PHASE II STUDY TO EVALUATE STEREOTACTIC BODY RADIATION THERAPY FOR PALLIATIVE MANAGEMENT OF UNRESECTABLE RECURRENT OR RESIDUAL PANCREATIC OR PERIAMPULLARY ADENOCARCINOMA

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PROTOCOL SYNOPSIS

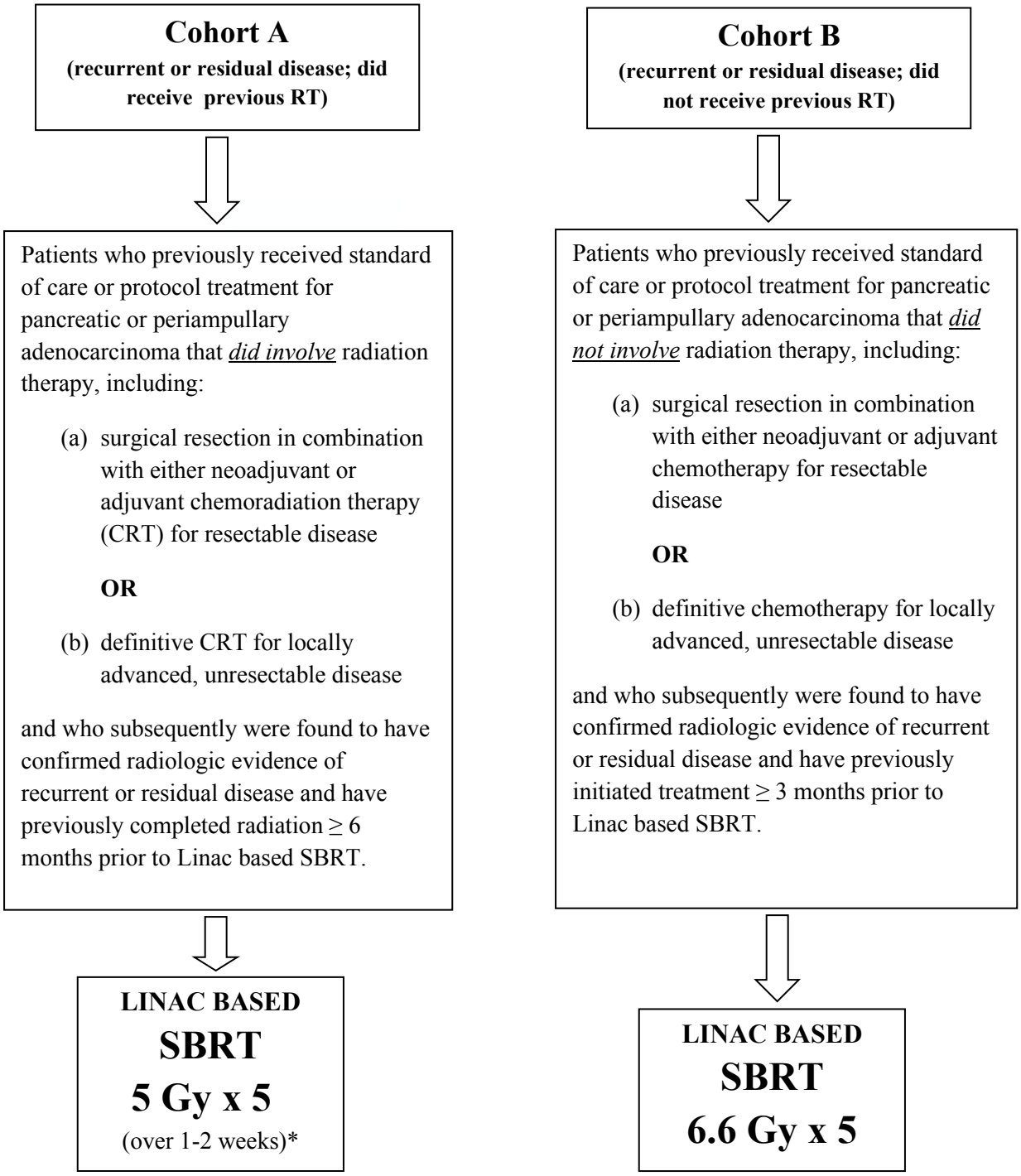
TITLE	**PHASE II STUDY TO EVALUATE STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR PALLIATIVE MANAGEMENT OF UNRESECTABLE RECURRENT OR RESIDUAL PANCREATIC OR PERIAMPULLARY ADENOCARCINOMA**
STUDY PHASE	**II**
INDICATION	**Unresectable recurrent or residual pancreatic or periampullary tumors**
PRIMARY OBJECTIVE	• To evaluate rates of **late** (> 3 months after treatment) gastrointestinal toxicity following fractionated Linac based SBRT for pancreatic tumors. Toxicities of note include grade 2 or greater gastritis, enteritis, fistula, or ulcer and any other grade 3 or greater gastrointestinal toxicity.
SECONDARY OBJECTIVES	• To evaluate rates of **acute** (within 3 months of treatment) gastrointestinal toxicity following fractionated Linac based SBRT for pancreatic tumors. Toxicities of note include any grade 3 or greater gastrointestinal toxicity. • To evaluate local progression free survival, overall survival, metastasis-free survival, and progression-free survival rates following Linac based SBRT in patients with unresectable recurrent or residual pancreatic or periampullary adenocarcinoma. • To evaluate the ability of Linac based SBRT to provide pain control among symptomatic patients as measured by pain medication requirement at 3, 6 and 12 months after treatment. • To evaluate the utility of FDG-PET for treatment planning and estimation of progression-free survival. • To develop and standardize Linac based SBRT delivery and dosimetric parameters. • To evaluate toxicity and outcomes among two cohorts of patients: a) patients with recurrent or residual disease after previous chemoradiation therapy, with or without surgery, who will be treated with 5 Gy x 5 and (b) patients with recurrent or residual disease after chemotherapy only, (with or without surgery), who will be treated with 6.6 Gy x 5.
HYPOTHESES	No standard treatment option has yet been established for patients with recurrent or residual disease after definitive treatment of pancreatic or

	periampullary cancers (duodenal, ampullary, bile duct). Linac based stereotactic body radiation therapy (SBRT) administered in 1-3 fractions has been shown to be an effective treatment option for patients with unresectable, locally advanced pancreatic adenocarcinoma, achieving local control rates of 84-92% at one year. Associated late gastrointestinal toxicity rates have been reported to be 22-25% at 1 year. We hypothesize that similarly excellent local control rates (80-90% at one year) with a reasonable rate of toxicity (≤20%) can be achieved using Linac based SBRT delivered as 5 Gy x 5 for patients with local failure after previous treatment with conventional chemoradiation therapy (CRT) with or without surgery and as 6.6 Gy x 5 for radiation-naïve patients with local failure after previous treatment with surgery and/or chemotherapy. The toxicities of note for this trial are grade 2 and greater gastritis, fistula, enteritis, ulcer, or any other grade 3 or greater gastrointestinal toxicity.
STUDY DESIGN	Prospective, non-randomized, phase II study.
PRIMARY ENDPOINT AND SECONDARY ENDPOINTS	Primary Endpoint: • Late (> 3 months after treatment) grade 2 or gastritis, enteritis, fistula, and ulcer, or any other grade 3 or greater gastrointestinal toxicity. Secondary Endpoints: • Acute (within 3 months of treatment) grade 3 or greater gastrointestinal toxicity. • Local progression free survival, progression-free survival, metastasis-free survival, and overall survival rates at 3, 6, and 12 months after therapy. • Symptom control as measured by pain medication requirement at 3, 6, and 12 months after Linac based SBRT. • Change in pancreatic or periampullary tumor volume with FDG-PET/CT compared to CT scan. • Health-related quality of life (QoL) before and after SBRT.
SAMPLE SIZE BY TREATMENT GROUP	120 (60 in Cohort A, 60 in Cohort B; see inclusion criteria below for cohort definitions)
SUMMARY OF SUBJECT ELIGIBILITY	

