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PILOT STUDY OF SHORT-COURSE PREOPERATIVE STEREOTACTIC BODY RADIATION THERAPY FOR RESECTABLE PANCREATIC CANCER

Primary Investigator

Alan W. Katz, MD, MPH, Department of Radiation Oncology, URMC, Box 647, Rochester, NY 14642

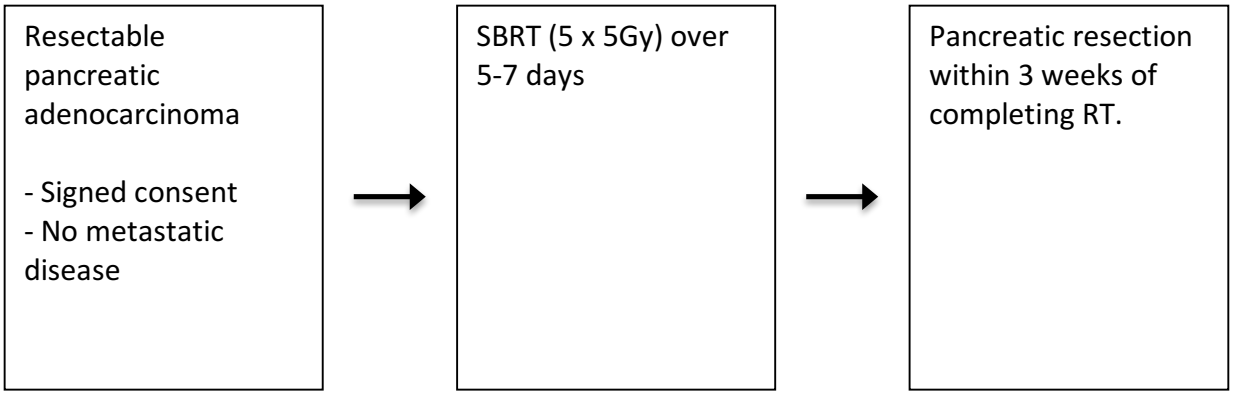
Co-Investigators

Haoming Qiu MD, Department of Radiation Oncology, URMC, Box 647, Rochester, NY 14642
Vivek Kaul MD, FACG, Department of Medicine, Division of Gastroenterology, URMC, Rochester, NY 14642
Shivangi Kothari MD MS, Department of Medicine, Division of Gastroenterology, URMC, Rochester, NY 14642

Sub-investigators:

Eva Galka, MD, Department of Surgery, URMC, Rochester, NY 14642
Luke Schoeniger, MD, PhD, Department of Surgery, URMC, Rochester, NY 14642
Aram Hezel, MD, Department of Medicine, Division of Hematology and Oncology, URMC, Rochester, NY 14642
Mohamedtaki Tejani, MD, Department of Medicine, Division of Hematology and Oncology, URMC, Rochester, NY 14642
Supriya Mohile, MD, Department of Medicine, Division of Hematology and Oncology, URMC, Rochester, NY 14642
Marcus Noel, MD, Department of Medicine, Division of Hematology and Oncology, URMC, Rochester, NY 14642

SCHEMA



Phase I: 12 patients who undergo SBRT and surgical resection

PURPOSE

The purpose of this study is to determine if giving stereotactic body radiation therapy (SBRT) to pancreatic adenocarcinoma before it is surgically resected is safe and feasible.

1. BACKGROUND

Adenocarcinoma of the pancreas is the fourth most common cause of cancer deaths in the United States. Most adenocarcinomas arise in the head of the pancreas in close approximation to the duodenum, celiac axis and superior mesenteric artery. Pancreaticoduodenectomy (Whipple resection) provides the only curative treatment, but only 10-15% of patients are eligible for upfront surgical resection. Unfortunately, even with resection, both locoregional and distant recurrence remains a common problem and 5 year survival rates is 25-30% for patients with node negative disease.[1] Both adjuvant and neoadjuvant therapy have been studied in an attempt to improve current results.

