


# BMJ Open Biologically effective doses of 60–70Gy versus >70Gy of stereotactic body radiotherapy (SBRT) combined with chemotherapy in locally advanced pancreatic cancer: protocol of a single-centre, phase II clinical trial

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## ABSTRACT

**Introduction** There is a paucity of studies about whether dose escalation of stereotactic body radiation therapy (SBRT) prolongs survival compared with de-escalation for patients with locally advanced pancreatic cancer (LAPC). Therefore, the aim of the study is to compare the survival benefits of biologically effective dose (BED<sub>10</sub>,  $\alpha/\beta=10$ ) of 60–70 Gy with those of BED<sub>10</sub> >70 Gy.

**Methods and analysis** This study is a single-centre, phase II trial. Patients with LAPC are randomly allocated to receive SBRT with BED<sub>10</sub> of 60–70 Gy or >70 Gy in 5–6 fractions combined with gemcitabine plus albumin-bound paclitaxel. The primary outcome is progression-free survival. The secondary outcomes are adverse events, local control and overall survival.

**Ethics and dissemination** The trial protocol has been approved by the Ethics committee of Shanghai Changhai Hospital. The ethics number is CHEC2020-100. Study results will be disseminated through peer-reviewed journals and released in related medical conferences.

**Trial registration numbers** NCT04603586.

## INTRODUCTION

Pancreatic cancer was the fourth leading cause of cancer death both for male and female patients in US with a dismal survival rate and slightly increasing incidence and mortality,<sup>1</sup> which was similar in China.<sup>2</sup> According to the National Comprehensive Cancer Network (NCCN) guideline, only patients with resectable pancreatic cancer, which implies no encasement of vessels by the tumour, are candidates for upfront surgery. However, due to insidious onset and rapid progress of pancreatic cancer, most patients had vascular involvement by the tumour at the first time, where surgery could not be given first priority. Only 15%–20% patients had the initial diagnosis of resectable pancreatic cancer, who

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A phase II trial comparing two radiation doses of stereotactic body radiation therapy (SBRT) for pancreatic cancer.
- ⇒ To identify the optimal dose of SBRT for pancreatic cancer.
- ⇒ A single-centre study, with a relatively small sample size.

were amenable to surgical resections.<sup>3–5</sup> For patients with locally advanced pancreatic cancer (LAPC), chemoradiotherapy may be the optimal modality. Recently, stereotactic body radiation therapy (SBRT) has been accepted as an alternative of intensity modulated radiotherapy (IMRT) due to the image-guided technique that results in highly precise delivery of doses, rapid dose fall-off outside targets and short courses without delay of subsequent treatment.<sup>6</sup>

However, there is limited evidence about the correlation between high radiation doses and better outcomes for LAPC, while it had been proven that high doses may be predictive of superior survival regarding lung cancer, liver cancer and prostate cancer.<sup>7–9</sup> Our previous studies have clarified that biologically effective dose (BED,  $\alpha/\beta=10$ )  $\geq 60$  Gy may be associated with better prognosis.<sup>10 11</sup> Additionally, it was also demonstrated that BED<sub>10</sub> >70 Gy was the only predictor of improved overall survival (OS) in another report.<sup>12</sup> Nevertheless, a recent meta-analysis has clarified that BED<sub>10</sub> >70 Gy did not correlate with improvement of 1-year local control (LC) rate.<sup>13</sup> Therefore, this study aims to compare the

**Table 1** The definition of locally advanced pancreatic cancer in the NCCN guideline

| Resectability status | Arterial  | Venous   |
|----------------------|---|--|
| Locally advanced     | Head/uncinate process: <ul style="list-style-type: none"> <li>▶ Solid tumour contact with SMA &gt;180°</li> <li>▶ Solid tumour contact with the CA &gt;180°</li> </ul> Pancreatic body/tail: <ul style="list-style-type: none"> <li>▶ Solid tumour contact of &gt;180° with the SMA or CA</li> <li>▶ Solid tumour contact with the CA and aortic involvement</li> </ul> | Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) |

CA, celiac axis; NCCN, National Comprehensive Cancer Network; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

efficacy and safety of BED<sub>10</sub> of 60–70 Gy of SBRT and that of >70 Gy of SBRT for LAPC.

