Biologically effective doses of 60-70Gy vs. >70Gy of stereotactic body radiotherapy (SBRT) combined with chemotherapy in locally advanced pancreatic cancer: protocol of a phase III study

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Study protocol

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Abstract

Background: There is controversial on the correlation between biologically effective dose (BED, α/β=10) of stereotactic body radiation therapy (SBRT) and clinical outcomes of patients with locally advanced pancreatic cancer (LAPC). Therefore, the aim of the study is to compare the survival benefits of BED_{10} of 60-70Gy with those of BED_{10} ＞70Gy.

Methods: This study is a multicenter study. Patients with LAPC are randomly allocated into two groups. Arm1: SBRT with BED_{10} of 60-70Gy in 5-6 fractions combined with gemcitabine plus albumin-bound paclitaxel; Arm2: SBRT with BED_{10} ＞70Gy in 5-6 fractions combined with gemcitabine plus albumin-bound paclitaxel. The primary outcome is progression-free survival (PFS). The secondary outcomes are radiation-induced gastrointestinal (GI) toxicity, local control (LC) and overall survival (OS).

Discussion: The pilot phase Ⅱ study could provide evidence for further decision making of prescription doses of SBRT for LAPC, which may improve survival outcomes without compromise of quality of life. The trial protocol has been approved by the Ethics committee of Shanghai Changhai hospital. The ethics number is CHEC2020-100.

Trial registration: Clinical trials number: NCT04603586. Date of registration: 10/27/2020.

Background

Pancreatic cancer is the fourth leading cause of cancer death among two genders with a dismal survival rate and slightly increasing incidence and mortality in US[1], which is similar in China[2]. Though radical surgical resection is recommended as the standard treatment, only 15–20% patients with initial diagnosis of resectable pancreatic cancer are indicated for upfront surgery[3, 4]. However, for the rest 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 its highly precise delivery of doses, rapid dose fall-off outside targets and short courses without delay of subsequent treatment.

However, there was limited evidence about the correlation between high doses and better outcomes in the case of radiotherapy of pancreatic cancer, while it had been proven that high doses may be predictive of superior survival regarding lung cancer and liver cancer. Our previous studies have clarified that biologically effective dose (BED, $\alpha/\beta = 10$) $\geq$ 60Gy may be associated with better prognosis [5, 6]. Additionally, it was demonstrated that $BED_{10} > 70$Gy was the only predictor of improved overall survival (OS) [7]. Nevertheless, a recent meta-analysis has clarified that $BED_{10} > 70$Gy did not correlate with improvement of 1-year local control rate [8]. Therefore, the aim of this study is to compare the efficacy and safety of BED_{10} of 60-70Gy of SBRT and that of > 70Gy of SBRT for LAPC.

Methods

Objectives

Due to limited investigations about radiation doses and the potential survival benefits, the pilot phase Ⅱ study was to compare the clinical outcomes of BED_{10} of 60-70Gy with those of Ⅱ70Gy delivered by SBRT for LAPC, which may be conducive to a comprehensive understanding about an appropriate dose range for LAPC.

Study design, setting and participants

This is a multicenter, double blinded, randomized phase Ⅱ trial designed and supervised by investigators of Changhai Hospital. Patients aged from 18-75, with radiographically and biopsy confirmed LAPC, no prior treatment, and without metastasis and severe morbidities are enrolled in our study. Therefore, fine needle aspirations guided by endoscopic ultrasound is required for all patients. Details about the inclusion and exclusion criteria are shown in Table1. The definition of LAPC is referred to the NCCN guideline [9](Table 2).

Eligible participants would receive personal interviews with physicians for a detailed explanation of the whole study and related treatment. If the patients agree to participate in this clinical study, it is mandatory to obtain the written informed consents before the study. Afterwards, patients are 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 tumor marker (CA19–9) tests, blood amylase and urine amylase tests, enhanced CT and MRI. Participants will be randomly allocated into two group to receive SBRT and sequential chemotherapy. The flow diagram of the study is illustrated in Figure 1.

Ethics

The study is in line 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 voluntarily decide to participate in the study. All physicians and patients involved in the study will be blinded to the allocations, and the randomization 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.

Intervention

1. Radiation therapy

SBRT will be delivered by CyberKnife with Synchrony Respiratory Tracking system. Before CT simulations, 1 to 4 fiducial markers will be implanted using endoscopic ultrasound adjacent to or in the tumor. A plain CT and a contrast-enhanced pancreatic parenchymal CT will be performed for simulations. Vacuum-bags will be used for immobilizing the body, the arms and the legs. The image of contrast-enhanced MRI will

be an auxiliary image for fusion. The radiation oncologists contour gross tumor volume (GTV), planning target volume (PTV) and organs at risk (OARs). GTV is defined as the visible lesion based on image examinations. PTV is delineated by uniform 3mm expansions of GTV. The participants are randomized into two groups, and receive the following regimens: Group1: SBRT with BED_{10} 60-70Gy in 5-6 fractions; Group2: SBRT with BED_{10} ≥70Gy in 5-6 fractions. Ninety percent of PTV should be covered by the prescription dose. The prescription isodose line is limited to 78-80%, which would restrict the tumor Dmax. Dose constraints of normal tissues comply with AAPM TG-101 report[10].