CRITERIA	
INCLUSION CRITERIA	• Age ≥18 years. • Karnofsky Performance Status ≥70% (see Appendix II). • Histologically confirmed pancreatic or periampullary adenocarcinoma; at least the majority of the histopathologic specimen must be identified as adenocarcinoma. If previously diagnosed, recurrence can be based on imaging findings of recurrence. • Either: (a) Previously completed standard of care or protocol treatment for pancreatic or periampullary adenocarcinoma consisting of either surgical resection with neoadjuvant/adjuvant CRT for resectable disease or conventional CRT as definitive treatment for unresectable disease. These patients who have received prior radiation therapy will constitute Cohort A and will receive SBRT as 5 Gy x 5. **OR** (b) Previously initiated standard of care or protocol treatment for pancreatic or periampullary adenocarcinoma consisting of chemotherapy (without radiation) for unresectable disease or surgical resection with neoadjuvant/adjuvant chemotherapy (without radiation) for resectable disease. Patients who have not previously received radiation therapy will constitute Cohort B and will receive Linac based SBRT as 6.6 Gy x 5. • Disease recurrence or residual disease at least 6 months after completing initial definitive therapy for patients who have received prior radiation and 3 months after initiating therapy for patients who have not received radiation. • Pancreatic or periampullary tumors must be less than 8 cm in greatest axial dimension at time of treatment planning. • No active infection requiring hospitalization • Patients must have acceptable organ and marrow function (see section 4.1.7). • Women who are not post-menopausal (as defined in Appendix III) should have a negative urine or serum pregnancy test. Women of childbearing potential must agree to use adequate contraception for the duration of study participation.

	• Ability to understand and the willingness to sign a written informed consent document. • Life expectancy > 3 months.
EXCLUSION CRITERIA	• Presence of metastatic disease. • Infections requiring systemic antibiotic treatment. • Unable to understand or unwilling to sign a written informed consent document. • Life expectancy < 3 months.
PROCEDURES	Endoscopically guided fiducial placement with optional biopsies obtained at the time of fiducial placement.
STATISTICAL CONSIDERATIONS	See statistics section.

SCHEMA



*It is recommended that patients in both cohorts discontinue any chemotherapy one week prior to Linac based SBRT and delay resumption of chemotherapy until 1 week following completion of Linac based SBRT. Patients must receive at least 2 consecutive radiation treatments per week if given over a 2 week period.

1. OBJECTIVES

1.1. Primary Objective

To evaluate rates of late (> 3 months after treatment) grade 2 gastritis, enteritis, fistula, and ulcer, or any other grade 3 or greater gastrointestinal toxicity.

1.2. Secondary Objectives

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

1.2.2 To determine rates of local progression free survival, overall survival, metastasis-free survival, and progression-free survival in patients with recurrent or residual disease treated with fractionated Linac based SBRT.

1.2.3 To evaluate the utility of FDG-PET before and following treatment in predicting local progression.

1.2.4 To evaluate patient quality of life before and after Linac based SBRT.

1.2.5 To evaluate the ability of Linac based SBRT to provide pain control in symptomatic patients with pain related to a pancreatic tumor.

1.2.6 To further develop standardization of Linac based SBRT delivery and dosimetric parameters.

1.2.7 To compare outcomes among patients treated with fractionated Linac based SBRT delivered as 5 Gy x 5 (Cohort A of current protocol) or 6.6Gy X 5 (Cohort B of current protocol) with patients treated with 25 Gy X 1.

2. BACKGROUND

2.1 Natural History and Management of Pancreatic Cancer

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

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

2.2 Current Adjuvant Management of Resectable Pancreatic Adenocarcinoma

Among the minority of patients who are able to undergo surgical resection, low median survival rates and cure rates imply the presence of residual local and/or systemic microscopic disease that may be amenable to adjuvant therapy. The standard of care for adjuvant therapy is controversial. Adjuvant chemoradiation has been frequently studied due to high rates of positive margins and locoregional recurrences seen in surgical series. The benefit of 5-fluorouracil-based chemoradiation was first seen in a small, randomized trial performed by the Gastrointestinal Tumor Study Group (GITSG) (2). This study, published in 1985, randomized patients to observation versus postoperative therapy with concurrent 5-FU and split-course radiation (40Gy), followed by two years of adjuvant 5-FU. It showed a striking benefit in median survival and 5-year overall survival among patients undergoing chemoradiation despite the fact that there was no difference in locoregional control among the two arms. The EORTC performed a similar study that enrolle patients with either

pancreatic or periampullary cancers, who were randomized postoperatively to observation or chemoradiation (split-course radiotherapy with concurrent 5-FU). This protocol also demonstrated a trend towards improved survival among patients with pancreatic cancer who received adjuvant chemoradiation (3, 4). Additionally, two large retrospective series, one from Johns Hopkins University (n=616) and one from the Mayo Clinic (n=472), have demonstrated median survival benefits consistent with the GITSG and EORTC studies (5, 6).

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

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

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

2.3 Current Neoadjuvant Management of Resectable Pancreatic Adenocarcinoma

Among patients who have undergone surgery, pancreatic cancer exhibits a strong tendency to recur locally and to metastasize after a brief median time interval of approximately 13 months from surgical resection (11). Early relapse after curative surgery is likely explained by the presence of micrometastases or minimal residual primary disease not detectable at the time of surgery,or by the spread of tumor cells into the portal vein, lymphatic vessels, and peritoneal cavity due to surgical manipulation. Therefore, preoperative treatment of resectable or borderline resectable pancreatic cancer has several potential benefits.

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

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

To date, no large RCTs have studied neoadjuvant therapy for resectable pancreatic cancer, and the sample size of existing prospective series has been small (see table II). Despite the theoretical advantages of neoadjuvant therapy, results obtained to date have shown only modest improvements compared to surgery alone. Median survival and 2-year OS for patients receiving neoadjuvant therapy range from 8-23 months and from 27-40%, respectively (19-23), compared to 11-17 months and 15-31% for surgery alone (24,25). Meanwhile, adjuvant CRT has produced a median survival of 27-44 months and 2-year OS of 53-58% (26-28). Thus, while neither neoadjuvant nor adjuvant CRT have achieved major degrees of improvement in OS, both have been demonstrated to be slightly more effective than surgery alone for pancreatic adenocarcinoma. The current prevailing management

strategy, therefore, is to combine neoadjuvant chemotherapy and/or radiation, surgical resection, and adjuvant chemotherapy and/or radiation to achieve the highest possible rate of long-term survival, though no RCTs have yet been done to conclusively prove the efficacy of this regimen.

2.4 Current Management of Locally Advanced, Unresectable Pancreatic Adenocarcinoma

First-line chemotherapy for locally advanced/metastatic pancreatic cancer is gemcitabine, a nucleoside analog. In the pivotal trial leading to FDA approval of this drug, patients with metastatic pancreatic cancer who were treated with gemcitabine had a modest improvement in survival compared to patients treated with 5-fluorouracil (5-FU) (3). The median survival improved from 4.41 months to 5.56 months. However, nearly 25% of patients receiving gemcitabine had clinical benefit, compared to 5% of patients receiving 5-FU. In a recent meta-analysis, the addition of platinum analogs to gemcitabine demonstrated a survival benefit in patients with a good performance status. However, additional studies are necessary to determine which drugs are best combined with gemcitabine (4).

A recent study compared full dose gemcitabine (1000 mg/m^2) to a lower dose of gemcitabine (600 mg/m^2) combined with standard fractionated radiation (50.4 Gy over 5.5 weeks) among patients with localized unresectable pancreatic cancer. Although the study was closed prior to reaching its planned accrual, there was a significant improvement in survival in patients receiving combined gemcitabine and radiation compared to gemcitabine alone (5). Objective responses were observed in 2.7% of patients in the gemcitabine alone arm (95% CI [0.09%, 14.1%]) and in 8.8% of patients in the combined arm (95% CI [1.9%, 23.7%]). In this trial, the dose of gemcitabine was reduced to 600 mg/m^2 with radiation, and patients required a 4 week break prior to resuming full dose gemcitabine. Grade IV toxicities, principally gastrointestinal and hematologic, was more common in the combined group (41.2 vs. 5.7%; $p<0.0001$). Although there was an improvement in survival, patients who received combined chemoradiation had substantially more toxicity compared to those who were treated with gemcitabine alone. Thus, there is currently no consensus regarding standard of care for treatment of locally advanced, unresectable pancreatic carcinoma, but either chemotherapy alone or combined CRT can be considered appropriate in this setting.

