A Dose Escalation Trial of SBRT After induction Chemotherapy for Locally Advanced Pancreatic Cancer

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PROTOCOL TITLE: A Dose Escalation Trial of Stereotactic Body Radiotherapy (SBRT) after Induction Chemotherapy for Locally Advanced Pancreatic Cancer

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

AE: adverse event

CBC: complete blood count

CBCT: cone beam CT

COMIRB: Colorado Multiple Institutional Review Board

CRC: clinical research coordinator

CRDB: clinical research database

CRF: case report form

DLT: dose-limiting toxicity

DSM: data safety monitoring

DSMC: data safety monitoring committee

EES: extracellular extravascular space

EKG: electrocardiogram

ERCP: endoscopic retrograde cholangiopancreatography

EUS: endoscopic ultrasound

FNA: fine needle aspiration

GCP: good clinical practice

GI: gastrointestinal

GTV: gross tumor volume

I: iodine

IMRT: intensity-modulated radiation therapy

IRB: institutional review board

ITV: internal target volume

KV: kilovoltage

LAPC: locally advanced pancreatic cancer

LC: local control

MTD: maximum tolerated dose

NTCP: normal tissue complication probability

OAR: organ at risk

OS: overall survival

PC: pancreatic cancer

PFS: progression free survival

PO: per os (orally)

QOL: quality of life

pCT: perfusion CT

PI: principal investigator

PB: privacy board

PTV: planning treatment volume

PV: portal vein

ROI: region of interest

RT: radiation therapy

SAE: serious adverse event

SBRT: stereotactic body radiotherapy

SIV: site initiation visit

SMA: superior mesenteric artery

SMV: superior mesenteric vein

UAP: unanticipated problem

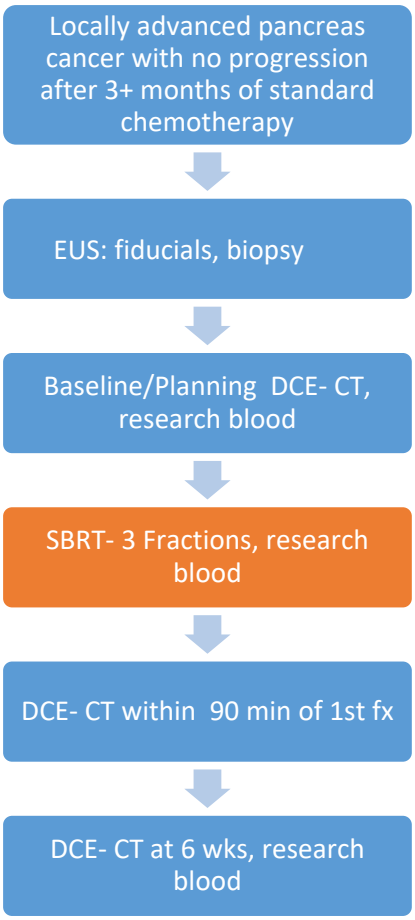
VMAT: volumetric modulated arc therapy

VS: vascular space

1.0 PROTOCOL SUMMARY AND SCHEMA

This is a dose escalation trial to evaluate the safety of stereotactic body radiotherapy (SBRT) delivered in 3 fractions for patients with locally advanced pancreatic cancer (LAPC) who have received induction chemotherapy (FOLFIRINOX or gemcitabine and nab-paclitaxel). The primary objective is to determine the maximum tolerated dose (MTD) of 3-fraction SBRT for patients with LAPC. We will develop and implement functional imaging methods to evaluate post-SBRT effects on normal tissue and tumor cellularity and perfusion/permeability that may provide quantitative biomarkers of tumor response as well as early indicators of bowel toxicity. We anticipate (up to) 18 patients to be accrued over 3 years.

SCHEMA



2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary objective:

To identify the maximum tolerated dose (MTD) of stereotactic body radiotherapy (SBRT) in locally advanced pancreatic cancer (LAPC) patients who have not developed distant progression after following induction chemotherapy (FOLFIRINOX or gemcitabine and nab-paclitaxel as per standard of care).

2.2 Secondary objectives:

1) To preliminarily assess the 2 year local control, progression free and overall survival rates for LAPC patients after induction chemotherapy and SBRT. Patterns of failure will also be investigated.
2) To identify early changes in the normal small intestine after SBRT for LAPC using Perfusion CT derived parameters to document changes in tissue perfusion kinetics and heterogeneity that predict for development of gastrointestinal toxicity such as duodenal ulcers, strictures, or enteritis.
3) To investigate vascular and cellular changes resulting from SBRT for LAPC using perfusion CT derived parameters that can predict treatment response and to assess any correlation between these perfusion CT derived parameters and local control and progression-free survival
4) Evaluate Quality of Life (QOL) in terms of global QOL, physical symptoms, physical functioning and emotional well-being after induction chemotherapy and SBRT. Testing will be prior to SBRT, 10-12 weeks after SBRT and 6 months after SBRT.

3.0 BACKGROUND AND RATIONALE

3.1 Stereotactic Body Radiotherapy for Locally Advanced Pancreatic Cancer

Pancreatic cancer (PC) remains a highly lethal cancer with 5-year survival rates of approximately 6% [1]. In 2016, an estimated 53,000 new cases of PC will be diagnosed with over 41,000 deaths [1]. Surgical resection is the only potentially curative option; however, fewer than 20% of patients are eligible. While systemic therapy remains vital, local therapy options are also paramount. In a recent autopsy series, 30% of PC patients died with extensive local progression and only minimal systemic disease [2]. Patients with unresectable, LAPC are committed to non-curative treatment options using concurrent chemotherapy and conventional, fractionated radiation therapy (RT) over 2-6 weeks, however, these regimens are associated with significant acute toxicity and minimal impact on resectability.

The mechanism of RT-induced tumor-cell death from fractionated RT is via induction of DNA double-strand breaks [3-6]. Fractionation requires daily treatment, leading to daily changes in tumor position, necessitating larger fields to ensure tumor coverage. SBRT allows delivery of focal RT with high precision using image guidance at the time of treatment to overcome uncertainties related to tumor positioning, thereby minimizing the dose to the surrounding normal tissues. Studies with 15-18 month follow-up have demonstrated excellent local control and minimal late toxicity (<5%) using single fraction SBRT for bone, nodal, liver, and lung tumors [7-10]. SBRT is particularly appealing for LAPC patients, as it may deliver a potentially more effective, focally ablative therapy over a short period, versus 5-6 weeks of conventional RT. This provides significant advantages for patients' quality of life and potential therapeutic benefit. Phase I and II studies have shown local tumor control rates of >90% and even metabolic response by PET/CT after a single fraction of 25Gy SBRT [11-14]. Distant metastasis was the most common site of failure. However, GI toxicity was significant, with development of Grade 2+ toxicities, particularly duodenal strictures and ulcers in approximately 40% of patients. Thus, a phase II, multi-institutional study, aimed at reducing toxicity, used a 5-fraction regimen of SBRT with a decreased dose of 6.6 Gy per fraction. This study has shown a reduced rate of Grade 2+ toxicities. Of 49 patients analyzed to date, 5 (10%) developed grade 2 acute toxicities and 1 (2%) an acute grade 4 duodenal ulcer. Late GI grade ≥3 toxicities occurred in 3 patients (6%) [15].

However, SBRT may be more effective at doses higher than 6.6Gy per fraction. Studies by Kolesnick and Fuks have demonstrated that high dose (>8Gy) per fraction rapidly activates the cell membrane enzyme acid sphingomyelinase (ASMase) that hydrolyzes sphingomyelin to generate the pro-apoptotic second messenger ceramide, thus initiating transmembrane signaling of apoptosis [39]. Endothelial cells are 20-fold enriched in secretory ASMase compared with any other cell in the body and are particularly sensitive to radiation-induced apoptosis in vitro and in vivo via the ASMase pathway[16]. High-dose RT appears to induce primarily sublethal lesions in tumor cells that become lethal due to apoptotic microvascular dysfunction. The proposed mechanism of tumor cell death related to microvascular damage may overcome the apparent radioresistance of pancreatic cancer evidenced by the poor local control with conventional RT.

