SBRT for close or positive margins after resection of pancreatic adenocarcinoma

A prospective evaluation in select patients with resected pancreas cancer (Version 4, 6/29/2011)

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List of Abbreviations

3D CRT	3 Dimension Conformal External Beam Radiation Therapy
5-FU	5-fluorouracil
AE	Adverse Event
CR	Complete Response
CT Scan	Computed Tomography Scan
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Treatment Volume
CXR	Chest X-Ray
DSMC	Data Safety Monitoring Committee
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy - General
FDG-PET/CT	[18F]-flourodeoxyglucose Positron Emissions Tomography / Computed Tomography
Fx	Fraction
Gy	Gray
LPFS	Local Progression-Free Survival
MD	Maximum Dose
OS	Overall Survival
PD	Prescription Dose
PD	Progressive Disease
PET/CT	Positron Emissions Tomography / Computed Tomography
PIV	Prescription Isodose Volume
PIV/TV	Prescription Isodose Volume/Tumor Volume
PTV	Planning Target Volume
QOL	Quality of Life
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SD	Stable Disease
SBRT	Stereotactic Body Radiotherapy
TTP	Time to Progression
TV	Tumor Volume
WOOCBP	Women of Child-Bearing Potential

PROTOCOL SUMMARY

Title

Stereotactic Body Radiotherapy (SBRT) for close or positive margins following resection of pancreatic adenocarcinoma

Objectives

The *primary* objectives of this study are to:

1. To determine the rate of local progression-free survival (LPFS) achieved in subjects with close (<2.5 mm) or positive margins after pancreatic cancer resection treated with SBRT

The *secondary* objectives of this study are to:

1. To determine the time to progression (TTP) and overall survival (OS)
2. To evaluate the acute and late toxicities associated with SBRT in this patient population
3. To evaluate quality of life (QOL) of locally-advanced pancreatic cancer subjects treated adjuvantly with SBRT

Subject population

Subjects with primary adenocarcinoma of the pancreas that has been resected with positive margins or close margins (<2.5 mm)

Specific inclusion and exclusion criteria are detailed in Section 4.0

Number of subjects

50

Study design and methodology

This is a phase II study.

Treatments administered

12 Gy x 3 fractions (36 Gy total)

Efficacy data collected

The following evaluations will be conducted to assess the efficacy of SBRT:

- Local progression-free survival (LPFS)
- Locoregional and distant control
- Time-to-progression (TTP)

Safety data collected

The following evaluations will be conducted to assess the safety of SBRT:

- Recording of all toxicity data per NCI CTCAE version 4.0
- Functional Assessment of Cancer Therapy – General (FACT-G)

1.0 BACKGROUND

1.1 Adenocarcinoma of the pancreas

Pancreatic cancer is the 4th leading cause of death from cancer of both men and women in the United States. There are expected to be 37,680 new cases and 34,290 deaths in the United States in 2008. Despite intensive research efforts into chemotherapy and radiotherapy, surgical resection remains the only treatment option associated with long-term survival. Unfortunately, pancreatic cancer is rarely resectable upon diagnosis, with approximately 40% presenting with locally-advanced but unresectable disease and an additional 40% presenting with metastatic disease. Within the United States, the 5-year survivals for local, locally-advanced and distant disease are 20%, 8% and 2% respectively, resulting in an overall 5-year survival for pancreatic cancer of only 5% (1). These values represent all pancreatic cancers. Adenocarcinoma of the pancreas, representing more than 90% of all cases, is believed to be the most aggressive malignancy with an even worse prognosis. For patients that are able to undergo surgical resection, the choice of adjuvant therapy remains controversial with data available for anything ranging from observation to chemoradiation.