3. RATIONALE

3.1 Rationale for Radiotherapy in Treatment of Pancreatic and Periampullary Adenocarcinomas

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

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 (31). 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 (32). 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 (33,34). Unfortunately, even among patients with resectable periampullary adenocarcinoma, over 50% will recur following definitive treatment (35). This trial, therefore, seeks to study SBRT as a means of providing patients with periampullary tumors with an additional treatment option in the case of locally recurrent or progressive disease.

3.2 Rationale for Fractionated Stereotactic Radiotherapy

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

Koong *et al.* previously used the Cyberknife™ stereotactic radiosurgery system to demonstrate that a single dose of 25 Gy Linac based stereotactic body radiotherapy (SBRT) was feasible for patients with locally advanced pancreatic cancer (36). Furthermore, this dose of radiation resulted in near 100% progression free survival and effectively palliated symptoms related to the local growth of pancreatic tumors. Based on this study, the same group also completed a phase II study assessing the efficacy of combining a standard five-week course of chemoradiotherapy followed by a stereotactic radiosurgery boost to the primary tumor in patients with locally advanced pancreatic cancer. In this cohort of 19 patients, 100% of tumors were without local progression. However, all patients eventually developed metastases, with a median time to progression of 5.5 weeks.

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

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

A recent protocol evaluated full dose gemcitabine before and after single fraction Linac based SBRT. Preliminary results indicate that the local progression free survival was comparable to what was previously observed (90%) with CyberKnife treatment (personal communication). All acute toxicity was grade 2 or less; however, a minority of patients developed late duodenal ulcers (15%), including 1 perforation (5%) with a single fraction of Linac based SBRT. Therefore, LInac based SBRT appears to achieve local control of

pancreatic tumors in a large majority of patients with reasonable rates of toxicity, suggesting that Linac based SBRT would be an effective treatment option for patients with locally recurrent disease, as we propose in this protocol.

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

We hypothesize that delivering fractionated Linac based SBRT (5 Gy x 5 or 6.6 Gy x 5) instead of single fraction treatment will result in equivalent tumor control with less late toxicity (≤20%). At this time, there is no clear consensus regarding an optimal fractionation schedule for unresectable pancreas cancer (38,39). Based on a recent study, this fractionation schedule is predicted to provide equivalent tumor control probability to 25 Gy x 1 while resulting in less normal tissue toxicity (40).

Although we believe this schedule (5 Gy x 5 or 6.6 Gy x 5) will result in good tumor control and acceptable toxicity, the potential clinical efficacy of this short-course, hypofractionated regimen is unknown. The choice of this regimen as a potentially effective approach for unresectable pancreatic cancer treatment is based on three observations. First, a similar schedule (5 Gy x 5) has been widely and efficaciously used in the neoadjuvant setting for rectal cancer, although a much larger field is used. Additionally, a series of patients with resectable pancreatic lesions treated at the M.D. Anderson Cancer Center strongly suggest that a 5-FU based chemoradiation regimen consisting of 30 Gy in 10 fractions over 2 weeks reduces treatment time and toxicity compared with a regimen consisting of 50.4 Gy in 28 fractions over 5 to 6 weeks without compromising overall survival or local control. Hong *et al.* from Massachusetts General Hospital have reported on a neoadjuvant regimen delivering 5 Gy x 5 to the pancreatic tumor plus adjacent lymph nodes using proton beam radiation (41). They show this regimen to be safe, with no instances of dose limiting toxicity observed and only 4 of 15 patients developing grade 3 toxicity (no patients experienced grade 4 toxicity). The phase I feasibility study outlined in this protocol proposes a 5 Gy x 5 (patients who previously received radiotherapy) or 6.6 Gy x 5 (radiation-naïve patients) fractionation schedule treating the region of local recurrence or unresectable pancreatic tumor plus a 3 mm margin. These volumes will be substantially smaller than the regimens outlined above for rectal and pancreatic cancer, likely leading to a lesser degree of toxicity. Using the linear-quadratic formulation, the biologically equivalent dose (BED) of the two proposed fractionation schedules are given in comparison to other commonly used schemes (table 1). 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.

Table 1:

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

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

The major benefit of Linac based SBRT/chemotherapy for unresectable, locally recurrent and locally progressive pancreatic and periampullary tumors is improved local control and palliation of symptoms related to local progression of these tumors. In addition, radiosurgical ablation of the tumor at the primary site can theoretically prevent distant seeding from the pancreatic tumor itself. Ultimately, these improvements in the treatment of pancreatic and periampullary cancer may translate into an improved quality of life and overall survival.

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

3.3 Rationale for Use in Treatment of Locally Progressive or Recurrent Disease

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 (45). 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 (46). 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 (47-50). However, virtually 100% of patients develop disease progression and succumb within 3 years (51-55).

The pattern of recurrence in pancreatic cancer is well known (11,18,56,57) and is similar to that of periampullary adenocarcinoma (35). Following resection, 71-77% develop distant metastases within 2 years, often accompanied by concurrent locoregional recurrence, while up to 30% (58, 59) exhibit isolated locoregional recurrence (60,61). 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 (60). 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 (61). Although survival is determined chiefly by systemic disease control, local control is an important factor contributing to quality of life (62,63). The symptoms associated with local recurrence require a mode of treatment that is swift and efficacious in order to restore patient quality of life and give patients the best chance at greater overall survival.

To date, no studies involving radiotherapy have been performed that primarily focus on this specific population of patients who have developed local failure after previous standard of care or protocol therapy for pancreatic or periampullary adenocarcinoma. Consequently, no standard treatment option has yet been defined. Current options include surgical re-exploration with possible re-resection, palliative chemotherapy or conventionally fractionated chemoradiotherapy (CRT), and best supportive care. Each of these has significant drawbacks, including: high degree of invasiveness and morbidity in the case of surgical re-resection (41,64); slow onset of effect, substantial systemic toxicity, and inferior local control rates (71.1%) with palliative chemotherapy or conventionally fractionated CRT (65); and lack of efficacy and diminished overall survival with best supportive care alone.

We propose that the drawbacks associated with the current treatment options above can be circumvented or mitigated by the use of fractionated SBRT, while simultaneously achieving excellent rates of local control and symptom palliation. Linac based SBRT is a non-invasive means of achieving effective local control in a large majority of patients (81 to nearly 100% at one year in previous studies) (36,37,66,67). Additionally, we propose to deliver the Linac based SBRT in 5 fractions over the course of 1-2 weeks, allowing for swift alleviation of symptoms associated with local tumor recurrence/progression. Conventionally fractionated radiation therapy (RT), on the other hand, delivers a similar BED (see table 1 in section 3.2) over a much longer period of 5-6 weeks. Furthermore, the tighter margins used in Linac based SBRT (0.2-0.3 cm) compared to conventional RT (2-3 cm) may result in less gastrointestinal toxicity (68). Therefore, we suggest that Linac based SBRT avoids the drawbacks associated with other existing treatment options for patients with recurrent pancreatic adenocarcinoma; that is, Linac based SBRT is effective, non-invasive, swift to take effect, and associated with a relatively mild toxicity profile.

Two recent studies support this assertion. In 2009, Chang *et al.* reported on the use of Linac based SBRT delivered as 25 Gy in a single fraction for patients with unresectable pancreatic adenocarcinoma (67). Of the 77 patients, 58% had locally advanced disease and 14% had medically inoperable disease, but the remainder were similar to our population in that they had either low-burden metastatic disease (19%) or locally recurrent disease (8%). Results were encouraging, with rates of freedom from local progression at 6 and 12 months of 91% and 84%, respectively. Overall survival at 6 and 12 months was 56% and 21%, respectively. Only 5% of patients experienced grade 2 or greater acute toxicity, 4% experienced grade 2 late toxicity, and 9% experienced grade 3 or greater late toxicity. Rates of grade 2 or greater late toxicity were 11% and 25% at 6 and 12 months, respectively.