In this study, we will introduce a 3-fraction regimen starting at 9Gy, a dose that should induce microvascular changes. This innovative therapy has potential to impact the majority of pancreatic cancer patients, i.e. who are ineligible for curative resection due to involvement of critical blood vessels. The proposed tumoricidal mechanism of tumor cell death related to microvascular damage may overcome the apparent radioresistance of pancreatic cancer as evidenced by the poor local control achieved by conventional RT techniques.

In addition, we will correlate dose to surrounding small bowel with the development of any acute or late gastrointestinal toxicity after SBRT. However, a limiting factor in predicting gastrointestinal toxicity is the variability in the accumulated radiation dose to organs at risk, in particular, the duodenum. Respiration-induced motion contributes to dose variability and requires accurately determining and controlling the motion trajectories of tissues during treatment delivery. The recent availability of intra-treatment kilovoltage cine radiography makes possible the tracking of implanted fiducial markers. We have developed a method of automatically tracking implanted markers in kV images during treatment. In a further study, we have developed a means of calculating and correcting for respiration-averaged drift in target position. We will use these capabilities to monitor and correct drift in the position of fiducials during respiration gated treatment, thereby controlling accumulated dose to the pancreas and to the duodenum, which is fixed to it.

This innovative therapy has potential to impact the majority of pancreatic cancer patients, i.e. those who are unable to undergo a curative resection due to involvement of critical blood vessels. Moreover, SBRT can be easily integrated into a regimen of aggressive chemotherapy, preventing unnecessary delays or discontinuation of effective chemotherapy regimens during more conventionally fractionated RT.

3.2 Functional Imaging

Conventional anatomical CT is routinely used to evaluate pancreatic neoplasms, however, standard bi-dimensional tumor measurements may underestimate response to treatment with radiotherapy. Signal intensity changes may be assessed, but are not reliable for demonstrating possible treatment responses. Apart from radiographic changes in tumor size, conventional CT offers no additional method of assessing the viability of the tumor, or the response of tumor to therapy. Furthermore, while tumor shrinkage is useful and is the gold standard for response assessment, tumor measurements alone may underestimate tumor necrosis and do not consider changes in tumor vascularity. More recently, functional imaging techniques that can assess biological parameters, such as vascularity or metabolism, have been explored to better predict tumor response either before or early after initiation of therapy. Functional imaging, including perfusion CT (pCT), can help assess the biological effects of therapy before changes in tumor size occur. Functional imaging can potentially 1) improve pre-treatment prediction of tumor response, 2) predict response early after initiating therapy, and 3) monitor tumor biology once size has stabilized.

Clinical CT examinations of the pancreas routinely include the use of iodine (I) based contrast agents to assess tumor vascularity and improve tumor conspicuity. Perfusion CT can be incorporated into routine CT simulation to quantitatively evaluate the passage and distribution of I contrast agents from the circulation to tumors over time. Quantitative

perfusion parameters obtained from pCT reflect the rate of exchange of I and include K^{trans} - a volume transfer constant between blood plasma or vascular space (VS) and extracellular extravascular space (EES), k_{ep} - the rate constant between EES and VS, BF – the rate of transfer of blood from the main vessels to the capillaries, and v_e - the fractional vascular volume. These parameters can be measured at baseline and compared on follow-up post treatment scans. This technique was initially applied for evaluation of antiangiogenic therapy, but its use has expanded to other cytotoxic agents and may be useful to evaluate rapid endothelial damage leading to vascular collapse after SBRT.

Tumor response to chemotherapy has traditionally been assessed by measurements of tumor size. Functional CT imaging can help assess the biological effects of therapy before changes in tumor size occur. Functional imaging can potentially 1) improve pre-treatment prediction of tumor response, 2) predict response early after initiating therapy, and 3) monitor tumor biology once size has stabilized.

While multiple studies have investigated perfusion imaging in pelvic tumors and breast cancers, there are still a limited number of studies exploring the role of perfusion for pancreatic cancers [43, 44]. Perfusion has been used to quantify regional perfusion/permeability in the normal pancreas or to distinguish pancreatitis and pancreatic cancer [44-46]. The use of perfusion to predict treatment response in pancreatic cancer is emerging. Changes in perfusion/permeability 3 days after treatment of a pancreatic tumor xenograft correlated with tumor volume changes 21 days after treatment with cetuximab and irinotecan [23]. Pancreatic tumors with high pre-treatment K^{trans} (measure of perfusion/permeability) responded better to concurrent chemo/radiotherapy. In another study of 11 pancreatic cancer patients treated with gemcitabine and sorafenib, pre-treatment K^{trans} were higher in 4 patients that showed a response by tumor marker levels [43]. While there were no significant changes in tumor size, an overall decrease in K^{trans} and other perfusion/permeability parameters was observed 4 weeks after treatment. There is also evidence that tumor blood flow can serve a useful predictive/prognostic role. There is evidence that decreased tumor blood flow combined with increased metabolic (i.e. PET) activity is associated with more malignant lesions, as well as evidence that tumor blood flow correlates with tumor histology.

Radiation-induced vascular damage can also affect normal organ function [47]. Traditional efforts to predict late toxicity have relied on normal tissue complication probability (NTCP) models derived from planned radiation dose distributions. Inclusion of clinical and imaging factors can improve prediction, thereby implying a range of patient radiosensitivities. For example, portal venous perfusion has been found to correlate with liver function following radiation therapy, which varied even among patients receiving the same dose and dose distributions [48]. Additionally, increased perfusion and permeability

can discriminate between actively inflamed and normal small bowel in Crohn's Disease [49]. In acute radiation GI toxicity, increased intestinal permeability and histological injury are observed partway into fractionated treatment [50]. Clinical studies [51-53], preclinical time-dose fractionation studies [54] and animal studies using modifiers of acute toxicity [55] have shown that acute toxicity often contributes to the development of late toxicity. The development of perfusion as a biomarker for pancreatic cancer and peripancreatic soft tissues following radiotherapy would represent an important clinical advance, in that it offers a noninvasive multiparametric approach to assess tumor response and predicting potential toxicities, monitor the vascular effects of SBRT and explore, in humans, the preclinical model of endothelial dysfunction. Ultimately, the goal of developing these functional imaging-based biomarkers would be to tailor the dose of SBRT for each patient based on early assessment of an individual patient's tumor responsiveness and risk of toxicity.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase I study of up to 18 patients to identify the maximum tolerated dose (MTD) of a 3-fraction regimen of SBRT for locally-advanced pancreatic cancer patients who have not developed distant progression following induction chemotherapy (FOLFIRINOX or gemcitabine and nab-paclitaxel as per standard of care). Using pCT to quantify tissue perfusion/permeability and associated heterogeneity after SBRT, we will define early normal tissue changes associated with GI toxicity requiring early interventions as well as tumor changes associated with local control or progression that can dictate further therapy choices for patients with LAPC.

4.2 Intervention

After completion of induction chemotherapy, stereotactic body radiotherapy (SBRT) will be administered in 3 fractions, every other day, on an outpatient basis. Dose escalation will start with dose level 1 (9 Gy x 3 fractions) and increase by 1 Gy per fraction at each dose level, dose level 2 will be 10 Gy x 3 fractions and dose level 3 will be 11 Gy x 3 fractions.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 EUS and Fiducial Placement:

Eligible patients will be enrolled on this protocol and will undergo endoscopic ultrasound (EUS)-guided placement of 3-5 fiducial markers for SBRT targeting purposes. The fiducials will be placed directly into or adjacent to the tumor under CT guidance, EUS or under direct visualization during laparoscopy.

