MELVIN AND BREN SIMON CANCER CENTER

INDIANA UNIVERSITY

PILOT STUDY OF RESPIRATORY-GATED STEREOTACTIC BODY RADIATION THERAPY FOR BORDERLINE RESECTABLE, UNRESECTABLE, OR RECURRENT/RESIDUAL ADENOCARCINOMA OF THE PANCREAS OR PERIAMPULLARY REGION

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1. SCHEMA

2. BACKGROUND & RATIONALE

Cohort A + Prior RT +Recurrent/Residual Disease	Cohort B No Prior RT +Recurrent/Residual Disease
• Any prior combination of surgery/chemo • Must have received ≥ 2 chemo cycles • ≥ 180 days since completing RT • ≥ 7 days since last chemo dose • To receive **5 Gy x 5**	• Any prior combination of surgery/chemo • Must have received ≥ 2 chemo cycles • ≥ 7 days since last chemo dose • To receive **6.6 Gy x 5**

2.1 Natural History and Management of Pancreatic Cancer

Over 40,000 cases of pancreatic cancer are diagnosed annually in the United States. Despite aggressive combined modality treatment approaches, the five-year survival of patients with pancreatic cancer is still less than 5%. (1) Surgical resection is considered to be the only potentially curative treatment option. (2) However, more than 85% of patients have locally advanced or metastatic disease when initially diagnosed, and treatment paradigms for patients with all stages of disease continue to evolve. Patients with resectable disease have high rates of both local recurrence and distant failure despite aggressive trimodality therapy, and controversy exists regarding whether or not radiation therapy should be included as part of routine postoperative therapy. (3-5) Neoadjuvant external beam radiotherapy is also frequently incorporated into treatment for borderline resectable pancreatic cancer in an attempt to increase the likelihood of margin-negative resection and improve local control. (6) Nonetheless, rates of local recurrence remain high even in patients who have undergone surgery, and more effective strategies to improve local control and to treat locally recurrent disease are needed.

Similarly, the role of radiation therapy in patients with unresectable disease continues to evolve. Unresectable pancreatic cancer is associated with high rates of occult distant metastatic disease; therefore, despite initially promising results associated with immediate chemoradiation in patients with unresectable disease, current treatment standards recommend the use of induction chemotherapy in this setting. (7, 8) For patients with unresectable disease, the use of induction chemotherapy can help to eliminate occult systemic micrometastases and to identify individuals with treatment-refractory distant metastases, who are unlikely to benefit from local therapies such as radiation. A prospective series testing this approach was recently reported by Huguet et al. (7) Patients were initially randomized to gemcitabine or gemcitabine plus erlotinib; those without progression on this regimen were then randomized to capecitabine-based chemoradiation versus chemotherapy alone. Forty percent of initially randomized patients developed progressive disease and did not proceed to the second randomization. Although the study did not demonstrate an overall survival benefit for RT, local failure rates and time to treatment resumption were both significantly improved in the RT arm. Furthermore, in patients with unresectable but localized pancreatic cancer at diagnosis, effective local therapy may play an important role in disease control. Autopsy studies suggest that approximately 30% of pancreatic cancer patients die due to local disease progression, a

statistic that is corroborated by clinical trial reports of local control rates of under 50% in patients with unresectable disease treated with definitive conventional chemoradiation. (9, 10) Pancreatic tumor progression is also associated with significant morbidity, including pain, jaundice, and gastrointestinal tract obstruction. (11)

Periampullary tumors are also frequently treated with radiation therapy. Patients with periampullary tumors have also been included in this trial because of anatomic and pathological similarities to patients with pancreatic cancer and the fact that the treatment paradigm for these cancers is similar to pancreatic cancer. Patients with periampullary tumors also have similar survival and recurrence patterns as patients with pancreatic cancers. (12) Periampullary adenocarcinoma is a rare malignancy, comprising less than 1% of all digestive cancers and occurring at an annual age-adjusted incidence of only 0.3 cases per 100,000 individuals. (13) As a consequence of this low prevalence, few studies have been performed in this population, and patients who fail definitive therapy (surgical resection in association with neoadjuvant or adjuvant CRT/chemotherapy for resectable disease; conventional CRT or chemotherapy for unresectable disease) have limited options for further treatment. (14, 15) Unfortunately, even among patients with resectable periampullary adenocarcinoma, over 50% will recur following definitive treatment (16).

This trial, therefore, seeks to study SBRT as a means of providing patients with borderline resectable, unresectable, or locally recurrent pancreatic/periampullary tumors with an additional treatment option after receiving prior combinations of surgery/chemotherapy.

2.2 Rationale for the use of stereotactic body radiation therapy in pancreatic cancer

Recent advances in radiation treatment technology, including improvements in planning systems, patient immobilization equipment, image-guided radiation therapy technologies, and radiation delivery mechanisms, have permitted the development of stereotactic body radiation therapy (SBRT), which permits the intensification of therapy by delivering increased daily doses of radiation to highly focused targets within the body. Several phase II trials of SBRT in patients with pancreatic cancers have been performed, showing that the technique is well tolerated and is associated with improvements in local control rates compared with historical series of conventionally fractionated chemoradiation. Koong et al. used the Cyberknife™ stereotactic radiosurgery system to demonstrate that a single 25-Gy dose stereotactic body radiotherapy (SBRT) was feasible for patients with locally advanced pancreatic cancer. (17) 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. However, all patients eventually developed metastases, with a median time to progression of 5.5 weeks. A more recent phase II study treated locally advanced pancreatic cancer patients with induction gemcitabine followed by single-fraction SBRT (25 Gy) 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%.(18) There were no significant acute GI toxicities; however, of the 15 patients alive >6 months after Linac

(linear-accelerator)-based SBRT, 7 (47%) experienced Grade 2 or greater GI toxicity, with 2 (13%) of the 15 experiencing Grade 3 or greater GI toxicity.