In 2010, Didolkar *et al.* reported on the use of Linac based SBRT doses ranging from 15 to 30 Gy delivered in 3 equal fractions, with mean dose of 25.5 Gy over 3 days (66). Eighty-five patients were studied; the majority (71 patients) had locally advanced disease, but a small number (14 patients) were included who were similar to our population in that they had locally recurrent disease. Results were again encouraging, with 78 patients (92%) achieving complete response, partial response, or stable disease for a duration of 3-36 months with a

median of 8 months. Pain relief was noted in the vast majority of patients lasting for 18-24 weeks. Median survival from time of Linac based SBRT was 8.65 months, which is comparable to or better than reported results for locally advanced pancreatic cancer (69-72). Nineteen patients (22.4%) developed grade 3-4 gastrointestinal toxicity, consisting of duodenitis, gastritis, and diarrhea in order of decreasing frequency. One patient developed renal failure.

We recently presented the preliminary results of our phase II multi-center trial of gemcitabine (GEM) and fractionated Linac based SBRT to determine if a high rate of LPFS with reduced toxicity could be achieved. After multidisciplinary review, 32 pts with locally advanced PDA received GEM in sequence with Linac based SBRT (6.6 Gy in 5 consecutive daily fractions, 33 Gy total). LPFS, metastasis free survival (MFS), and overall survival (OS) were measured from date of tissue diagnosis. Objective tumor response (OTR) was assessed by RECIST/PERCIST. EORTC QLQ-C30/PAN26 questionnaires were used to measure QOL. Median f-up was 12 mos (range, 2-23). Mean age was 69.9 yrs (SD, 9.8) and 62% were male. Patients received a mean of 2.2 (SD, 1.0) GEM doses prior to SBRT and 8.3 (SD, 5.6) doses total. All pts completed SBRT. Median OS was 15.9 months (95% CI, 12.7-18.8). Stratification by CA19-9 > or < 90 at diagnosis yielded a hazard ratio of 6.2 for > 90 (p=0.021). Median LPFS has not been reached and median MFS was 10.2 mos (95% CI, 2.9-17.5). LPFS rate at 1 year was 87%. OTR on CT was seen in 41%, while 41% had stable disease and 18% progressed. Tumor metabolic activity decreased in 17/18 patients with pre/post- Linac based SBRT PET available. Mean peak SUV was 4.0 pre- Linac based SBRT versus 2.4 post- Linac based SBRT (p=0.002). Median CA19-9 was reduced from 124.7 prior to SBRT to 43.9 afterwards. Acute toxicity included: grade 2 anorexia (37%), fatigue (28%), nausea (22%), abd pain (19%), weight loss (9%), diarrhea (3%); gr 3 nausea (9%); and gr 4 nausea (6%). Late gr ≥3 GI toxicity was seen in 9%. Mean QOL score 4 wks post-Linac based SBRT was similar to baseline (p=0.38). At 6 mos there was a trend towards improved QOL (p=0.07). Overall, fractionated Linac based SBRT with GEM achieved high rates of LPFS and tumor response. Minimal grade ≥3 acute and late toxicity was observed. Linac based SBRT is more likely to benefit patients with Ca-19-9 <90. A combination of Linac based SBRT with more aggressive chemotherapy may further improve outcomes.

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 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.

4. PATIENT SELECTION

4.1 Inclusion Criteria

4.1.1 Age ≥18 years.

4.1.2 Karnofsky Performance Status ≥70% (see Appendix II).

4.1.3 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.

*If histological confirmation of adenocarcinoma cannot be obtained by biopsy, the following procedures may be employed:

4.1.3.1 Attempt a repeat biopsy to obtain a diagnosis.

4.1.3.2 Present the case at JHU tumor board and if the candidate has one of the following: a rising CA 19-9 or radiographic evidence of recurrence on MRI, CT, and/or PET scan then the patient can be considered for treatment on protocol.

However, if these objectives cannot be met, the patient will not be a candidate.

4.1.4 Pancreatic or periampullary tumors must be less than 8.0 cm in greatest axial dimension at the time of treatment planning.

4.1.5 Either:

Patients who have received RT: Previously (≥6 months before retreatment) completed treatment for pancreatic or periampullary adenocarcinoma consisting of either surgical resection with neoadjuvant/adjuvant conventional CRT for resectable disease or conventional CRT as definitive treatment for unresectable disease. These patients who have received prior radiation therapy will constitute Cohort A and will receive SBRT as 5 Gy x 5.

*patients may be receiving continued chemotherapy post initial CRT.

OR

Patients who have not received RT: Previously (≥3 months before retreatment) initiated treatment for pancreatic or periampullary adenocarcinoma consisting of chemotherapy alone for unresectable disease or surgical resection with neoadjuvant/adjuvant chemotherapy for resectable disease. These patients who have not received prior radiation therapy will constitute Cohort B and will receive SBRT as 6.6 Gy x 5.

*patients must have attempted chemotherapy upon initial diagnosis.

4.1.6 Patients must have acceptable organ and marrow function as defined below (within 2 weeks prior to radiotherapy):

- Leukocytes ≥2,000/μL
- Absolute neutrophil count ≥1,000/μL
- Platelets ≥75,000/μL
- Total Bilirubin ≤1.5X normal institutional limits
- 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

4.1.7 Ability to understand and the willingness to sign a written informed consent document.
4.1.8 Must be a patient to be treated with SBRT only at Johns Hopkins Hospital.
4.1.9 Life expectancy > 3 months.
4.1.10 Patient must be able to have fiducials placed. If not, the tumor must be posterior and adjacent to the aorta and treatment will only be permitted at the discretion of the Principal Investigator.

4.2 Exclusion Criteria

4.2.1 Children (< 18 years) are excluded because pancreatic and periampullary tumors rarely occur in this age group. Furthermore, treatment requires a great deal of patient cooperation including the ability to lie still for several hours in an isolated room.
4.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
4.2.3 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.
4.2.4 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.
4.2.5 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.
4.2.6 Patients with a life expectancy of < 3 months.
4.2.7 Patients with metastatic disease.

5. REGISTRATION PROCEDURES

5.1 General Guidelines

Subjects will be identified per the recommendation of surgeons or GI Combined Modality Tumor Board or equivalent combined modality assessment. Subjects will be recruited through self-referral and the advice of their attending physician. No advertisement will be used to recruit subjects.

5.2 Registration Process

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

6. SBRT ADMINISTRATION AND RADIATION TREATMENT PLANNING

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

The following will be completed prior to Linac based SBRT:

a. Medical history and clinical examination.
b. CBC with differential, Chemistry Panel, CA19-9.
c. Gold fiducial seed placement percutaneously, intraoperatively, or under endoscopic ultrasound guidance, which may be performed prior to enrollment.
d. Pathologic confirmation of malignancy. (Core biopsies during gold fiducial placement as needed or optional).
e. CT Pancreas or C/A/P scan required; FDG-PET or FDG-PET/CT (dual phase) recommended at the discretion of the treating physician.
f. Signed informed consent document.
g. Baseline collection of EORTC QLQ C-30/ PAN26 QOL.
h. Optional whole body dynamic PET/CT

6.1.1 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. Also, if a patient had an attempted surgical resection that was aborted, fiducials may have been implanted intraoperatively, which is also allowable prior to study enrollment.

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.

6.1.2 Simulation

1) Simulation should be done following placement of fiducials; however, this may vary and is at the discretion of the principal investigator.
2) Typically, patients will be positioned supine in an Alpha Cradle or equivalent immobilization device that will be custom-made for each patient.
3) 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).
4) A research dMRI may be conducted at the time of simulation. In order to derive a set of 4D anatomic images that are directly comparable to 4D-CT, the Department of Radiation Oncology has developed a retrospective, slice-stacking, sorting technique that relies on a respiratory trace collected simultaneously with multi-slice 2D dMRI sequences (bSSFP and HASTE). The final rendered “4D-MRI,” or set of phase-binned 3D-MR volumes, represents a statistically-averaged breathing cycle over the long-duration imaging session. Because this frame-averaging approach can result in image blurring in the context of breathing variability, secondary anatomic-based sorting methods are employed to improve on image quality (contrast). Further,

for each imaged slice location and breathing phase bin a sufficiently large number of samples permits derivation of meaningful, image-based strategies to convey variability information, such as via rendering a corresponding "4D-MRI standard deviation" image. This method is independent of the imaging sequence employed and is generically suitable for multiple sites of disease.