1.2 Radiation therapy as adjuvant treatment in pancreatic adenocarcinoma

For many years chemoradiation was considered the standard of care after patients underwent resection of pancreatic carcinoma. This was mainly based on a small phase III randomized control trial by the Gastrointestinal Tumor Study Group (GITSG) (2). This trial randomized 43 patients to surgery with or without adjuvant 5-FU based chemoradiation. The radiation was delivered using outdated techniques (AP/PA and in a split course) to a total dose of 40 Gy. The patients in the experimental arm also received 2 years of adjuvant 5-FU. The experimental arm had a median OS of 20 months compared to 11 months in the control arm. Regardless, 50% of patients in both arms still developed local recurrence. There are also two large retrospective series from Johns Hopkins and the Mayo clinic. The JHU series contains over 600 patients, with 44% having received 5-FU based CRT to a median dose of 50 Gy. The other 44% did not receive adjuvant therapy. The CRT group had a median OS of 21.2 months compared to 14.4 months in the observation group (3). The Mayo series had 472 patients, all with an R0 resection. The median RT dose was 50.4 Gy and almost all patients received 5-FU. The median OS again favored CRT with a median OS of 25.2 months compared to 19.2 months in patients who were observed (4).

A few other studies have examined other adjuvant CRT regimens utilizing non-5-FU-based chemotherapy. RTOG 9704 compared gemcitabine to 5-FU before and after 5-FU based CRT. The study included 451 patients with gross total resection. The radiation dose was 50.4 Gy delivered using modern methods. There was a trend towards improved 3 year OS (31% vs. 22%) with the use of gemcitabine. Local recurrence remained a significant source of failure, but was lower compared to older studies at approximately 25%. Distant metastasis remained the most significant site of failure at greater than 70%, highlighting the importance of systemic therapy (5). The ACOSOG also published a small phase II trial of 89 patients with R0/1 resection of pancreatic head adenocarcinoma treated to 50.4 Gy along with chemotherapy. The chemotherapy was relatively intense, consisting of 5-FU, cisplatin, and alpha interferon and 96% of patients had grade 3 toxicity or greater. Despite such intense therapy local recurrence still remained around 50%, but systemic therapy only made up 35% of failures (6).

1.3 Chemotherapy alone as adjuvant therapy

There are a few key studies supporting the adjuvant use of chemotherapy alone after resection of pancreatic cancer. ESPAC-1 was a complex 2x2 factorial designed study with over 500 patients. The arms were 5-FU based CRT (split course technique), adjuvant 5-FU/leucovorin alone, both

CRT followed by chemo, or observation. For all patients, chemotherapy improved median survival from 14 months to 19.7 months. For patients that received chemotherapy the 5 year OS was 21% compared to 8%. When analyzing the effect of CRT, it appeared to have a detriment, with a 5 year OS of 10% compared to 20% when chemoradiation was not given. Drawbacks of this study include its complex design, use of outdated radiation techniques, lack of RT quality assurance, and the ability of treating physicians to give "background" therapy (7). The CONKO-001 study randomized 368 patients with a R0/R1 resection to observation of gemcitabine alone for 6 cycles. The use of adjuvant gemcitabine improved disease free survival from 7 months to 14 months, but not OS (22 months vs. 20 months) (8). There was also a metaanalysis published in 2005 examining outcomes of patients in randomized adjuvant trials. This study included 875 patients from 6 trials. The investigators found that chemotherapy improved median OS from 14 months to 19 months. Chemoradiation did not provide a statistically significant benefit (15.2 months to 15.8 months). Of interest, on subgroup analysis it was determined that CRT was more effective for patients with a positive margin resection (9).

1.3 Stereotactic body radiotherapy (SBRT)

SBRT is technique that combines highly conformal radiotherapy with real-time imaging to deliver high doses of radiation in a small number of fractions. Modeled after intracranial stereotactic radiosurgery, SBRT has now been studied in a variety of extracranial locations including the spine, lung, liver, pancreas, and head and neck cancers. Because of the precise targeting, SBRT has the potential to improve upon the local control achieved with conventional EBRT while minimizing the dose to normal tissue. Most prospective randomized trials of conventionally fractionated EBRT for the treatment of locally-advanced pancreatic cancer have reported local control rates of 35%-55% (2-5). Koong, et al established the feasibility of using SBRT for locally-advanced pancreatic cancer in a phase I dose escalation study which achieved 100% local control with no treatment limiting toxicities at 25 Gy in a single fraction (10). A follow-up study combined conventionally fractionated 5-FU chemoradiotherapy with an SBRT boost resulting in 94% local control but no improvement in overall survival and an increase in toxicity compared to SBRT alone (11). A recent study combining full dose gemcitabine with single fraction SBRT reported 81% local control and 100% 1-year freedom from local progression. While acute toxicities were minimal, a significant number of subjects (47%) experienced Grade 2 or greater late toxicities, primarily duodenal ulcers (12). It is possible that these late toxicities may be reduced by increasing the degree of conformance of the radiation dose cloud and increasing the number of fractions, as studies comparing conventionally fractionated RT with hypofractionated RT have found an increased incidence of late GI toxicities in the hypofractionated group (13).