To decrease the risk of late GI toxicity, subsequent studies have therefore reduced the per-day dose and prolonged the treatment schedule. For example, Hong et al. reported a neoadjuvant regimen delivering 5 Gy x 5 to the pancreatic tumor plus adjacent lymph nodes using proton beam radiation. (19) This regimen was shown 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). Herman et al. recently published the largest phase II study to date of definitive 5-fraction SBRT in pancreas cancer, which reported a median overall survival rate of 13.8 months. (20) The regimen was also well tolerated, with acute and late grade 2 or greater toxicity rates of 2 and 11%, respectively. SBRT was associated with stable quality of life scores and improving pain scores. Similarly, a grade 3 or greater toxicity rate of 7% was reported in an institutional series of 159 patients treated using five-fraction regimens for both borderline resectable and unresectable tumors. (21)

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), including conventionally fractionated radiation, which is typically administered in 28 1.8-Gy fractions for a total dose of 50.4 Gy, usually with concurrent capecitabine-, 5-FU-, or gemcitabine-based chemotherapy. While the BED for the 5 Gy x 5 schedule (early/late 37.5/66.7) must necessarily be lower because it will be used in patients who have already been treated with radiation to the pancreatic region, that 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 a smaller tumor margin (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. Finally, the use of five-fraction SBRT regimens may be able to spare circulating lymphocytes from radiation-induced toxicity that is mediated by high radiation doses to circulating blood. As radiation-induced lymphopenia has been linked to inferior overall survival in patients with both unresectable and resectable pancreatic cancers, it is logical to explore potential ways to decrease the risk and severity of this toxicity. (22, 23) Circulating blood dose is directly proportional to radiation field size and fraction number, suggesting that SBRT is a potentially promising strategy to reduce the risk of radiation induced lymphopenia, perhaps leading to improved outcomes, in patients with pancreatic cancer.

Table 1. Comparison of Radiation Fractionation Schemes in Pancreatic Cancer.				
RT Dose (Gy) /# Fractions	Regional Nodes Treated?	Concurrent chemo?	Early BED (Gy) ($\alpha/\beta = 10$)	Late BED (Gy) ($\alpha/\beta = 3$)
50.4/28	Yes	Yes	60 Gy	83.3 Gy
30/10	Yes	Yes	39	60
25/5	No	No	37.5	66.7
33/5	No	No	54.8	105.6
25/1	No	No	87.5	233.3

2.3 Rationale for Selection of Patient Population

As noted previously, local control rates remain unsatisfactory in patients with unresectable pancreatic cancer, up to 30% of whom die with uncontrolled local disease. Local progression of pancreatic cancer can cause distressing symptoms including pain, biliary and gastrointestinal tract obstruction, and pancreatic insufficiency. Furthermore, preliminary data suggest that some patients treated with stereotactic body radiation therapy for unresectable disease achieve sufficient tumor response to proceed to surgical resection; (20) in patients with borderline resectable disease, neoadjuvant SBRT has also been associated with high rates of margin-negative resection. (21)

The development of recurrent pancreatic cancer after definitive treatment with surgery, radiation, chemotherapy, or a combination of these universally portends a dismal prognosis, with the 5-year survival for such patients being 5.6% or less. (24) Unfortunately, this scenario is not uncommon; even among the small number of patients (10-15%) able to undergo potentially curative surgical resection, more than 80% subsequently develop recurrent disease.(25) Following resection, 71-77% develop distant metastases within 2 years, often accompanied by concurrent locoregional recurrence, while up to 30% exhibit isolated locoregional recurrence. (26-29) Patients who develop combined distant/locoregional recurrence have a median survival of 3 months from the time of recurrence, while those with isolated locoregional recurrence have a median survival of 7 months. (28) Locoregional recurrence is, therefore, a common and serious problem both in the setting of metastatic disease and as an isolated entity. Symptomatic manifestations include pain, gastric outlet/small bowel obstruction, portal hypertension, biliary obstruction, and malnutrition. Although survival is determined chiefly by systemic disease control, local control greatly affects quality of life in pancreatic and periampullary cancer patients. (29, 30) Among the majority of patients with pancreatic cancer who present with unresectable disease, chemoradiation is able to transiently stabilize the disease in some patients and to prolong median survival to 8-14 months. (8, 9, 31) Regardless of whether a tumor is resectable or unresectable at diagnosis, the symptoms associated with local recurrence or persistence of disease require swift and effective treatment.

Preliminary data also supports the safety of re-irradiation of the upper abdomen in patients with pancreatic/peri-ampullary tumors who have previously been treated with conventionally fractionated radiation regimens. In 2013, Herman et al. published their institutional experience of re-irradiation in a group of 18 patients. (32) No grade 3 or greater toxicities were reported with a dose of 5 Gy x 5; reported one-year local control rates were 62%, and 57% of patients who had symptoms of pain before treatment

experienced pain relief. This data provides initial support for exploring a 5 Gy x 5 regimen in patients with a history of radiation treatment in the upper abdomen.

Considering the difficulty of surgical re-exploration due to extensive adhesions after previous resection, the risks of surgery and general anesthesia for patients who often have impaired performance status, and the prolonged time course and inferior local control associated with conventional CRT, we propose that SBRT may be a viable alternative treatment option for patients who have failed other modes of therapy through local recurrence or local progression. The paucity of studies focusing on this population and lack of a standardized treatment paradigm for these patients underscore the need for further investigation. The recent studies delineated above suggest that Linac-based respiratory gated SBRT is a safe and promising therapeutic option for pancreatic and periampullary cancers that merits further study in the specific patient population that will be treated using this protocol. However, further investigation of pancreatic SBRT should be performed in patients who have been more heavily pre-treated with intensive chemotherapy regimens such as FOLFIRINOX (5-FU, irinotecan, oxaliplatin), and gemcitabine in combination with nab-paclitaxel, which are currently commonly used in this setting but were not part of the standard approach in the previously cited phase I and II studies of pancreatic SBRT.

3. OBJECTIVES

3.1 Primary Objective

- To estimate rates of acute (within 3 months of treatment) grade 3 or greater gastrointestinal and hematologic toxicity in patients treated with Linac-based SBRT for pancreatic or periampullary cancers who have previously received other treatment.

3.2 Secondary Objectives

- To estimate rates of late (> 3 months after treatment) grade 2 gastritis, enteritis, fistula, and ulcer, or any other grade 3 or greater gastrointestinal toxicity in patients treated with Linac-based SBRT for pancreatic or periampullary cancers
- To estimate rates of local progression, overall survival, metastasis-free survival, and progression-free survival in patients with pancreatic or periampullary cancers treated with fractionated Linac-based SBRT.
- To evaluate the ability of Linac-based SBRT to provide pain control in patients with pain related to a pancreatic or periampullary tumor.
- To evaluate quality of life in patients undergoing treatment with Linac-based SBRT for pancreatic or periampullary cancers.

