UCCI-GI-002- PHASE I STUDY TO EVALUATE THE FEASIBILITY OF NEOADJUVANT STEREOTACTIC BODY RADIATION THERAPY FOR RESECTABLE AND/OR BORDERLINE RESECTABLE ADENOCARCINOMA OF THE PANCREATIC HEAD AND/OR BODY

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ABBREVIATION LIST

SBRT	Stereotactic Body Radiotherapy
RCT	Randomized Controlled Trial
IORT	Intraoperative Radiation Therapy
IGRT	Image Guided Radiation Therapy
CBCT	Cone Beam CT
EUS	Endoscopic Ultrasound
BED	Biologic Equivalent Dose
GTV	Gross tumor volume
ITV	Gross Tumor Volume
PTV	Internal Target Volume
QA	Planning Target Volume
PPI	Quality Assurance
RTOG	Proton Pump Inhibitor
CTCAE	Common Toxicity Criteria for Adverse Events
AE	Adverse Event
CR	Complete Response
PR	Partial Response
SD	Stable Disease
PD	Progressive Disease
IHC	Immunohistochemistry
NK Cells	Natural Killer Cells
HA	hyaluronan
D1R	Dopamine Receptor 1

PROTOCOL SYNOPSIS

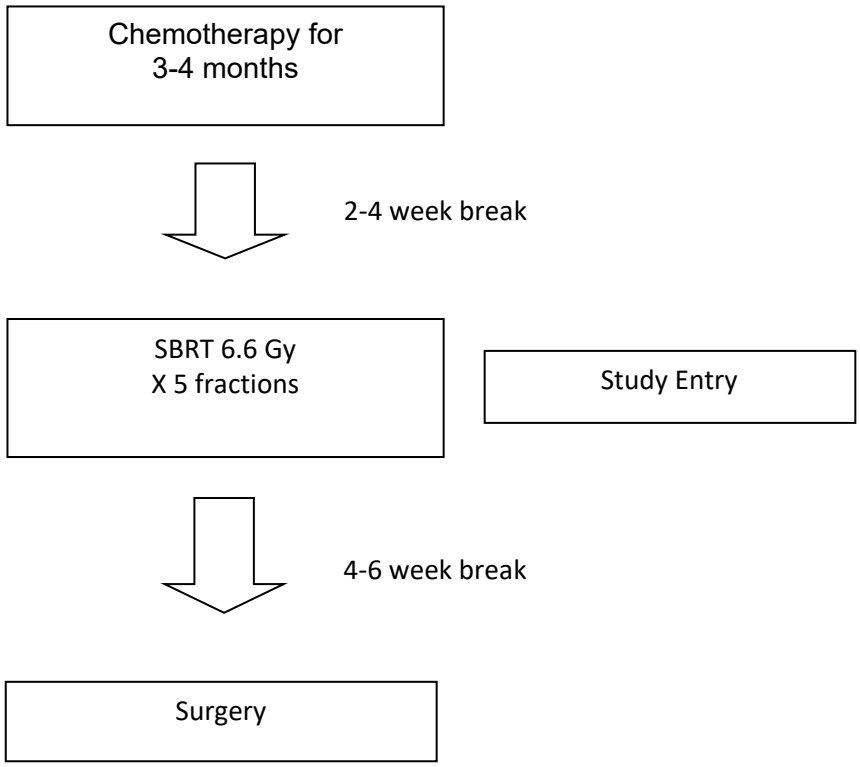
TITLE	PHASE I STUDY TO EVALUATE THE FEASIBILITY OF NEOADJUVANT STEREOTACTIC BODY RADIATION THERAPY FOR RESECTABLE AND/OR BORDERLINE RESECTABLE PANCREATIC ADENOCARCINOMA
STUDY PHASE/DESIGN	Prospective, non-randomized phase I study of 20 patients
INDICATION	Resectable and/or borderline resectable adenocarcinoma of the pancreas
PRIMARY OBJECTIVE	To evaluate rates of acute (within 3 months of treatment) gastrointestinal toxicity following fractionated Linac based SBRT for pancreatic tumors. Toxicities of note include any grade 3 or greater gastrointestinal toxicity.
SECONDARY OBJECTIVES	To evaluate rates of late (> 3 months after treatment) gastrointestinal toxicity following fractionated Linac based SBRT for pancreatic tumors. Toxicities of note include grade 2 or greater gastritis, enteritis, fistula, or ulcer and any other grade 3 or greater gastrointestinal toxicity. To evaluate local progression free survival, overall survival and metastasis-free survival rates after Linac based SBRT and subsequent resection in patients with resectable and/or borderline resectable pancreatic adenocarcinoma of the head and/or body. To develop and standardize Linac based SBRT delivery and dosimetric parameters. To estimate resection margin positivity (R0/R1) and pathologic complete response rate after neoadjuvant SBRT To evaluate pre- and post- SBRT patient reported quality of life (QOL)
TREATMENT	After 3- 4 monthsof chemotherapy, patients will be enrolled to a single arm trial of stereotactic body radiotherapy (SBRT) in 5 fractions given over 15 days. They will then proceed to surgery after a break of 4-6 weeks.

INCLUSION CRITERIA	• Age >18 years. • Karnofsky Performance Status >70% (see Appendix IV). • Histologically confirmed pancreatic adenocarcinoma of the head and/or body; at least the majority of the histopathologic specimen must be identified as adenocarcinoma. • Pancreatic tumors must be considered at least borderline resectable and/or borderline resectable at time of treatment planning. Definition of resectable and/or borderline resectable: no metastases, less than 180 degree involvement of hepatic artery, superior mesenteric artery or celiac artery • No active infection requiring hospitalization • If bilirubin > 2, patients must have a biliary stent placed prior to SBRT. • Patients must have acceptable organ and marrow function (see section “Inclusion Criteria, page 17-18). • Women who are not post-menopausal (as defined in Appendix V) should have a negative urine or serum pregnancy test. Women of childbearing potential must agree to use adequate contraception for the duration of study participation. • Ability to understand and the willingness to sign a written informed consent document. • Life expectancy > 3 months. • Patients are to have received neoadjuvant chemotherapy prior to enrollment. Approved regimens may consist of 3-4 months of gemcitabine-based chemotherapy or FOLFIRINOX. Patients will have a 2-4 week break between last chemotherapy administration and start of

EXCLUSION CRITERIA	• Presence of metastatic disease. • Infections requiring systemic antibiotic treatment. • Unable to understand or unwilling to sign a written informed consent document. •
PROCEDURES	Endoscopically guided fiducial placement with optional biopsies obtained at the time of fiducial placement.
STATISTICAL CONSIDERATIONS	See statistics section.

SCHEMA

Eligibility: resectable or borderline resectable adenocarcinoma of the pancreas. Definition of resectable: no metastases, less than 180 degree involvement of hepatic artery, superior mesenteric artery or celiac artery



I. OBJECTIVES

Primary Objective

- To evaluate rates of acute (within 3 months of treatment) grade 3 or greater gastrointestinal toxicity.

Secondary Objectives

- To evaluate rates of late (> 3 months after treatment) grade 2 gastritis, enteritis, fistula, and ulcer, or any other grade 3 or greater gastrointestinal toxicity
- To determine rates of local progression free survival, overall survival, and metastasis- free survival in patients with resectable and/or borderline resectable pancreatic adenocarcinoma of the head and/or body undergoing neoadjuvant SBRT
- To evaluate patient quality of life before and after Linac based SBRT.
- To evaluate the margin positivity rate and pathologic complete response rate after Linac based SBRT.
- To further develop standardization of Linac based SBRT delivery and dosimetric parameters.

II. BACKGROUND

Natural History and Management of Pancreatic Cancer

More than 40,000 individuals are diagnosed with pancreatic cancer annually in the United States. Despite aggressive combined modality treatment approaches, five-year survival of patients with pancreatic cancer is still less than 5% (1). Clearly, more innovative treatments are needed to improve survival in this group of patients.

Surgical resection is considered to be the only potentially curative treatment option (2). However, the majority of pancreatic cancer patients do not have resectable and/or borderline resectable disease at presentation. More than 85% of patients have locally advanced or metastatic disease when initially diagnosed.

Current Adjuvant Management of Resectable and/or borderline resectable Pancreatic Adenocarcinoma

Among the minority of patients who are able to undergo surgical resection, low median survival rates and cure rates imply the presence of residual local and/or systemic microscopic disease that may be amenable to adjuvant therapy. The standard of care for adjuvant therapy is controversial. Adjuvant chemoradiation has been frequently studied due to high rates of positive margins and locoregional recurrences seen in surgical series.

