Official title: Stereotactic body radiation therapy with sequential S-1 for patients with locally advanced pancreatic cancer and poor medical conditions --a phase II clinical trial (SILAPANC trial)

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1. 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.

Inclusion criteria:

1. Unresectable without metastasis:

    (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).

2. Without any other treatment before SBRT.

3. A life expectancy of >3months.

4. ECOG: 2 or 3 points.

5. Age of more than 18 years old.

6. Blood routine examination: Absolute neutrophil count (ANC) ≥ 1.5 $\times 10^9$ cells/L, leukocyte count≥ 3.5 $\times 10^9$ cells/L, platelets ≥ 70×10^9 cells/L, hemoglobin ≥ 8.0 g/dl.

7. Liver and kidney function tests: Albumin > 2.5 g/dL, total bilirubin < 3 mg/dL, creatinine < 2.0 mg/dL, AST <2.5 × ULN (Upper Limit of Normal) (0-64 U/L), ALT<2.5 × ULN (0-64 U/L).

8. INR < 2 (0.9-1.1).

9. Ability of the research subject or authorized legal representative to understand and the willingness to sign a written informed consent document.

Exclusion criteria:

1. Prior surgery, chemotherapy or radiation for the pancreatic cancer.

2. Evidences of metastatic disease such as nodal or distant metastases by abdomen CT and chest CT or FDG PET-CT.

3. Contraindication to receiving radiotherapy.

4. ECOG: 0-1 point.

5. Age<18

6. Abnormal results of blood routine examinations, liver and kidney function and coagulation tests.

7. Patients with active inflammatory bowel diseases or peptic ulcer.

8. Gastrointestinal bleeding or perforation within 6 months.

9. Heart failure: NYHA III-IV.

10. Women who are pregnant.

11. Participation in another clinical treatment trial while on study.

12. Patients in whom fiducial implantation was not possible.

13. Inability of the research subject or authorized legal representative to understand and the willingness to sign a written informed consent document.

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.

2. Doses of S-1

The doses of S-1 are calculated by the body surface. Hence, patients will receive S-1 orally, twice daily, at a dose of 80 mg/m^2 for 28 days, followed by a 14-day interval, which would repeat for 6 cycles. It was initiated one month after SBRT.

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.

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. 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.

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 prescribed dose of PTV varies from 35-40Gy/5f with a single dose of 7-9Gy. 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.

6. 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 three 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, and imaging studies every month within the first three months. Subsequent examinations in later follow-ups are the same.

7. Statistical analysis

All outcomes would be analyzed based on intention-to-treat principle. Continuous and categorical data were expressed as median (interquartile range, IQR) and n (%), respectively. Overall survival and progression free survival are calculated *via* the Kaplan-Meier method compared by the log-rank test. A two-sided α of less than 0.05 was considered statistically significant. Statistical testing is performed using SPSS version 20.0 (IBM Corp, Armonk, NY, USA).