The optimal adjuvant treatment after surgical resection is not currently known. The CONKO-001 trial showed that adjuvant gemcitabine chemotherapy increased 5 year overall survival to 21% from 10% in those who did not receive adjuvant therapy.[2] Whether the addition of radiation therapy to adjuvant chemotherapy is beneficial is controversial. The EORTC 40013/ FFCD-9203/GERCOR phase II study of 90 patients showed that gemcitabine based chemoradiotherapy resulted in improved local control compared with gemcitabine chemotherapy alone with similar median time of disease free and overall survival.[3] The ESPAC-1 trial was a complex study in which patients were randomized to one of 4 adjuvant arms, chemoradiotherapy, chemotherapy, both or none. In a subset analysis of 289 patients, intention to treat analysis showed significantly improved overall survival in patients randomized to receive chemotherapy. On the other hand, patients randomized to chemoradiotherapy had a trend towards worse overall survival.[4] This trial was heavily criticized due to methodological flaws and for using outdated split course radiation techniques. A currently ongoing study RTOG 0848 is seeking to further answer this question by randomizing patients who have received adjuvant chemotherapy to further chemotherapy alone or chemoradiotherapy.[5]

Although upfront surgery with adjuvant therapy is generally chosen, there are many reasons to consider the use of neoadjuvant therapy. The morbidity of surgical resection often prevents the timely delivery of adjuvant therapy. Despite careful technique, there still remains a significant fraction of patients who have positive surgical margins and these patients have a poorer prognosis than those who are able to undergo an R0 resection. Lastly, post-operative

radiation therapy results in the radiation of significant volumes of bowel which often fall into the space previously occupied by the pancreatic head. This can result in significant GI toxicity. As a result, investigators have evaluated the use of neoadjuvant chemoradiation therapy for resectable patients. A study of 50.4 Gy of radiation given over 5.5 weeks in combination with 5-FU demonstrated improved local control versus historical controls.[6] However, toxicity from preoperative treatment resulted in hospital admission for one third of patients. This prompted a consideration of short course preoperative chemoradiation therapy in which 30 Gy in 2 weeks was delivered with concurrent 5-FU which resulted in similar efficacy but decreased grade 3 toxicity.[7,8] As with most other studies, distant metastases to the liver accounted for a majority of disease progression. Therefore, efforts were made to shorten the interval of neoadjuvant radiation therapy to allow patients to proceed more quickly to surgery and adjuvant chemotherapy which would presumably decrease the rate of metastatic disease.

Short course radiation of 25 Gy in 5 fractions has been extensively studied in Europe for the neoadjuvant treatment of resectable rectal cancer and has been found to improve local control compared to surgery alone.[9,10] In the Swedish Rectal Cancer Trial, patients underwent resection within 1 week after radiotherapy. [9] A comparison of 25 Gy in 5 fractions to conventional chemoradiation therapy to 50.4 Gy with 5-FU and Leucovorin showed similar rates of survival, local control and late toxicity. In addition, 25 Gy in 5 fractions was associated with less grade 3 or 4 toxicities (3.2% vs. 18.2%, p=<0.001) and higher compliance (97.9% vs. 59.2%) compared with conventional CRT.[11]

Building upon this experience, a prospective study of 15 patients from Harvard demonstrated that neoadjuvant short course RT using 25 Gy in 5 fractions to the pancreatic bed and regional lymph nodes using proton therapy and concurrent capecitabine was feasible and well tolerated. Acute grade 3 toxicity was noted in 4 of 15 patients. 11 of 15 patients underwent surgical resection but no patients experienced delays or exclusion from surgery due to toxicity from neoadjuvant treatment. Evaluation of 30 day post-operative results showed no deaths or anastomotic leaks. 9 of 11 patients who underwent surgery had R0 resections and 10 of these patients were able to receive post-operative gemcitabine. After a median follow up of 12 months, one year overall survival was 75% for the entire group. Of 11 surgical resected patients, 10 are still alive at last follow up. Of 15 patients treated with neoadjuvant therapy, only 1 patient with a positive surgical margin experienced local progression. No patient experienced nodal or regional failure but 8 patients developed metastatic disease.[12]

A similar study was repeated, also at Harvard, using photon (conventional x-rays) instead of proton radiation therapy. However, compared with the proton study a higher rate of fibrosis (63% vs. 27%) was noted during surgery leading to a mean increase in operative time of 69

minutes. Dosimetric comparisons revealed that patients undergoing photon irradiation had significantly increased low dose radiation exposure to the abdominal organs. Due to this complication, the study was terminated after accrual of 10 of 12 planned patients.[13]

While the Harvard study with neoadjuvant proton therapy achieved excellent results, protons are not widely available at most centers including ours. Therefore, we believe that there is a need for continued investigation of neoadjuvant photon radiation therapy for pancreatic cancer. We hypothesize that delivering high dose photon radiation to the gross disease using stereotactic localization (SBRT) without elective nodal irradiation can effectively reduce local recurrence while minimizing the fibrosis noted in the Harvard Photon study.[13]