The benefit of 5-fluorouracil-based chemoradiation was first seen in a small, randomized trial performed by the Gastrointestinal Tumor Study Group (GITSG) (2). This study, published in 1985, randomized patients to observation versus postoperative therapy with concurrent 5-FU and split-course radiation (40Gy), followed by two years of adjuvant 5- FU. It showed a striking benefit in median survival and 5-year overall survival among patients undergoing chemoradiation despite the fact that there was no difference in loco-regional control among the two arms. The EORTC performed a similar study that enrolled patients with either pancreatic or periampullary cancers, who were randomized postoperatively to observation or chemoradiation (split-course radiotherapy with concurrent 5-FU). This protocol also demonstrated a trend towards improved survival among patients with pancreatic cancer who received adjuvant chemoradiation (3, 4). Additionally, two

large retrospective series, one from Johns Hopkins University (n=616) and one from the Mayo Clinic (n=472), have demonstrated median survival benefits consistent with the GITSG and EORTC studies (5, 6).

The comparative benefit of chemotherapy and chemoradiation was challenged by the European Study Group for Pancreatic Cancer (ESPAC) study, which randomized 541 patients with pancreatic adenocarcinoma who had undergone surgical resection to the following four treatment arms using a two-by-two factorial design: a) observation; b) concomitant chemoradiotherapy (20 Gy in 10 fractions over 2 weeks) with 500 mg/m2 5- FU IV bolus during the first three days of radiation therapy, repeated after a planned 2- week break without additional chemotherapy; c) chemotherapy alone (leucovorin 20 mg/m2 bolus followed by 5-FU 425 mg/m2 administered for 5 consecutive days repeated every 28 days for 6 cycles); and 4) chemoradiotherapy (as in arm 2) followed by chemotherapy. For the same subset randomized through the original two by two design, chemotherapy alone demonstrated a trend towards improved survival alone (median survival 17.4 months) versus observation alone (15.9 months), but the difference was not statistically significant (p=0.19). The study authors concluded that there was no survival benefit for adjuvant chemoradiotherapy but that a potential benefit existed for adjuvant chemotherapy alone. Unfortunately, this trial had many flaws, including a questionable study design and lack of surgical/pathological/radiation quality control measures, rendering its results difficult to interpret. However, ESPAC does highlight the importance of adjuvant chemotherapy.

While the above-mentioned adjuvant studies were being conducted, gemcitabine emerged as a more effective chemotherapy than 5-FU in the setting of advanced disease (8). Because of this, gemcitabine was evaluated in the post-operative setting. The Radiation Therapy Oncology Group (RTOG) reported on a phase III study of 518 resected pancreatic cancer patients randomized to either 5-FU or gemcitabine. Dosing for the 5-FU group consisted of continuous infusion (250 mg/m2/d for 3 weeks), followed by 5-FU continuous infusion (250 mg/m2/d) during radiation therapy (50.4 Gy in 1.8 Gy/fractions), followed by 2 cycles of 5-FU continuous infusion. Patients assigned to the gemcitabine arm received gemcitabine 1000 mg/m2 weekly X 3, followed by 5-FU continuous infusion during radiation therapy, followed by 3 cycles of gemcitabine alone (9). Although there was a higher incidence of grade 3-4 neutropenia among patients in the gemcitabine arm, the median survival was 20.3 months for the gemcitabine-treated patients versus 16.3 months for 5-FU treated patients (p=.03). In the final manuscript, RTOG reported a survival benefit on multivariable analysis of 20.6 versus 16.9 months (p=.03) in favor of the gemcitabine chemotherapy arm, restricted to patients with cancer of the pancreatic head. The European CONKO-1 study recently published a phase III study of 354 resected patients randomized to observation or 6 months of gemcitabine chemotherapy (10). The primary endpoint of this study was DFS; patients in the treatment arm had a significant improvement in DFS (13.4 months v. 6.9 months, p<0.001). Further follow-up has shown a survival benefit to chemotherapy.

From these studies, it is evident that a single standard adjuvant treatment approach for patients with resected disease has not yet been determined. However, given the above data, gemcitabine- or 5-FU based CRT (RTOG 9704) or gemcitabine/bolus 5-FU (CONKO- 1/ESPAC-3) can both be viewed as a reasonable standard of care in the adjuvant setting.

Current Neoadjuvant Management of Resectable and/or borderline resectable Pancreatic Adenocarcinoma

Among patients who have undergone surgery, pancreatic cancer exhibits a strong tendency to recur locally and to metastasize after a brief median time interval of approximately 13 months from surgical resection (11). Early relapse after curative surgery is likely explained by the presence of micrometastases or minimal residual primary disease not detectable at the time of

surgery, or by the spread of tumor cells into the portal vein, lymphatic vessels, and peritoneal cavity due to surgical manipulation. Therefore, preoperative treatment of resectable and/or borderline resectable or borderline resectable and/or borderline resectable pancreatic cancer has several potential benefits.

First, patients who undergo surgery up front must wait at least 6-8 weeks after surgery for healing to occur before starting adjuvant CRT. Furthermore, 20-30% of patients are unable to receive planned adjuvant therapy due to surgical complications or inability to tolerate adjuvant therapy after surgery (12, 13). Thus, there is a potentially harmful delay in treatment of micrometastatic disease, which is thought to exist in a majority of resectable and/or borderline resectable patients. Neoadjuvant therapy avoids this delay, allowing for immediate treatment of micrometastatic disease. Second, approximately 30% of patients who undergo surgery have positive resection margins (11,14); if radial margins are examined, it appears that as many as 75% of resections are margin-positive (15). Any partial response to treatment reduces the tumor volume, potentially increasing the likelihood of an R0 resection while decreasing both the burden of microscopic residual disease and intraoperative tumor spillage. Third, the resected tumor can serve as its own biological marker of treatment response; that is, an in vivo assessment of tumor chemo/radio-sensitivity can be performed. Fourth, the undisturbed tumor microenvironment may permit better delivery of chemotherapy to the tumor through the vasculature. An intact vascular supply will also allow for better oxygenation of tumor, which may enhance the effects of radiation by allowing for increased generation of oxygen free radicals. Fifth, without the prior trauma of surgery, the normal tissue surrounding the tumor may better tolerate CRT, decreasing rates of treatment-postponing toxicities and allowing for higher-dose radiotherapy. Sixth, patients who experience disease progression prior to surgical resection despite neoadjuvant therapy likely have tumors of an exceedingly aggressive biology that cannot be cured by extensive surgery and can therefore be spared the considerable risk of surgical morbidity and mortality. Finally, neoadjuvant CRT raises the possibility of downstaging unresectable and/or borderline resectable and borderline resectable and/or borderline resectable/unresectable and/or borderline resectable disease so that more patients ultimately are able to undergo potentially curative surgical resection.

The main drawbacks of neoadjuvant treatment include: (a) possible delay of surgery due to complications of therapy, (b) the generally low response rate of advanced pancreatic cancer to multimodality treatments, and (c) the potentially higher surgical complication rate due to prior irradiation of tissue at the resection site. Encouragingly, no increase in surgical complications after neoadjuvant therapy has been reported to date (16-18).

To date, no large randomized controlled trials have studied neoadjuvant therapy for resectable and/or borderline resectable pancreatic cancer, and the sample size of existing prospective series has been small (see table II). Despite the theoretical advantages of neoadjuvant therapy, results obtained to date have shown only modest improvements compared to surgery alone. Median survival and 2-year OS for patients receiving neoadjuvant therapy range from 8-23 months and from 27-40%, respectively (19-23), compared to 11-17 months and 15-31% for surgery alone (24,25). Meanwhile, adjuvant chemoradiation (CRT) has produced a median survival of 27-44 months and 2-year OS of 53-58% (26-28). Thus, while neither neoadjuvant nor adjuvant CRT have achieved major degrees of improvement in OS, both have been demonstrated to be slightly more effective than surgery alone for pancreatic adenocarcinoma. The current prevailing management strategy, therefore, is to combine neoadjuvant chemotherapy and/or radiation, surgical resection, and adjuvant chemotherapy and/or radiation to achieve the highest possible rate of long-term survival, though no RCTs have yet been done to conclusively prove the efficacy of this regimen.

III. RATIONALE

Rationale for Radiotherapy in Treatment of Pancreatic and Periampullary Adenocarcinomas

Radiation therapy is a widely accepted treatment for pancreatic cancer. The Gastrointestinal Tumor Study Group (GITSG) carried out a series of landmark studies demonstrating the effectiveness of radiation therapy as both adjuvant and definitive treatment in pancreatic cancer (6,7). Modern radiation treatments have increasingly used conformal fields and dose escalation to enhance tumor control (8, 9). Efforts to increase radiation dose to the pancreatic tumor without risking normal tissue injury have generally required relatively invasive techniques such as interstitial implantation of radioactive metals or intraoperative radiotherapy (IORT) (10, 29). Historically, the local control rates for conventionally fractionated radiotherapy have ranged from 25-50%. Local progression of pancreatic cancers can result in considerable morbidity, including gastric outlet obstruction, biliary obstruction, and pain (30).