## METHODS AND ANALYSIS

### Study design

This is a single-centre, single-blinded, randomised phase II trial designed and supervised by investigators of Changhai Hospital. Patients aged from 18 to 75, with histologically confirmed or clinical diagnosis of LAPC via multidisciplinary consultation, no prior treatment and no metastasis and severe morbidities will be enrolled in our study. Fine needle aspirations guided by endoscopic ultrasound should be considered in all patients. However, for those who are intolerant of it after evaluations by physicians, careful diagnosis by multidisciplinary approach is mandatory. The definition of LAPC is referred to the NCCN guideline<sup>14</sup> (table 1).

Eligible participants will receive personal interviews with physicians about a detailed explanation of the whole study and related treatment. If the patients agree to participate in this clinical trial, it is mandatory to obtain the written informed consents before the study. Afterwards, patients will be required to complete the pretreatment evaluations including medical history, demographic data, physical examinations, blood routine tests, urine routine tests, liver and renal function tests, coagulation

function tests, serum tumour biomarker (CA19–9) tests, blood amylase and urine amylase tests, contrast-enhanced pancreatic parenchymal CT and MRI. Participants will be randomly allocated into two groups to receive different doses of SBRT and sequential chemotherapy. The flow diagram of the study is illustrated in figure 1. This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.<sup>15</sup>

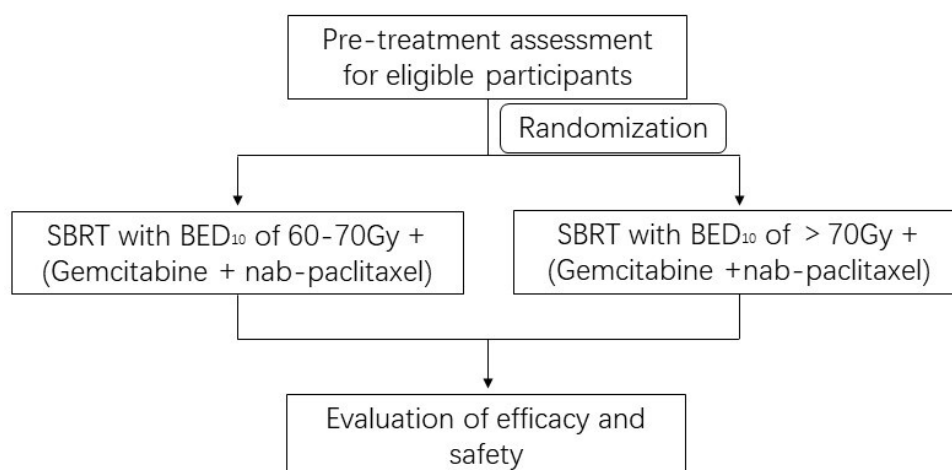
### OBJECTIVES

Due to limited investigations about radiation doses and the potential survival benefits, the phase II trial aims to compare the clinical outcomes of BED<sub>10</sub> of 60–70 Gy with those of >70 Gy delivered by SBRT for LAPC.

### Study participants

#### Inclusion criteria

- ▶ Aged from 18 to 75 years. Patients with LAPC and the age over 75 may have a poor performance status. Therefore, they may be intolerant of a high dose of SBRT. Additionally, these patients may be at a high risk of severe adverse events after SBRT and chemotherapy. As a result, the upper limit of the age was set at 75 years.