3.3 Outcome Measures:

3.3.1 Primary Outcome Measure

- Rates of grade 3 acute GI and hematologic toxicity (as raw percentage)

3.3.2 Secondary Outcome Measures

- Late (> 3 months after treatment) toxicity rates (as raw percentage), as related to the RTOG Late Radiation Toxicity Grading Scale.

- One-year rates of overall, progression-free, and metastasis-free survival (will continue to obtain data on these outcomes at subsequent visits beyond 1 year, but the 1 year time point will represent the outcome measure of interest)
- Pain control at one and three months after treatment (based on reporting of standard pain score (0-10) with an option to record pain score based on FACES assessment scale) –will continue to obtain data on pain control at subsequent visits but these 2 time points will represent the main outcome measures of interest
- Quality of life at each follow-up visit (measured by EORTC QOL-Q scale) - will continue to obtain data on quality of life at subsequent visits but these 2 time points will represent the main outcome measures of interest

4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

- Age ≥18 years.
- Karnofsky Performance Status >70% (see Appendix II).
- Histologically confirmed adenocarcinoma of the pancreas or ampulla of Vater; at least the majority of the histopathologic specimen must be identified as adenocarcinoma as opposed to another histologic subtype. In patients with a diagnosis of recurrent disease (based on radiographic progression and/or rising CA19-9 levels) and a history of a biopsy-proven adenocarcinoma of the pancreas or the ampulla of Vater, repeat biopsy of the recurrence site is not required for participation of the trial.
- Pancreatic or periampullary tumors must be less than 8.0 cm in greatest axial dimension at the time of treatment planning.
- Patients who have been treated with any combination of surgical resection and neoadjuvant/adjuvant conventional chemoradiation therapy for resectable disease or conventional chemoradiation as definitive treatment for unresectable or borderline resectable disease are eligible for the study, provided that at least 180 days have elapsed since completing any previous radiation treatment. Patients who have been receiving continued chemotherapy following their initial radiation treatment are eligible regardless of when the most recent chemotherapy was received. Those patients who have received prior radiation therapy will constitute Cohort A and will receive SBRT as 5 Gy x 5.
- Patients who have not previously undergone radiation therapy can have a history of treatment with either chemotherapy (for unresectable/borderline resectable disease) or any combination of surgery and chemotherapy (for resectable disease). Patients with no history of prior radiation treatment will constitute Cohort B and will receive SBRT as 6.6 Gy x 5. Please note that patients must have received at least two cycles of chemotherapy (with selection of drugs at the discretion of the treating oncologist) before SBRT treatment on protocol.
- Acceptable organ and marrow function as defined below (taken no earlier than time of CT Simulation, within 3 weeks prior to radiotherapy):
    - Leukocytes >3,000/μL

  - Absolute neutrophil count >1,500μL
  - Platelets >100,000/μL
  - Total Bilirubin ≤1.5x institutional upper limit of normal
  - AST(SGOT)/ALT(SGPT) <2.5x institutional upper limit of normal
  - Creatinine ≤ institutional upper limit of normal OR creatinine clearance >60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
- Ability to understand and the willingness to sign a written informed consent document.
- Life expectancy > 3 months.
- Radio-opaque markers must be present within the tumor bed. In patients who have undergone surgical resection, radio-opaque surgical clips within the tumor bed can be used as fiducials. Patients without surgical clips in the tumor bed must be able to have fiducials placed endoscopically, laparoscopically, or through a CT- or ultrasound-guided technique. 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.

4.2 Exclusion Criteria

- Age < 18 years.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), active upper GI ulceration or hemorrhage, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Any concurrent malignancy other than non-melanoma skin cancer, non-invasive bladder cancer, early stage prostate cancer, or carcinoma in situ of the cervix. Patients with a previous non-pancreatic, non-periampullary malignancy without evidence of disease for > 5 years will be allowed to enter the trial.
- 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. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- Women who are not post-menopausal (as defined in Appendix III) and have a positive urine or serum pregnancy test or refuse to take a pregnancy test.
- Patients with a life expectancy of < 3 months.
- Patients with metastatic disease.
- Patients with evidence of gross tumor invasion into the lumen of the stomach or small bowel are not eligible; if imaging suggests luminal invasion of tumor, this must be ruled out endoscopically before the patient can be enrolled on study.

5. STUDY DESIGN

This is a single center, single arm unblinded prospective study of the safety of pancreatic SBRT in patients with unresectable, borderline resectable, or recurrent pancreatic/periampullary cancers who have previously undergone treatment with chemotherapy, surgery, photodynamic therapy, conventionally fractionated radiation treatment, or any combination of these therapies.

6. PATIENT REGISTRATION

Potential patients will be identified per the recommendation of surgeons or GI Combined Modality Tumor Board or equivalent combined modality assessment. Potential patients will be recruited through self-referral and the advice of their attending physician. No advertisement will be used to recruit subjects. This trial will be registered at clinicaltrials.gov.

Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. 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. Eligible patients who complete the Informed Consent Process will be registered in the OnCore® database and assigned a patient ID number. Regulatory files will be maintained by the Radiation Oncology Research Office or the IU Simon Cancer Center Clinical Trials Office. Applicable regulatory documents must be completed and on file prior to registration of any patients.

7. SBRT ADMINISTRATION AND RADIATION TREATMENT

7.1 Pre-Linac-based SBRT Tests, Procedures, and Planning

The following will be completed prior to Linac-based SBRT:

- Medical history and clinical examination.
- CBC with differential, chemistry panel, and CA19-9 measurement.
- Gold fiducial seed placement percutaneously, intraoperatively, or under endoscopic ultrasound guidance, which may be performed prior to enrollment.
- Pathologic confirmation of malignancy. (Core biopsies may be obtained during gold fiducial placement as needed; however, repeat biopsy is NOT required for study enrollment in patients who already have pathologically proved adenocarcinoma of the pancreas or periampullary region.)
- Pancreatic-protocol CT or CT of the chest/abdomen/pelvis
- Baseline FDG-PET/CT (dual phase) may be obtained for tumor staging and treatment planning purposes; however, patients who are unable to undergo PET CT scanning (e.g., due to insurance refusal of coverage) can still participate in the study.
- Signed informed consent document.
- Baseline collection of EORTC QLQ C-30/ PAN26 QOL.