Rationale for Fractionated Stereotactic Radiotherapy

The mortality rate for pancreatic cancer approaches 100%. Current therapies provide only partial palliation of symptoms and slight prolongation of survival. More effective therapies are clearly needed. Several clinical trials have shown that Linac based SBRT has the potential to significantly improve progression-free survival of patients with pancreatic tumors, which could translate into both more effective palliation and longer patient survival.

Linac based SBRT is delivered using linear accelerators and image-guided radiation therapy (IGRT). These machines combine a conventional high-energy linear accelerator with a kV imager capable of volumetric, cone beam CT (CBCT). Because of these innovations, it is possible to deliver highly accurate, stereotactic radiation treatments.

Koong et al. previously used the CyberknifeTM stereotactic radiosurgery system to demonstrate that a single dose of 25 Gy Linac based stereotactic body radiotherapy (SBRT) was feasible for patients with locally advanced pancreatic cancer (36). Furthermore, this dose of radiation resulted in near 100% progression free survival and effectively palliated symptoms related to the local growth of pancreatic tumors. Based on this study, the same group also completed a phase II study assessing the efficacy of combining a standard five- week course of chemoradiotherapy followed by a stereotactic radiosurgery boost to the primary tumor in patients with locally advanced pancreatic cancer. In this cohort of 19 patients, 100% of tumors were without local progression at 1 year median follow-up. However, all patients eventually developed metastases..

More recently, another phase II study treated locally advanced pancreatic cancer patients with gemcitabine followed by 25 Gy of Linac based SBRT delivered with Cyberknife and maintenance gemcitabine chemotherapy. In this study, the excellent progression free survival was confirmed from previous studies (81%). The median overall survival was 11.4 months, median time to progression was 9.7 months and the 1 year survival was 50% (37). There were no significant acute GI toxicities however, of the 15 patients alive >6 months after Linac based SBRT, 7 (47%) experienced Grade 2 or greater GI toxicity, with 2 (13%) of the 15 experiencing Grade 3 or greater GI toxicity.

A multi-institutional study (Johns Hopkins, Stanford, Memorial Sloan Kettering) of fractionated SBRT (6.6Gy x 5) in 70 patients with locally advanced or borderline resectable and/or borderline resectable pancreatic adenocarcinoma has thus far shown very promising results. Median overall survival of the locally advanced patients was 13.9 mo (comparable to national standard) with 83% local control at 1 year. Furthermore, patients reported improved global and pancreas specific

quality of life post-SBRT (Herman, ASTRO oral presentation, Sept 2013). Rates of acute and late GI toxicity have been < 15%, Grade 2 or less with no grade 3 or higher toxicity seen. Seventeen of these patients have gone to resection thus far, with no complications, and 50% pathologic complete response rate, 90% negative margin resection rate, and 80% node negative rates (Herman, personal communication). Given these very encouraging pathologic results, while SBRT can be delivered faster and with fewer side effects than traditional fractionated radiotherapy, we are interested in fractionated SBRT for resectable and/or borderline resectable patients.

To date, Stanford has treated more than 150 patients with Linac based SBRT for locally advanced or borderline resectable and/or borderline resectable pancreatic cancer, and this treatment has resulted in local control rates of >90% with acceptable acute GI toxicity. We predict that this treatment will not adversely impact patients' quality of life. Although QOL measures have not been thoroughly studied among pancreatic cancer patients treated with Linac based SBRT, the majority of patients treated with Linac based SBRT appear to derive a clinical benefit as assessed by decreased pain, decreased fatigue, and increased weight. A single fraction of Linac based SBRT (25 Gy x 1) has resulted in excellent tumor control. However, close to 50% of these patients developed late duodenal toxicity within one year, primarily because of the proximity of the duodenum to the pancreas.

Although we believe this schedule (5 Gy x 5 or 6.6 Gy x 5) will result in good tumor control and acceptable toxicity, the potential clinical efficacy of this short-course, hypofractionated regimen is unknown in resectable and/or borderline resectable pancreas cancer. The choice of this regimen as a potentially effective approach for resectable and/or borderline resectable pancreatic cancer treatment is based on the following observations: First, a similar schedule (5 Gy x 5) has been widely and efficaciously used in the neoadjuvant setting for rectal cancer, although a much larger field is used. Additionally, a series of patients with resectable and/or borderline resectable pancreatic lesions treated at the M.D. Anderson Cancer Center strongly suggest that a 5-FU based chemoradiation regimen consisting of 30 Gy in 10 fractions over 2 weeks reduces treatment time and toxicity compared with a regimen consisting of 50.4 Gy in 28 fractions over 5 to 6 weeks without compromising overall survival or local control. Hong et al. from Massachusetts General Hospital have reported on a neoadjuvant regimen delivering 5 Gy x 5 to the pancreatic tumor plus adjacent lymph nodes using proton beam radiation (41). They show this regimen to be safe, with no instances of dose limiting toxicity observed and only 4 of 15 patients developing grade 3 toxicity (no patients experienced grade 4 toxicity). Finally, in the multi-institutional study of patients with locally advanced or borderline tumors treated with 6.6Gy x 5 at Johns Hopkins, Stanford or Memorial Sloan Kettering, there have been no significant peri-operative complications seen with very encouraging pathologic results previously mentioned above (Herman, personal communication).

The phase I feasibility study outlined in this protocol proposes a 6.6 Gy x 5 fractionation schedule treating the region of tumor plus a 3 mm margin. These volumes will be substantially smaller than the regimens outlined above for rectal and pancreatic cancer, likely leading to a lesser degree of toxicity. Using the linear-quadratic formulation, the biologically equivalent dose (BED) of the two proposed fractionation schedules are given in comparison to other commonly used schemes (table 1). The BED of the proposed 6.6 Gy x 5 schedule (BED early/late 54.8/105.6) closely approximates that of standard chemoradiation (BED early/late 60/83.3), but without concurrent chemotherapy and treating (0.3 cm vs. ~2 cm). Furthermore, the proposed 6.6 Gy x 5 fractionation schedule has a much lower late BED (105.6 vs. 233.3) with a similar early BED (54.8 vs. 87.5) as the previous 25 Gy x 1 regimen that has resulted in higher toxicity.

Table 1:

	Nodes Tx	Concurrent Chemo	BED early	BED late
			a/b=10	a/b=-3
50.4	Yes	5-FU	60	83.3
30 Gy/10	Yes	Gemcitabine	39	60
25 Gy/5	No	No	37.5	66.7
33 Gy/5	No	No	54.8	105.6
25 Gy/1	No	No	87.5	233.3

In this study, we will refine our current understanding of radiation tolerance of the pancreas and adjacent organs, thereby making it possible to treat future patients more safely and aggressively.

The major benefit of Linac based SBRT/chemotherapy for resectable and/or borderline resectable pancreatic tumors is improved local control from improved sterilization of primary tumor and lymph nodes, and well as faster delivery with lower side effects. In addition, radiosurgical ablation of the tumor at the primary site early after diagnosis can theoretically prevent distant seeding from the pancreatic tumor itself. Ultimately, these improvements in the treatment of pancreatic cancer may translate into an improved quality of life and overall survival.

Quality of life will be assessed using the European Organization for Research and Treatment in Cancer quality of life core cancer questionnaire with the pancreatic cancer module (EORTC QLQ-C30/PAN26). The EORTC QLQ-C30 is a multidimensional, 30- item questionnaire, which assesses five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health/QOL scale, as well as 6 single items (42). The EORTC QLQ-PAN26 supplements the core questionnaire with 26 items specific for patients with pancreatic cancer (43,44). These instruments have been validated in patients receiving treatment for metastatic and resected pancreatic cancer and are sensitive to identify treatment related changes in quality of life. The quality of life of patients in this study will be compared to historical cohorts of patients treated with conventional chemoradiation at University of Cincinnati and other institutions.

IV. METHODS

REGISTRATION PROCEDURES

General Guidelines

Subjects will be identified per the recommendation of Surgeons, Medical Oncologists, Radiation Oncologists or GI Combined Modality Tumor Board or equivalent combined modality assessment. Subjects will be recruited through self-referral and the advice of their attending physician. Patients will be enrolled prior to start of SBRT. Patients will have chemotherapy (3-4 months) for pancreas cancer prior to study enrollment.

Registration Process

A member of the research team (most likely the research coordinator) will enroll the patient into the trial. Consent will be obtained after a clear and thorough discussion between the patient and the principal investigator or any of the co-investigators in clinic. Any patients that are deemed by the principal investigator or co-investigators to be mentally or physically incapable of consent will not be included in the study.