Another advantage to SBRT is the fractionation schedule. First, the entire course of treatment is often completed over 1 to 7 days versus the 5 to 8 weeks required for conventionally fractionated EBRT. Second, the accelerated fractionation schedule could improve overall survival by allowing earlier systemic doses of chemotherapy. Because pancreatic cancer is often characterized by progression to metastatic disease, early delivery of systemic chemotherapy is imperative to address potential sites of microscopic disease. In fact, some studies have evaluated the delivery of systemic chemotherapy followed by combined chemoradiotherapy for those subjects without evidence of disease progression. This strategy selects those subjects most likely to benefit from the local control provided by radiotherapy and in two separate studies has resulted in significant increases in TTP and OS for subjects treated with chemoradiotherapy compared to those receiving chemotherapy alone (14-15).

1.3.1 Experience with SBRT at the University of Pittsburgh Cancer Institute

A retrospective review from our institution evaluated the outcome in 71 subjects with intact pancreatic cancer treated with SBRT (16). With a median follow-up of 12.7 months the freedom from local progression at 6 months and 1 year was 72% and 49%, respectively. Median overall survival for the entire group was 10.3 months. Treatment-related toxicity was minimal with only 3 patients experiencing acute grade 3 toxicity (4%). There was no recorded late toxicity. We have been treating patients with close or positive margins with SBRT as well. We recently examined outcomes in 24 patients treated post-operatively with SBRT (17). Sixty-six percent of the patients had positive margins and the remainder had close margins of 1-2.5mm. The median follow-up was 1 year. The freedom from local progression at 6 months and 1 year was 95% and 66%. There was no acute or late grade 3-4 toxicity, and two patients (8%) had late grade 1-2 toxicity, again demonstrating that when done properly, SBRT has a low potential for toxicity.
The current study seeks to further investigate the impact of SBRT following resection with a close or positive margin. We hope to improve local control, and through the use of a shortened treatment schedule, allow patients to begin systemic therapy earlier.

2.0 OBJECTIVES

Primary

2.1 To determine the rate of local progression-free survival (LPFS) with two years of follow-up in subjects with margin positive or close margins following resection of pancreatic adenocarcinoma treated with SBRT.

Secondary

2.2 To determine the time to progression (TTP) and overall survival (OS) in this patient population

2.3 To evaluate the impact of SBRT on the QOL of subjects in the adjuvant setting

2.5 To evaluate the acute and late toxicities associated with SBRT for pancreas cancer

3.0 INVESTIGATIONAL PLAN

3.1 Overall design and plan of the study

Detailed visit-by-visit study procedures and a study flow chart are provided in Section 6.0. Prior to enrollment, all subjects will be evaluated with physical examination, review of surgical pathology, discussion in a multi-disciplinary setting, review of imaging with the operating surgeon, and review of post operative imaging to establish the target volume.

3.2 Radiation simulation

Contrast-enhanced CT based simulation will be obtained prior to any adjuvant treatment (2-4 weeks post-op depending on healing). The target volume will be indentified based on fiducial marker placement at time of surgery as well as a detailed discussion and image review with the operating surgeon. This area will be contoured on axial CT images obtained at 1.25 mm slice thickness. These volumes will then be reconstructed into a 3-dimensional image set for SBRT planning. Subjects will be simulated in the treatment position (supine with arms raised) on the CT scanner table the appropriate immobilization. Optiray® contrast (125 mL Optiray 350; 350 mg/mL organically bound iodine; Ioversol; Mallinckrodt Inc., St. Louis, MO, USA) will be administered intravenously at a flow rate of 2.5 mL/s. A helical CT scan of the abdomen will be acquired with intravenous contrast starting 30 seconds prior to CT acquisition.