5) IV and oral contrast must be used for simulation, unless the patient has an allergy that cannot be adequately premedicated. In these situations, the plan should be fused with an IV contrast CT scan or MRI (ideally in a similar treatment position).
6) Motion management can be addressed using respiratory gating, breath-hold, respiratory tracking, or abdominal compression. Specialized compression belts may be utilized for some patients. They come in 4 sizes: S, M, L, and XL. Each belt has an adjustable pressure cuff which can be used to reduce breathing motion. Fluoroscopy is used to assess motion of implanted gold markers before and after compression. The goal is to reduce motion from typically 11-22 mm peak to less than 5 mm. If the fiducial motion cannot be decreased to 5 mm or less, then respiratory gating using either the Varian Respiratory Management (RPM) system or the Elekta Active Breathing Coordinator (ABC) will be utilized for treatment delivery. Prior to simulation, standard guidelines will be followed.
7) As long as the specified dosimetric parameters for SBRT are reached, patients may be treated on any IGRT-enabled machine.
8) All patients must start Linac based SBRT within 4 weeks of the simulation scan.

6.1.3 Treatment Planning

1) When available, an FDG-PET scan is preferred for treatment planning purposes and will be acquired on a flat table top with the same immobilization devices used for the treatment planning CT simulation.
2) An SBRT treatment plan will be developed using Pinnaclebased on tumor geometry and location. Institutional standards for radiation quality assurance and radiation delivery will be utilized.
3) The tumor volume (GTV), as identified on the treatment planning CT, will be contoured by an attending physician from Johns Hopkins Hospital. The final GTV will be defined by the attending radiation oncologist after reviewing the diagnostic CT, respiratory-correlated 4D-CT scan, pancreas protocol CT, and/or the FDG-PET/CT scan. These scans will be used to define the ITV (internal target volume). The final PTV (planning treatment volume) expansion will consist of an additional 2-3mm of margin expansion, except if the margin results in expansion into the duodenum or stomach. In these cases, margin expansion is allowed to be non-uniform. The dose will be prescribed to the isodose line that completely surrounds the PTV. It is recommended that 6-12 co-planar fields be used in the radiation treatment plan.
4) Contours of the fiducials used for target localization will be generated on the applicable image sets, to be used for patient setup on treatment.
5) Radiation dose to the adjacent normal tissue will be minimized. Based on an analysis of duodenal toxicity representing pooled data from 3 previous prospective studies, the following dose constraints must be met: V15<9cc, V20<3cc. The duodenum (duo@PTV) as defined for these dosing parameters includes the entire duodenum on the same axial plane as the PTV and duodenum 1 cm above and 1 cm below the PTV. 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 1cc of the proximal duodenum or proximal stomach may exceed 33 Gy for cohort B (25 Gy for cohort A, re-irradiation patients). 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, (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).

6) 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).
7) Greater than 90% of the PTV should receive 100% of the prescription dose (3300cGy for 6.6Gy x 5; 2500cGy for 5Gyx5).
8) If above constraints cannot be achieved, then 100% of the GTV must receive at least 25 Gy (20 Gy for cohort A) (an allowed minor deviation, which will be documented).

   If this constraint cannot be met, the patient should be removed from the protocol.

6.1.4 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. Ideally all 5 fractions should be delivered Monday through Friday; however, treatment may be delivered over 2 weeks, as long as the patient receives at least 2 fractions per week.

Treatment Delivery (LINAC-based):

1) Initial patient positioning will be based on volumetric kV (cone-beam CT) imaging with shifts to bony anatomy as appropriate.
2) Orthogonal kV/MV or kV/kV projection imaging will be used to verify the location of the fiducials prior to delivery of first treatment beam. A secondary shift based on the location of fiducials may be utilized, as indicated by the position of the fiducials. For free-breathing treatments, kV fluoroscopic images should be obtained to confirm the anticipated position of these fiducials during the entire respiratory cycle.
3) 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.

4) Patient-specific dosimetric quality assurance (QA) will be performed as per standard practice in the Department of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins Hospital.

6.1.5 Post-Linac based SBRT Follow-Up

Following Linac based SBRT, all patients will be monitored clinically and with serial imaging (CT scans and/or PET/CT if possible and as deemed necessary by the treating physician).

A detailed medical history with physical examination and quality of life assessment will be performed at 4-6 weeks, 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.

6.2 General Concomitant Medication and Supportive Care Guidelines

6.2.1 Antidiarrheals and Anti-emetics

For symptoms of diarrhea and/or abdominal cramping, patients will be instructed to take anti-diarrheals. Additional antidiarrheal measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

For symptoms of nausea and vomiting, anti-emics will be given one hour prior to Linac based SBRT and for up to 5 days following Linac basedSBRT 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.

6.2.2 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.

6.2.3 Supportive Care Guidelines

All commonly accepted supportive care guidelines will be used.

6.2.4 Use of Radioisotopes/Rad Machines

Stereotactic radiotherapy will be performed using Linac based radiation machines. The radiation treatment plan will be designed to use multiple beams of radiation to

concentrate large doses of radiation within a tumor. The Linac machines are equipped with cone beam CT imaging that can be used to deliver image-guided radiation therapy (IGRT). IGRT allows delivery of highly accurate, stereotactic radiation treatment. The use of cone beam CT images during IGRT is considered standard of care treatment.

Uncertainties in tumor location are minimized because these machines have on-board, volumetric imaging for accuracy in initial patient setup; kV and MV projection imaging during treatment is used to monitor delivery accuracy and/or make corrections to the patients' position. 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.

6.2.5 Risk Information

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

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

6.3 Duration of Study

It is anticipated that this study will last approximately 42 months (30 months of accrual and 12 months while cohort matures).

6.4 Duration of Follow Up

We estimate that most patients will remain a subject in this study for approximately one year Patients will remain enrolled on this protocol for a maximum of 5 years or until patient withdrawal. One year after Linac based SBRT, patients should undergo standard follow-up every 3-6 months, as determined by the treating physician. Patients that have completed the 5 year follow-up will continue being followed for survival information until death. The administration of subsequent chemotherapy and/or other antineoplastic treatment following Linac based SBRT will be at the discretion of each patient's attending medical oncologist.

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

6.5 Criteria for Removal from Study

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

6.6 Alternatives

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

6.7 Compensation

Subjects will not be paid to participate in the study.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Adverse Events and Potential Risks List

Based upon our prior phase I and phase II studies evaluating the toxicities associated with Linac based SBRT for pancreatic cancer, we estimate that ≤20% of patients will experience grade 2 or higher late GI toxicity within one year. Late GI toxicities are those events occurring more than 3 months after Linac based SBRT. Acute GI toxicities are those events occurring within 3 months following Linac based SBRT. The major toxicity in this group of patients is the development of duodenal/gastric ulcers. Most of these are successfully managed medically. However, Stanford has observed 2 cases of duodenal perforation associated with Linac based SBRT. 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. We anticipate that the risk of ulcer formation should be lower in this study. Hepatic and renal 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 RTOG Gastrointestinal Toxicity Scale and/or CTCAE v4.0.

7.2 Reporting of Serious of Unexpected Adverse Events

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

7.2.2 **Important** Adverse Events that are **unanticipated** must be reported to the JHM IRB within a time period as specified by current institutional guidelines. If the Important Adverse Event requires changes to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the JHM IRB.

7.2.3 All other **unanticipated** Adverse Events or changes to the protocol and consent form must be reported to the JHM IRB, within a time period as specified by current institutional guidelines

Addendum (8/15/2014):
Adverse events will be recorded using Mosaiq software, 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. Hospitalizations that occur greater than 30 days from completion 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, though provide realistic expectations based on the sickness of this patient population.