7.1.1 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 locally advanced pancreatic or periampullary cancer. Patients who have undergone surgical resection or attempted surgical resection may already have clips or fiducials in the tumor bed, which are acceptable markers for the purposes of this study.

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.

7.1.2 Simulation

Simulation should be done following placement of fiducials; however, this may vary and is at the discretion of the principal investigator. Patients will be positioned supine in a standard custom immobilization device. 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 a contrast-enhanced CT scan or MRI (ideally in a similar treatment position).

Motion management can be addressed using respiratory gating, breath-hold, or respiratory tracking. Fluoroscopy will be used to assess the motion of the implanted gold fiducials during simulation. If the fiducial motion is greater than 5 mm, then the Varian Respiratory Management (RPM) system will be utilized for treatment delivery in either the breath hold or respiratory gating modes (dependent on patient's ability to comply with breath hold). If motion is less than 5 mm, an internal target volume (ITV) will be generated based on the 4-D CT scan, and no respiratory management will be required during radiation treatment. As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled linear accelerator. All patients must start Linac-based SBRT within 4 weeks of the simulation scan.

7.1.3 Treatment Planning

When available, an FDG-PET scan can be used for treatment planning purposes and will be acquired on a flat table top with the same immobilization devices used for the simulation CT scan to enable accurate image fusion. An SBRT treatment plan will be developed using the Eclipse treatment planning system, based on tumor geometry and location. All treatment plans will be stored in their entirety on the Radiation Oncology Eclipse Servers for future reference. Institutional standards for radiation quality assurance and radiation delivery will be utilized. Target volumes will be contoured on the treatment planning CT by an attending physician in

radiation oncology at the IU Simon Cancer Center. Data from prior diagnostic CT scans, respiratory-correlated 4D-CT scan, and/or the FDG-PET/CT scan may be used to assist in treatment planning. The following three target volumes will be contoured:

1) **Gross tumor volume (GTV)**. This will consist of all visible tumor based on the free-breathing, IV contrast-enhanced CT scan. Data from the FDG-PET scan may be used to assist in contouring this volume if the patient has undergone a PET scan.
2) **Tumor-vessel interface (TVI)**. This will include the entire circumferential contour of any major upper abdominal blood vessel [including the portal vein (PV)], superior mesenteric artery/vein (SMA/SMV), celiac artery (CA), and/or common hepatic artery (CHA)] that is in direct contact with the tumor. The craniocaudal extent of the TVI contour should match that of the GTV for any vessel that is included in the TVI.
3) **Tumor-gut interface (TGI)**. This volume is defined as GTV or TVI that directly abuts the stomach, duodenum, small bowel, or large bowel. It will be delineated by creating a planning organ at risk volume (gut PRV) that will consist of the stomach, duodenum, small bowel, and large bowel plus a 3-mm expansion margin. Any areas of the GTV-PTV or the TVI-PTV that overlap with the gut PRV will be considered as TGI.

Table 2. Target volume expansion guide.

Target Volume	Base Structure	Dose	Expansion
TGI	GTV (minus gut PRV)	30 Gy (6 Gy x 5)	n/a
GTV-PTV	GTV	33 Gy (6.6 Gy x 5)	3 mm
TVI-PTV	TVI	36 Gy (7.2 Gy x 5)	3 mm

The final PTV (planning treatment volume) expansion will consist of an additional 3 mm of margin expansion to the GTV and TVI, except if the margin results in expansion into the duodenum or stomach. In these cases, margin expansion is allowed to be non-uniform. Please refer to Table 2. In patients who cannot tolerate or are otherwise not candidates for breath-hold radiation treatment (determination to be made at the discretion of the treating radiation oncologist), an internal target volume (ITV) for each of the above contours will be contoured based on the 4D CT scan in order to account for respiratory motion. The PTV expansion margins will then be added to the ITV in such cases. The dose will be prescribed to the isodose line that completely surrounds the PTV. It is recommended that 6-12 co-planar fields be used in the radiation treatment plan. Contours of the fiducials used for target localization will be generated on the applicable image sets for use in patient setup and 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< 9 cc, and V20< 3 cc. The duodenum, 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. In patients who have undergone pancreaticoduodenectomy, the regions of the pancreaticojejunostomy, gastrojejunostomy, and hepaticojejunostomy that lie 1 cm above or below or lateral to the PTV will also be delineated as structures of interest. V15 and V20 are defined as the percent volume receiving 15 Gy and 20 Gy, respectively. No more than 1 cc of the proximal duodenum or proximal stomach may exceed 33 Gy for cohort B or 25 Gy for cohort A (re-irradiation patients). Dose to the remainder of the normal tissues will be limited as follows:

- Liver (excluding tumor): 50% should be limited to <12 Gy (<8 Gy for cohort A/re-irradiation patients)
- Kidney: Combined volume for both should have 75% <12 Gy (<8 Gy for cohort A/re-irradiation patients)
- Stomach and duodenum: V15<9cc (V12<9 cc for cohort A) and V20<3cc (V15<3 cc for cohort A). 50% should be limited to <12 Gy (<8 Gy for cohort A). No more than 1 cc of proximal stomach can receive >33 Gy for cohort B, and no more than 1 cc of proximal stomach can receive >25 Gy for cohort A/re-irradiation patients.
- Spinal cord: no more than 1cc can receive >8 Gy (>6 Gy for cohort A).
- No more than 1cc of the PTV can receive >130% of the prescription dose (4290cGy for 6.6Gy x 5; 3250cGy for 5Gyx5, cohort A).
- Greater than 90% of the PTV should receive 100% of the prescription dose (3300cGy for 6.6Gy x 5; 2500cGy for 5Gyx5).
- If the above constraints cannot be achieved, the dose to the TGI will first be decreased to from 30 to 25 Gy in 0.5 Gy increments. If the TGI dose is reduced to 25 Gy without meeting constraints, the dose to GTV-PTV will then be decreased from 33 to 25 Gy in 0.5-Gy increments. If constraints still cannot be met, then the TVI-PTV dose can be decreased in similar fashion. In such cases, 100% of the GTV-PTV and the TVI-PTV must receive at least 25 Gy (20 Gy for cohort A) (an allowed minor deviation, which will be documented). The highest dose that permits the above stomach and duodenal constraints to be achieved will be used. However, if even this constraint cannot be met, the patient should be removed from the protocol.