SBRT ADMINISTRATION AND RADIATION TREATMENT PLANNING

Pre-Linac based SBRT Tests, Procedures, and Planning

The following will be completed prior to Linac based SBRT:

- Signed informed consent document.
- Medical history and clinical examination.
- CBC with differential, Chemistry Panel, CA19-9.
- Gold fiducial seed placement percutaneously, intraoperatively, or under endoscopic ultrasound guidance, technique will be determined clinically. Fiducial placement may be performed prior to enrollment.
- Pathologic confirmation of malignancy. (Core biopsies during gold fiducial placement as needed or optional). Patients are encouraged but not required to have tissue banked in UCCI Tumor Bank per Tumor Bank protocol.
- Pancreas protocol CT required; if patient allergic to contrast and allergy can not be premedicated with steroids prior to IV contrast, pancreas protocol MRI will be obtained
- Baseline collection of EORTC QLQ C-30/ PAN26 QOL.

Fiducials

Treatment on this protocol requires placement of 1-5 gold (99.9% pure, 1-5 mm length, or visicoils) fiducials for targeting purposes. The fiducials will be used as surrogates for targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor and/or periphery under endoscopic ultrasound or CT guidance. When possible, clips or fiducials will also be placed in the proximal duodenum directly adjacent to the pancreatic tumor. Fiducials may be implanted prior to enrollment as this is an acceptable standard of care procedure for any patient receiving radiotherapy for pancreatic cancer.

If fiducials are not placed intraoperatively and/or prior to enrollment, placement will be done and is expected to be done on an outpatient basis. In rare occurrences when fiducials/clips cannot be placed, patients may be treated at the discretion of the PI.

Simulation

Simulation should be done following placement of fiducials; however, this may vary and is at the discretion of the principal investigator. Typically, patients will be positioned supine in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient. Standard free-breathing CT and respiratory-correlated 4-D pancreatic protocol CT will be obtained on each patient. The 4D-CT scan will be used for characterizing target motion during quiet respiration. For more accurate tumor delineation, an arterial phase pancreatic protocol CT may be obtained (typically during expiration breath hold, 1.25 mm slices). Fiducial to fiducial fusions between these scans should be utilized whenever possible. The simulation scan should include T4/T5 to L5/S1 (upper abdomen). IV and oral contrast must be used for simulation, unless the patient has an allergy that cannot be adequately premedicated. In these situations, the plan should be fused with an IV contrast CT scan or MRI (ideally in a similar treatment position). Motion management can be addressed using respiratory gating, breath-hold, respiratory tracking, or abdominal compression. Specialized compression belts may be utilized for some patients. Each belt has an adjustable pressure cuff which can be used to reduce breathing motion. Fluoroscopy is used to assess motion of implanted gold markers before and after compression. The goal is to reduce motion from typically 11-22 mm peak to less than 5 mm. If the fiducial motion cannot be decreased to 5 mm or less, then respiratory gating will be utilized for treatment delivery. Prior to

simulation, standard guidelines will be followed. As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled machine.
All patients must start Linac based SBRT within 4 weeks of the simulation scan.

Treatment Planning
An SBRT treatment plan will be developed based on tumor geometry and location. Institutional standards for radiation quality assurance and radiation delivery will be utilized. The tumor volume (GTV), as identified on the treatment planning CT, will be contoured by an attending physician from UC Radiation Oncology. The final GTV will be defined by the attending radiation oncologist after reviewing the diagnostic CT, respiratory-correlated 4D-CT scan, pancreas protocol CT scan. These scans will be used to define the ITV (internal target volume). The final PTV(planning treatment volume) expansion will consist of an additional 2-3mm of margin expansion of the primary tumor to generate the PTV primary, except if the margin results in expansion into the duodenum or stomach. In these cases, margin expansion is allowed to be non-uniform. The dose will be prescribed to the isodose line that completely surrounds the PTV primary. It is recommended that 6-12 co-planar fields be used in the radiation treatment plan. A low dose clinical target volume will also be incorporated in the treatment volume called CTV vasculature. This customized CTV volume covers the immediately abutting vasculature (SMA, celiac, SMV), the pathway of perineural spread to the root of the mesentery, and extrapancreatic tissue immediately adjacent to the primary tumor at the discretion of the radiation oncologist. A 3 mm PTV margin will be added to the CTV vasculature to generate the PTV vasculature. The dose to this structure will receive 25 Gy over the 5 fraction SBRT course.

Contours of the fiducials used for target localization will be generated on the applicable image sets, to be used for patient setup on treatment. Radiation dose to the adjacent normal tissue will be minimized. Based on an analysis of duodenal toxicity representing pooled data from 3 previous prospective studies, the following dose constraints must be met: V15<9cc, V20<3cc. The duodenum (duo@PTV) as defined for these dosing parameters includes the entire duodenum on the same axial plane as the PTV and duodenum 1 cm above and 1 cm below the PTV. V15 and V20 are defined as the percent volume receiving 15 Gy and 20 Gy, respectively. The remainder of the normal tissues will be limited as follows:

- Liver (excluding tumor): 50% should be limited to <12 Gy
- Kidney: Combined volume for both should have 75% <12 Gy
- Stomach and duodenum: V15<9cc and V20<3cc. 50% should be limited to <12 Gy (no more than 1 cc of proximal stomach can receive >33 Gy)
- Spinal Cord: no more than 1cc can receive >8 Gy

No more than 1cc of the PTV primary can receive >130% of the prescription dose (4290cGy for 6.6Gy x 5).
Greater than 90% of the PTV primary should receive 100% of the prescription dose (3300cGy for 6.6Gy x 5)
Greater than 90% of the PTV Vasculature should receive 100% of the prescription dose (2500 for 5 Gy x 5)

If above constraints cannot be achieved, then 100% of the GTV must receive at least 25 Gy (an allowed minor deviation, which will be documented). If this constraint cannot be met, the patient should be removed from the protocol.

Linac based SBRT Treatment Delivery
Patients will receive 5 fractions of 6.6 Gy delivered twice weekly, with each fraction separated by

> 48 hours. Radiotherapy will be delivered Monday- Friday at Precision Radiotherapy or Barrett Cancer Center. Initial patient positioning will be based on volumetric kV (cone-beam CT) imaging with shifts to bony anatomy as appropriate. Orthogonal kV/MV or kV/kV projection imaging will be used to verify the location of the fiducials prior to delivery of first treatment beam. A secondary shift based on the location of fiducials may be utilized, as indicated by the position of the fiducials. For free-breathing treatments, kV fluoroscopic images should be obtained to confirm the anticipated position of these fiducials during the entire respiratory cycle. Active monitoring of treatment delivery accuracy will be accomplished using kV and/or MV projection imaging, either immediately before or during all (or a subset of) treatment fields.
Patient-specific dosimetric quality assurance (QA) will be performed as per standard practice in the Department of Radiation Oncology at University of Cincinnati.

Post-Linac based SBRT Follow-Up
Following Linac based SBRT, all patients will be monitored clinically and with serial imaging (CT scans and/or PET/CT if possible and as deemed necessary by the treating physician). A detailed medical history with physical examination and quality of life assessment will be performed at 4-6 weeks, 3 months, 6 months, 9 months and 1 year after radiation treatment. In years 2-5, the follow up interval will be every 3-6 months, as determined by the principal investigator. Follow up intervals may also be more frequent as indicated clinically. A complete blood count (CBC) with differential, comprehensive chemistry panel, tumor marker studies, and quality of life assessment will be performed at each follow-up interval.

GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Anti-diarrheals and Anti-emetics
For symptoms of diarrhea and/or abdominal cramping, patients will be instructed to take anti-diarrheals. Additional antidiarrheal measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea. For symptoms of nausea and vomiting, anti-emetics will be given one hour prior to Linac based SBRT and for up to 5 days following Linac based SBRT on an as- needed basis. Additionally, patients will be instructed to increase fluid intake. All patients will be prescribed proton pump inhibitors (PPIs), which should begin by the start of Linac based SBRT and continue for a minimum of 6 months following Linac based SBRT.

Other Concomitant Medications
Therapies considered necessary for the patient's well being may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. Specifically, if the patient is being treated with chemotherapy, it is recommended that chemotherapy be discontinued at least one week prior to initiation of Linac based SBRT and that resumption of chemotherapy be delayed for at least one week following the conclusion of Linac based SBRT. In general, prescription of these medications will be presided over by the patient's attending medical oncologist.

Supportive Care Guidelines
All commonly accepted supportive care guidelines will be used.