5.2 Simulation and baseline pCT:

The patient will undergo a treatment planning simulation after the re-staging CT scan. In preparation for the planning CT scan, patients will be asked to fast for 2 hours prior to simulation and treatment to minimize the volume of stomach contents. A nurse will remind patient of these procedures. In order to visualize the bowel and lymph nodes, the patient may also be given bowel and IV contrast prior to the treatment planning CT. All patients will be immobilized in a cradle in order to prevent any inadvertent patient motion. Patients who can tolerate the abdominal compression belt will be fitted with the belt and motion of the fiducials with the compression belt inflated will be evaluated by fluoroscopy. For patients who are unable to use the compression belt or there is greater than 5mm of motion of the fiducials by fluoroscopy, we will use respiratory gating for motion management.

With patients in the treatment position, a thin-cut pancreatic protocol CT scan (1 mm cuts) is performed with IV contrast for high resolution delineation of the tumor and surrounding structures. For patients who will be treated with respiratory gating, the intravenous contrast is administered in a rapid bolus when the patient is being coached to remain in the expiratory phase. For the respiratory gating patients, we will also perform four-dimensional (4D) CT scans, in which CT data (3 mm cuts) are acquired synchronously with a respiratory signal, to evaluate temporal changes of the anatomy as a function of the respiratory phase during the imaging, in order to correct for respiratory related liver tumor movement. All patients will have been given an audio coaching CD to review prior to the set-up procedure to determine a comfortable breathing rhythm.

A pre-SBRT pCT image will be performed at the time of simulation in the treatment position on the Siemens AS Open CT scanner. 50-100 mL of Iodine contrast will be injected at a rate of 3 mL/s followed by a saline flush of 20 mL. A series of axial images with an 8 cm field of view in the superior-inferior direction will be acquired over a period of 60-120 s at intervals of 3-5 s.

5.3 Target Definition:

The gross tumor volume (GTV) is delineated on cross-sectional images from the planning CT scan. For patients who will be treated using respiratory gating, the 4DCT scans are reconstructed and tumor motion is evaluated on the Eclipse planning station. The respiratory gating interval is selected based on the degree of tumor motion. These scans are registered with the IV contrast breath-hold CT scan and the primary tumor is contoured. If there is greater than 5 mm of motion during the expiratory phase/gating window, the GTV will be expanded at the extremes of the gating window and an internal target volume (ITV) is created. Any adjacent duodenum, small/large bowel, and stomach will be expanded by 2 mm to create a planning organ at-risk volume (PRV). A GTV/ITV to PTV margin expansion of 5mm will be added and the PRV of the duodenum, small/large bowel or

stomach, will be excluded from the PTV using a boolian function. For compression belt patients, a GTV to planning treatment volume (PTV) margin expansion of 5mm will be added to account for internal motion. The same process of excluding the PRVs will be performed to minimize PTV overlap with OARs.

5.4 Radiation Treatment Planning:

Intensity-modulated radiation therapy (IMRT) with or without Volumetric Modulated Arc Therapy (VMAT) treatment planning will be done to create a multi-field or arc plan or to deliver the assigned dose to the target as a single dose. Dose to the adjacent normal tissue will be minimized. Since the small bowel is the most radiosensitive normal structure in this region, the dose to it will be limited to no more than 16cm^3 can receive >10 Gy, no more than 5 cm^3 can receive >20 Gy, and the maximum point dose is ≤23 Gy [36]. For other abdominal organs at risk (OAR), the institutional normal tissue guidelines for 3-fraction SBRT treatments will be used. Dose shall be prescribed to the periphery of the PTV and a hot spot of up to 10% of the prescribed dose will be accepted. In the case where normal tissue criteria cannot be met, the dose constraints will take priority over tumor coverage. Dose painting will be allowed to achieve the protocol dose constraints.

5.5 Radiation Dose Constraints

Duodenum	V15Gy<20cc, V20Gy<10cc
Other Small Bowel	V20Gy<5cc
Spinal cord	Dmax 21Gy
Stomach	V20Gy<5cc
Liver	V15Gy<33%
Large Bowel	V20Gy<5cc
Kidney	V15Gy<33%

5.6 On Line Image-Guided Localization and Treatment Delivery:

Image–guided IMRT is the delivery of IMRT with on-line imaging capabilities and verification. This is accomplished with standard IMRT treatment planning with position verification using 2-dimensional kilovoltage (KV) images to evaluate the position of the fiducial markers as well as 3-dimensional cone beam imaging. 3D kilovoltage cone beam CT (CBCT) scan is a CT scan taken of the patient and target structure of interest while the patient is immobilized on the treatment table. During the treatment, the patient is immobilized in a cradle with the compression belt on. Fluoroscopic images are taken to verify that motion of the fiducials or stent is <5mm. For respiratory gated patients, the fluoroscopy is not performed. The patient is then set-up in the treatment position according to tattoos, then live images of the patient are obtained with diagnostic x-ray

tubes and amorphous silicon detectors. Then the therapists can either initially obtain a KV image (gated KV for the respiratory gating patients) to align the fiducial markers or a CBCT will be obtained and image registration is performed based on the location of the fiducial markers and visible tumor abnormality (if possible) noted in the CT. The patient position is then adjusted to move the patient into the exact position corresponding to the designed treatment plan.

Another CBCT scan is then obtained to verify visualization of the fiducial markers, tumor, and normal tissues. In the CBCT image, the target structure and surrounding normal tissue structures can be visualized. We will upload the target and normal tissue contours on the treatment CBCT images. If necessary, adjustments can be made to the patient's position at this time to ensure that the fiducial markers line up with the fiducial markers on the planning CT and that the critical normal tissues are not within the high dose region. If the patient requires additional repositioning, another set of KV orthogonal images will be obtained to confirm tumor localization. Once the latter is confirmed, the treatment will be delivered. Treatment will be delivered with the abdominal compression belt or using respiratory gating using the gating interval as determined from the 4DCT obtained at the simulation. The patient will be monitored during treatment with intra-fraction imaging (IMR) to prevent non-respiratory body motions greater than 3 mm.

5.7 Early Post-SBRT CT Imaging:

To evaluate the effect of the high-dose radiotherapy on the tumor vasculature, patients will undergo a pCT within 90 minutes of the first fraction of SBRT.

5.8 Follow-up CT Imaging:

Patients will undergo a follow-up abdominal pCT to evaluate the response to SBRT 6 weeks (± 1 week) after completion of SBRT. The patients can resume systemic therapy per the discretion of the treating physician after the pCT scan at 6 weeks.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Histologically or cytopathologically confirmed adenocarcinoma of the pancreas.
2. Locally advanced, unresectable pancreatic cancer as confirmed by the multidisciplinary input from a hepatobiliary surgeon and as defined on CT as having tumor abutment of >180° (> 50%) of the circumference of the superior mesenteric artery (SMA) or celiac axis, unreconstructable superior mesenteric vein (SMV) or portal vein (PV) involvement.

3. No evidence of distant metastasis either prior to or after induction chemotherapy.
4 Completion of at least 3 months, but no more than 12 months of standard induction chemotherapy for LAPC, which may include FOLFIRINOX or gemcitabine and nab-paclitaxel, preferably within 2-4 weeks but no longer than 8 weeks.
5. Pancreatic tumor size ≤ 5 cm.
6. Age ≥18 years.
7. ECOG 0-1.
8. Patients must have acceptable organ and marrow function as defined below:

Leukocytes	>3,000/μL
Absolute neutrophil count	>1,500/μL
Platelets	>70,000/μL
Total bilirubin	Within 2 x upper limit of normal
AST (SGOT)/ALT (SGPT)	<2.5 x institutional upper limit of normal
Creatinine	Within 1.5 x upper limit of normal OR
Creatinine clearance	>60 mL/min for patients with creatinine levels above institutional normal

9. Ability to understand and follow the breathing instructions involved in the respiratory gating procedure or to tolerate compression sufficient to reduce fiducial motion to <= 5mm.
10. Ability to understand and the willingness to sign a written informed consent document.
11. Residual or on-going ≥ Grade 3 treatment-related toxicity from previous chemotherapy should be resolved.