**Figure 1** Flow diagram of the study. BED, biologically effective dose; SBRT, stereotactic body radiation therapy.

- ▶ Cytologically or histologically confirmed pancreatic ductal adenocarcinoma (PDA) or clinical diagnosis of pancreatic cancer by multidisciplinary consultation.
- ▶ LAPC proven by imaging examinations via multidisciplinary approaches according to NCCN guidelines<sup>14</sup>.
- ▶ Eastern Cooperative Oncology Group performance status of 0–1.
- ▶ Written informed consents according to International Council for Harmonization/Good Clinical Practice regulations before any trial-specific procedures.

#### Exclusion criteria

Patients may not be included in the study if any of the following applies:

- ▶ Patients who have previously received related treatment because of pancreatic cancer, such as radiotherapy, chemotherapy, molecular targeted therapy or immunotherapy.
- ▶ Patients with severe liver (serum total bilirubin >3.0 mg/dL, serum aspartate aminotransferase (AST) >2.5 times of the upper limit of normal, serum alanine aminotransferase (ALT) >2.5 times of the upper limit of normal or Child-Pugh class B or C) or kidney dysfunction (serum creatinine >2.0 mg/dL).
- ▶ Patients without remissions of obstructive jaundice albeit with implantation of stents.
- ▶ Patients with massive ascites.
- ▶ Patients participating in other clinical trials.
- ▶ Patients with other malignancies, or acute infections or severe chronic infections, ulcerative colitis, inflammatory bowel disease.
- ▶ Patients with peptic ulcer who have not recovered from it.
- ▶ Gastroscopy or imaging examination indicates that the tumour invades the duodenum or stomach.
- ▶ Inappropriate participation of this clinical trial judged by the investigator.

#### Dropout or suspension of the trial

- ▶ Unresolved severe adverse event or frequent occurrence of adverse events that may result in a high risk of death, which include grade 3 or more adverse events evaluated by Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.
- ▶ Requests from patients to withdraw from the trial.
- ▶ Lost to follow-up.
- ▶ Other potential situations that necessitate the termination of the trial.

#### Randomisation

Patients will be enrolled by the investigators and randomly assigned (1:1) to receive SBRT with BED<sub>10</sub> of 60–70 Gy or >70 Gy in 5–6 fractions combined with gemcitabine plus albumin-bound paclitaxel by an interactive voice or web response system. A randomisation list will be produced by the response technology provider, which ensure random assignment of patients' ID to randomisation numbers after they are eligible. Each number will be linked to a treatment group. The study is open-label and

treatment allocation will be not masked to the patients or the investigators.

This is a single-blinded study. Patients and study designers will be aware of the randomisation results. However, all the study members who conduct data collection will be blinded to the randomisation.

#### Intervention

##### Radiation therapy

SBRT will be delivered by CyberKnife with Synchrony Respiratory Tracking system. Before CT simulations, 1–4 fiducial markers will be implanted using endoscopic ultrasound adjacent to or in the tumour. A plain CT and a contrast-enhanced pancreatic parenchymal CT will be performed for simulations. Vacuum-bags will be used for immobilising the patients' body, arms and legs. The image of contrast-enhanced MRI will be an auxiliary image for fusion. The radiation oncologists contour gross tumour volume (GTV), planning target volume (PTV) and organs at risk (OAR). GTV is defined as the visible lesion based on image examinations. PTV is delineated by uniform 3 mm expansions of GTV. The participants will be randomised into two groups and receive the following regimens: group1: SBRT with BED<sub>10</sub> 60–70 Gy in 5–6 fractions; group2: SBRT with BED<sub>10</sub> >70 Gy in 5–6 fractions. Ninety per cent of PTV should be covered by the prescription dose. The prescription isodose line is limited to 70%–80%, which would restrict the tumour Dmax. Dose constraints of normal tissues comply with AAPM TG-101 report.<sup>16</sup>

##### Chemotherapy

Chemotherapy will be performed after completion of SBRT. The initiation of gemcitabine plus albumin-bound paclitaxel will be within 1 month after SBRT. Intravenous administration of gemcitabine (1000 mg/m<sup>2</sup>) plus albumin-bound paclitaxel (125 mg/m<sup>2</sup>) will be delivered on days 1 and 8 during each 3-week cycle, which will repeat for 4–6 cycles.