Use of Radioisotopes/Rad Machines
Stereotactic radiotherapy will be performed using Linac based radiation machines. The radiation treatment plan will be designed to use multiple beams of radiation to concentrate large doses of radiation within a tumor. The Linac machines are equipped with cone beam CT imaging that can

be used to deliver image-guided radiation therapy (IGRT). IGRT allows delivery of highly accurate, stereotactic radiation treatment. The use of cone beam CT images during IGRT is considered standard of care treatment. Uncertainties in tumor location are minimized because these machines have on- board, volumetric imaging for accuracy in initial patient setup; kV and MV projection imaging during treatment is used to monitor delivery accuracy and/or make corrections to the patients' position.

V. STUDY POPULATION

PATIENT SELECTION

Inclusion Criteria

- Age >18 years.
- Karnofsky Performance Status >70% (see Appendix IV).
- Histologically confirmed adenocarcinoma of the pancreatic head and/or body; at least the majority of the histopathologic specimen must be identified as adenocarcinoma as opposed to another histologic subtype.
    - *If histological confirmation of adenocarcinoma cannot be obtained by biopsy, the following procedures may be employed:
        - Attempt a repeat biopsy to obtain a diagnosis.
        - Present the case at UC tumor board and if the candidate has one of the following: a rising CA 19-9 or radiographic evidence of pancreas tumor on MRI, CT, and/or PET scan then the patient can be considered for treatment on protocol.
        - However, if these objectives cannot be met, the patient will not be a candidate.
- Pancreatic tumor must be considered at least borderline resectable by UC multi-disciplinary tumor board at the time of treatment planning.
- Patients who have not received RT to the abdomen.
- Patients must have acceptable organ and marrow function as defined below (within 2 weeks prior to radiotherapy):
- Leukocytes >3,000/μL
- Absolute neutrophil count >1,500μL
- Platelets >100,000/μL
- Total Bilirubin ≤2X normal institutional limits
- AST(SGOT)/ALT(SGPT) <2.5X institutional upper limit of normal
- Pre-menopausal women must have a negative serum pregnancy test
- If bilirubin > 2, all patients must have a biliary stent placed prior to radiotherapy. After stent placement, bilirubin must be <1.5x normal prior to study entry.
- Creatinine ≤ institutional upper limit of normal
  OR
- Creatinine clearance >60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal
- Ability to understand and the willingness to sign a written informed consent document.
- Patients are to have received neoadjuvant chemotherapy prior to enrollment (3-4 months). Approved regimens may consist of 3-4 months of gemcitabine-based chemotherapy or FOLFIRINOX. Patients will have a 2-4 week break between last chemotherapy

administration and start of SBRT.
- Patient must be able to have fiducials placed. If not, the tumor must be posterior and adjacent to the aorta and treatment will only be permitted at the discretion of the Principal Investigator.

Exclusion Criteria
- Children (< 18 years) are excluded because pancreatic tumors rarely occur in this age group. Furthermore, treatment requires a great deal of patient cooperation including the ability to lie still for several hours in an isolated room.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant and breastfeeding women are excluded as are women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for the duration of the study treatment. Should a woman become pregnant or suspect she is pregnant while undergoing radiotherapy in this study, she should inform her treating physician immediately.
- Women who are not post-menopausal (as defined in Appendix V) and have a positive urine or serum pregnancy test or refuse to take a pregnancy test.

VI. RISK / BENEFIT

Risk Information
It is difficult at this time to predict with confidence the percentage rate of complications from the proposed Linac based SBRT treatment. However, it is reasonable to extrapolate from the current experience with radiotherapy in and around the pancreas. Based upon prior phase I and phase II studies, we anticipate that the toxicities associated with this treatment will be acceptable.

Toxicities commonly associated with such treatment include nausea, vomiting, fatigue, anorexia and weight loss. Severe side effects such as gastrointestinal (GI) obstruction, perforation, or hemorrhage are uncommon complications, occurring in <5% of patients undergoing standard radiation therapy for pancreatic cancer. Although we expect a comparable rate of complications with fractionated Linac based SBRT, it is important to note that vomiting, GI obstruction, GI hemorrhage, anorexia and weight loss are also commonly associated with pancreatic cancer progression. Clinical and radiographic assessments will be performed in an effort to identify these effects, ascertain their etiology and provide the most appropriate palliative measures. Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs. Complications, if any, will be graded according to the CTCAE, National Cancer Institute, version 4.0. We will also utilize the RTOG scale for grading acute and chronic radiotherapy toxicities.

Duration of Study
It is anticipated that this study will last approximately 36 months (24 months of accrual and 12 months while cohort matures).

Duration of Follow Up
We estimate that most patients will remain a subject in this study for approximately one year. Patients will remain enrolled on this protocol for a maximum of 5 years or until patient withdrawal.

One year after Linac based SBRT, patients should undergo standard follow-up every 3-6 months, as determined by the treating physician. Patients that have completed the 5 year follow-up will continue being followed for survival information until death. The administration of subsequent chemotherapy and/or other antineoplastic treatment following Linac based SBRT will be at the discretion of each patient's attending medical oncologist.

Criteria for Removal from Study

Patients will be removed from the study for any of the following reasons: death or patient withdrawal. The protocol director may also withdraw a patient from the study for one or more of the following reasons: failure of the patient to follow the instructions of the protocol study staff, the protocol director decides that continuing participation could be harmful to the patient, pregnancy (if applicable), the patient needs treatment not allowed in the study, the study is cancelled, other administrative reasons, or unanticipated circumstances. Patients that have been removed from or discontinue the study will be followed for survival information until death.

Alternatives

Alternative therapies include chemotherapy alone, standard chemotherapy/radiation, upfront resection of pancreas tumor, palliative symptomatic relief, or no further treatment. Additionally, patients may choose to receive treatment to improve quality of life but that may have no effect on the growth of their cancer. The risks of chemotherapy and standard chemotherapy/radiation include nausea, vomiting, diarrhea, fatigue, bone marrow suppression, and sepsis. The potential benefits of chemotherapy or standard chemotherapy/radiation are prolonged survival. The risk of pursuing no further treatment is tumor progression or spread.

VII. COMPENSATION

Subjects will not be paid to participate in the study.

VIII. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse Events and Potential Risks List

Based upon prior phase I and phase II studies evaluating the toxicities associated with Linac based SBRT for pancreatic cancer, we estimate that ≤20% of patients will experience grade 2 or higher late GI toxicity within one year. Late GI toxicities are those events occurring more than 3 months after Linac based SBRT. Acute GI toxicities are those events occurring within 3 months following Linac based SBRT. The major toxicity in this group of patients is the development of duodenal/gastric ulcers. Most of these are successfully managed medically. However, Stanford has observed 2 cases of duodenal perforation associated with Linac based SBRT in patients who did not undergo surgical resection of their tumors. We anticipate that because of refinements in radiation treatment planning techniques and because the dose will be divided over five treatments (as opposed to one), the biological equivalent and actual dose to the duodenum will be less than prior studies. Furthermore, the Stanford observed perforations occurred in duodenal locations that are routinely removed with pancreaticoduodenectomy, and all of our patients are anticipated to go to surgery. We anticipate that the risk of ulcer formation should be low (< 5%) in this study. Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs.

Reporting of Serious of Unexpected Adverse Events

All fatal events, both anticipated and unanticipated, must be reported to the UC IRB within a time period as specified by current institutional guidelines after the PI learns of the event, whether or

not the PI believes the event to be related to the study. All other events, which are both serious and unanticipated, must be reported to the UC IRB within a time period as specified by current institutional guidelines after the PI learns of the event. Events which are serious, but anticipated, should be reported as part of the continuing review application. If any of these Serious Adverse Events requires a change to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the UC IRB. Important Adverse Events that are unanticipated must be reported to the UC IRB within a time period as specified by current institutional guidelines. If the Important Adverse Event requires changes to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the UC IRB. All other unanticipated Adverse Events or changes to the protocol and consent form must be reported to the UC IRB, within a time period as specified by current institutional guidelines.

IX. STATISTICAL CONSIDERATIONS

Study Overview
This pilot study is designed to assess the feasibility of giving neoadjuvant SBRT in resectable and/or borderline resectable pancreas cancer patients. The feasibility demonstration will establish the infrastructure for future randomized phase II clinical trials in a single or multi-center setting. Twenty patients with resectable and/or borderline resectable pancreas cancer, confirmed by multi-disciplinary radiologic review, will be enrolled and treated. The decision regarding whether this study demonstrates sufficient feasibility to support a phase II study testing novel regimens in this disease population will be based on three key considerations:

- The study can meet the accrual goal.
- The proposed preoperative SBRT will result in no more toxicity than has been established previously in the borderline resectable and locally advanced setting by evaluating the prevalence of grade 3+ toxicities and treatment delay rate (> 4 weeks).
- The completion rate of preoperative and operative therapy meets the goals.