7.3 Definitions

Serious Adverse Event: means an event that is

- fatal
- life-threatening
- persistent or significantly disabling or incapacitating
- inpatient hospitalization or prolongation of hospitalization
- congenital anomaly or defect and/or
- a significant medical incident (considered to be a serious study related event because, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)

Important Adverse Event: means an event, although not a Serious Adverse Event, which still presents an undesirable occurrence that interferes with the subject's usual activities and may be persistent or require treatment. (For example, serious rash, cough, or fever.)

Unanticipated Adverse Event: means an event that results from a study intervention and was not expected or anticipated from prior experience. This includes expected events that occur with greater frequency or severity than predicted from prior experience.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

8.1.1 Analysis of patient plasma for biomarker development.

8.1.1.1 Collection of Specimen(s) (optional):

Patients will elect whether they want to participate in this portion of the study on the consent form.

Blood Samples

a) Blood (EDTA preserved) for research purposes will be drawn prior to radiation treatment (prefer before chemotherapy if possible) and at each follow-up along with the patient's regular labs. For each collection, up to 8 ml (1 large purple/violet tube or 2 small purple/violet tubes at 4 ml each) will be drawn.

b) Within two hours from collection, blood will be centrifuged at 3000 RPM for 10 minutes and plasma collected. The supernatent will be aliquotted for storage at -80°C into separate tubes. The pellet will also be aliquotted and stored in separate tubes at -80°C.

Tumor Biopsy Tissue Samples

a) Consent for obtaining tumor samples: All patients with a presumed diagnosis of pancreatic or periampullary cancer can give consent or decline consent to obtain additional tumor tissue for research purposes. In this situation, the research biopsy should be obtained only after a final diagnosis (preliminary if determined by the pathologist during the diagnostic biopsy) of pancreatic or periampullary adenocarcinoma has been reached by the pathologist. Once a preliminary/final diagnosis has been obtained, gold fiducials can be placed into the tumor for tumor tracking. In the event the patient already has a confirmed pathologic diagnosis of pancreatic or periampullary cancer, a repeat endoscopic ultrasound, CT, or laparoscopic procedure may be used to place gold fiducials into the tumor for tumor tracking. Following fiducial placement, additional tumor samples can be obtained for research purposes if the patient gives permission in the study consent.

b) Tumor sample processing: Fine needle aspirations (FNA) and core biopsies (if possible) of tumor tissue will be immediately placed into small cryovial tubes that can be stored at -80°C. Sample tubes are immediately immersed into a canister of liquid nitrogen with forceps/tube holder until completely frozen. Samples are then transferred into the -80°C freezer until utilization for biomarker analysis.

8.1.1.2 Storage of Specimen(s)

All samples will be stored at Johns Hopkins Hospital in Cancer Research Building II at -80°C or in liquid nitrogen until utilized for analysis of biomarkers.

8.1.1.3 Site(s) Performing Correlative Studies

All biomarker studies will be performed at Johns Hopkins Hospital by Dr. Narang or his staff or in the laboratory of a research collaborator. Specimen

samples will also be processed in the laboratories of Stanford Cancer Institute, Memorial Sloan Kettering Cancer Center, and Metabolon, Inc.

We will utilize proximity ligation assay (PLA) to simultaneously interrogate a panel of 60-100 secreted proteins that we have developed for pancreatic cancer patients. PLA is an antibody based method of detection in which complementary single- stranded oligonucleotides are linked to each antibody pair. When the 2 antibodies bind in close enough proximity, the local concentration increases, allowing for PCR amplification of this signal. PLA is more sensitive than conventional ELISA and can be reliably multi-plexed for the detection of multiple protein panels (Fredrikkson et al). In a pilot study, we have shown that when using this method of detection (Chang et al), we can accurately identify patients with pancreatic cancer. In this study, we will expand the number of biomarkers and collect plasma at multiple time points during therapy. The goal is to identify a biomarker panel that is predictive of patient outcome and/or response to therapy. We hypothesize that not only is the pattern of secreted biomarkers important but the change in these biomarkers may be even more critical for prediction of clinical outcomes.

8.1.1.4 Coding of specimens for privacy protection

At the time of consent, each patient will be given a specific confidential identification number (IDN). Specimens will be stored under the patient's IDN. The information can be shared with other investigators listed on this protocol. Study data will be maintained in password protected computer files (protected online database through Johns Hopkins). Only research personnel will have access to this information.

8.2 Collection of Pre and Post Treatment CT/PET Scans, Treatment Planning Scans, and Treatment Plans

8.2.1 Data and Image Collection

8.2.1.1 Pre-Linac based SBRT PET scan is recommended but not required. Post - SBRT PET scans will be optional for all patients based on the opinion of the treating physician. Pre- and post-Linac based SBRT CT scans will be mandatory for all patients (PET/CT may supplement protocol CT). All images (CT and PET) will be stored electronically by JHU through the Oncospace network and be registered to each patient using the IDN. Radiation treatment plans will also be retrospectively reviewed and stored at JHU via Oncospace. The JHU database is set up to store ROI geometries and dose distributions along with the CT. This design facilitates the investigation of dosimetric effects on tumor response and complications utilizing DVH or other attributes of the 3D dose.

For Pinnacle, the data can be directly placed in the JHU database via scripts.

8.2.1.2 All treatment planning scans will be stored electronically by JHU through the Oncospace network and be registered to each patient using the IDN. Specific parameters will be prospectively collected such as treatment volume and dose to adjacent structures in oncospace

8.2.1.3 Dynamic Whole Body PET/CT

Up to 17 patients will be recruited to a sub-project that will assess the feasibility of acquiring a quantitative dynamic whole body PET/CT early after treatment. The aim of this sub-project is to assess the extent to which dynamic PET can be used to aid in the discrimination of tumor from radiation induced inflammation in a therapy assessment setting. This could potentially enable future PET/CT-based response assessment at an earlier time than the current protocol and clinical practice, 4-6 weeks post-treatment. This will allow therapy decision (success or failure) to be made earlier and management is personalized.

Unlike conventional PET imaging, which performs single-pass multi-bed imaging of the subject, the proposed framework performs multiple-pass multi-bed imaging of the subject. The objective of this alternative imaging framework as developed and validated by Johns Hopkins Department of Nuclear Medicine, and implemented by major vendors, is to quantify the pattern of tracer uptake within the imaging duration, moving beyond conventional static imaging. This approach enables enhanced quantification of radiotracers uptake by tumors, and has the potential to enable improved differentiation of tumor recurrence from inflammation, and is hypothesized to arrive at improved assessment of therapy response and prediction of outcome.

In this sub-set of patients who consent to undergo this research imaging, two ^{18}F-FDG dynamic whole body PET/CT scans will be obtained using the novel protocol of dynamic whole body data acquisition. Patients participating in this sub-project will have a PET/CT study performed in a dynamic whole-body mode at baseline and on day 5 of SBRT treatment.
All PET/CT studies will be acquired on the Biograph mCT at the Johns Hopkins PET Center. Dynamic whole-body PET/CT scanning will last approximately 45 minutes, while single-pass whole-body PET/CT imaging last under 30 minutes, although the total duration of the patient visit is likely to be 2-3 hours. Each PET/CT study will involve intra-venous administration of 0.15 mCi / kg of ^{18}F-FDG (maximum 17.5 mCi), similar to clinical FDG dose. Low-dose CT will be acquired at the same imaging session, similar to clinical protocol. The total effective dose for each PET/CT study is <0.4 rem for the CT and <1.2 rem for the PET.

9. INVESTIGATOR RESOURCES

9.1 Qualifications

The study staff will include, but is not limited to, the Principal Investigator, Co-Investigators, research coordinators, research nurses, and any residents or fellows working with the physicians.

All study staff have completed the required training specific for their responsibilities in this study. Furthermore, each member of the research team will be given a thorough explanation of the protocol and their responsibilities, including helping with scheduling, procedures, follow-up, data entry, or analysis. All research investigators will be required to complete proper training through their institutional review boards.