6.2 Subject Exclusion Criteria

1. Patients who have had prior abdominal radiotherapy.
2. Patients receiving any investigational agents.
3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
4. Contraindication to IV contrast
5. Patients in which iodine contrast is contraindicated.
6. Pregnant and breastfeeding women are excluded. Women of childbearing potential who are unwilling or unable to use an acceptable method of birth

control to avoid pregnancy for the entire study period and for up to 4 weeks after the study are excluded. This applies to any woman who has experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months, or women on hormone replacement therapy with serum FSH levels greater than 35 mIU/mL. A negative urine or serum pregnancy test must be obtained within 14 days prior to the start of study therapy in all women of childbearing potential. Male subjects must also agree to use effective contraception for the same period as above.

7.0 RECRUITMENT PLAN

This study will be available to all patients seen at University of Colorado who meet the eligibility criteria. University of Colorado is a referral center for pancreatic cancer and all patients considered for this study will be presented at a weekly multidisciplinary Pancreatic Multidisciplinary Conference. In addition, the study will be placed on the University of Colorado Website to maximize patient recruitment. Patients will be identified from surgical, gastroenterology and medical oncology clinics for treatment of their disease. The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations.

Patient recruitment will continue for a period of 3 years. Based on past census values at University of Colorado, we expect 10-15 local pancreatic cancer patients will be eligible for this study per year. The target accrual is 18 patients over 3 years.

8.0 PRETREATMENT EVALUATIONS (PRE-SCREENING)

To be completed:

- Histologic or cytologic confirmation of malignancy.
- Endoscopic retrograde cholangiopancreatography (ERCP) as clinically indicated for placement of a biliary stent for obstructive jaundice and/or for brushings/washings to confirm malignancy.
- Endoscopic ultrasonography (EUS) will be performed. Cytologic confirmation of malignancy will be obtained during EUS by core biopsy or Fine Needle Aspiration (FNA), if possible.
- A 12-lead Electrocardiogram (EKG).
- Within 2-4 weeks of completion of induction chemotherapy (at least 3 months but no more than 12 months of standard of care chemotherapy for LAPC, either FOLFIRINOX or gemcitabine and nab-paclitaxel), patients will be evaluated with a repeat CT of the chest, abdomen and pelvis with a dedicated pancreatic protocol/angiogram series. If there is no evidence of distant disease and the pancreatic

tumor is still deemed to be unresectable by a hepatobiliary surgeon, the patient may be eligible for the protocol. If the patient is eligible and enrolled on the study, treatment should be initiated within 30 days of the CT scan or it must be repeated.

- Patients will be seen by a radiation oncologist to discuss the radiotherapy options and if the tumor is felt to be amenable to SBRT, the patient can be enrolled on the dose escalation protocol.

9.0 STUDY PROCEDURES - SCREENING

9.1 To be completed within 30 days prior to SBRT:

- History and physical examination and performance status.
- CT chest, abdomen, pelvis with a dedicated pancreatic protocol.
- Review of CT or MRI scans at Multidisciplinary Conference to determine if tumor is locally advanced.
- Documentation of all measurable or non-measurable disease parameters including radiographic imaging procedures within four weeks of study entry. The definitions of measurable and non-measurable disease will be those definitions used in the RECIST criteria as defined by CTEP (http://ctep.info.nih.gov/Policies).
- Placement of gold fiducial markers (via EUS or, if not feasible by EUS, by direct visualization under laparoscopy). No specific location within the tumor is required. In conjunction with the imaging system, fiducials will serve to identify the precise location of the pancreas tumor relative to these markers during SBRT and confirm that the tumor does not move significantly with respect to the bony skeleton over the course of treatment. It is expected that such fiducial placement will be done on an outpatient basis. If the patient has a plastic stent, this can be exchanged for a metal wall stent.
- Core biopsy or Fine Needle Aspiration (FNA) will be obtained during EUS if possible -The sample will be sent for immunomonitoring assays.
- Complete blood count (CBC) with differential and platelet count, serum chemistries (Na, Cl, BUN, Creatinine, K, Bicarb, and glucose), LFTs (AST, ALT, alkaline phosphatase, total bilirubin), calcium, albumin, total protein, LDH, INR and CEA, CA19-9.

9.2 To be completed within 14 days prior to SBRT:

- Serum pregnancy test for all women of childbearing potential. If the test result is positive, the patient will not be allowed to participate in this study.
- Research blood draw for immune monitoring analysis
- Completion of quality of life (QOL) assessment

- Simulation for radiotherapy planning: At least 4 days after the fiducial placement, patients will undergo a simulation for RT treatment planning at which time the patient is immobilized in a cradle. While immobilized, a thin-sliced CT with IV and PO contrast is performed. A 4DCT scan is obtained for patients treated with respiratory gating (see section 4.2). A pCT will also be performed in the treatment position.

10.0 STUDY PROCEDURES - TREATMENT/INTERVENTION PLAN

- The interval between completion of induction chemotherapy and initiation of SBRT should be preferably within 2-4 weeks but no longer than 8 weeks.
- Based on the planning CT scan performed at the simulation, an SBRT treatment plan is developed using inverse planning methods. A dose distribution in which the target receives the prescription dose, and the relevant normal tissues are exposed to less than the tolerance dose levels is evaluated. VMAT arc therapy or multi-field IMRT plans will be acceptable.
- A total dose of 900cGy will be delivered to the tumor with each fraction for the first 3-patient cohort. Dose escalation will start with dose level 1 (9 Gy x 3 fractions) and increase by 1 Gy per fraction at each dose level, dose level 2 will be 10 Gy x 3 fractions and dose level 3 will be 11 Gy x 3 fractions.
- Motion management will be achieved by either placement of an abdominal compression belt or using respiratory gating per standard of care.
- At the time of treatment, kilo voltage images are taken to evaluate positioning based on the fiducial markers.
- Initial shifts are made to bring the patient into the correct position.
- A cone beam CT (CBCT) scan is performed.
- The CBCT scan is registered with the planning CT scan in 3D by aligning the fiducial markers from the two scans.
- The position of the fiducial markers or stent on the simulation CT is then compared with the position of the fiducial markers or stent seen in the CBCT scan. Any adjustment to the position of the volume to be treated is made by the physician using software developed for this purpose.
- If an adjustment is to be made, it is implemented by correcting the position of the treatment couch.
- A second CBCT scan is taken to confirm patient is in the correct treatment position. Any additional shifts can be made as needed.
- A 2D-KV orthogonal pair is obtained for confirmation of treatment position
- The first fraction of SBRT is then delivered.

- A pCT is performed within 90 minutes of SBRT.
- 2 more fractions of SBRT are delivered.
- A pCT is performed at 6 weeks post SBRT.
- Research blood draw during SBRT and at 6 weeks follow-up.

10.1 **Research Samples**

A research biopsy will be performed prior to treatment to analyze tumor and stromal expression of biomarkers and correlate these with clinical outcomes. The biopsy will be performed, if possible, at the time of the EUS-guided fiducial placement. The research coordinator will bring the tissue in formalin directly to research histology. Research histology will embed the biopsy to deliver the de-identified sample to the Human Immune Monitoring Shared Resource for further analyses. Peripheral blood will be prior to SBRT treatment, during SBRT treatment, and 6 weeks following treatment according to the schedule outlined in section 11. Two 8 ml EDTA blood tubes will be collected at each time point for experimental research that will be performed in the University of Colorado Denver School of Medicine Human Immune Monitoring Shared Resource. Blood samples will be de-identified prior to transfer to the Human Immune Monitoring Shared Resource using study numbers that will be assigned to each blood sample in the order they are drawn. A sample information form will be included with each sample describing the de-identified study number, the time the blood was drawn, and the time the blood was submitted. All research samples will be labeled with de-identified study numbers. The PI will maintain a secure record of patient and study ID's.

10.2 **Specimen Analysis**

Peripheral blood mononuclear cells (PBMCs) will be isolated and flow cytometry will be used to quantify immune cell phenotypes, to measure tumor-specific T cell responses, and to measure cytokines present in plasma. Biopsy samples from the primary pancreas tumor will be obtained by fine needle aspiration and if feasible, core needle biopsy by the gastroenterologists at the time of fiducial placement. Specimen processing will be performed by the Tissue Banking Shared Resource and submitted for further analyses as described below by the Human Immune Monitoring Shared Resource.