Sample Size
A maximum of 20 patients will be enrolled if the trial completes accrual.

Accrual time
The anticipated monthly accrual rate is approximately 1-2 patients per month. The trial is expected to accrue in approximately 24 months.

Statistical Design for Primary Endpoints

Primary Endpoints

- The primary endpoint is the rate of acute (within 3 months of treatment) G3+ gastrointestinal toxicities as assessed by CTCAE v4.0.

Study Design and Decision Rules
The purpose of this study is to demonstrate the feasibility of conducting a study assessing the proposed regimen. The sample size of twenty patients with confirmed resectable or borderline resectable pancreas cancer is selected based on financial and logistic considerations. However, we still propose decision rules based on testable hypotheses whenever possible. If, at the conclusion of the trial, none of the following stopping rules has been crossed, we will conclude that the proposed regimen and trial design warrants further phase II study for assessing SBRT followed by surgery in this disease population.

Accrual stopping rules
If, 4 months following the date IRB approval is obtained, no patients have been accrued, we will conclude the study does not demonstrate sufficient feasibility. Thereafter, the accrual rate will be monitored bi-monthly. If at any evaluation time point, the accrual rate is less than 0.5 per month, we will conclude the study does not demonstrate sufficient feasibility.

Toxicity Stopping Rules
The toxicity feasibility stopping rules are specified as the following:

- The toxicity rate is defined as the proportion of treated patients with resectable and/or borderline resectable pancreas cancer who experience at least one grade 3+ adverse event, and is considered at least possibly related to the preoperative treatment (i.e. an adverse event with attribute specified as "possibly," "probably," or "definitely" related to SBRT). The toxicity rate will be evaluated when the first 10, the first 15 and then 20 patients are enrolled and the toxicity data are available.
    - When toxicity data are available on the first 10 evaluable patients, if the toxicity rate is greater than 0.54 (> 5 patients experienced defined AEs), we will conclude the study does not demonstrate sufficient feasibility. Otherwise, continue accrual.
    - When toxicity data are available on the first 15 evaluable patients, if the toxicity rate is greater than 0.46 (> 6 patients experience defined AEs), we will conclude the study does not demonstrate sufficient feasibility. Otherwise, continue accrual.
    - When toxicity data are available on all 20 evaluable patients, if the toxicity rate is greater than 0.42 (>8 patients experience defined AEs), we will conclude the study does not demonstrate sufficient feasibility.
        - This decision rule based on a sample size of 20 patients will have more than 80% chance to conclude the study does not demonstrate sufficient feasibility if the toxicity rate is ≥ 50% and only have less than 17% chance to conclude the study does not demonstrate sufficient feasibility if the toxicity rate is ≤ 30%.
    - If 4 or more patients in the first 10, or after 10 patients, 40% or more treated patients experience treatment delay (> 4 weeks), we will conclude the study does not demonstrate sufficient feasibility.

Completion of Therapy Stopping Rules
The completion of therapy stopping rules are specified as the following:

- If at least 6 patients among 20 evaluable patients complete all preoperative and operative therapy including R0 or R1 resection, we will conclude the study warrants further phase II study, provided that none of the other feasibility stopping rules are crossed at any time.

- If 5 or less than 5 patients among 20 evaluable patients complete all preoperative and operative therapy we will conclude that the study does not demonstrate sufficient feasibility.

    - This decision rule based on a sample size of 20 patients will have more than 80% chance to conclude the study does not demonstrate sufficient feasibility if the R0/R1 resection rate is ≤ 20% and only have less than 13% chance to conclude the study does not demonstrate sufficient feasibility if the R0/R1 resection rate is ≥ 40%.

Analysis Plan
All acute AE (within 3 months after treatment) and the maximum grade for each type of adverse events (including all adverse events and those that are possibly, probably or definitely related to study treatments) will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. Point estimate and confidence interval will be reported for binary endpoints.

Supplementary Analysis Plans (Secondary Endpoints)
All late AE and the maximum grade for each type of adverse events (including all adverse events and those that are possibly, probably or definitely related to study treatments) will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. Point estimate and confidence interval will be reported for binary endpoints. All patients meeting the eligibility criteria and confirmed by central review who have signed a consent form and have begun any dose of treatment will be evaluable for the following secondary endpoints, unless otherwise specified.

- The positive margin resection rate is defined as number of patients achieved R0 versus R1/R2 resection during surgery divided by number of evaluable patients. (R0= negative margin, R1= microscopically positive margin, R2= macroscopically positive margin). Point estimate and confidence interval of the rate will be reported.
- The histopathologic response rate is defined as number of patients achieved CR or PR determined according to histopathologic examination during pre-operative chemo or chemoradiotherapy divided by number of evaluable patients. Point estimate and confidence interval of the rate will be reported.
- Time to locoregional recurrence is defined as time from the date of registration to the date of the first documented locoregional recurrence. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).
- Time to distant recurrence is defined as time from the date of registration to the date of the first documented distant recurrence. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).
- Overall survival is defined as time from the date of registration to the date of the death due to all causes. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).

Safety Stopping Rules
In addition to toxicity feasibility stopping rules, accrual will be temporarily suspended to the study, if at any time, we observe events considered at least possibly related to study treatment an adverse event with attribute specified as (“possible,” “probably,” or “definite”) that meet the following:

- The rate of treatment-related deaths during treatment, or within the first 60 days following completion of treatment, is 2 or more in the first 10 patients, or after 10 patients, 20% or more of all treated patients.
- We will also review grade IV and V adverse events deemed “unrelated” or “unlikely to be related” to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event

X. DATA REPORTING / REGULATORY CONSIDERATIONS

Study Monitoring

This study will be monitored by the University of Cincinnati DSMB and IRB. The PI will be responsible for maintaining the clinical protocol and subjects' study charts, reporting adverse events, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to their IRB and trail monitoring group(s) as per UC protocol. There will be password-protected limited access to the database in order to maintain privacy (See Confidentiality below).

Monitoring Plan
UCCI DSMB will conduct study audits after enrollment of each 10 patients to review subjects' timely and complete enrollment, registration into the electronic database, and follow-up per study calendar. More frequent monitoring will take place as needed. Trial monitoring with subject chart and trial binder reviews will be done by the UCCI Clinical Trials office.

Data Entry and Compilation
Subject data will be documented and stored in the electronic database Oncore, the software and infrastructure being supplied by UCCI clinical trials office. Research Staff (Coordinators, Nurse, or Co-Investigators) will enter/scan subject data into Oncore, which will include:

- Eligibility or Inclusion/Exclusion Criteria
- Patient Demographics
- Pre-Study Evaluation including H & P, Allergies, and Review of Systems
- Surgical Procedures, with dates and findings (including EUS, biopsy (if needed), seed placement, and/or stent (if recommended)
- Scan dates (pancreas protocol CT)
- Treatment planning date
- Pre-Study Labs including hematology, chemistry, and tumor markers (CBC, CMP and CA 19-9)
- Radiation therapy dates and toxicities reported
- Pre-study chemotherapy records including drugs, doses, and schedules
- Surgery records including pathology reports (pathologic staging, margin status, histology), length of hospitalization and postop complications according to Appendix VI.
- Follow-up Evaluations including H&P, Review of Systems, and toxicities
- Follow-up labs and dates
- Completion of QOL questionnaires
- Subject study withdrawal, date, and reason
- Concomitant medications, specifically PPIs and anti-emetics, prescribed per protocol and if reportedly taken by subject

Confidentiality
Study data will be maintained in password protected computer files. Only research personnel listed on this protocol will have access to this information. Only the patients unique IDN will be used. The patient's name or other public identifiers will not be included in any information shared with other investigators. The study data with identifiers will be kept at in Oncore.

XI. CORRELATIVE STUDIES

Correlative studies to develop predictive and prognostic information will focus on molecular markers of interest in pancreatic cancer. For all of the markers described below, tissue from both pre-treatment biopsies and post-resection specimens will be subjected to immunohistochemical (IHC) analysis. Funding for correlative studies will come from either pending grant applications or

supported by the UCCI GI Center of Excellence.

Differential expression of these markers correlated with clinical outcomes can provide invaluable prognostic data, as well as a basis for future clinical trials with a personalized, molecular profile-targeted approach. The markers of interest are:

Hyaluranon- Tumor stroma microenvironment has been very important in pancreas cancer. The interstitial pressure is very high, which limits the diffusion of chemo and blood flow in the tumor[10]. Hyaluronan (HA) is one component of the stroma thought to be responsible for this and HA can be evaluated by IHC. Hyaluronan inhibitor (PEGPH20) is currently under investigation in metastatic pancreatic cancer and HA could potentially be used as a radiosenitizer. This would be a completely new mechanism of sensitization. We would plan to evaluate HA concentration by IHC, and would consider decreased post-SBRT concentration as a preliminary indicator that SBRT has some synergy with HA inhibition warranting further study.