We are not aware of any prospective reports of using SBRT alone as neoadjuvant treatment for resectable pancreatic cancer. However, there are several single institution experiences which show that SBRT can be safely delivered for locally advanced pancreatic cancer (LAPC). Choung et al. reported treating LAPC with induction chemotherapy followed by 5 fraction SBRT. Dose painting technique of 7-10 Gy/ Fraction to the region of vessel abutment and 5-6 Gy/fraction to the reminder of the tumor was utilized. Of 73 patients evaluated, no patients developed grade 3 or higher acute toxicity and only 5% developed grade 3 or higher late toxicity.[14]

Since SBRT requires large doses of radiation to be accurately delivered, Chuong et al and many other authors have utilized fiducial placement in the tumor for more precise radiotherapy targeting.[12-14] Although biliary stents have sometimes been used as a surrogate for tumor location, a study of 11 patients demonstrated that biliary stents are not reliable enough to substitute for fiducials in SBRT targeting.[15] Fiducial placement using endoscopic ultrasound (EUS) has been demonstrated to be both feasible and safe. [16]

Based on data from the aforementioned studies, we believe that our protocol which uses photon irradiation of 25 Gy in 5 fractions to the gross disease alone using fiducial localization and stereotactic guidance without chemotherapy will be able to achieve a favorable therapeutic ratio. The rationale is to deliver a dose of radiation that will sterilize microscopic disease at the margins thus decreasing the risk of local recurrence. By targeting the gross disease alone, we hope to minimize the volume of tissue treated and avoid the increase in fibrosis noted in the Harvard photon study. Using radiation therapy alone without chemotherapy will decrease the duration and toxicity of neoadjuvant therapy thereby allowing patients to proceed quickly to definitive surgical resection. After, resection, full dose chemotherapy can then be delivered without interruption with the aim of reducing distant metastatic disease.

2. STUDY DESIGN

2.1 Overview

This will be a Phase I, single center, prospective, single arm feasibility study of the use of stereotactic body radiotherapy (SBRT) for the preoperative treatment of surgically resectable pancreatic adenocarcinoma.

2.2 Primary Objectives

a) To evaluate the feasibility and tolerability of short course preoperative stereotactic body radiation therapy for resectable pancreas cancer
b) To determine the rate of Grade 2 or greater acute toxicity of neoadjuvant stereotactic body radiation therapy
c) To determine intraoperative and postoperative surgical morbidity following neoadjuvant treatment including the amount of fibrosis and total operative time.

2.3 Secondary Objectives

a) To determine local control and recurrence patterns of treated patients relative to historical controls.
b) To determine progression free survival of treated patients
c) To determine overall survival of treated patients

3. CHARACTERISTIC OF THE RESEARCH POPULATION

3.1 Subject Characteristics

We aim to enroll 18 patients into this Phase I trial with the goal of 12 evaluable cases. We will recruit from the population of patients who are referred to URMC for diagnosis and workup of their suspected pancreatic adenocarcinoma. We expect that patients will be approximately 50-70 years old with an equal distribution of males and females and racial and ethnic backgrounds. No vulnerable subjects will be enrolled.

3.2 Inclusion Criteria

a) Patient with pathologically proven diagnosis of adenocarcinoma of the head of the pancreas
b) CT w/ contrast or MRI of the abdomen with contrast within 6 weeks prior to registration
c) CT chest or PET/CT within 6 weeks prior to registration
d) Clinically determined to be resectable based on NCCN Criteria:

e) No radiographic evidence of superior mesenteric vein or portal vein distortion
f) No evidence of distant metastasis
g) Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery
h) No enlarged lymph nodes per CT criteria or PET avid lymph nodes
i) No lymphadenopathy outside the surgical field (i.e. celiac or para-aortic adenopathy)
j) Adequate cardiopulmonary reserves to tolerate surgery
k) Karnofsky performance status ≥ 70
l) Age ≥ 18
m) Adequate bone marrow function defined as follows:
    - Absolute neutrophil count (ANC) ≥ 1800 cells/mm^3
    - Platelets ≥ 100,000 cells/mm^3
    - Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8 g/dl is acceptable.)
n) Pregnancy test must be negative for women of childbearing potential within 7 days prior to study entry
o) Patient must sign study specific informed consent prior to study entry