- **Baseline and post-treatment immune monitoring.** Participants will be asked to provide 16 mls of blood prior to initiating treatment, during treatment, and after completion of treatment to evaluate changes in immune cell frequency and activation status by flow cytometry. Approximately five million PBMCs will be used to determine the frequency of tumor-specific T cell responses by stimulating the cells with a mixture of peptides derived from known tumor antigens and measuring IFN-gamma production by ELISPOT.

Approximately five million PBMCs will be used to analyze the frequency of T cell populations and their activation status by flow cytometry. Any remaining cells will be securely stored for up to five years.

- **Cytokine analysis.** Up to 10 ml of plasma will be securely stored for five years following study completion for subsequent cytokine analysis. Multiplex cytokine array will be used for subsequent cytokine analysis. Concentration of cytokines related to the function of MDSCs (GM-CSF, VEGF, MIP-1 alpha, MIP-1 beta, IL-10, IL-6, and IL-8) and T cells (IFN-gamma, TNF-alpha, IL-1-beta, IL-2, IL-4, IL-5, IL-12p70, IL-17) will be analyzed.
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- **Tissue analysis:** Immune cells with also be quantified and characterized in tumor biopsies using the Vectra 3 imaging system that enables immunohistochemical analysis of up to six immune markers (plus DAPI) in formalin-fixed paraffin-imbedded tissue samples on a single slide. The powerful accompanying inForm software uses trainable algorithm-based tools to recognize and segment tissue morphology, phenotype and quantify infiltrating immune cells, score positive regions in the tissue, and provide mean fluorescence intensities and two-dimensional geometric locations for each cell in the tissue.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

Tests/Procedures	Before SBRT		During SBRT[5]	Follow-up						
	Within 30 days	Within 14 days	SBRT	6 wks ± 1 wk	10-12 wks	6 mos±2 wks	9 mos±2 wks	12 mos±2 wks	18 and 24 months ± 4 wks	
Placement of gold fiducial markers + EUS-guided FNA or core biopsy	X									
Review at Multidisciplilnary Conference	X									
Medical History	X[7]				X	X	X	X	X	
Physical Exam and ECOG[6]	X				X	X	X	X	X	
CBC, Metabolic panel, LFTs, Ca-19-9, CEA	X			X	X	X	X	X	X	
Pregnancy test[1]		X[1]								
Research Blood		X	X	X						
CT (chest, abd & pelvis)	X[3]				X	X	X	X	X	
Simulation CT, 4DCT[4]		X								
Cone beam scan			X							
Abdominal pCT		X	X[2]	X						
3 fractions of SBRT delivered			X							
Toxicity Assessments		X	X	X	X	X	X	X	X	
EORTC QLQ-C30, EORTC QLQ-PAN26		X			X	X				
Survival Status										

[1] For women of child bearing potential

[2] To be performed within 30-120 minutes following the first fraction of SBRT

[3] CT scans of the chest/abdomen/pelvis can be done prior to enrollment but must be within 30 days of initiating SBRT.

[4] For respiratory gating patients only

[5]Set-up and treatment procedure repeated for each of 3 fractions

[6]Physical exam includes HEENT, Pulmonary, Cardiovascular, GI/Abdomen, Extremities, Neurological, Skin and hair

[7] Including smoking history

12.0 TOXICITIES/SIDE EFFECTS

12.1 Preparation for SBRT

Toxicities may occur from the pancreas core biopsies and placement of the fiducial markers. Potential adverse effects include cholangitis, pancreatitis, bleeding, and infection.

All patients will get standard antibiotic prophylaxis at the time of biopsy.

12.2 SBRT planning and treatment

No side effects are expected to result from the CB imaging used for on-line target localization. The additional patient dose from the two cone beam scans is approximately 10 cGy, which represent less than 1% of the prescription dose.

Toxicities will be assessed using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0). Possible toxicities may occur from the single fraction high dose treatment include:

12.2.1 Anticipated Toxicities of SBRT

Likely:

- stomach pain and intestinal discomfort
- abdominal bloating and gas
- nausea
- diarrhea
- fatigue
- tanning
- skin redness
- hair loss within the radiation area - which is temporary
- permanently dry skin in the radiation treatment area
- loss of appetite and weight loss
- mild muscle aches in the area treated

Less Likely:

- vomiting
- low blood counts, which could lead to an increased risk of infection
- weakness and/or bleeding and bruising easily

Rare, but serious:

- change in liver or kidney function, which is unlikely to cause symptoms

- bowel obstruction, which could result in abdominal pain, nausea and vomiting and may require surgery
- gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain, nausea and vomiting, and bleeding, and may require surgery

The risk of significant toxicity would depend on the presence of normal tissue structures in close proximity to the target. These normal tissue doses will be constrained by the treatment plan to deliver doses no more than those listed in section 4.2 (Intervention: Radiation Treatment Planning).

Patients will be assessed for late toxicities (>3 months post radiation) every 3 months for the first year.

13.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

13.1 Primary objective:

To identify the maximum tolerated dose (MTD) of stereotactic body radiotherapy (SBRT) in locally advanced pancreatic cancer (LAPC) patients who have not developed distant progression after induction chemotherapies per standard of care.

The primary objective is to determine the MTD of SBRT after for patients with LAPC (induction FOLFIRINOX and nab-paclitaxel and gemcitabine per standard of care). This will be accomplished by the standard 3+3 dose escalation design. Dose limiting toxicities (DLT) are defined by ≥ Grade 3 treatment-related GI toxicity within 3 months of SBRT. These include: (1) Bowel (includes bowel perforation, obstruction, or hemorrhage) and (2) Stomach (bleeding ulcer, perforation) as determined by imaging or endoscopic evaluation.

13.2 Secondary objectives:

13.2.1 *To preliminarily assess the 2 year local control, progression free and overall survival rates for LAPC patients after induction chemotherapy and SBRT. Patterns of failure will also be investigated.*

Patients will be followed approximately every 3 months after SBRT. To assess recurrence, serum CA19-9 level will be obtained at each visit and CT or MRI imaging will be obtained every 3 months (± 2 weeks) until 12 months, and then every 6 months (± 4 weeks) for year 2.

Local control (LC) will be measured from completion of SBRT to the time of identification of any local progression by imaging or surgical exploration. Overall

survival (OS) will be measured from completion of SBRT until death due to any cause. Progression free survival (PFS) will be measured from completion of SBRT to the time of tumor progression or death due to any cause. PFS and OS will be estimated using the method of Kaplan and Meier. The pattern of patients experiencing local, distant or local with distant failure will be estimated using competing risks method. First site of failure will be recorded.

13.2.2. *To identify early changes in the normal small intestine after SBRT for LAPC using pCT derived parameters to document changes in tissue perfusion kinetics and heterogeneity that predict for development of gastrointestinal toxicity such as duodenal ulcers, strictures, or enteritis.*

We will measure changes in the perfusion/permeability related parameters of peripancreatic small intestine before, during and after SBRT for LAPC using pCT and correlating these changes with the development of gastrointestinal toxicity such as duodenal ulcers, strictures, or enteritis. Patients will undergo baseline, post-first-fraction SBRT and post-treatment CT scans on the Siemens AS Open scanner in the Department of Radiation Oncology. Perfusion/permeability parameters reflect the rate of exchange of I and include K^{trans} (transfer rate of contrast agent between vascular space and extravascular and extracellular space (EES), v_e and v_p (volume fraction of EES and vascular space, respectively), F (blood flow at the capillary level), and τ (mean transit time across capillary) [68, 74]. These derived parameters will be measured at baseline and re-measured for comparison on post-treatment scans. Patients will be followed approximately every 3 months after SBRT. Follow-up evaluations will include history and physical with assessment for presence of late toxicity using NCI CTCAE v 4.0.