A 4D CT data acquisition for the same axial extent will be obtained. The images will then be electronically transferred from the CT workstation via DICOM3 to the appropriate treatment planning workstation in the department of radiation oncology. Based on axial CT images, fiducial marker placement, review of the pathology report, and a detailed discussion with the operating surgeon, contours will be drawn of the clinical target volume (CTV), which is defined as the area at risk for microscopic disease. The planning target volume (PTV) will be equivalent to the CTV unless motion is detected on the 4D motion study. If there is motion, the amount of motion in the superior-inferior, lateral, and anterior-posterior directions will be the margin given. Surrounding normal and critical structures will also be contoured by the treating radiation oncologist including the kidneys, liver, small bowel, spinal cord, and stomach if necessary.

3.3 Stereotactic Body Radiotherapy Planning

An SBRT plan will be created by a medical physicist based on the PTV contoured on the CT scan. The plan will be to deliver fractionated SBRT to the isodose line best encompassing the PTV:

12 Gy x 3 fractions (36 Gy total)

In determining the radiation dose and fractionation scheme for this protocol, we used the linear-quadratic formalism for radiation cell killing to “equate” schemes that vary the dose/fraction and number of fractions. This concept of biologically equivalent dose (BED) states that the total effect is given by:

nd x (1 + d/□□ (α/β))

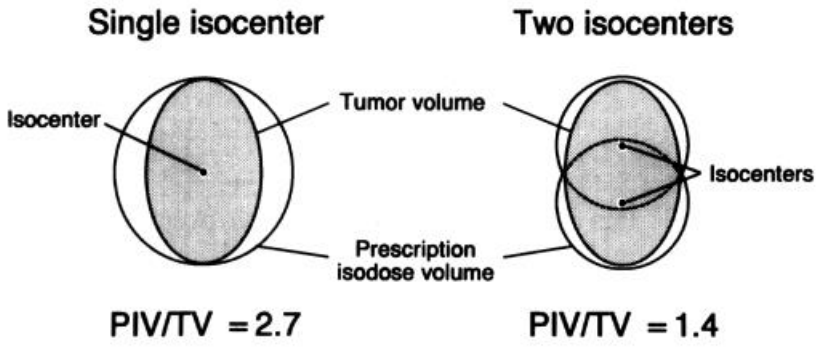
where n is the # of fractions and d is the dose/fraction. The “alpha-beta ratio” characterizes the radiation response of a particular tissue; a higher value is indicative of a tissue that responds acutely to the effects of radiation. Due to their highly proliferative nature, most tumors fall into this category.
This dose scheme (36 Gy in 3 fractions) is biologically equivalent to the previously studied doses in the literature (24 Gy in 1 fraction). We would favor treating in three fractions, as opposed to one, to

allow more repair of normal tissue, reoxygenation of tumor cells, and redistribution of tumor cells to more radiosensitive parts of the cell cycle. Using a smaller fraction size, 12 Gy compared to 24 Gy, will also help reduce late effects of radiation therapy. SBRT treatment will be given on an every other day schedule, excluding weekends. The prescription dose will be prescribed to the isodose line best encompassing the planning target volume (PTV) depending on the volume of tumor.

Careful evaluation of each plan will be conducted by the radiosurgical team to ensure that normal tissues and critical structures tolerances are maintained.

The maximum dose (in Gy) within the treatment volume (MD), prescriptions dose (PD), and the ratio of MD/PD (as a measure of heterogeneity within the target volume), prescription isodose volume (PIV in mm^3), tumor volume (TV in mm^3), and the ratio of PIV/TV (as a measure of dose conformity of the treatment relative to the target) will be recorded. This concept is illustrated in **Figure 2**.

Figure 2: Example illustrating the concept of PIV/TV



3.4 Quality of Life Assessment

Quality of life assessment using the Functional Assessment of Cancer Therapy – General (FACT-G) tool, which is a validated tool, will be administered to all subjects prior to treatment and at each follow-up visit (Appendix A).