2.Chemotherapy

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

Date collection

The schematic diagram for data collections and evaluations of efficacy and safety is shown in Table 3. All the pre-treatment data, and follow-up information of patients 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 authorized researchers.

Follow-up

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

Outcomes

The primary outcome is PFS. PFS is the time period from the initiation of SBRT to identification of disease progression including local relapse or metastases or death or the last follow-up. The secondary outcomes are LC, GI toxicity and OS. LC is the time period from the initiation of SBRT to identification of local progression according to RECIST criteria, version 1.1[11]. Radiation-induced acute GI toxicities are determined by the Radiation Therapy Oncology Group, "Acute radiation morbidity scoring criteria". Late GI toxicity morbidity scoring schema". OS is the time period from the initiation of SBRT to the death by any cause or the last follow-up.

Statistical analysis

Normally and Non-normal distributed continuous data will be described by mean±SD and median (range), respectively, Categorical data will be expresses as n (%). Student t-test or Mann-Whitney U test was used for analysis in the case of normally or non-normally distributed continuous covariates. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test. PFS, OS and LC of two groups are estimated by the Kaplan-Meier method and compared via the log rank test. Univariate and multivariable hazard ratios are calculated with the Cox proportion hazard model. P values< 0.05 is considered statistically significant. Statistical analyses will be performed using SPSS software v18.0(SPSS Inc.,Armonk,NY).

Discussion

The role of chemo-radiotherapy for LAPC has been discussed for many years. In the recent LAP07 study, the absence of an OS benefit compared to gemcitabine chemotherapy alone seems to has increased the controversy of chemoradiation therapy in LAPC[12]. 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. However, IMRT has been the mainstay modality of radiotherapy, whose benefits have 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 compromise of organs at risk have been feasible. Additionally, some clinical studies have clarified that higher doses may be predictive of superior survival.

Based on the National Cancer Database of the United States, Sung Jun Ma et al. concluded that under the premise of maximum induction chemotherapy, combined chemotherapy will bring survival benefits to LAPC patients when the radiation dose increases to > 55Gy[13]. As stated above, our previous studies have clarified that $BED_{10} \geq 60Gy$ may be associated with better prognosis, which was also proven by another study that demonstrated the correlation between BED_{10} >70Gy and better outcomes [9]. In terms of hypofractionated IMRT, a Korean study evaluating almost 500 patients with LAPC also found that patients receiving ≥ 61Gy had improved LC, PFS and OS[14].

Similarly, according to the preclinical studies, in the lower dose range, PDA cell line appeared highly radioresistant. The result was consistent with the poor radiosensitivity of pancreatic tumors indicated by classical radiation biology[15-18]. 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 tumor cell immunogenicity[19]. 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 indicated milder radiation toxicities and effectiveness in LAPC. However, no phase Ⅲ trials have investigated role of higher doses of SBRT in LAPC. Hence, it is necessary to assess the efficacy and safety of SBRT with

BED_{10} of 60-70Gy and that of ≥70Gy to identify a dose range that can both provide survival benefits and low risk of radiation-induced toxicities.

Abbreviations

SBRT: stereotactic body radiotherapy; LAPC: locally advanced pancreatic cancer ; BED: biologically effective dose PFS: progression-free survival; OS: overall survival; LC: local control; GI: gastrointestinal; CT: computed tomography MRI: magnetic resonance imaging; WHO: World Health Organization; ICH/GCP: International Council for Harmonization/ Good Clinical Practice; GTV: gross tumor volume; PTV: planning target volume; OARs: organs at risk; CA19-9: cancer antigen 199;

Declarations

Ethics approval and consent to participate

Signature of the informed consent will be obtained from all patients before inclusion in the study. This study was approved by the Ethics committee of the Shanghai Changhai Hospital (CHEC2020-100) and is registered on clinicaltrail.gov. (NCT04603586).

Consent for publication

Not applicable

Availability of data and materials

Material and methods are available in the clinicaltrail.gov.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Study conception: H.J.Z Initial Study design: H.J.Z., X.F.Z. and Y.S.Y. Revision of study design and protocol: H.J.Z, X.F.Z., Y.S.Y. and X.Z.Z. Study coordination: Y.S.Y., X.F.Z., X.Z.Z. and L.G.J. Drafting the manuscript: Y.S.Y., X.Z.Z., and X.F.Z. All authors read and approved the final manuscript.