D1R-DA acts as a neurotransmitter in the brain and as a hormone in the periphery. It binds to five G-protein-coupled receptors (DAR), grouped by structure and function into D2-like (D2R, D3R and D4R) and D1-like (D1R and D5R). The D2R-like are classified by inhibition of cAMP, whereas the D1R-like stimulate cAMP. In addition to their distinct distribution and functions within the brain, several DAR subtypes are expressed in peripheral tissues, where they participate in the control of kidney, cardiovascular, immune and adipose functions; DAR have also been detected in some adrenal, ovarian, lung, and colon cancers.

Drugs that affect DA functions constitute one of the largest classes of pharmaceuticals. They are widely used as oral medications for Parkinson's disease, schizophrenia, hyperprolactinemia, renal hypertension, erectile dysfunction and gastrointestinal motility disorders. Among these, Fenoldopam (Fen) is of particular interest. Fen is an FDA-approved, selective D1R agonist (Kd=2.3 nM) which does not penetrate the brain and does not activate D2R-like or adrenergic receptors. Fen is clinically used to treat severe renal hypertension, and has a wide margin of safety for normotensive patients, causing only mild hypotension.

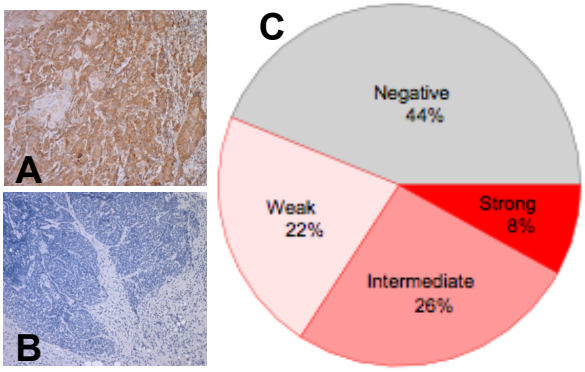


Fig 2: Examples of SCCHN primary tumors that stain strongly positive (**A**) or negative (B) by IHC for D1R. **C:** Pie chart showing the D1R-staining distribution pattern of 27 SCCHN primary tumors.

D1R expression in breast cancer: Using rabbit monoclonal antibodies (mAb) with high selectivity for D1R, Dr Ben-Jonathan's lab (UC Cancer Biology) has discovered robust D1R expression in several BCC. They found moderate to strong D1R staining by immunohistochemistry in ~30% of 751 primary breast carcinomas in tissue microarrys, while D1R was undetectable in 30 normal breast tissue samples. D1R expression correlated with high tumor grade, size, and advanced disease and overall survival. Treatment of D1R-expressing BCC with low nM doses of D1R agonists reduced cell viability in vitro, induced apoptosis, and augmented cell sensitivity to doxorubicin. Fen dramatically suppressed the growth of D1R-expressing breast cancer xenografts in nude mice. We plan to evaluate D1R expression by IHC in all pre- and post- SBRT paraffin embedded tissue with mAb purchased through Epitomics with the assistance of Dr Ben Jonathans lab.

SapC-DOPS

SapC-DOPS is a nanovesicle technology developed at CCHMC/UC with very promising results in pancreas cancer models. A Phase I trial of this drug will begin at multiple sites including UC in the next 2-3 months treating all solid tumors. These vesicles are assembled from saposin C (SapC) and dioleylphosphatidylserine (DOPS) bind to phosphatidylserine (PS), preferentially expressed in cancer cell surfaces, and are internalized into tumor cells where they induce apoptosis. Dr. Qi (collaborator in Hematology Oncology at UC) has shown that the vesicles target to surface exposed PS and decrease cell viability in human pancreatic cancer cells and in subcutaneous as well as orthotopic pancreas models.

Synergistic tumor kill between SapC-DOPS and RT has been demonstrated in braincancer cells by Dr. Qi and his collaborators. In addition, Timmerman, et al. have demonstrated in an orthotopic lung cancer model that SBRT increases the extracellular expression of PS on tumor vessels from 4% to 26% using an antibody to PS called bavituximab. Moreover in a radiation resistant animal lung model, they demonstrated that SBRT + bavituximab produced higher clinical and pathologic response rates than either alone. This raises the possibility that SBRT may increase the effectiveness of SapC-DOPS in terms of tumor cell kill in *in vivo* pancreas models.

We plan to evaluate tumor expression of PS pre- and post-SBRT in human tissue. In pre-SBRT core biopsies specimens and post-SBRT resection specimens from the above mentioned UC investigator initiated “Phase I feasibility study of SBRT in resectable adenocarcinoma of pancreas”, we will plan to evaluate the tumor expression of PS by IHC using bavituximab and fluorescently labeled SapC-DOPS . These stains and interpretation will be performed by Dr. Jiang Wang in Pathology and Dr. Qi.

Alternatively spliced Tissue Factor (asTF)

Tissue Factor (TF) present in blood cells and plasma is referred to as blood-borne or circulating TF. TF has been implicated in the pathogenesis of several chronic disease states, most notably cardiovascular disease and cancer. Full-length TF is an integral membrane protein while alternatively spliced TF can be secreted in a free form and features a unique C-terminal domain enabling its selective detection in bio-specimens. Recently, asTF was shown to circulate in the blood of metastatic breast cancer patients at concentrations exceeding 1 ng/mL (Kocaturk et al, PNAS 2013), and it promoted tumor growth and spread in an orthotopic model of pancreatic ductal adenocarcinoma (PDAC, Unruh et al, Int J Cancer, 2014). asTF protein acts as a cell agonist driving angiogenesis, cancer cell proliferation, and monocyte recruitment via integrin binding. It is not known whether circulating asTF may contribute to or serve as a biomarker in patients with solid cancers including PDAC. We evaluated circulating asTF in healthy subjects and individuals with PDAC.

Samples of platelet poor plasma from 43 subjects were obtained from University of Cincinnati Cancer Institute’s Tumor Bank and Diagnostica Stago collections. Blood was drawn into tubes containing acid citrate dextrose (PDAC) or sodium citrate (healthy subjects), centrifuged at 3000 rpm for 15 min at 4°C, and stored at -80°C until use. Blinded asTF ELISA was performed on platelet poor plasma samples (each in triplicate, 200 ul per well) as per the prototype-tailored procedure (Diagnostica Stago). Samples with asTF concentrations ≥0.2 ng/mL were deemed positive. asTF concentrations are presented as mean±SD. Kruskal-Wallis one-way analysis of variance was used to compare differences in concentration levels between the cohorts; Chi-Square and/or Fisher’s exact test were used to compare proportions.

asTF protein was detectable in the plasma of 3/19 (15.8%) subjects in the healthy cohort (CORE Set 50, George King Bio-Medical) and 20/43 (46.5%) in the PDAC cohort; the proportion of PDAC patients

positive for asTF was significantly higher compared to that in all other cohorts ($p<0.01$, Chi-Square test). The mean asTF concentrations in the cohorts were as follows: PDAC, 0.403±0.912 ng/mL; healthy subjects, 0.169±0.596 ng/mL; the differences between mean asTF levels in the cohorts did not reach significance. Next, we evaluated asTF's potential as a biomarker to help detect a more aggressive PDAC phenotype. Among the 43 patients with PDAC, 36 were initially deemed resectable and 7 unresectable due to the presence of metastatic disease as determined by diagnostic screening; following exploratory laparoscopic surgery, 11 out of 36 patients initially deemed resectable were deemed unresectable due to the presence of metastatic disease. When the entire PDAC cohort was split into bona fide resectable (25) and unresectable (18) sub-cohorts, positivity for asTF was significantly more prevalent in the unresectable sub-cohort irrespective of the results of initial evaluation and/or pre-operative CA19-9 levels (asTF ≥0.2 ng/mL: 13 unresectable and 7 resectable patients; asTF<0.2 ng/mL: 5 unresectable and 18 resectable patients, $p=0.0059$, Fisher's exact test).

Our findings suggest that asTF at levels ≥0.2 ng/mL occurs more frequently in the plasma of patients with PDAC compared to healthy subjects. Further, PDAC patients whose plasma asTF levels were equal to or exceeded 0.2 ng/mL had a significantly lower chance to qualify for tumor resection, irrespective of initial pre-surgical diagnostic evaluation. asTF may thus comprise a novel marker of aggressive PDAC phenotype with potential utility in patient stratification, warranting prospective evaluation of larger PDAC patient cohorts.