9.2 Use of Cancer Center Facilities

Patients will be evaluated and treated in at Sidney Kimmel Cancer Center at Johns Hopkins Hospital. All radiotherapy for this study will be performed in the department of Radiation Oncology at JHH. Other procedures related to this study (i.e., blood draws, fiducial placement, imaging studies) will be carried out at JHH.

9.3 Conflict of interest

There is no potential conflict of interest among the research personnel involved in this study.

10. STUDY CALENDAR

	Pre-Study	Pre-SBRT[9]	SBRT Treatment[10,11]	Follow-Up [6] (Post-Radiation Treatment)					
				4-6 weeks	4 mos	6[4] mos	9 mos	12[4] mos	Yrs 2-5 Q 3-6 mos
Initial Consult	X								
Demographics	X								
History / Physical Exam	X			X	X	X	X	X	
Informed consent	X								
Biopsy (confirmed adenocarcinoma)	X								
Labs: CBC, CMP, CA19-9		X[7]		X	X	X	X	X	X
Research Blood Sample (optional)		X[7]		X	X	X	X	X	X
Negative Pregnancy Test[8]		X							
Seed Placement (EUS, CT, intraoperatively)		X							
Research Biopsy (optional)		X							
Simulation Scan		X							
Radiologic Evaluation (CT[1], PET-CT[2])		X		X[3]	X	X	X	X	X
Dynamic Whole Body PET/CT		X[12]	X[12]						
Research dMRI		X							
QoL Questionnaire[5]		X		X	X	X	X	X	X
AE Evaluation[13]	X			X	X	X	X	X	X

[1]CT pancreas or chest/abdomen/pelvis, as per treating physician, required pre- and post-SBRT. However, may be supplemented by PET/CT (dual phase).

[2]Pre-SBRT PET-CT scans and subsequent PET-CT scans are recommended but not required and may be ordered at the discretion of the treating physician.

[3]If being reevaluated for resection, scans will be conducted at 4-6 weeks or as determined necessary by treating physician.

[4]It is preferred that patients have the 6MFU and 12MFU evaluation and imaging at the treating institution. Other evaluations may be done at a local center however records must be submitted to SBRT treating facility.

[5]QoL questionnaires may be completed and returned by mail or email if preferred.

[6]Follow-up appointments have a +/- 30 day tolerance window. (ex. 6MFU may occur between 5-7 months)

[7]Pre-SBRT labs should be done within 4 weeks prior to treatment.

[8]Pregnancy test by urine or serum, for women who are not post-menopausal as defined in Appendix III.

[9]Pre-SBRT procedures should be completed within 45 days of beginning treatment.

[10]It is recommended that patients in both cohorts discontinue any chemotherapy one week prior to SBRT and delay resumption of chemotherapy until one week following completion of SBRT

[11]Ideally all 5 fractions should be delivered Monday through Friday; however, treatment may be delivered over 2 weeks, as long as the patient receives at least 2 fractions per week.

[12] Required if participant consents to PET scan research correlative. To be performed at baseline and Day 5 SBRT

[13]Toxicity evaluation may be completed via telephone if participant cannot return for follow up.

11. MEASUREMENT OF EFFECT

11.1 Anti-tumor Effect

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

11.1.1 Definitions

Patients will be evaluable for toxicity and evaluable for objective response at the follow-up intervals specified above.

11.1.2 Disease Parameters

Pancreatic and periampullary tumor response will be based upon standard radiographic criteria for the treated lesion and will be prospectively recorded in the JHU secure 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

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

Local tumor progression will be defined as >=20% increased size on CT scan compared to a CT scan from prior to treatment. Distant progression will be defined as any new tumor found outside of the pancreas or periampullary region on CT scan. Local and/or distant progression by both PET (if available) and CT scan will be recorded separately. We will also determine PET response with the new PERCIST criteria as reported by Wahl et al. (J Nuc Med 2009; 50:122S-150S).

11.1.3 Methods for Evaluation of Measurable Disease

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

CR = complete alleviation of pain or other symptoms thought to be related to the index lesion

PR = improvement, but not complete elimination, of pain or other symptoms thought to be related to the index lesion
PD = worsening of pain or other symptoms thought to be related to the index lesion
SD = does not meet criteria for PR or PD

Radiographic response will be defined as outlined in section 11.1.2.

11.1.4.2Evaluation of Non-Target Lesions
Standard radiographic criteria will be utilized for non-target lesions. Any disease outside of the pancreas or periampullary region will be considered metastatic disease. If possible a biopsy should be obtained to confirm metastasis.

11.1.4. 3Evaluation of Best Overall Response
This will be based upon the response of the treated lesion as described above.

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

11.1.6 Progression-Free Survival (or other parameters)
The criteria for time to progression and progression-free survival (PFS) will be the duration from Linac based SBRT treatment to documented local/regional or distant progression or death. Local PFS will be measured as the duration from Linac based SBRT treatment to local progression or death from any cause.

11.1.7 Response Review
All responses will be reviewed independently by a board certified radiologist at the study's completion. Each image will be reviewed by the PI. Simultaneous review of the patient's chart will also occur at this time. PET/CT images (if available as per the recommendation of the treating physician) and PERCIST measurements will be made by Jeff Leal and a staff member in the nuclear medicine department.

12. DATA REPORTING / REGULATORY CONSIDERATIONS

12.1 Monitoring Plan

Johns Hopkins University will conduct yearly study audits to review subjects' timely and complete enrollment, registration into the electronic database, and follow-up per study calendar. More frequent monitoring will take place as needed. Trial monitoring with subject chart and trial binder reviews will be done by Johns Hopkins University per Sidney Kimmel Cancer Center guidelines.

Subject data will be documented and stored in the electronic database Oncospace & Mosaiq, the software and infrastructure being supplied by JHH.

12.1.1 Data Management
This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (9/22/2011). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI is responsible for monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety

reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study.

12.1.2 Data Entry and Compilation

Research Staff (Coordinators, Nurse, or Co-Investigators) will enter/scan subject data into Oncospace, which will include:

- Eligibility or Inclusion/Exclusion Criteria
- Patient Demographics
- Pre-Study Evaluation including H & P, Allergies, and Review of Systems
- Surgical Procedures, with dates and findings (including EUS, biopsy (if needed), seed placement, and/or stent (if recommended)
- Scan dates (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, Review of Systems, and toxicities
- Follow-up labs and dates
- Completion of QOL questionnaires
- Subject study withdrawal, date, and reason
- Concomitant medications, specifically PPIs and antiemetics, prescribed per protocol and if reportedly taken by subject

Information will be entered from source documents or from Case Report Forms which are formatted to capture data as it will be entered into the database. If information is entered from source documents directly into Oncospace, Case Report Forms can be printed out and signed or signed electronically.

The PI will be responsible for maintaining the clinical protocol and subjects' study charts, reporting adverse events, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to their IRB and trail monitoring group(s) as per JHH protocol.

There will be password-protected limited access to the database in order to maintain privacy (See Confidentiality below).

12.2 Stopping Rules

All outcome data (toxicity and efficacy) will be reviewed every 6 months by the Principal Investigator and key Co-Investigators. This study will be monitored by the JHH IRB. All potential adverse events will be reported to the SKCCC Data Safety Monitoring Committee and the JHH IRB. An interim analysis is planned to assess late grade 2 or greater gastritis, enteritis, fistula, ulcer, or late grade 3 or greater GI toxicity when 16 patients are accrued. If 7 or more patients have late grade 2 or greater gastritis, enteritis, fistula, ulcer, or late grade 3 or greater GI toxicity within one year, the trial will be halted (note: accrual will continue while interim analysis is being conducted). After the first 16 patients are followed up for one year, we will also estimate the 1-year local progression free survival. If the upper bound of a two-sided 98% confidence interval (alpha = 0.02) of local progression free survival is below 30% in cohort A, or less than 50% in cohort B, the accrual at that cohort will be halted for lack of efficacy.

12.3 Confidentiality

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

13. STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Primary Endpoint

To evaluate late (>3 months after Linac based SBRT) grade 2 or greater gastritis, fistula, enteritis, or ulcer, or any other grade 3 or greater gastrointestinal toxicity attributable to fractionated Linac based SBRT.