The region of interest (ROI) will be placed by an experienced radiologist on the entire tumor. Tumor margins will be evaluated by reviewing all prior imaging, including CT and possible conventional MR sequences (T1 and T2). For pancreas cancer, the actual tumor extent is unknown, especially after treatment, so the ROI placement will be inherently limited by interobserver variability, which can be studied on its own.

Data will only be analyzed if seen on functional images. ROI's will be placed on the entire tumor. Tumor heterogeneity will be addressed by measuring standard deviation and skewness of the derived metrics. The experienced radiologist will draw the ROI on the normal tissue. A physicist and radiologist will review the images being acquired together to ensure the same region ROIs are covered in pre and post treatment images. The results from the study will provide the minimum size deemed measurable for the derived metrics.

13.2.3 *To investigate vascular and cellular changes resulting from SBRT for LAPC using pCT derived parameters that can predict treatment response and to assess any correlation between these pCT derived parameters and local control and progression-free survival.*

We will measure changes in diffusion and perfusion/permeability related parameters. Comparisons will be made between the pre- treatment, post-first-fraction SBRT and post-treatment pCT (K^{trans}, v_e and v_p, F, and τ) derived parameters. The baseline measurements as well as intra- and post-treatment changes in these parameters will be correlated to disease response of the primary tumor, as defined by RECIST 1.1 i.e. complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). K^{trans} is a reproducible biomarkers of response in cancers such as brain, prostate and breast tumors and has been comprehensively investigated. We expect similar results in this study. However, the other metrics derived from pCTare exploratory in nature.

Progression free survival and local control for LAPC patients treated with FOLFIRINOX followed by SBRT will be determined as described in 12.2.1. The clinical outcomes will be compared with finding on pCT. Each MRI biomarker outcome will be studied for potential association with local control and progression-free survival.

We will use ROI analysis with mean parameter values to see which measure correlates better with disease response. We will analyze heterogeneity using voxel based analysis by measuring the standard deviation and skewness.

13.2.4. *To evaluate Quality of Life (QOL) in terms of global QOL, physical symptoms, physical functioning and emotional well-being after induction chemotherapy and SBRT. Testing will be 14 days prior to SBRT, 10-12 weeks after SBRT, and 6 months after SBRT.*

The primary objective of the QOL study is to document the patient's experience of treatment for locally advanced pancreatic cancer by examining global QOL, physical symptoms, physical functioning and emotional well-being at baseline, during treatment, and after treatment. Subjects will be giving 2 questionnaires: (1) EORTC-PAN26 and (2) EORTC-QLQ-C30. The two questionnaires have a total of 56 questions, 54 out of which have answers on a scale of 1-4 and 2 questions have answers on a scale of 1-7.

QOL measures including EORTC-QLQ-C30[80] and the Pancreatic Cancer subscale (EORTC-PAN26)[81] will be assessed 14 days prior to SBRT (Time 0), 10-12 weeks

after SBRT (Time 1), and 6 months after SBRT (Time 2). The primary QOL endpoints include the EORTC global QOL, physical symptoms, physical functioning and emotional well-being.

14.0 CRITERIA FOR REMOVAL FROM STUDY

- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
- Patient is not treated according to the prescription dose
- The investigator removes the patient from the trial in the best interests of the patient
- Patient death
- Study completion or discontinuation
- Patient withdraws consent to continued participation in the trial or is lost to follow-up

15.0 BIOSTATISTICS

15.1 Dose Escalation Study and Clinical Outcomes Analysis

The primary objective of this trial is to determine the maximum tolerated dose (MTD) of SBRT after at least 3 months of induction chemotherapy for patients with LAPC. Dose limiting toxicities (DLT) are defined by ≥ Grade 3 treatment-related GI toxicity within 3 months of SBRT. These include: (1) Bowel (includes bowel perforation, obstruction, or hemorrhage) and (2) Stomach (bleeding ulcer, perforation). We will employ a modified 3+3 dose-escalation scheme.

Dose escalation will be evaluated after 3 evaluable patients who have completed 90 days of follow-up. Due to dropout during the 90-day follow-up period, up to 6 patients may be accrued at each dose level to yield a cohort of at least 3 evaluable patients. The dose level will be escalated if none of the evaluable patients followed for 90 days exhibits any DLT within 90 days of completion of SBRT. If a DLT is observed in one patient, an additional cohort of patients will be treated at that dose to achieve having at least 6 evaluable patients at that dose level. The dose will be escalated if none of the additional patients exhibits any DLT (i.e. at most 1 DLT is observed at that dose level). Dose-escalation stops and the previous dose will be considered the MTD if 2 or more patients have a DLT. If the previous dose level has been administered to fewer than 6 patients, an additional cohort of patients will be enrolled to achieve having at least 6 evaluable patients at that dose level. If at most 1 DLT is observed among all evaluable patients treated at that dose level, that dose level will be declared to be the maximum tolerated dose (MTD). If, however, there are a total of 2 or more DLTs, the dose will be de-escalated again. The MTD will be the greatest dose at which at least 6 evaluable patients are treated with at most 1 of them experiencing a DLT.

If 3 patients have completed the 90 day follow-up without a DLT and there have been more patients accrued at that dose level, the dose may be escalated based on 0 DLTs among the first 3 evaluable patients. However, if one of the additional patients treated at the lower dose subsequently experiences a DLT, the dose escalation will halt. At that point accrual will continue at the lower

dose level to achieve a total of 6 evaluable patients who have completed the 90 day follow up at the lower dose; if at most 1 of all patients at that dose level experienced a DLT then dose escalation occur and accrual at the higher dose level will resume. If 2 or more patients have a DLT at that level, the previous dose will be considered the MTD (as described above).

For this design, the probability of escalation is as follows:

True toxicity rate	5%	10%	15%	20%	25%	30%	40%	50%
Probability of escalation	0.97	0.91	0.81	0.71	0.60	0.49	0.31	0.17

Dose escalation will start with dose level 1 (9 Gy x 3 fractions) and increase by 1 Gy per fraction at each dose level, dose level 2 will be 10 Gy x 3 fractions and dose level 3 will be 11 Gy x 3 fractions. The maximum number of patients needed for this dose escalation design is 18. A patient must be successfully treated according to prescription dose before he/she can be evaluated for the safety point, otherwise he/she will be replaced by a new patient. We expect to finish the enrollment (up to 18 patients) within 3 years. All toxicity profiles will be summarized and tabulated by dose level.

For the first secondary objective, the 2 year local control (LC) rate, progression free-survival (PFS), overall survival (OS) and patterns of failure for LAPC patients after induction chemotherapy and SBRT will be assessed using survival analysis tools such as Kaplan-Meier method or cumulative incidence curves if competing risks exist. To provide some simple comparison to the historical efficacy rates we will focus on OS due to its simplicity. The historical 2-year OS rate is approximately 20% and we expect to improve it to 40% by using the proposed treatment modality. Thus we expect that, out of the 22 patients at MTD level, we shall have at least 8 patients surviving beyond 2 years. Under the null hypothesis of 20%, the probability of observing at least 8 patients surviving beyond 2 years (i.e., type I error rate) is 5.6%. Due to the small sample size and lack of power, we will not use “at least 8 patients (out of 22) surviving beyond 2 years” as a formal decision rule for declaring the success of this study. The anticipation of at least 8 patients (out of 22) surviving beyond 2 years is merely to provide us a preliminary estimation of the efficacy signal relative to the historical control in this population.

For the above efficacy secondary objective, patients at different dose levels will be examined separately.

For the two secondary objectives involving pCT parameters (see Section 12 for details of how to obtain these parameters), all relative changes (i.e., percentage of change from the baseline, note that there will be two sets of changes, one based on the 90-minute CT and the other the 6-week CT) will be computed and correlated with the toxicity and response at

6 months post-SBRT by logistic regression. For correlation with OS, LC and PFS, survival analysis tools such as Cox model or Fine-Gray competing risks regression model will be used. For these two objectives all patients will be combined for statistical analyses.