7.2 Linac-based SBRT Treatment Delivery

Patients will receive 5 fractions of 5 Gy or 6.6 Gy delivered over a five-day period, as delineated above, based on whether or not they have received prior radiation therapy to the pancreatic region. Treatment may be delivered over 2 weeks, provided that the patient receives at least 2 fractions per week. 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 the 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, Indiana University School of Medicine.

7.3 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, 4 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.

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. 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. If participants become very ill and cannot travel to IU for follow-up appointments, the study team will mail Quality of Life Questionnaires and request relevant medical records from local providers. This situation is expected due to progression profile, and if all protocol parameters are met, will not constitute a protocol deviation.

7.4 General Concomitant Medication and Supportive Care Guidelines

7.4.1 Antidiarrheals and Anti-Emetics

For symptoms of diarrhea and/or abdominal cramping, patients will be instructed to take over-the-counter anti-diarrheal medication (loperamide). Additional antidiarrheal therapies 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. Prophylactic anti-emetics (generally ondansetron, unless patient has intolerance/allergy) will be encouraged 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.

7.4.2 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.

7.4.3 Use of Radioisotopes/Rad Machines

Stereotactic radiotherapy treatments will be delivered using a linear accelerator ("linac"). The radiation treatment plan will be designed to use multiple beams of radiation to concentrate large doses of radiation within a tumor. Cone beam CT imaging and diagnostic-energy (kV) imaging will 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. 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. The radioactive tracer FDG will be used to perform PET scans (when available), a special imaging procedure. Positron emission tomography (PET) is a type of nuclear medicine examination, which is based on the administration of a small amount of a radioactive FDG agent. The tracer (FDG) is a modified form of glucose, a sugar normally found in the bloodstream and used by cells in the body for energy. FDG is eliminated in the urine. With special imaging equipment, it is possible to detect radiation from the administered radioactive agent and obtain images of the body.

8. TOXICITIES TO BE MONITORED/DOSAGE MODIFICATIONS

It is difficult at this time to predict with confidence the percentage risk 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. We estimate that ≤20% of patients will experience grade 2 or higher late Radiation-related 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. Acute 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. The major serious 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. 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.

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 radiation toxicity is not anticipated given the expectation of limited incidental irradiation of these organs and we have not observed any to date in the patients treated with Linac-based SBRT. Complications, if any, will be graded according to the CTCAE, National Cancer Institute, version 4.0 (see Appendix I). We will also utilize the RTOG scale for grading acute and chronic radiotherapy toxicities.

9. STUDY PARAMETERS/CALENDAR

	Pre-Study[1]	**Treatment**		**----------Follow-Up[4]----------**					
		Week 1	Week 2	4-6 weeks[6]	3 months	6 months	9 months	12 months	Yrs 2-5
Initial Consult	X								
Demographics	X								
History/Physical	X	X[5]	X[5]	X	X	X	X	X	Q6 months
Informed Consent	X								
Biopsy confirmation of adenocarcinoma	X								
CBC with differential	X	X	X	X	X	X	X	X	Q 6 months
CMP	X	X	X	X	X	X	X	X	Q 6 months
CA 19-9	X			X	X	X	X	X	Q 6 months
Negative Pregnancy Test[2]	X								
Fiducial Placement	X								
Simulation Scan	X								
SBRT		X	X						
Radiographic Eval[3]	CT			CT	CT	CT	CT	CT	CT
QoL/Pain Questionnaires	X	X	X	X	X	X	X	X	Q 6 months
AE Evaluation				X	X	X	X	X	Q 6 months

Footnotes:

[1]Within 45 days of commencing study treatment.
[2]Urine or serum pregnancy test must be negative in all premenopausal women who have not undergone surgical sterilization procedures.
[3]FDG PET scan optional at baseline and at all follow-up intervals.
[4]All follow-up visits subsequent to the 4-6 week visit may be completed at an outside hospital. However, all records and imaging (copies of images in addition to reports) must be reviewed at IU. Follow-up appointments have a 30-day tolerance window. QoL surveys may be returned by mail for patients who are completing follow-up visits at an outside clinic.

[5]A treatment evaluation will be done in lieu of history/physical exam at these visits.

[6] Surgical oncology visit note is acceptable if patient has undergone surgical procedures and is limited to travel to clinic

10. CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

10.1 Anti-Tumor Effect and Response Evaluations

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 or PET/CT that was performed for radiation treatment planning. Evaluation of pancreatic and periampullary tumor response will be based on standard radiographic criteria for the treated lesion and will be prospectively recorded in the study database. Radiographic response of the pancreatic or periampullary 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.

Pancreatic or periampullary tumor response will also be assessed by FDG-PET scans (when available) according to the following criteria:

- CR = target lesion becomes photopenic or standardized uptake value (SUV) ratio of tumor/liver less than or equal to 1
- PR = decrease in SUV ratio of tumor/liver (at least 30%) PD = increase in SUV ratio of tumor/liver (at least 20%)
- SD = no significant change in SUV ratio of tumor/liver

We will also determine PET response (in those patients who have undergone follow-up FDG PET scanning) with the new PERCIST criteria as reported by Wahl et al., defined as follows: (33)

- Complete metabolic response (CMR): complete resolution of 18F-FDG uptake within the measurable target lesions so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels with no new 18F-FDG avid lesions
- Partial metabolic response (PMR): reduction by a minimum of 30% in the target lesion's 18F-FDG peak
- Stable metabolic disease (SMD): disease other than CMR, PMR, or progressive metabolic disease
- Progressive metabolic disease (PMD): 30% or greater increase in 18F-FDG peak in the target lesion or the development of new 18F-FDG avid lesions that are typical of cancer.