3.3 Exclusion Criteria

a) Prior surgical resection of any pancreatic malignancy
b) Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years
c) Any prior chemotherapy or radiation for treatment of the patient's pancreatic tumor.
d) Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields
e) Severe, active comorbidity, defined as follows:
    1. Unstable angina and/or congestive heart failure requiring hospitalization within the last 12 months
    2. Transmural myocardial infarction within the last 6 months
    3. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
    4. Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration.
f) Severe, uncorrectable hepatic insufficiency and/or coagulation defects due to liver failure
g) Any evidence of distant metastases (M1)
h) Pregnancy or women of childbearing potential and men who are sexually active and not

willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic

4. METHODS AND STUDY PROCEDURES

4.1 Pretreatment Evaluation (please see schedule in Appendix B for table layout)

Within 6 weeks prior to study enrollment patients must undergo the following evaluations:

a) History and physical by Radiation Oncologist, Gastroenterologist and Surgical Oncologist
b) CT or MRI scan of the abdomen and pelvis with IV contrast or PET/CT
c) CT chest or PET/CT within 6 weeks prior to registration
d) Informed Consent obtained by a member of the study team
e) Lab studies [CBC with diff, Na, K, BUN, Cr, Glucose, Phosphorous, Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase, CA19-9, CEA, INR and a pregnancy test (urine or serum HCG) for women of childbearing potential].
f) If clinically indicated, fiducial placement in/near the tumor via endoscopic ultrasound by gastroenterology service at least one week prior to CT simulation
g) Patients will be placed on proton pump inhibitors 1 week prior to SBRT to continue until the day of surgery to minimize bowel toxicity.
h) Any bile stent manipulation should be done 7-10 days prior to SBRT

4.2 Evaluation during study Period

a) History, physical and vital signs during the weekly “on treatment visit” during radiation therapy
b) History, physical and vital signs and laboratory evaluation obtained by surgery team prior to resection. Specific tests needed will be determined by surgical team.
c) Following resection, patients will be assessed within 30 days after discharge for post-operative morbidity by the surgery team.
d) Patients will be followed at least every 6 months for a minimum of 5 years by a physician from either radiation, surgical or medical oncology service. Closer follow up may be needed based on clinical situation.

4.3 Treatment

4.3.1 Radiation Therapy

4.3.1a Simulation and Planning

Patients should abstain from oral intake for 2 hours prior to CT Simulation. Water and medications are acceptable. Patients will be simulated supine and Exac-trac body markers will be placed on the skin for patient positioning and respiratory management. In order to minimize treatment volume, patients will be asked to perform end-expiratory breath hold during simulation and treatment. If patient is unable to tolerate and/or comply with breath hold, simulation and treatment will be done using shallow free breathing. A Vac-bag custom immobilization device will be made.

With the patient in the treatment position and in end-expiratory breath hold, a non-contrast CT will be first performed. This will be followed by a contrast CT scan (if no contraindications) also using breath hold technique. The maximum slice thickness will be 2.5mm. If intravenous contrast is not used during CT Simulation, a diagnostic CT or MRI using intravenous contrast or PET/CT must be available as a reference for target delineation.

Gross tumor volume (GTV) will be defined on the basis of CT and MRI imaging findings. The GTV alone will be treated with a planning target volume (PTV) margin of -5 mm to account for setup inaccuracy and patient and organ movement. If needed, PTV can be reduced to 3mm or less in order to avoid high doses to the duodenum and stomach. 25 Gy in 5 fractions will be prescribed to the 70-90% isodose line. Patients will be treated in 5 fractions delivered over 5-7 days.

4.3.1b Plan Evaluation

Prior to starting treatment, the radiation plan for each patient will be evaluated by the radiation oncologists who will review the isodose curves on the treatment planning scan and evaluate the dose-volume histograms (DVH).

Target Dose

25 Gy in 5 fractions will be prescribed to the 70-90% isodose line. The prescription isodose line will be chosen so that at least 95% of the PTV is conformally covered by the prescription isodose surface. Target doses less than 95% of prescription dose are limited to areas adjacent to an organ at risk (OAR).