3.5 Treatment following SBRT

As described above, all patients will have been seen in a multi-disciplinary pancreatic cancer clinic. As such, they will be set up with a medical oncologist. Following completion of SBRT as described in this protocol, the patient's medical oncologist may, at his/her discretion, administer systemic therapy according to the current standard of care or the UPMC pathways.

4.0 SUBJECT SELECTION AND ELIGIBILITY

4.1 Selection of subjects

Enrollment is defined as the first day of protocol therapy.

4.1.1 Number of subjects

50 patients will be enrolled to the study. The study has been designed to detect a 20% improvement in the rate of local progression-free response over that of historical controls.

4.1.2 Inclusion criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

- Histologically or cytologically proven adenocarcinoma of the pancreas that has been resected with a close (<2.5mm) or positive margin based on surgical and pathological findings.
- Subjects will be staged according to the 2010 AJCC staging system (Appendix D) with pathologic stage T1-4, N0-1 being eligible; and have a primary tumor of the pancreas (i.e., pancreatic head, neck, uncinate process, body/tail
- PTV must be encompassed in a reasonable SBRT "portal" as defined by the treating radiation oncologist
  - Karnofsky performance status $\geq$ 70 (ECOG 0-1)
  - Age $\geq$ 18
  - Estimated life expectancy > 12 weeks
- Patient must have adequate renal function as defined by serum creatinine<-2.5 mg/dl obtained within 28 days prior to registration
- Patient must have adequate hepatic function as defined by total bilirubin <2.5 xIULN(institutional upper limit of normal) and either SGOT or SGPT <3.0 xIULN, obtained within 28 days prior to registration.
- Patient must be able to swallow enteral medications. Patient must not require a feeding tube. Patient must not have intractable nausea or vomiting, GI tract disease resulting in an inability to take oral medication, malabsorption syndrome, or uncontrolled inflammatory bowel disease (Chron's, ulcerative colitis).
- Ability to provide written informed consent
- Patient must not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, history of myocardial infarction or cerebrovascular accident within 3 months prior to registration, uncontrolled diarrhea, or psychiatric illness/social situations that would limit compliance with study requirements.
- Patient must not be pregnant because of the risk of harm to the fetus. Nursing women may participate only if nursing is discontinued, due to the possibility of harm to nursing infants from the treatment regimen. Women/men of reproductive potential must agree to use an effective contraception method.

4.1.3 Exclusion criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

- Non-adenocarcinomas, adenosquamous carcinomas, islet cell carcinomas, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct, and ampullary carcinomas are not eligible.
- Evidence of distant metastasis on upright chest x-ray (CXR), computed tomography (CT) or other staging studies
- Subjects with recurrent disease

- Prior radiation therapy to the upper abdomen or liver
- .
- Subjects in their reproductive age group should use an effective method of birth control. Subjects who are breast-feeding, or have a positive pregnancy test will be excluded from the study
- Any co-morbidity or condition of sufficient severity to limit full compliance with the protocol per assessment by the investigator
- Concurrent serious infection
- Previous or current malignancies of other histologies within the last 5 years, with the exception of cervical carcinoma in situ, adequately treated basal cell or squamous cell carcinoma of the skin, and treated low-risk prostate cancer.

5.0 TREATMENT EVALUATION, ADMINISTRATION, AND MODIFICATION

SBRT guidelines

5.1 Tissue constraints

Appropriate beam "nodes" or angles shall be selected to treat the primary site and areas at risk for occult disease spread. Careful target definition of these areas at risk is essential for optimal outcome. Beam shaping for treatment delivery shall be via conical or multi-leaf collimation (MLC). Treatment shall be via linear accelerator (LINAC) commissioned and equipped to deliver SBRT. Normal tissues and sensitive critical structures (e.g. duodenum, spinal cord, stomach, bowel, kidneys, liver, etc) shall be countered and the dose to these organs limited. See table below.

Normal Tissue Constraints	
Organ	Maximum Dose in 3 fractions
Liver (700 cm3)	15 Gy
1/3 of total kidney volume (left and right)	15 Gy
Spinal Cord	18 Gy
Stomach	30 Gy
Duodenum/small bowel	18 Gy

As discussed above the CTV will be equivalent to the PTV, unless the motion study reveals motion in the target volume. In that case, margins will be given to account for that motion.