13.1.2 Secondary Endpoints

- To determine rates of local progression free survival, overall survival, metastasis-free survival, and progression-free survival at 3, 6, and 12 months from Linac based SBRT.
- To evaluate acute toxicity, defined as any grade 3 or greater gastrointestinal toxicity within 3 months of treatment.
- To use FDG-(if available as per the recommendation by your treating physician) /CT scans for assessment of tumor response and progression.
- To evaluate the role of FDG-PET scans in treatment planning.
- To assess the quality of life before and after fractionated Linac based SBRT.
- To further standardize Linac based SBRT delivery and dosimetric parameters.
- To compare toxicity and outcomes among patients treated with fractionated Linac based SBRT delivered as 5 Gy x 5 (Cohort A of current protocol), 6.6 Gy X 5 (Cohort B of current protocol), 25 Gy X 1 (previous study), and 5-10 Gy x 3 (previous study).
- To evaluate pain control (as define by pain medication requirements at 3, 6, and 12 months following Linac based SBRT.

13.2 Analysis Populations

Efficacy analysis will be conducted on all patients who complete Linac based SBRT.

13.3 Plan of Analysis

Demographic and clinical characteristics of patients and the characteristics of treated lesions (volume, location, and modality) will be summarized by means, medians, standard deviations, ranges and proportions as applicable. Toxicities will be tabulated by type and grade at each follow-up interval. All adverse events will be reported to the SKCCC Data Safety Monitoring Committee and the JHH IRB. The study may be stopped before reaching the accrual goal at the recommendation of any of these groups. The level of progression free survival (and other categorical outcomes) will be tabulated at each follow-up interval. The percentage of individuals free from local progression will be computed with exact 95% confidence intervals. Time to event outcomes (overall survival, metastasis free survival, and progression free survival) will be summarized using Kaplan-Meier curves and medians with 95%

confidence intervals calculated using Greenwood's formula. A competing risks analysis of local progression at 6, 12, and 18 months will be conducted. The measurements of the volume of the pancreatic tumors based upon CT and/or PET-CT scans will be compared using paired t-tests or Wilcoxon signed-rank tests as appropriate. Quality of life at each interval will be calculated and compared using the recommended guidelines from the module (available by E-mail: c.d.johnson@soton.ac.uk). Vincent Bernard from MD Anderson will also help with data analysis. Data will be transferred via secure JH Box and totally anonymized.

13.4 Sample Size

13.4.1 Accrual Estimates

This is a single institution, phase II study to evaluate the safety and efficacy of fractionated stereotactic body radiation therapy in subjects with unresectable or locally recurrent pancreatic or periampullary cancer. The study will recruit two cohorts of patients; one will be patients who had recurrent or residual disease after previous chemoradiation therapy (Cohort A), and the other will be patients who had recurrent or residual disease after surgery and/or chemotherapy without radiation (Cohort B). Cohort A will be treated with 5 Gy x 5 for palliative retreatment, and Cohort B will be given 6.6 Gy x 5 for definitive treatment. We anticipate recruiting 2-3 patients per month for each cohort.

13.4.2 Sample Size Justification

The primary goal of this study is to access the late gastrointestinal toxicity rates including grade 2 or greater gastritis, fistula, or ulcer and any other grade 3 or greater gastrointestinal toxicity in Linac based SBRT patients. Two cohorts will be accrued in this study; one will be patients who recurrent or residual disease after previous chemoradiation therapy (Cohort A), and the other will be patients who had recurrent or residual disease after surgery and/or chemotherapy without radiation (Cohort B). Cohort A will be treated with 5 Gy x 5 for palliative retreatment, and Cohort B will be given 6.6 Gy x 5 for definitive treatment. Two cohorts will be evaluated separately.

The sample size is 60 patients per cohort. The primary outcome used to determine the sample size is the percentage of individuals with a late gastrointestinal toxicity (grade 2-4) at one year. The late grade 2 or greater toxicity rates was previously observed for other treatment regiments for locally advanced pancreatic cancer were approximately 40% .We hypothesize that in each cohort, the toxicity rate for this regimen will be 20%, a 50% reduction. The stopping rules for futility were calculated based upon a two-stage design with a total sample size of 60 and an interim analysis of 16 patients (note: accrual will continue while interim analysis is being conducted). Within 16 patients, if 7 or more patients have late grade 2 or greater gastritis, enteritis, fistula, ulcer, or late grade 3 or greater GI toxicity, the trial will be stopped. If 6 or fewer patients have late grade 2 or greater gastritis, enteritis, fistula, ulcer, or late grade 3 or greater GI toxicity, then the study will continue enrolling patients until 60 patients have been accrued. After 60 patients are enrolled, if 17 or more of the patients have late grade 2 or greater gastritis, enteritis, fistula, ulcer, or late grade 3 or greater GI toxicity, the null hypothesis will not be rejected. If 16 or fewer of the patients have late grade 2 or greater gastritis, enteritis, fistula, ulcer, or late grade 3 or greater GI toxicity, we will conclude that one year late toxicity is below 40%. This design will reach 91% power with 2% type I error for grade 2 or greater late toxicity, and the probability of early termination is 0.47. In addition, this sample size will reach 89% and 90% power to test the increase of 1-year local progression free survival from 30% to 45% in cohort A and 50% to 65% in cohort B, respectively.

The calculation is based on a one-sided test at significance level 0.04, assuming exponential distribution for local progression time and 2.5 year uniform accrual time with 1 year follow up.

13.5 Interim Analyses for Efficacy

After the first 16 patients are followed up for one year, we will estimate the 1-year local progression free survival. If the upper bound of a two-sided 98% confidence interval (critical value alpha = 0.02) of local progression free survival does not exceed 30% in cohort A, or less than 50% in cohort B, the accrual at that cohort will be halted and trial will be re-evaluated.

13.6 Data Analysis

We will perform separate analyses for Cohorts A and B. Descriptive summary statistics (mean, median, standard deviation, range, or proportion) will be presented for demographic and clinical characteristics of patients or treated lesions.

Toxicity will be summarized by type and grade for each cohort. The rate of grade 3 or higher GI toxicity will be estimated along with its 95% CI. This study will evaluate the efficacy of fractionated Linac based SBRT based on local-regional progression free survival (LFSP). LPFS is defined as the elapsed time from the start date of Linac based SBRT treatment to the date of documented local/regional tumor progression or death, whichever occurs first. We will plot the Kaplan-Meier curve for LPFS and estimate 1-yr local control and its 95% confidence interval based on KM estimate and Greenwood's formula. In addition, we will consider death without local progression as a competing event, and estimate cumulative incidence rate of local-regional progression using a competing risk analysis.

Other outcomes to be studied in this group of patients include, overall survival (OS), progression free survival (PFS) and quality of life. OS is defined as the elapsed time from the start date of Linac based SBRT treatment to death due to any cause; PFS is the time from the start date of Linac based SBRT treatment to disease progression or death, whichever occurs first. OS and PFS will be summarized using Kaplan-Meier plot.

Quality of life will be assessed via EORTC QLQ-C30 (v3.0) questionnaires. Our study population is pancreatic cancer subjects, and the analysis will be focused on Global Health Status/QoL scale, symptom scale (fatigue, pain), and functional scale (physical functioning, role functioning, emotional functioning). For each module, summary statistics of the score will be reported as baseline and follow up time. Changes of quality of life score before and after treatment will be tested via paired t-test. In addition, mixture effect models will be fitted for accessing the quality of life changes over time. The frequency of patients who reach minimal clinically important difference of 10-points change from baseline will be tabulated by time. The time to definitive deterioration in quality of life will be analyzed using the Kaplan Meier method.

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Appendix I

EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

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

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

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

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

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

During the past week:

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

Please go on to the next page

ENGLISH/US

EORTC QLQ - PAN26

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

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

Please go to the next page

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

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Appendix II

Karnofsky Performance Status

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

Appendix III
Definition of Menopausal Status:

Menopausal status will be defined according to the following criteria:

Post-menopausal:

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

Pre- or peri-menopausal: Not meeting definition for postmenopausal as outlined above.