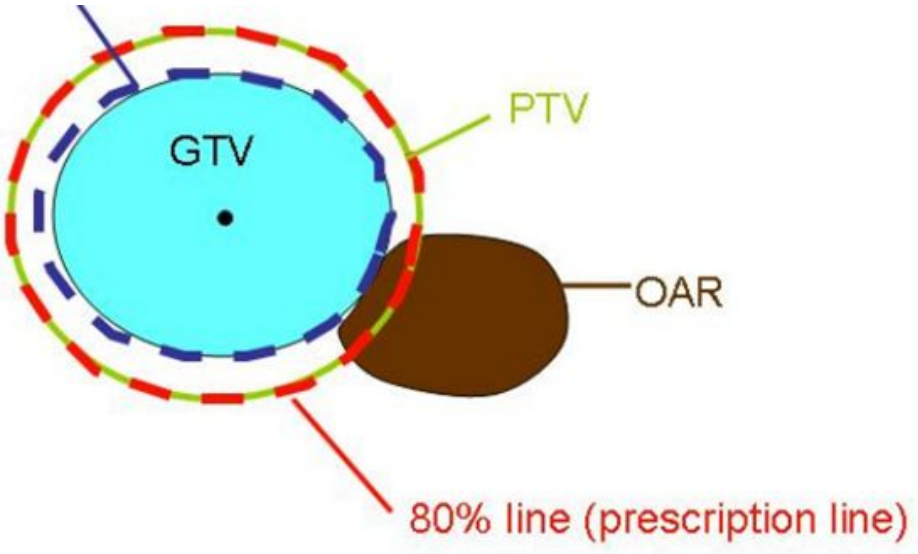


Figure 1. Schematic of Radiation Prescription

1. Prescription dose 25 Gy
2. Prescription isodose 70-90%
3. At least 95% of PTV covered by prescription isodose
4. Normalization to be at isocenter

Normal Tissue Tolerance adapted from Chuong et al. [14]:

- Mean kidney dose <10 Gy
- Duodenum/small bowel/stomach: maximum dose (0.5cc) <35 Gy, mean dose <20 Gy, volume receiving 30 Gy <5 cc
- Liver: volume receiving 30 Gy <10%
- Spinal cord maximum point dose -20 Gy

4.3.1c Quality Assurance

The prescription isodose line selected will be 70-90% of the maximum dose within the PTV. As a result a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (e.g. 25 Gy/0.8 = 31.25 Gy when 25 Gy is prescribed to the 80% isodose line). Doses higher than the prescription dose (i.e. hotspots) must occur within the target and not within an OAR.

4.3.1d Treatment

Patients will be immobilized in the Vac-Bag device. They will be treated in the manner in which they were simulated; either expiratory breath hold or shallow breathing. They will initially be positioned using ExacTrac body markers. Treatment position will then be confirmed by fiducials alignment via ExacTrac KV imaging. Final anatomic confirmation will be made by cone-beam CT immediately prior to treatment.

4.3.2 Supportive Treatment During Radiation

a) Narcotic pain medications and anti-nausea medications will be prescribed as needed
b) NSAID medications will be stopped prior to SBRT and not restarted until after surgery.

4.3.3 Surgery

Surgery will be performed no more than 3 weeks after completion of radiation therapy. A pancreaticoduodenectomy (Whipple procedure) with standard lymphadenectomy will be done. Restaging is not required prior to surgery. However if re-staging scans are obtained and demonstrate metastatic disease, surgery will not be performed.

An attempted resection may also be aborted when more advanced or metastatic disease is found at the time of laparotomy. If surgical resection cannot be completed due to the presence of advanced disease, the patient will be withdrawn from the protocol at that time and will continue their care with standard treatment and follow up based on their clinical characteristic.

4.3.4 Adjuvant Therapy

Adjuvant chemotherapy may be given after pancreaticoduodenectomy at the discretion of the medical oncologist.
Postoperative radiotherapy would not routinely be given after SBRT.

4.4 Cost of Treatments to the Subject

Some of the tests/procedures/exams involved in the study such as imaging and laboratory analysis for oncologic staging and the surgical resection are standard care. The patient and/or his/her insurance company will be responsible for paying for any tests/procedures/exams that are done as part of the standard of care. The patient and his/her insurance company will also be required to pay for the SBRT radiation received through this study. The provider will attempt to obtain prior authorization for the radiation treatment from the subject's insurance provider. Any difficulties obtaining authorization will be discussed with the subject prior to your treatment.

The patient will be encouraged to discuss their coverage with the insurance provider prior to initiating treatment. The cost of SBRT will be offset by omitting fractionated radiotherapy that would otherwise be given as the standard of care after surgery and chemotherapy.

There will be no payments made to patients on the study.

5 EVALUATION OF EFFICACY

5.1 After Radiation

No routine oncologic evaluation will be performed after SBRT therapy. Further workup may be needed if patients demonstrate clinical signs of disease progression.