5.2 Dose Specification, Homogeneity Considerations & Plan Evaluation

The treatment plan used shall be based on the assessment of the dose-volume histogram (DVH) with attention to coverage of the planning tumor volume (PTV) and critical normal structures.

The prescription dose is the isodose cloud that encompasses at least 95% of the PTV.
No more than 20% of any PTV shall receive doses >110% its prescribed dose
No more than 2% of any PTV shall receive <93% of its prescribed dose
No more than 5% of any normal tissue shall receive doses in excess of 110% of the primary PTV dose.

5.3 On-Treatment assessment and post-treatment toxicity evaluation

All subjects will be seen prior to delivery of each fraction of SBRT with toxicity evaluated by physical examination. Subsequently, subjects will be evaluated for toxicity 10-12 weeks later and then every 3 months until at least 2 years. Toxicities will be scored by the NCI CTC AE version 4.0. Also see Section 6.0.

5.4 Stereotactic Body Radiotherapy Risks

Short-term side effects include but not limited to skin reaction, local hair loss, fatigue, abdominal pain, nausea, vomiting, diarrhea, increasing liver function abnormality, GI bleeding or perforation which may require surgical intervention. Long term side effects are less likely to occur but if they do occur are more likely to be permanent. They include local hair loss, liver function abnormality, diarrhea, small bowel obstruction which may require surgical intervention, spinal cord injury which could result in paralysis, and kidney function abnormality.

5.3.4 Fidiucial placement

It is currently standard practice at our institution for the operating surgeon to place fiducial markers intraoperatively at the areas he feels will be at risk for positive or close margins. As such, patients will not need to undergo a separate procedure for fiducial marker placement.

5.3.5 CT Risks

The subject will be exposed to radiation associated with the CT scans performed to assess response to therapy. CT scans are routinely performed as standard-of-care for tumor staging and to monitor response to therapy, and the radiation dose associated with these diagnostic scans are felt to represent minimal risk.

Claustrophobia: Possible anxiety, claustrophobia, and/or temporary discomfort may occur as a result of being placed in the scanning devices. Subjects will be monitored and removed from the scanner if required

6.0 STUDY EVALUATIONS

6.1 Pretreatment evaluation

The following tests/procedures will be performed in order to ascertain subject eligibility within 28 days prior to registration unless otherwise specified.

6.1.1 Medical history

6.1.2 Physical examination, including Karnofsky status, ECOG performance status and vital signs.

6.1.3 Signed informed consent

6.1.4 Subject body weight and height taken within 1 week of the study start.

6.1.5 Histologic and/morphologic confirmation of diagnosis as well as margin status

6.1.6 CBC including: WBC with complete differential, platelets, RBC, hemoglobin, hematocrit, within 30 days prior to study start.

6.1.7 Blood chemistries including BUN, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, calcium, phosphorus, chloride, magnesium within 30 days of study start.

6.1.8 Urine or blood HCG test for female subjects of child-bearing potential (women who are not at least 1 year post-menopause or who have not undergone a surgical sterilization procedure) within 14 days prior to study start. Female subjects of child-bearing potential will be instructed to use contraception from the time of the screening pregnancy test until study completion.

6.1.9 CT of the abdomen and pelvis

6.2 Evaluation during treatment

The subjects will be carefully followed while on active treatment and post-treatment for 24 months, or until death. Evaluation during treatment will consist of the following activities:

6.2.1 Administration of SBRT

6.2.3 Interim medical history and physical examination at baseline, prior to SBRT treatment, at the end of SBRT, and 10-12 weeks after SBRT then every 3 months thereafter for up to 24 months.

6.2.4 Serum chemistry and electrolytes to include BUN, creatinine, sodium, potassium, bicarbonate, chloride, calcium, magnesium, glucose, total bilirubin, AST, ALT, alkaline phosphatase post-treatment as clinically indicated

6.2.5 Hematologic studies to include CBC with differential and platelet count prior to SBRT and repeated 10-12 weeks later and then at follow-up as clinically indicated.