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

10.2 Definitions

- Duration of Response: time elapsed between SBRT completion (i.e., the last day of treatment) and the first sign of local progression or the development of new metastatic disease.
- Progression-Free Survival: time elapsed from SBRT completion to documented local/regional or distant progression or death. Local PFS will be measured as the duration from SBRT to local progression or death from any cause.
- Overall Survival: Duration from SBRT completion to patient death.

10.3 Response Review

All responses will be reviewed independently by a board certified radiologist at the study's completion. Each image also will be reviewed by the PI with a concurrent review of the patient's medical records.

10.4 Criteria for Removal from Study

Patients will be removed from the study if consent is withdrawn or death occurs. 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 who have been removed from or discontinue the study for administrative reasons will be followed for survival information until death.

11. STATISTICAL METHODS

11.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outlined below.

11.2 Study Design

This is an open-label pilot study. No randomization or blinding is involved. Patients will be placed into dosing cohorts (A or B) depending on previous radiation therapy and followed for at least 1 year post-SBRT.

11.3 Criteria for Stopping Study

We expect the safety profile to be similar for Cohort A and B so will evaluate the stopping rule in the combined cohort. The expected Grade 4 or 5 treatment related AE rate from gemcitabine with SBRT is approximately 6% (Herman ref), and we would consider a 10% rate in our study to be unacceptable. An interim safety analysis is planned after every six patients are accrued and followed for 1 year to assess Grade 4 or 5 treatment-related AEs. If 3 or more out of 6, 4 or more out of 12, 5 or more out of 18, or 6 or more out of 24 patients have a Grade 4 or 5 treatment-related AE within one year, accrual will be terminated. These stopping boundaries represent where the lower bound of a 90% exact binomial confidence interval would be in excess of 10%.

11.4 Analysis Datasets

- Enrolled Population - The enrolled population consists of all patients who enroll in the study.
- Efficacy Population - The efficacy population comprises all patients who meet the eligibility criteria, are registered onto the study, get at least one session of Linac-based SBRT, and have at least one follow-up evaluation. This set will be used for efficacy analysis.
- Safety Population - The safety population comprises all patients who have received at least one session of Linac-based SBRT. This set will be used for safety analysis.

11.5 Sample Size

It is anticipated that this study will last approximately 42 months (30 months of accrual and 12 months of additional follow-up while cohort matures). The total enrollment will be 38. With a 1 to 5 ratio of prior RT treatment to no prior RT treatment, we expect to enroll approximately 6 subjects in Cohort A and 30 in Cohort B. Six subjects in Cohort A will allow us to obtain only a preliminary sense of efficacy; however, we do not want to exclude this important cohort from the study since our focus is on safety. A sample size of 38 will allow us to estimate the primary outcome of acute (within 3 months of treatment) grade 3 or greater gastrointestinal and hematologic toxicity to within approximately 12% using a 90% exact confidence interval assuming the rate is similar to Herman et al. (28%).

11.6 Patient Characteristics and Significant Protocol Violations

Baseline patient characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics will be displayed combined and by cohort. Significant protocol violations such as with respect to eligibility criteria and treatment plan will be tabulated by cohort.

11.7 Concomitant Medications

Medications that might affect the study treatment will be tabulated.

11.8 Disposition

Frequencies and percentages of all patients enrolled, discontinuing the study, and completing the study will be presented by cohort. The reasons for discontinuation will also be summarized.

11.9 Analysis of Primary Objective

The primary outcome of acute (within 3 months of treatment) grade 3 or greater gastrointestinal and hematologic toxicity will be estimated with a 90% exact binomial

confidence interval in the two cohorts combined, since the safety profile is expected to be similar for Cohort A and B.

11.10 Analysis of Secondary Objectives

Acute toxicities according to CTCAE 4.0 will be summarized by frequencies and rates calculated as the proportion of patients in the safety population experiencing SAEs, discontinuations due to AEs, and AEs for the two cohorts combined. For the secondary objective of estimating rates of late (> 3 months after treatment) grade 2 gastritis, enteritis, fistula, and ulcer, or any other grade 3 or greater gastrointestinal toxicity, the proportion of patients with each condition and its 90% confidence interval will be calculated.

In Cohort B only, Kaplan-Meier estimates will be used to estimate the median and 90% confidence intervals for time to local progression, overall survival, metastasis-free survival and progression-free survival. The 1-year rates and 90% confidence intervals will be also be estimated from these curves. A listing of clinical outcomes will be generated for Cohort A.

Pain control (based on reporting of standard pain score (0-10) with the option to use the FACES 0-10 scale) will be evaluated before and after Linac-based SBRT and the change in pain scores will be evaluated and summarized through descriptive statistics separately for each cohort. For Cohort B, linear mixed models will be used to model changes in pain over time. A similar approach will be used for the EORTC QOL-Q scale.

11.11 Interim Analysis

No interim analyses are planned other than assessing Grade 4 or 5 treatment-related AEs after every 6th patient.

11.12 Subgroup Analysis

No subgroup analyses are planned other than the separation of efficacy analyses for Cohorts A and B.

12. DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore®**.** The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCC Clinical Trials Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI).

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center Data Safety Monitoring Committee.

Participant data that will be collected include the following:

- Eligibility or inclusion/exclusion criteria
- Patient demographics
- Pre-study evaluation

- Surgical procedures, with dates and findings (including EUS, biopsy (if needed), fiducial placement, and/or stent placement (if recommended)
- Scan dates (PET/CT (if available) and/or 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
- Follow-up evaluations including H&P data, laboratory studies, imaging, and toxicity data
- QOL and pain questionnaires
- Subject study withdrawal, date, and reason
- Participant report of compliance with protocol prescribed medications, specifically PPIs and antiemetics

13. PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Radiation Oncology Research Office or Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

14. DATA AND SAFETY MONITORING PLAN

Investigators will conduct continuous review of data and patient safety. Monthly review meetings for moderate risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Monthly meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted and reviewed monthly by the IUSCC Data Safety Monitoring Committee (DSMC). Submit to DSMC@iupui.edu.

14.1 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring. Reports will be reviewed by the full DSMC at the time of study review. Moderate risk trials are reviewed annually by the DSMC.

14.2 Early Study Closure

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC. Alternatively, the DSMC may

initiate suspension or early closure of the study based on its review of the investigator reports.