5.2 After Surgery

5.2.1 Pathology

Following surgical resection, all patients will undergo pathologic staging according to the AJCC Cancer Staging Manual, 7th Edition including T,N,M staging. Pancreatic transection margin, bile duct, and uncinate margin will be evaluated on frozen section. Recorded on permanent section will be: tumor size, degree of differentiation (well, moderate, poor), lymph node status, margin status. The amount of necrosis in the tumor and any other effects of treatment should also be noted.

5.2.2 Post-Treatment Surveillance

NCCN guidelines will be followed. Surveillance will be every 3-6 month for 2 years then annually thereafter and will include:

- History and Physical
- CA 19-9 Levels
- CT or MRI imaging with IV contrast

6. ADVERSE EVENTS

6.1 Definition of Adverse Event

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study intervention.

The investigator will be responsible for assessing the etiology of any adverse events and determining if these can be considered a treatment related adverse event (TRAE) which arose directly or indirectly as a result of SBRT. Adverse events will be graded according to the NCI CTCAE Version 4.0. TRAE will be considered “acute” if they occur within 1-4 weeks post SBRT and prior to surgical resection and “late” if they occur after this time period.

6.2 Evaluation of Adverse Events

Patients will be assessed for treatment related adverse events weekly during on treatment visit during radiation therapy, at the pre-operative evaluation visit and at follow up visits for at least 5 years. Additional patient visits may be needed as clinically indicated. At these visits, study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical, radiologic and laboratory features as indicated by the schedule in Appendix B and as clinically warranted. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

6.3 Documentation of Adverse Events

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, will be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, and the relationship to SBRT, contributing factors, and any action taken with respect to the planned radiation therapy. In addition, any toxicity leading to radiation treatment break and delay in surgical resection beyond 3 weeks post SBRT will noted.

All patients are expected to undergo surgical resection within 3 weeks after radiation therapy. Any Intraoperative complications including blood loss, total operative time and amount of fibrosis noted by the surgeon will be recorded in the operative report. Post-operative complications including delayed wound healing, blood loss, infection, length of hospital stay, incidence of pancreatic leak, hospital readmissions for complications will also be recorded. Appendix A lists the data the surgical oncology team is responsible for recording.

Treatment related late complications including but not limited to duodenal and intestinal ulceration, perforation, gastritis, bowel adhesions and obstruction, will be recorded at follow ups up to 5 years after treatment.

6.4 Serious Adverse Events (SAEs)

A serious adverse event is any adverse event that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

Any serious adverse events will be communicated directly to the primary investigator (Dr. Alan Katz) within 24 hours and documented in the patient's medical chart. Dr. Katz will determine how to respond to the event and whether the patient will continue on the study.
All SAEs will be reported to the IRB per local institutional policy.

6.5 Treatment Modification due to adverse events

We do not anticipate any serious treatment related adverse events will take place during or immediately following SBRT treatment. We expect that the most common acute toxicities of radiation therapy will be mild nausea, fatigue and loose bowel movements.

Patients will finish planned radiation if they experience up to grade 2 treatment related toxicity. If patients develop any serious adverse event or any grade 3 or higher treatment related toxicity, SBRT radiation will be stopped and the patients will proceed directly to surgical resection if deemed appropriate by surgical oncology.

7. RISK/BENEFIT ASSESSMENT

This study is being conducted because the investigators believe that treating pancreatic adenocarcinoma with preoperative SBRT may improve outcome compared with more conventional treatment. There have been several small-scale studies at other institutions (as documented in the introduction) which have shown delivering SBRT to the pancreas can be safe and effective. However, this technique has not been attempted at URMC. We aim to study whether neoadjuvant SBRT is feasible at URMC. There are benefits and risks associated with this study as documented below. The investigators believe that the benefits outweigh the potential risks for patients enrolled on this study.

7.1 Benefits of Participation

a) In conventional treatment, radiation is delivered to the surgical bed which contains a large of bowel that has been surgically manipulated. This study calls for radiation to be delivered prior to surgery. This allows the radiation to be targeted at the gross tumor directly which will decrease the amount of normal bowel that is treated. In addition, the tumor vascular supply preoperatively is generally more robust than postoperatively allowing better oxygenation to the tissue which is critical for the tumoricidal effect of radiation.
b) In conventional treatment, radiation is delivered in conjunction with radio-sensitizing chemotherapy over a period of 5-6 weeks. This chemotherapy is generally not as effective at controlling micrometastatic disease compared to definitive chemotherapy which may increase the risk of metastatic progression. This study calls for a shorter

course of radiation treatment to be delivered over 1-2 weeks preoperatively. This will allow the patient to receive full dose chemotherapy without interruption after surgery. This could reduce the risk of metastatic disease which is a major problem in the treatment of pancreatic cancer.

c) Conventional radiation treatment delivers a small dose of radiation spread over 5-6 weeks. It is known that pancreatic cancer is relatively resistant to radiation therapy. The radiation in this study is delivered in larger doses over a shorter period of time which may help to overcome some of the resistance of pancreatic cancer.