##### Date collection

The schematic for data collections and evaluations of efficacy and safety is shown in [table 2](#). All patients' pretreatment data, and follow-up information, will be evaluated by physicians, and then checked again by the researchers not involved in the study to ensure accuracy and completeness. At the same time, all patients' information will be strictly kept confidential. Treatment and follow-up data will be retrieved from the database when they need to be reviewed by the ethics committee or authorised researchers.

##### Follow-up

CA19-9 level will be monthly evaluated. Additionally, contrast-enhanced CT and MRI will be performed every 2–3 months during follow-up or at the physician's discretion. If CA19-9 level continuously rises for 3 months or new lesions are found by enhanced MRI or CT of the

**Table 2** The schematic diagram for data collections and assessment

| Test items               | Screening | Before radiotherapy or chemotherapy | Follow-up |
|--------------------------|-----------|-------------------------------------|-----------|
| Medical history          | ●         | ●                                   | ●         |
| Physical examination     | ●         | ●                                   | ●         |
| Vital signs              | ●         | ●                                   | ●         |
| CA19-9                   | ●         | ●                                   | ●         |
| Blood amylase            | ●         | ●                                   | ●         |
| Urine amylase            | ●         | ●                                   | ●         |
| Blood routine            | ●         | ●                                   | ○         |
| Urine routine            | ●         | ●                                   | ○         |
| Blood biochemistry       | ●         | ●                                   | ○         |
| Coagulation function     | ●         | ●                                   | ○         |
| Pancreatic-enhanced CT   | ●         | ●                                   | ●         |
| Pancreatic-enhanced MR   | ●         | ●                                   | ●         |
| Chest CT                 | ●         | ●                                   | ●         |
| PET/CT                   | ○         | ○                                   | ○         |
| Biopsies of the pancreas | ○         |                                     |           |
| Adverse effects          |           | ●                                   | ●         |
| Combined drug record     | ●         | ●                                   | ●         |

PET, positron emission tomography.

pancreas and chest CT, positron emission tomography-CT will be recommended.

### Outcomes and measurements

The primary outcome is progression-free survival (PFS). PFS is the time period from the randomisation to identification of disease progression including local recurrence or metastases or death or the last follow-up. The secondary outcomes are LC, treatment-related adverse events and OS. LC is the time period from the randomisation to local progression according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria, V.1.1.<sup>17</sup> Adverse events are reported and graded based on CTCAE V.5.0. OS is the time interval from the randomisation to the death by any cause or the last follow-up.

### Determination of sample size

Previous studies showed that PFS of patients receiving BED<sub>10</sub> of 60–70 Gy was about 7 months. Additionally, we assume that the PFS is increased by 5 months in the case of BED<sub>10</sub> >70 Gy. Therefore, we need to include 69 patients in each group to be able to reject the null hypothesis that survival curves of BED<sub>10</sub> of 60–70 Gy and BED<sub>10</sub> >70 Gy are equal, with probability (power) of 0.8 and a type I error probability of 0.05.

### Data management and monitoring

Patients' data regarding basic characteristics, medical histories, results of clinical and laboratory examinations will be stored in our database. The accuracy of data entry into the database will be verified by two administrators,

and the Ethics Committee of Shanghai Changhai Hospital will be responsible for the data monitoring. The interim results will be reported to the Ethics Committee of Shanghai Changhai Hospital.

### Statistical analysis

Normally and skewedly distributed continuous data will be described by mean±SD and median (range), respectively. Categorical data will be expressed as n (%). Student t test or Mann-Whitney U test will be used for analysis in the case of normally or non-normally distributed continuous variables. Categorical variables will be compared using the  $\chi^2$  test or Fisher's exact test. PFS, OS and LC of two groups will be estimated by the Kaplan-Meier method and compared via the log rank test. Hazard ratios will be calculated with the Cox proportional hazards model. A two-sided p values <0.05 are considered statistically significant. Statistical analyses will be performed using SPSS software V.22.0 (SPSS, Armonk, New York).