14.3 Reporting Guidelines

The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

14.4 Reporting Death

Death will be reported per local IRB reporting guidelines.

14.5 Study Accrual Oversight

Accrual data will be entered into the IUSCC OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

14.6 Protocol Deviations

Protocol deviations are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

15. REPORTING ADVERSE EVENTS

Low-grade toxicities are to be expected given the disease profile. Any toxicity below CTCAE v4.0 grade 3 will not be reported on the Master AE Log or Case Report Forms. However, this information will be retained in patient charts. Towards end of life, hospitalization events increase within this patient population. Unplanned hospitalizations that occur greater than 30 days from the last fraction of SBRT and that are not attributable to research intervention will be recorded on the Master AE Log and reported at the time of continuing review and SMC monitoring. These parameters are drafted in accordance with CFR21, and provide realistic expectations based on the sickness of this patient population.

15.1 Definitions of Adverse Events

15.1.1 Adverse Event (AE)

An **adverse event** is defined as untoward medical occurrence associated with the use of a medical intervention in humans, whether or not considered related to the medical intervention. An adverse event can be **ANY** unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Acute adverse events will be graded according to the NCI Common Toxicity Criteria, Version 4.0.

15.1.2 Serious Adverse Event (SAE)

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

- Results in death or ANY death occurring within 28 days of the last fraction of SBRT (even if it is not felt to be related to the medical intervention)

- 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

  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to first administration of study treatment
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study treatment
- 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.
- Pregnancy

  Pregnancy of a patient during the study or within 30 days after the last fraction of SBRT should be reported via an SAE report. Should pregnancy occur in a female participant during the treatment period, SBRT should be discontinued.

15.1.3 Unexpected Adverse Event

An adverse event not mentioned in the informed consent or the specificity or severity of which is not consistent with the informed consent, or is not common within the patient population.

15.2 Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	**Attribution**	**Description**
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**

	Definite	The AE **is clearly related**

15.3 Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

Acute adverse events (CTCAEs) will be recorded from the time of first SBRT and for at least 90 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to SBRT. All Acute AEs considered related to SBRT will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

All SAE's should be collected from the first fraction of SBRT until death or the patient enrolls in hospice. SAE's related or possibly related to study treatment or a study procedure should be reported until the patient is off study. Any death occurring within 30 days after the last fraction of SBRT or last study procedure must be reported as an SAE regardless of attribution.

15.3.1 Reporting to the IRB

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

15.3.2 Reporting to the IUSCC Data Safety Monitoring Committee (DSMC)

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is **in addition to any other** regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

16. REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010 Sep-Oct;60(5):277-300.

2. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006 Jul;244(1):10-5.

3. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after

resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011 May;18(5):1319-26.

4. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007 Jan 17;297(3):267-77.

5. Hsu CC, Herman JM, Corsini MM, Winter JM, Callister MD, Haddock MG, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Ann Surg Oncol. 2010 Apr;17(4):981-90.

6. Franke AJ, Rosati LM, Pawlik TM, Kumar R, Herman JM. The role of radiation therapy in pancreatic ductal adenocarcinoma in the neoadjuvant and adjuvant settings. Semin Oncol. 2015 Feb;42(1):144-62.

7. Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP study. Journal of Clinical Oncology. 2014;32(5S):4001.

8. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer. 1981 Oct 15;48(8):1705-10.

9. Chauffert B, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouche O, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol. 2008 Sep;19(9):1592-9.

10. Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009 Apr 10;27(11):1806-13.

11. Erdek MA, King LM, Ellsworth SG. Pain management and palliative care in pancreatic cancer. Curr Probl Cancer. 2013 Sep-Oct;37(5):266-72.

12. Winter JM, Cameron JL, Olino K, Herman JM, de Jong MC, Hruban RH, et al. Clinicopathologic analysis of ampullary neoplasms in 450 patients: implications for surgical strategy and long-term prognosis. J Gastrointest Surg. 2010 Feb;14(2):379-87.

13. Benhamiche AM, Jouve JL, Manfredi S, Prost P, Isambert N, Faivre J. Cancer of the ampulla of Vater: results of a 20-year population-based study. Eur J Gastroenterol Hepatol. 2000 Jan;12(1):75-9.

14. Ross WA, Bismar MM. Evaluation and management of periampullary tumors. Curr Gastroenterol Rep. 2004 Oct;6(5):362-70.

15. Abrams RA, Yeo CJ. Combined modality adjuvant therapy for resected periampullary pancreatic and nonpancreatic adenocarcinoma: a review of studies and experience at The Johns Hopkins Hospital, 1991-2003. Surg Oncol Clin N Am. 2004 Oct;13(4):621,38, ix.

16. Talamini MA, Moesinger RC, Pitt HA, Sohn TA, Hruban RH, Lillemoe KD, et al. Adenocarcinoma of the ampulla of Vater. A 28-year experience. Ann Surg. 1997 May;225(5):590,9; discussion 599-600.

17. Koong AC, Le QT, Ho A, Fong B, Fisher G, Cho C, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004 Mar 15;58(4):1017-21.

18. Schellenberg D, Goodman KA, Lee F, Chang S, Kuo T, Ford JM, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2008 Nov 1;72(3):678-86.

19. Hong TS, Ryan DP, Blaszkowsky LS, Mamon HJ, Kwak EL, Mino-Kenudson M, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys. 2011 Jan 1;79(1):151-7.

20. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015 Apr 1;121(7):1128-37.

21. Mellon EA, Hoffe SE, Springett GM, Frakes JM, Strom TJ, Hodul PJ, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol. 2015 Jul;54(7):979-85.

22. Balmanoukian A, Ye X, Herman J, Laheru D, Grossman SA. The association between treatment-related lymphopenia and survival in newly diagnosed patients with resected adenocarcinoma of the pancreas. Cancer Invest. 2012 Oct;30(8):571-6.

23. Wild AT, Ye X, Ellsworth SG, Smith JA, Narang AK, Garg T, et al. The Association Between Chemoradiation-related Lymphopenia and Clinical Outcomes in Patients With Locally Advanced Pancreatic Adenocarcinoma. Am J Clin Oncol. 2013 May 2.

