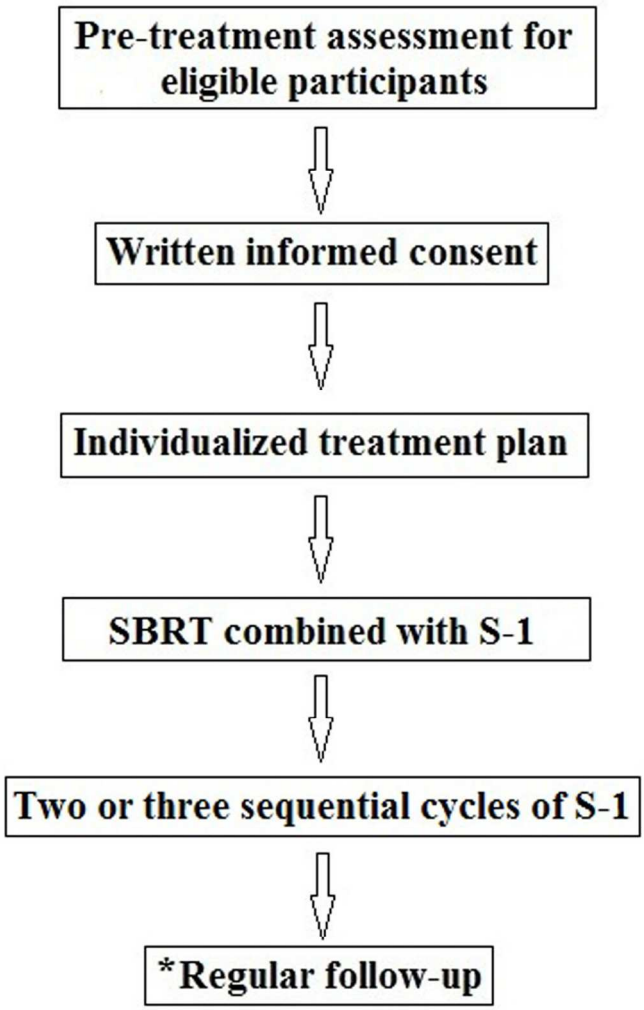

Figure 1 illustrates the flow diagram of the study.

135x166mm (300 x 300 DPI)

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P3_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4_____
	2b	All items from the World Health Organization Trial Registration Data Set	P4_____
Protocol version	3	Date and version identifier	P4_____
Funding	4	Sources and types of financial, material, and other support	None_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P11_____
	5b	Name and contact information for the trial sponsor	P11_____
	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	P11, 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)	None_____

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	P5-6_____
	6b	Explanation for choice of comparators	P5-6_____
Objectives	7	Specific objectives or hypotheses	P12_____
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)	P10_____
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	P10, 11_____
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)	P12-16_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P18-22_____
	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)	P22_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P16-17_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P17_____
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	P23-25_____
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)	P19, 23_____

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	P25_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P25_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			Non-controlled trial
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	None_____
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	None_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	None_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	None_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	None_____
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	P16, 17_____
	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	P18_____

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	P17, 26
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	P25
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P25
	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)	P25
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	P26
	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	P26
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	P24, 25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P26
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P17, 18
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)	None

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P18_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P18_____
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	P18, 26_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P33_____
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	P18, 26_____
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	P17_____
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	P18_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	None_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P17, 18_____
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	P12, 16_____

*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" license.