7.2 Risks of Participation

a) Preoperative SBRT could cause toxicities that could delay or even prevent surgical resection which is the most important treatment for resectable pancreatic cancer. However, previous studies have demonstrated that the vast majority of patients who undergo preoperative radiation can safely undergo surgery in a timely fashion.

b) Radiation therapy can cause both acute and delayed side effects. Acute side effects that take place during or immediately after treatment can include fatigue, nausea, vomiting, diarrhea, loss of appetite and weight loss. These effects are expected to be uncommon and can be managed with supportive care such as anti-nausea or anti-diarrheal medicines. Delayed side effects can take place months to years after radiation and can include delayed wound healing, scar tissue formation and bowel obstruction and structuring. These effects are expected to be very rare. These effects are expected to be similar or decreased compared with the toxicities associated with conventional radiation.

c) There is a risk of invasion of patient privacy. All the information gathered from patient chart or records, including name and any other identifying information will be strictly confidential and will be kept under lock and key. The patients will not be identified nor will any information that would make it possible for anyone to identify the patient be used in any presentation or written reports about this study. Only summarized data will be presented at meetings or in any publications.

8. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

All protected health information will be de-identified prior to storage in the research database. Subjects in the research database will be only identified by an ID number based on their order of enrollment (i.e. Subject 1, Subject 2 etc.). The primary investigator, Dr. Katz will maintain a password-protected file that will link the subject ID code to the patient's medical record number in the electronic medical record system at URMC. All research data will be kept in

secure data servers in the department of radiation oncology. All research spreadsheets will have passwords protection that will only be known to the study investigators.

The patient's enrollment on the trial and any clinical data relevant to the patient's care will be documented in the patient's electronic medical record at URMC.

9. DATA ANALYSIS AND MONITORING

The purpose of this pilot study is to determine feasibility of preoperative SBRT followed by surgical resection at URMC and to determine its safety and tolerability in a small population of patients. For this phase 1 trial, we plan to enroll 18 patients over 1-2 years with a goal of 12 evaluable cases. This is a generally accepted number of patients for phase 1 trials and will minimize the risks to patients in case the treatment is found to be unsafe. We will stop recruitment and analyze the safety data if there appears to be any grade 3 or greater toxicity on any subject that can be directly attributed to SBRT or if any patients are made ineligible for surgical resection solely due to toxicities from SBRT.

In the case where any patient becomes ineligible for resection due solely to toxicity from SBRT, the study will be immediately closed to accrual. We will stop recruitment and any patient who has not started radiation therapy will have their planned radiation treatment canceled. A patient who has started radiation therapy will undergo an individual discussion with Dr. Katz about the risks and benefits of continued treatment.

If a patient experiences grade 3 or greater toxicity directly attributable to SBRT that is reversible and ultimately able to undergo resection, we will analyze the event and attempt to prevent/reduce the adverse event from taking place again. We will discuss the risks and benefits of continued recruitment into the study with our co-investigators and determine whether or not to continue the study. If we believe that modifications can be made that will reasonably reduce the risk of a future event from occurring, we will continue recruitment to the study.

The investigators plan to evaluate the rates of acute toxicity after 12 patients have been enrolled and undergone SBRT and surgical resection. Long term safety and efficacy will be evaluated after all 12 patients have undergone surgical resection and have either been followed for at least 6 month or have died. The primary investigator, Dr. Alan Katz will have access to all of the study data.

The Cancer Center Data & Safety Monitoring Committee will monitor the study for safety. Study

Investigators will conduct continuous review of data and patient safety. The Investigator will submit quarterly progress reports of these data to the Clinical Trials Monitoring Committee for review [Appendix C]. The review will include for each treatment arm/dose level: the number of patients enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the AE spreadsheet along with the Progress Report to the Clinical Trials Monitoring Committee for review. Actual review dates will be assigned when the 1st patient is accrued.