6.2.6 CT scan will be obtained at 10-12 weeks post-treatment and will be reviewed for evidence of response. Since these subjects will likely have no gross disease on imaging, the main goal of the follow-up scans is to monitor for local and distant progression as defined below.

6.3 Treatment schedule

Parameter	Pre-Study	SBRT			10-12 weeks post-treatment	Q 3 months until 24 months
		Fx 1	Fx 2	Fx3		
History	X	X		X	X	X
Physical exam	X	X		X	X	X
Measurement of disease	X				X	X
Performance Status	X				X	X
Serum Chemistry	X*				X▲	X▲
Hematologic Studies including CBC	X*				X	X▲
CT Scan	X				X	XΩ
Serum or Urine Pregnancy Test for WOCBP	X					
Histologic and Morphologic Confirmation and Margin Status	X					
QOL assessment	X				X	X

* Within 30 days of study start

▲If clinically indicated

Ω May be modified by oncology team if patient receives system therapy

6.4 Post-treatment evaluation and plan

6.4.1 Evaluation of CT Imaging

A follow-up CT scan will be obtained at 10-12 weeks post-SBRT and then every 3 months until end of study. If the patient goes on to receive systemic therapy, the follow-up CT schedule can be modified at the discretion of the oncology team.

6.4.2. Definition Local Progression Free Survival

In this study, LPFS is defined as the time from enrollment to first documentation of progressive disease (PD) in the target lesion. Death or development of distant disease is not regarded as an event. For patients that undergo surgical resection, local progression will be defined as disease recurrence detected on follow-up imaging (CT or FDG-PET/CT) that is located within the SBRT target volume.

6.4.3 Definition of OS and TTP

TTP is defined as the time from enrollment to disease progression. Disease progression will be defined as PD in the target volume, or development of distant disease. OS is defined as the length of time from enrollment to confirmed death from any cause.

6.4.4 QOL evaluation

QOL evaluation will be carried out according to the treatment schema in section 6.0. The survey will be the FACT-G and will be administered prior to SBRT, after completion of SBRT, and at each follow-up. See appendix A for more details.

6.4.5 Safety evaluation

All patients will be monitored for potential treatment-related toxicity throughout treatment as detailed in the schema. Toxicity will be graded according to the CTCAE, which is further detailed in section 8.2.1. Acute toxicity is defined as toxicity occurring within 3 months of completion of SBRT. Late toxicity is defined as toxicity occurring greater than 3 months after treatment.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Objectives and Design

The primary objective is to determine the LPFS in subjects with resected pancreatic adenocarcinoma with close or positive margins treated with SBRT. Secondary objectives include the evaluation of TTP, OS, acute and late toxicities, and QOL. These study endpoints are defined in Section 6.4.

This clinical trial is planned as a prospective single-arm phase II study. The treatment schema is shown in Section 6.3a.

7.2 Sample Size and Accrual Rate
7.2.1 Sample Size

From the Investigators' treatment experience, the 2-year local progression-free survival rate for the standard of care is 40%. This phase II study aims to improve it to 60% with SBRT. We plan to have 24 months of accrual, and 24 months of follow-up beyond the last patient enrolled on study. Under assumption of exponential survival, a total of 50 patients will provide 94% power to detect a statistically significant improvement in survival by one-sided log-rank test at significance level 0.05. Assuming that there will be no loss to follow up and no ineligible case, a total of 50 patients will be accrued for this trial.

7.2.2 Rate of Accrual

We anticipate that 2 to 4 study-eligible patients will be enrolled per month. Thus, our planned study size of 50 patients to be enrolled within 24 months is well within our capacity.

7.3. Statistical Analyses

7.3.1. Analysis Set

The data from all evaluable patients will be used in the analyses of survival, safety, tumor response, and health related QOL. Evaluable patients are those meeting all of the protocol inclusion/exclusion criteria and receiving at least one fraction of SBRT.

7.3.2. Baseline Characteristics

Baseline descriptive statistics on all evaluable patients will be provided on demographic variables (age, sex, race/ethnicity), ECOG performance status, laboratory parameters, the chemotherapy regimens that were previously used, the number of treatment cycles and irradiation fractions involved, and disease characteristics, including tumor size and stage.