### Patient and public involvement

Patients or public are not involved in the design, conduct, reporting, dissemination plans of the research.

### Ethics and dissemination

This study has been approved by the Ethics Committee of Shanghai Changhai Hospital (CHEC2020-100) and registered in ClinicalTrials.gov and initiated on 20 October 2020. The study complies with the Declaration of Helsinki. All patients will be informed of the details about the procedures, benefits and risks of chemotherapy and



SBRT by physicians. Afterwards, patients could decide whether to participate in the study. All physicians and patients involved in the study will be blinded to the allocations, and the randomisation procedures will be carried out by researchers not involved in the study. Patients could withdraw from the study at any time for any reason. Physicians need to record all adverse effects promptly in case that the treatment may be stopped temporarily or patients may be excluded from the study due to chemotherapy or radiotherapy-induced toxicities. Findings of the study will be published in peer-reviewed scientific journals and released in related medical conferences.

## DISCUSSION

The role of chemoradiotherapy for LAPC has been discussed for many years. In the recent LAP07 study, the absence of an OS benefit compared with gemcitabine chemotherapy alone seems to have increased the controversy of chemoradiation therapy in LAPC.<sup>18</sup> With the development of more effective regimens including targeted therapies and immunotherapy and radiotherapy techniques in recent years, attempts to improve PFS and OS have facilitated clinical practice of combinations of radiotherapy and other treatment. Though IMRT has been the mainstay modality of radiotherapy, prolonged survival has not been confirmed in recent studies. This may be ascribed to the relatively low biological effective doses delivered by IMRT. As SBRT has been more commonly used in LAPC than before, higher doses to targets without excessive irradiation to OAR has been feasible. Additionally, it has been clarified that higher doses may be predictive of superior survival in some studies.

Based on the National Cancer Database of the USA, it was concluded that under the premise of maximum induction chemotherapy, combined chemotherapy would bring survival benefits to LAPC patients when the radiation dose increased to >55 Gy.<sup>19</sup> As stated above, our previous studies have identified that BED<sub>10</sub> ≥60 Gy may indicate prolonged survival, which was also proven by another study that demonstrated the correlation between BED<sub>10</sub> >70 Gy and better outcomes.<sup>9</sup> In terms of hypofractionated IMRT, a Korean study evaluating almost 500 patients with LAPC also found that patients receiving ≥61 Gy had improved LC, PFS and OS.<sup>20</sup>

Similarly, according to the preclinical studies, in the lower dose range, PDA cell lines appeared highly radioresistant. The result was consistent with the poor radiosensitivity of pancreatic tumours indicated by classical radiation biology.<sup>21–24</sup> This was proven by the dose-dependent response of KRAS-driven PDA cell lines to conventional radiation biological endpoints (such as clonogenicity) and the current concept of radiation-induced tumour cell immunogenicity.<sup>25</sup> Therefore, higher doses delivered by SBRT may be a promising way to improve outcomes.

SBRT has been proven with higher accuracy and shorter course without delay of subsequent systemic therapies compared with conventional radiotherapy. Moreover,

previous studies have also shown milder radiation toxicities and effectiveness of SBRT in LAPC. However, no phase II trials have investigated the role of higher doses of SBRT in LAPC. Hence, it is necessary to assess the efficacy and safety of SBRT with BED<sub>10</sub> of 60–70 Gy and that of >70 Gy to identify the optimal dose that can both provide survival benefits and low risks of radiation-induced toxicities.

**Contributors** Study conception: HZ. Initial Study design: HZ, XfZ and YY. Revision of study design and protocol: HZ, XfZ, YY and XzZ. Study coordination: YY, XfZ, XzZ, LJ and YC. Drafting the manuscript: YY, XzZ and XfZ. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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**Data availability statement** The unpublished data from the study are available in peer-review journals and conferences.

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