- Any serious adverse event that is serious, related AND unexpected must be reported within 10 calendar days to both the Safety Coordinator and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.
- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the Committee for review at the quarterly meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

We plan to publish a descriptive analysis of the results including acute and late toxicity including surgical morbidity. We plan to report oncologic outcomes including median overall survival, progression free survival, local progression free survival and distant progression free survival. Analysis will be using Kaplan-Meier method. Survival time will be measured from the date of diagnosis. A local recurrence will be defined as any evidence of tumor recurrence within the PTV. Whether local recurrence occurred in conjunction with, before or after distant recurrence will be noted.

Appendix A

Assessment of Acute Toxicity Form to be completed by Surgical Team immediately after resection and at the Post Op Visit.

Field	Result
To be Recorded in the Operative Note	
Operating Time (min)	
Estimated Blood Loss (ml)	
Surgeon's Assessment of Fibrosis (Expected, Increased, Markedly Increased)	
To be Recorded at the Post Op Visit	Date of Visit:
Length of Hospitalization post-surgery including any re-admissions (days). Described any re-admissions	
Anastomotic Leak (yes/no) If so described	
Post-Surgery Infection Requiring Antibiotics (yes/no) If so described	
Wound healing complications that are worse than usual? (yes/no) If so described	

Name of person completing the form:

Date form completed:

Appendix B
Required Evaluations

Tests and Observation	Within 6 weeks prior to Study enrollment	On Treatment visit during RT	Post-Op Toxicity Eval by surgery team	Clinical Follow Up every 3-6 months for 2 years, then annually per NCCN
Signed informed consent	X			
History + Physical Examination	X	X	X	X
Complete blood count with differential, Comprehensive metabolic panel, creatinine clearance, Phosphorous, INR	X*			
Pregnancy test**	X			
CA 19-9 Level	X			X
CEA Level	X			
CT or MRI scan of the abdomen and pelvis with IV contrast or PET/CT.	X			X
CT chest or PET/CT	X			

* Other laboratory tests such as coagulation studies may be ordered by surgical team as needed

** Pregnancy test results need to be obtained within 7 days of study entry for those of childbearing potential.

Appendix C

James P. Wilmot Cancer Center (JPWCC)
Data Safety Monitoring Committee (DSMC)
Study Progress Summary Report

Study name and URCC #
PI:

DSMC Review Date:

Date of 1st accrual: _____Status: open___ closed to accrual___ closed _____
(date)

DATA SUMMARY:

1. ENROLLMENT
Since last Report: _____ Total to Date: _____ Total Planned: _____
Comments:

2. ADVERSE EVENTS			
	Serious / Related / Unexpected[1]:	Other Serious[2]:	Non-Serious:
Since Last Report:			
Total:			
Comments:			

[1]Serious, possibly/probably/definitely related events that are considered unexpected require prompt reporting to RSRB and DSMC.
[2]Serious events which are unrelated and/or expected require reporting to the RSRB at least annually and to the DSMC per DSMC reporting requirements.

3. SUBJECT WITHDRAWALS				
	Investigator-initiated:	Reason(s):	Subject-initiated:	Reason(s):
Since last report:				
Total:				

DMSC RECOMMENDATIONS:
*<indicate DSMC recommendations, if any – i.e., requested actions **or** state 'No recommendations at this time; study should continue as planned.'>*

10. References

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2. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: The CONKO-001 randomized trial. *JAMA*. 2013;310(14):1473-1481.

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6. Evans DB, Pisters PW. Preoperative chemoradiation therapy for pancreatic cancer. *Surg Clin North Am*. 2001;81(3):709-713.

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11. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*. 2006;93(10):1215-1223.

12. Hong TS, Ryan DP, Blaszkowsky LS, 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;79(1):151-157.

13. Wo JY, Mamon HJ, Ferrone CR, et al. Phase I study of neoadjuvant accelerated short course radiation therapy with photons and capecitabine for resectable pancreatic cancer. *Radiother Oncol*. 2014;110(1):160-164.

14. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys*. 2013;86(3):516-522.

15. van der Horst A, Lens E, Wognum S, et al. Limited role for biliary stent as surrogate fiducial marker in pancreatic cancer: Stent and intratumoral fiducials compared. *Int J Radiat Oncol Biol Phys*. 2014;89(3):641-648.

16. Kothari S, Kaul V. Therapeutic applications of endoscopic ultrasound. *Ultrasound Clinics*. 2014;9(1):53-65.