7.3.3 Analysis of Study Endpoints

Survival (LPFS, OS, TTP) will be estimated by the Kaplan-Meier method for all evaluable patients and the corresponding median survival times (with 95% confidence interval) reported. The 2-year LPFS will also be estimated along with its 95% confidence interval. The effect of variables listed in Section 7.3.2 will be explored with Cox regression models.

For the QOL data analysis, each item of the FACT-G will be individually assessed. The mean and standard deviation of the observed data will be summarized at each collection time and plotted against time, from baseline through the end of patient follow-up. Generalized linear models (such as cumulative logit models[18]) for repeated measures will be used to explore if there are significant changes in HRQOL over time.

Using NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0), the number of patients experiencing adverse events over their course of treatment will be characterized by type of adverse event and grade, by the time of onset in relation to the first day of therapy, and whether the event is clinically significant. Attribution of adverse events to treatment (unrelated, unlikely, possibly, probably, or definitely) will also be summarized for any serious adverse events (SAEs), CTCAE grade 3 or higher. The percentage of patients experiencing SAEs that are considered to be treatment-related (probable or definite) will be determined. The percentage of patients experiencing the acute and late toxicities associated with SBRT (as defined in Section 6.4) will also be estimated along with its 95% confidence interval.

7.4. Early Stopping for Toxicity

Toxicity will be monitored continuously, with protocol amendment being made as needed. For safety, we will consider that regimen to be excessively toxic and stop accrual if, at any time, the observed rate of grade 3-5 acute or late toxicity as defined above in Section 6.4.5 $\geq 33\%$ and at least 4 toxicities have been observed.

8.0 DATA SAFETY AND MONITORING

8.1 Data safety monitoring plan

All subject data will be collected by the University of Pittsburgh Cancer Institute's Protocol Office. All data will be secured in a password protected file with observance of all applicable HIPAA regulation. A data safety monitoring board will meet monthly to evaluate toxicity for this trial. Subjects/adverse events will be discussed at these monthly disease center meetings. Unexpected serious adverse events will be reported to the IRB and DSMC, and minutes of the monthly disease center meetings will be reviewed at the DSMC meetings.

8.1.1 Subject Removal Criteria

1. Disease progression
2. Development of a serious medical illness
3. Evidence of dose-limiting toxicity
4. Voluntary withdrawal
5. Protocol violation
6. Discretion of the principal investigator
7. Development of grade 4 toxicity related to experimental therapeutic

8.2 Safety Reporting

8.2.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas will have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication.

Exacerbation of a pre-existing illness should be considered when a subject requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the study. Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect should not be recorded as an adverse event. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

In addition, abnormal objective test findings (e.g., electrocardiogram changes, abnormal

laboratory test results) that can result in a change in study drug dosage or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the subject, should also be recorded as adverse events. Clinically significant changes in physical examination findings should also be recorded as adverse events. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to UPCI or its designated representative.

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study drug will be recorded on the adverse event page(s) of the CRF. The investigator will record all adverse events in the CRF and assess each event as to severity and causal relationship to study drug.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality, (i.e., study drug or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse events that continue, or emerge within 30 days, after the subject's discontinuation or completion of the study will be followed until the events resolve, are considered stable, or can be ascribed to causes other than study treatment.

All serious AE shall be reported meeting criteria for reporting can be found on the University of Pittsburgh Institutional Review Board's website at http://www.irb.pitt.edu. In the event of such adverse event, the investigator must report the event(s) via phone within 24 hours and a written report filed within 24 hours to the Principal Investigator, or the UPCI's Clinical Research Office.

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APPENDIX A: Functional Assessment of Cancer Therapy - General (FACT-G)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

APPENDIX B: Karnofsky Performance Scale

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX C: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

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APPENDIX D: Staging for Pancreas

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis in situ carcinoma
T1 Tumor limited to the pancreas 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas more than 2 cm in greatest dimension
T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage Ia	T1	N0	M0
Stage Ib	T2	N0	M0
Stage IIa	T3	N0	M0
Stage IIb	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

From American Joint Committee on Cancer. *AJCC Cancer Staging Manual, 6th ed.* New York: Springer-Yearlab, 2010:157-164