For the QOL objective, patients will be assessed at the following time points: within 14 days prior to SBRT (Time 0); 10 to 12 weeks after SBRT (Time 1), and 6 months after SBRT (Time 2). Questionnaires will be administered in the clinic or by e-mail at all assessments. The quality of life assessment will include quality of life measures (EORTC QLQ-C30 Quality of Life Questionnaire) and the Pancreatic Cancer subscale (EORTC-PAN26). See Section 12 for more details about the quantification of the answers. The time required to complete the assessment is 20 minutes. Analysis of the QOL outcomes will be descriptive. Summary statistics will be used to characterize the patient's experience of treatment. Means, standard deviations, medians, and ranges of the QOL endpoints (scales and subscales) will be tabulated by dose level and by assessed time.

For the last secondary objective, we will assess the feasibility of obtaining adequate cytology samples for next generation sequencing using sample proportion (the number of patients who yielded sufficient material for next generation sequencing at any three time points divided by the number of patients who went through the procedure) and its confidence intervals. All patients will be combined for this objective.

16.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

[Section Intentionally Omitted]

17.0 DATA MANAGEMENT

17.1 Data and Safety Monitoring

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits

- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this six month report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review. The Colorado Multiple Institutional Review Board (COMIRB) will be the IRB of record for this study.

17.2 Quality Control and Quality Assurance

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the electronic case report forms (eCRFs) will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

17.3 Study Monitoring and Frequency of Monitoring Visits

The monitoring for this trial will be carried out in full compliance with all Good Clinical Practice (GCP) Guidelines, COMIRB policies and regulations and all applicable federal regulations. This study will be monitored for its entire duration until the investigation is completed.

A site initiation visit (SIV) will be conducted for all participating sites prior to enrolling any subjects into this trial to document full training of all study personnel who will be delegated any specific task on the study. This visit includes but is not limited to training on the IRB approved study protocol, regulatory requirements for study conduct including but not limited to GCP guidelines, reporting of adverse events, the review of study personnel's roles and responsibilities, completion of the Delegation of Authority Log and Protocol Training, review of the monitoring plan as outlined in the protocol, and to review data collection and proper source documentation procedures.

The monitor will perform both on-site interim monitoring visits and remote monitoring off-site for all participating sites in this study. Data that is collected during the duration of this trial will be reviewed by the sponsor to identify data discrepancies, inconsistencies or any unclear information both on-site and remotely. In order to reconcile data discrepancies, queries will be sent electronically to the site(s) for data that requires clarification.

This study is considered to be high risk and will need consistent routine monitoring visits. An initial monitoring visit will be performed within 2-4 weeks of the first subject being enrolled into the trial. Subsequently, this study will then be monitored every 8-12 weeks on-site, with remote monitoring in-between scheduled on-site visits, as necessary based on the study needs, at all participating sites.

The monitor will perform routine on-site monitoring visits that include but are not limited to:

- Interface with the Principal Investigator at each visit, if possible, to discuss any findings, address concerns, and to update the PI and site staff on current study progress.
- Subject source documentation verification
- Verify subject eligibility
- Informed Consent review
- Verify radiation treatment
- Protocol adherence
- Review Case Report Forms and the electronic database
- Regulatory documents review

Review and determine if all Adverse Events and Serious Adverse Events have been appropriately reported within the specified time periods required by the protocol, GCP, the IRB and any other applicable regulatory requirements

After monitoring visits are completed, the monitor will evaluate and summarize the results after each monitoring visit in a written report. This report will include all pertinent findings during the monitoring visit including all identifiable and reportable data and non-compliant problems ongoing in the study and recommend resolutions for noted deficiencies. Any noted deficiencies that are in need of resolution will need a corrective plan of action by the Investigator and/or research staff.

The Investigator will receive a post interim monitoring visit follow-up letter 7 to 10 business days following the completion of the monitoring visit, documenting study progress and any pertinent findings and outstanding action items that need to be resolved. The Investigator will need to sign and date the letter after reviewing, and keep the original on site. The Monitor may review the letter at the next subsequent visit to ensure it has been reviewed, signed and dated by the Investigator in a timely manner.

Upon completion or termination of the study, the sponsor will ensure that each participating site undergo a site Close-out Monitoring visit prior to final closure of the study. The Monitor will assure that all necessary site close-out procedures and activities have been completed which include but are not limited to query resolution, Case Report Form completion, notification to local IRB and regulatory authorities of study closure, record retention arrangements finalized, AE and SAE resolution, and all essential documents are available and present in the Principal Investigator's file. The Monitor will complete a final close-out report documenting completion of the Close-out Monitoring visit and forward a study Close-out follow up letter to the Investigator(s) at the participating site(s) to be reviewed, signed and dated, and file a copy on site for record retention.

18.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: We take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 7.0 (Recruitment Plan).

Exclusion of Children: Children have been excluded from this study. Pancreatic adenocarcinoma is an adult cancer.

Exclusion of Lactating or Pregnant Women: Lactating and pregnant women are also excluded because of potential teratogenic effects of radiotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is possible that this treatment will result in shrinkage of pancreatic cancer or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including, CT scans and SBRT. Patients will not be responsible for the costs of the pCT following SBRT.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: For patients with localized pancreatic cancer, alternative treatments may include other chemotherapy regimens as well as standard chemoradiation. Patients may be eligible for other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. A limited data set will be shared with Memorial Sloan Kettering Cancer Center. A similar was conducted by Dr. Karyn Goodman at MSKCC and these data will be combined and analyzed for publication. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study.

18.1 Privacy

University of Colorado's Institutional Review Board may allow the use and disclosure of protected health information pursuant to a completed and signed Informed Consent Form. The use and disclosure of protected health information will be limited to the individuals described in this form which must be approved by the IRB.

18.2 Procedures for Adverse Events – Definitions and Reporting Criteria

18.2.1 Definitions

The definition of "related" being that there is a reasonable possibility that the treatment caused the adverse event.

An adverse event is UNEXPECTED when the specificity or severity is not consistent with the current expectations of treatment complications.

Adverse Event (AE)

An AE will be defined as any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with the 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 medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic testing.

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

18.2.2 Procedures for Recording and Reporting Adverse Events

As noted above in section 17.1, per the CU Cancer Center Institutional DSM Plan, SAEs and AEs are reported to the DSMC, IRB. If the AE or SAE occurs at CU

Cancer Center, it will be reported to the PI who will then report it to the DSMC and IRB. All AEs and SAEs are to be reported within 5 business days of receiving notification of the occurrence. The PI will also follow their IRB requirements regarding AE or SAE reporting.

Any SAE must be reported to the COMIRB as soon as possible but no later than 5 calendar days.

19.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information and participants will sign an Informed Consent Form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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21.0 APPENDICES

Appendix 1. ECORTC QLQ-C30 (version 3)

Appendix 2. EORTC QLQ – PAN26

APPENDIX 1

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

APPENDIX 1

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 2

ENGLISH/US

EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Were you uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did your arms and legs feel weak?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel a sudden urge to have a bowel movement?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

APPENDIX 2

ENGLISH/US

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Have you worried about what your health might be like in the future?	1	2	3	4
52. Were you limited in planning activities in advance (e.g. meeting friends)?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

Principal Investigator: Sana D. Karam, MD, PhD.

COMIRB No: 16-1139
Protocol Version Date: October 1, 2019

Study Title: A Dose Escalation Trial of Stereotactic Body Radiotherapy (SBRT) after Induction Chemotherapy for Locally Advanced Pancreatic Cancer

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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about the safety of stereotactic body radiotherapy (SBRT) given in 3 fractions (doses) and how well it works to treat your kind of cancer when used after standard chemotherapy.

You are being asked to be in this research study because you have advanced pancreatic cancer that has not spread to other areas of your body but cannot be removed with an operation.

Other people in this study

Up to 18 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive. The goal of the study is to see what the highest dose can be for 3-fraction SBRT. Subjects with advanced cancers that have already had at least three months of standard chemotherapy will be asked to join the study.

Study Procedures

While you are taking part in this study, many of the tests and procedures that will be performed are standard of care for your disease. Some "research" procedures are performed just for this study and are identified below.