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Tables

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age≥18years old and≤75years old • Cytologically or histologically verified pancreatic adenocarcinoma or clinically diagnosed as pancreatic cancer by multidisciplinary consultation. • Locally advanced pancreatic cancer proven by imaging examinations via multidisciplinary approaches according to NCCN guidelines. • SBRT is not preceded by any targeted antitumor therapy. • Eastern Cooperative Oncology Group (ECOG) performance status 0–1. • Written informed consents according to International Council for Harmonization/ Good Clinical Practice (ICH/GCP) regulations before registration and prior to any trial specific procedures.	• Patients who have previously received related treatment because of pancreatic adenocarcinoma, such as radiotherapy, chemotherapy or other treatment. • Patients with severe liver or kidney dysfunction. • 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, with ulcerative colitis, inflammatory bowel disease. • Patients with peptic ulcer who are not completely cured or patients with acute peptic ulcer. • Gastroscopy or imaging examination indicates that the tumor invades the duodenum or stomach. • Inappropriate in this clinical trial judged by the investigator.

Table 2 The definition of locally advanced pancreatic cancer in the NCCN guideline

Resectability status	Arteral	Venous
Locally Advanced	Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

SMA: superior mesenteric artery; CA: celiac axis; SMV: superior mesenteric vein; PV: portal vein

Table 3 The schematic diagram for data collections and assessment

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

l Required items ¡ Selected items

Figures

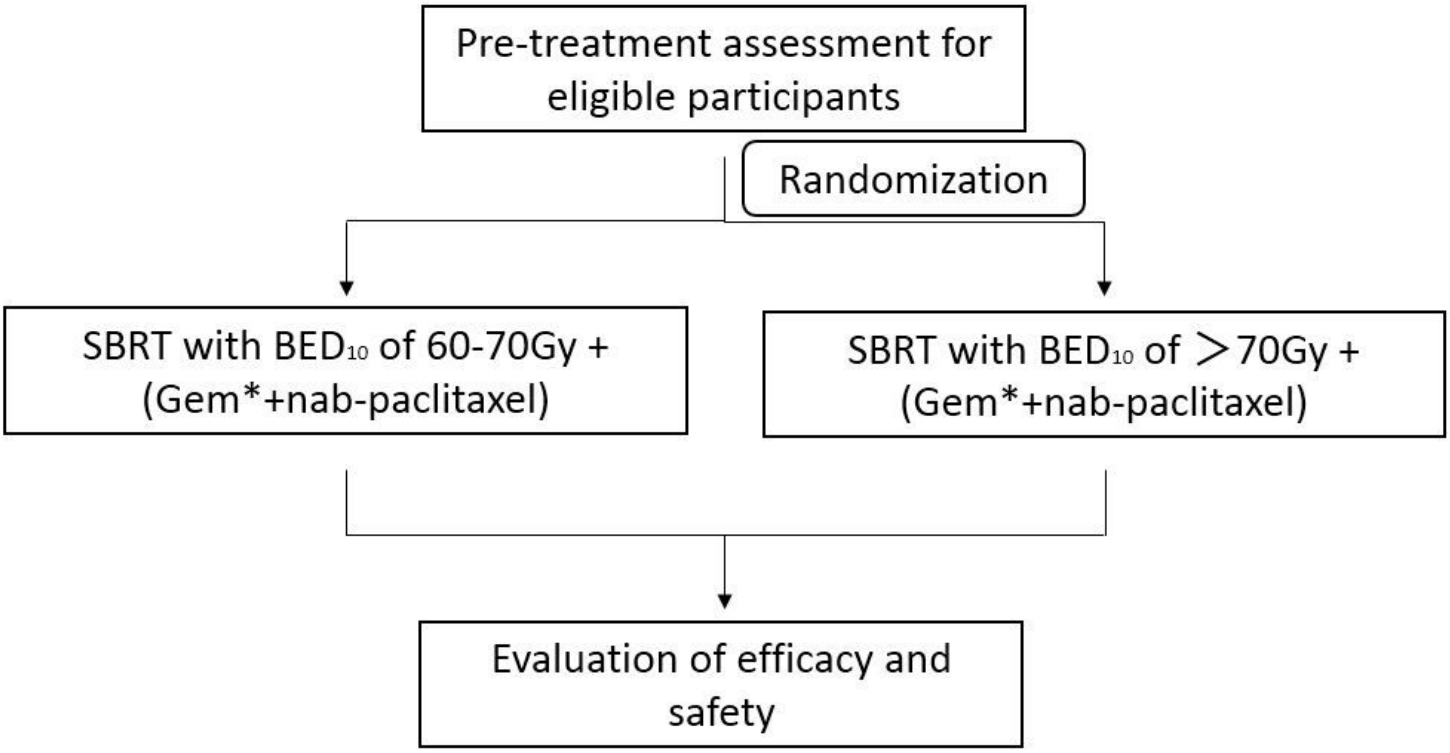

Figure 1

Flow diagram of the study.