Proposed research: prospective evaluation of asTF levels in circulation of patient with PDAC at 3 time points pre / post-SBRT (time point 0-14 days before surgery) and post-operative. Blood will be drawn in 3 ml sodium citrate tubes, ~1.5 ml of platelet poor plasma isolated, frozen until use, and assayed for asTF using ELISA as described above. We hypothesize that asTF levels will i) drop post-SBRT, ii) further drop post-resection, and iii) rise either concomitantly or shortly before recurrence. We also hypothesize that higher asTF levels at the onset and/or during the study will positively correlate with more aggressive disease and, consequently, poorer response to treatment.

XII. MEASUREMENT OF EFFECT

Anti-tumor Effect

Patients will be evaluated for anti-tumor effect by follow-up imaging (pancreas protocol CT and/or PET-CT imaging) as outlined above. All subsequent scans (post-treatment) will be compared to the same pretreatment CT that was used in conjunction with radiation treatment planning. Patients will be evaluable for toxicity and evaluable for objective response at the follow-up intervals specified above.

Disease Parameters

Pancreatic tumor response will be based upon standard radiographic criteria for the treated lesion and will be prospectively recorded in the UC secure database. Radiographic response of the pancreatic tumor by diagnostic CT scans will be defined according to RECIST criteria as described below:

- CR = complete disappearance of index lesion
- PR = at least 30% decrease in the longest diameter of the index lesion
- PD = more than 20% increase in the longest diameter of the index lesion
- SD = does not meet criteria for PR or PD

Local tumor progression will be defined as >=20% increased size on CT scan compared to a CT

scan from prior to treatment. Distant progression will be defined as any new tumor found outside of the pancreas or periampullary region on CT scan. Local and/or distant progression will be evaluated by both PET/CT (if available) and CT scan as deemed by treating physician.

Methods for Evaluation of Measurable Disease
Pancreas protocol CT scans (biphasic imaging, 1.25 mm cuts) and/or FDG PET-CT scans (optional and if recommended by the treating physician) will be obtained at all follow-up intervals as described in the treatment calendar.

XIII. RESPONSE CRITERIA

Evaluation of Target Lesions
Patients' responses to therapy will also be evaluated clinically after completion of their Linac based SBRT. The following are clinical definitions for response:

- CR = complete alleviation of pain or other symptoms thought to be related to the index lesion
- PR = improvement, but not complete elimination, of pain or other symptoms thought to be related to the index lesion
- PD = worsening of pain or other symptoms thought to be related to the index lesion SD = does not meet criteria for PR or PD
- Radiographic response will be defined as outlined in section 11.1.2.

Evaluation of Non-Target Lesions
Standard radiographic criteria will be utilized for non-target lesions. Any disease outside of the pancreas region will be considered metastatic disease. If possible a biopsy should be obtained to confirm metastasis.

Evaluation of Best Overall Response
This will be based upon the response of the treated lesion as described above.

Duration of Response
The criteria for overall response will be the time between treatment and first sign of local progression or development of new metastatic disease.

Response Review
All responses will be reviewed independently by a board certified radiologist at the study's completion. Each image will be reviewed by the PI. Simultaneous review of the patient's chart will also occur at this time.

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APPENDIX I

STUDY CALENDAR

	Pre-Study	Pre-SBRT[8]	SBRT Treatment[9,10]	Follow-Up [5] (Post-Radiation Treatment)					
				4-6 weeks	4 mos	6[3] mos	9 mos	12[3] mos	Yrs 2-5 Q 3-6 mos
Initial Consult	X								
Demographics	X								
History / Physical Exam	X			X	X	X	X	X	X
Informed consent	X								
Biopsy (confirmed adenocarcinoma)	X								
Labs: CBC, CMP, CA19-9		X[6]		X	X	X	X	X	X
Post-op complication assessment (appendix 6)				X					
Negative Pregnancy Test[7]		X							
Seed Placement (EUS, CT, intraoperatively)		X							
Simulation Scan		X							
Radiologic Evaluation (CT)		X		X[2]	X	X	X	X	X
QoL Questionnaire		X		X	X[4]	X	X[4]	X	X
AE Evaluation	X			X	X	X	X	X	X
Research tubes		X		X[11]					

1 - CT pancreas or chest/abdomen/pelvis, as per treating physician, required pre- and post-SBRT.
2 - If being reevaluated for resection, scans will be conducted at 4-6 weeks or as determined necessary by treating physician.
3 - It is preferred that patients have the 6MFU and 12MFU evaluation and imaging at the treating institution. Other evaluations may be done at a local center however records must be submitted to SBRT treating facility.
4 - QoL questionnaires may be completed and returned by mail if preferred.
5 - Follow-up appointments have a +/- 30 day tolerance window. (ex. 6MFU may occur between 5-7 months)
6 - Pre-SBRT labs should be done within 2 weeks prior to treatment.
7 - Pregnancy test by urine or serum, for women who are not post-menopausal as defined in Appendix III.
8 - Pre-SBRT procedures should be completed within 45 days of beginning treatment.
9 - It is recommended that patients discontinue any chemotherapy one week prior to SBRT
10 - Ideally all 5 fractions should be delivered Monday through Friday; however, treatment may be delivered over 2 weeks, as long as the patient receives at least 2 fractions per week.
11- Pre-surgery

APPENDIX II

EORTC QLQ - 30

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

	Not at All	A Little	Quite a Bit	Very Much
Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suit case?	1	2	3	4
Do you have any trouble taking a LONG walk?	1	2	3	4
Do you have any trouble taking a SHORT walk outside of the house?	1	2	3	4
Do you need to stay in bed or a chair during the day?	1	2	3	4
Do you need help eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
Were you limited in doing either your work or other daily activities?	1	2	3	4
Were you limited in persuing your hobbies or other leisure time activities?	1	2	3	4
Were you short of breath?	1	2	3	4
Have you had pain?	1	2	3	4
Did you need to rest?	1	2	3	4
Have you had trouble sleeping?	1	2	3	4
Have you felt weak?	1	2	3	4
Have you lacked appetite?	1	2	3	4
Have you felt nauseated?	1	2	3	4
Have you vomited?	1	2	3	4
Have you been constipated?	1	2	3	4
Have you had diarrhea?	1	2	3	4

Were you tired?	1	2	3	4

	Not at All	A Little	Quite a Bit	Very Much
Did pain interfere with your daily activities?	1	2	3	4
Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
Did you feel tense?	1	2	3	4
Did you worry?	1	2	3	4
Did you feel irritable?	1	2	3	4
Did you feel depressed?	1	2	3	4
Have you had difficulty remembering things?	1	2	3	4
Has your physical condition or medical treatment interfered with your FAMILY life?	1	2	3	4
Has your physical condition or medical treatment interfered with your SOCIAL activities?	1	2	3	4
Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please select the number between 1 (Very Poor) and 7 (Excellent) that best applies to you.

	Very Poor						Excellent
How would you rate your overall HEALTH during the past week?	1	2	3	4	5	6	7
How would you rate your overall QUALITY OF LIFE during the past week?	1	2	3	4	5	6	7

APPENDIX III

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 checking the number that best applies to you.

	Not at All	A Little	Quite a Bit	Very Much
Have you had abdominal discomfort?	1	2	3	4
Did you have a bloated feeling in your abdomen?	1	2	3	4
Have you had back pain?	1	2	3	4
Did you have pain during the night?	1	2	3	4
Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
Were you restricted in the TYPES of food you can eat as a result of your disease or treatment?	1	2	3	4
Were you restricted in the AMOUNT of food you can eat as a result of your disease or treatment?	1	2	3	4
Did food or drink taste different from usual?	1	2	3	4
Have you had indigestion?	1	2	3	4
Were you bothered by gas (flatulence)?	1	2	3	4
Have you worried about your weight being too low?	1	2	3	4
Did you feel weak in your arms and legs?	1	2	3	4
Did you have dry mouth?	1	2	3	4
Have you had itching?	1	2	3	4

To what extent was your skin yellow?	1	2	3	4
Did you have frequent bowel movements?	1	2	3	4
Did you feel the urge to move your bowels quickly?	1	2	3	4
Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

	Not at All	A Little	Quite a Bit	Very Much
Have you been dissatisfied with your body?	1	2	3	4
To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
Were you worried about your health in the future?	1	2	3	4
Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
Have you received adequate support from your health care professionals?	1	2	3	4
Has the information given about your physical condition and treatment been adequate?	1	2	3	4
Have you felt less interest in sex?	1	2	3	4
Have you felt less sexual enjoyment?	1	2	3	4

APPENDIX IV

Karnofsky Performance Status

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

APPENDIX V

Definition of Menopausal Status

Menopausal status will be defined according to the following criteria:

Post-menopausal:

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to
- registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)
- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

Pre- or peri-menopausal:

- Not meeting definition for postmenopausal as outlined above.