- **Physical Examination**
  A physical examination will be completed as part of your standard of care. We will also assess if the study drug is affecting your body functions including lungs, heart,

abdomen, extremities, skin, head (eyes, ears, noses, hair, etc.), and neurologically.

- **Vital Signs**
  We will take your blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

- **Concomitant Medications**
  Your study doctor will let you know which other medications you can and cannot take while taking part in this study. From the time you first receive the study drugs through 30 days after the last dose, we will record other medications you may be taking.

- **Blood**
  These tests are sometimes referred to as safety labs so the study doctor can be sure it is safe for you to take part in this study and to be given the study drugs. Serum pregnancy tests will be performed in women who are able to become pregnant. A positive pregnancy test prior to being given the study drugs, will exclude you from starting or continuing to take part in the study.

- **EUS and Fiducial Placement**
  Endoscopic ultrasound (EUS)-guided placement of 3-5 fiducial markers for SBRT targeting purposes. The fiducials will be placed directly into or adjacent to the tumor under CT guidance, EUS or under direct visualization during laparoscopy.

Description of Research Procedures

- **Perfusion CT (pCT) Scan.** A computerized tomography scan (CT scan) is a series of detailed pictures of areas inside the body taken from different angles. A perfusion CT (pCT) will look at the effects on the blood flow to the tumor following the SBRT treatment

- **Questionnaires for quality of life.** These questionnaires will ask about you, your health, and any symptoms or problems you may be having.

- **Biopsy**
  At the time of the EUS and Fiducial Placement Procedure, a fresh biopsy of your tumor tissue will be taken and kept for research.

- **Blood draw**
  We will be collecting approximately 2 tablespoons of blood for research purposes at the time of your normal blood work at 5 time points.

Screening Study Procedures

Within 30 days prior to SBRT:

- Placement of gold seed into the tumor to help guide the delivery of radiation therapy
- Medical history
- Physical exam and performance test
- Blood tests
- CT scan (chest, abdomen and pelvis)
- Tumor biopsy – ***research procedure***

Within 14 days prior to SBRT:

- Pregnancy test for women of child-bearing potential
- Simulation CT scan
- Toxicity (side effects) assessment
- Abdominal perfusion CT (pCT) scan – ***research procedure***
- Quality of Life Questionnaires – ***research procedure***
- Blood tests for Immune monitoring analysis – ***research procedure***

During Treatment Procedures

- Cone beam CT scan prior to each treatment with SBRT
- SBRT – 3 treatments
- Toxicity (side effects) assessment
- Abdominal perfusion CT (pCT) scan – ***research procedure***
- Blood tests for Immune monitoring analysis - ***research procedure***

Follow-up Procedures (*after SBRT)*:

Week 6 (plus or minus 1 week):

- Toxicity (side effects) assessment
- Abdominal perfusion CT (pCT) scan – ***research procedure***
- Blood tests for Immune monitoring analysis – ***research procedure***

Week 10-12:

- Medical History
- Physical exam and Performance Test
- Blood tests

- CT scan (chest, abdomen and pelvis)
- Toxicity (side effects) assessment
- Quality of Life Questionnaires – ***research procedure***

6 Months (plus or minus 2 weeks):

- Medical History
- Physical exam and Performance Test
- Blood tests
- CT scan (chest, abdomen and pelvis)
- Toxicity (side effects) assessment
- Quality of Life Questionnaires – ***research procedure***

9 Months and 12 Months (plus or minus 2 weeks):

- Medical History
- Physical exam and Performance Test
- Blood tests
- CT scan (chest, abdomen and pelvis)
- Toxicity (side effects) assessment

Every 6 Months during Years 2-5 (plus or minus 4 weeks):

- Medical History
- Physical exam and Performance Test
- Blood tests
- CT scan (chest, abdomen and pelvis)
- Toxicity (side effects) assessment

Annually (Year 5+)

- In person or by phone call health check. We may also use publically available sources to obtain this information if we are unable to reach you.

How long will I be in this study?

We think that your active participation in the study will last about 5 years. After 5 years, we will continue to collect information on your health status.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include:

Anticipated Toxicities of SBRT

Likely:

- stomach pain and intestinal discomfort
- abdominal bloating and gas
- nausea
- diarrhea
- fatigue
- tanning
- skin redness
- hair loss within the radiation area - which is temporary
- permanently dry skin in the radiation treatment area
- loss of appetite and weight loss
- mild muscle aches in the area treated

Less Likely:

- vomiting
- low blood counts, which could lead to an increased risk of infection
- weakness and/or bleeding and bruising easily

Rare, but serious:

- change in liver or kidney function, which is unlikely to cause symptoms
- bowel obstruction, which could result in abdominal pain, nausea and vomiting and may require surgery
- gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain, nausea and vomiting, and bleeding, and may require surgery

The risk of significant toxicity would depend on the presence of normal tissue structures in close proximity to the cancer that will be treated.

Risks of Having Blood Taken:

In this study, depending on study visit, we will need to get about 8-26 tablespoons (4-13 tubes) of blood from you over the course of the study. We will get blood by putting a needle into one of your veins and letting the blood flow into a vacuum tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risk of CT Scan:

Other possible risks include as part of this study we will perform a CT scan of your chest. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation.

You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will deliver to your body (give you) is about the same as you would get from living in your environment for 1 year.

Risks of EUS and Fiducial Placement:

In this study, you will be asked to provide one biopsy for research, which will happen at the same time as the EUS and Fiducial Placement. There is a small chance that you could get an infection where the needle goes in. You may also experience pain, redness, swelling, minor bleeding or bruising at the site where the cut was made or the needle inserted. You may experience mild to moderate pain at the site of the needle puncture. There is also a small chance that you could have an allergic reaction to the numbing medicine. After your skin heals up, you may have a small scar where we take the samples.

Risk of Biopsy:

There are some risks to having a biopsy at the time of your fiducial placement into the pancreas. There is a small chance that you could get an infection where the needle goes in. You may also experience pain, swelling, or minor bleeding at the site where the needle inserted. You may experience mild to moderate abdominal pain after the procedure

Risks of loss of confidentiality:

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Other possible risks include:

While you take part in this study, you will have tests and procedures that are standard of care for your disease. These include CT scans, MRIs, endoscopic ultrasound (EUS), and stereotactic body radiation therapy (SBRT). There are risks associated with these procedures. You should talk to your study doctor about any questions you may have about these risks.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the shrinkage of pancreatic tumors and the potential of stabilizing the progression the cancer. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your cancer. You have the following choices available to you:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Get treatment only for your pain and symptoms, but no treatment for the cancer itself
- Get no treatment at all

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

This research is being sponsored by The University of Colorado Cancer Center.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

It will not cost you anything to be in the study for research treatments. All standard of care costs will be billed to you or your insurance. Check with your insurance company for their coverage of participation in studies.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Karam immediately. Her phone number is 720-848-0141.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care

Who do I call if I have questions?

The researcher carrying out this study is Sana D. Karam, MD, PhD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Karam at 720-848-0141. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Karam with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov. This Web site will not include information that can identify you. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Sana D. Karam, MD, PhD.
University of Colorado Denver
Department of Radiation Oncology
Anschutz Cancer Pavilion Campus
Mail-Stop: F-706
1665 Aurora Court
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The University of Colorado Cancer Center, who is the institution paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make *all or some* **of the following health information about you collected in this study available to:** Memorial Sloan Kettering Cancer Center, which we are sharing a limited data set.

Information about you that will be seen collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Your social security number
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results

- Research Visit and Research Test records
- Billing or financial information

What happens to Data and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data and specimens collected from you during this study are important to this study and to future research.

If you join this study:

- The data and specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study the data and specimens collected from you.
- If data or specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:_____ Date: _____

Print Name: _____

Consent form explained by:_____ Date: _____

Print Name: _____

A signature line for a witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature:_____ Date: _____

Witness Print Name: _____

Witness of Signature

Witness of consent process