24. Kleeff J, Reiser C, Hinz U, Bachmann J, Debus J, Jaeger D, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg. 2007 Apr;245(4):566-72.

25. Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg. 1997 May;225(5):621,33; discussion 633-6.

26. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg. 1997 Feb;21(2):195-200.

27. Sharma C, Eltawil KM, Renfrew PD, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of pancreatic carcinoma: 1990-2010. World J Gastroenterol. 2011 Feb 21;17(7):867-97.

28. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, Goodman SN, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg. 1995 Jun;221(6):721,31; discussion 731-3.

29. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg. 1993 Jan;165(1):68,72; discussion 72-3.

30. Cupp JS, Koong AC, Fisher GA, Norton JA, Goodman KA. Tissue effects after stereotactic body radiotherapy using cyberknife for patients with abdominal malignancies. Clin Oncol (R Coll Radiol). 2008 Feb;20(1):69-75.

31. Moertel CG, Childs DS,Jr, Reitemeier RJ, Colby MY,Jr, Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet. 1969 Oct 25;2(7626):865-7.

32. Wild AT, Hiniker SM, Chang DT, Tran PT, Khashab MA, Limaye MR, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. J Gastrointest Oncol. 2013 Dec;4(4):343-51.

33. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009 May;50 Suppl 1:122S-50S.

17. APPENDICES

A1. Appendix I: NCI Common Toxicity Criteria Version 4.0

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site, http://ctep.cancer.gov/reporting/ctc.html

A2.Appendix II: Performance Status Scales/Scores

ECOG or Zubrod		Karnofsky		Lansky	
Score	Activity	Score	Activity	Score	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

A3.Appendix III: DSMC Check Sheet

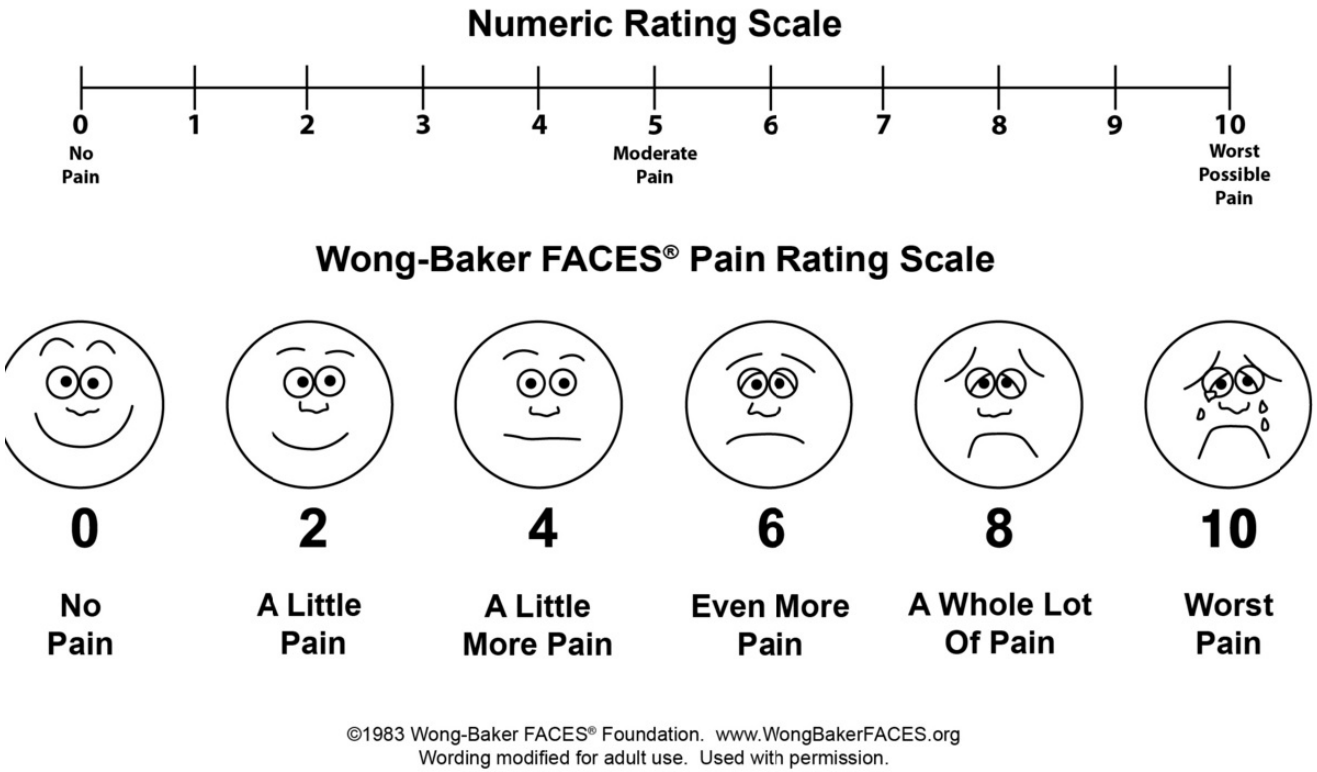
Meeting Minutes Form for DSMC

send to dsmc@iupui.edu or file in binder

Meeting Date:			
Team/Program: **(include meeting sign in sheet)**			
Protocol & Status (open/closed to accrual) (**one protocol per sheet**)			
PI:			
	Y	N	
Weekly and Monthly meetings should include discussion on data, dose levels, accrual numbers, deviation summaries and SAE reports (per IUSCC DSMP).			
Has accrual been reviewed and entered into Oncore?			
Have all SAE's been entered into Oncore?			
Is there documentation for study discontinuation?			
Have all deviations been entered into OnCore?			
Have study deviation summaries been reviewed by the team *(CTO continue to keep deviation logs signed by PI) ?*			
Record any dose limiting toxicities (DLT's) on this form for any phase I investigator initiated trial, HOG or on a multi-site trial in which IUSCC is the lead site.			
If any of your answers are "NO" please explain in the space below.			
***Notes**			

This form is to be used for Investigator Initiated and HOG trials (High risk weekly, Moderate risk Monthly, Low risk quarterly)

A4.Appendix IV: Pain Scale



A5.Appendix V: QOL Questionnaire

See attached PDF “EORTC QLQ-30 (version 3)”