**Official Title: MR Guided Phase II Radiotherapy Dose Escalation in Unresectable Non-Metastatic Pancreatic Cancer**

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# MR-guided Phase II Radiotherapy Dose Escalation in Unresectable Non-metastatic Pancreatic Cancer

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**Schema:**

All patients will receive radiation to doses ≥50.4 Gy, five days per week over six to seven weeks. The Planning Target Volume (PTV) (PTV low dose) will include the pancreatic head or body or tail, where the tumor originated, as well as the major associated blood vessels and any suspicious nodes. This PTV will be treated with traditional dose per fraction radiation. The MR-defined tumor (PTV boost) will be treated with a simultaneous integrated boost (SIB) to a higher dose per fraction and will get the escalated dose. Patients will be treated with 28, 29, 30, or 31 fractions dependent on meeting the normal tissue dose constraints as shown in the table below. Treatment planning will be done to achieve the highest dose plan (31 fractions) if the normal tissue dose constraints can be met. If the normal tissue dose constraints are not met, the dose will be adjusted down incrementally from 31 to 30 to 29 to 28 fractions until the dose constraints are met.

| Fractions | 28 fractions | 29 fractions | 30 fractions | 31 fractions |
|---|---|---|---|---|
| $PTV_{low\ dose}$ | 28 x 1.8Gy 50.4 Gy | 29 x 1.75Gy 50.75Gy | 30 x 1.70Gy 51 Gy | 31 x 1.65Gy 51.15Gy |
| $PTV_{boost(SIB)}$ | 28 x 2.25 Gy 63 Gy | 29 x 2.25Gy 65.25Gy | 30 x 2.25Gy 67.5 Gy | 31 x 2.25Gy 69.75Gy |

- Dose level depends on duodenal, small bowel and gastric doses
- Chemotherapy: concurrent Gemcitabine or Capecitabine

**Patient Population**: (See Section 3.0 for Eligibility)

Pathologically confirmed (histologic or cytologic), unresectable non-metastatic adenocarcinoma of the pancreas (Appendix I). Patients must have received at least four months of any type of systemic chemotherapy prior to enrolling in the trial. Any type or duration of prior chemotherapy beyond four months is acceptable as long as there is no evidence of distant metastases. Patients may have responding, stable, or locally progressive disease as long as there is not definite metastatic disease. Patients with bulky tumors (> 7cm) may not be eligible if the MR-defined SIB PTV volume is too large (>400 cc). Additionally, patients with a suboptimal performance status will not be considered for the study (Zubrod Performance Status < 0–1), A minimum of two weeks is required between the last cycle of chemotherapy and the first fraction of radiation.

Patients must be able to undergo MR scans for baseline evaluation, radiation planning, and follow-up.

**Required Sample Size**: 23 patients

## 1.0 INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States. Despite aggressive combined modality treatment approaches, the overall five-year survival remains less than 7%. (Sener 1999; Herman 2010; Cooke 2010; Siegel 2015) Although surgery is historically the only curative option, the majority of patients have unresectable or metastatic disease at presentation.

Conventional treatment for locally advanced pancreatic cancer is unsatisfactory. The emergence of more effective chemotherapy may help to decrease the risk of failure outside of the pancreas and make radiation more pivotal in contributing to cure.

The advent of contemporary advanced radiation therapy technology allows for escalation of radiation dose to levels previously unobtainable. (Ben-Josef 2004; Ben-Josef 2012) Select patients with unresectable pancreatic cancer may be curable with high-dose chemoradiation if they do not develop metastatic disease.

## 1.1 Rationale for Selected Approach and Trial Design

### 1.1.1 Locally Advanced Pancreatic Cancer

Of the 48,960 patients diagnosed with pancreatic carcinoma in the United States from 2007 to 2011, approximately 40% presented with locally advanced disease. (Jemal 2015) These patients have pancreatic tumors that are surgically unresectable due to encasement or occlusion of the superior mesenteric vein (SMV), SMV/portal vein confluence, or direct involvement of the superior mesenteric artery (SMA), celiac axis, inferior vena cava, or aorta. These patients are now approached initially with systemic chemotherapy and radiation is used selectively based on response to chemotherapy and performance status. (Huguet 2007)

### 1.1.2 Chemoradiation for Locally Advanced Pancreatic Cancer

The Mayo Clinic had a randomized trial in the 1960s in which 64 patients with surgically staged locally unresectable, non-metastatic pancreatic adenocarcinoma received 35 to 40 Gy of radiation and concurrent fluorouracil (5-FU/RT) versus radiation alone. A significant survival advantage was seen for patients receiving 5-FU/RT (10.4 months vs. 6.3 months, respectively). (Moertel 1969) The Gastrointestinal Tumor Study Group (GITSG) followed with a study of 194 patients comparing RT alone (60 Gy split course) to 5FU (bolus)/RT (40 Gy or 60

Gy split course) and maintenance 5-FU. A survival benefit was demonstrated with the combined modality arms (Moertel 1981). The RT alone arm closed early due to inferior survival. The one-year survival rates in the two CRT arms were 38 and 36%, respectively vs. 11% in the RT arm. (Moertel 1981)

A follow-up GITSG trial compared chemotherapy alone to chemoradiotherapy in surgically confirmed unresectable tumors. Forty-three patients were randomized to receive combination streptozocin, mitomycin, and 5-FU (SMF) chemotherapy or 5-FU (bolus)/XRT (54 Gy) followed by adjuvant SMF chemotherapy. The chemoradiotherapy arm demonstrated a significant survival advantage over the chemotherapy-alone arm (one-year survival, 41% vs. 19%) (GITSG 1998).

Contrastingly, the Eastern Cooperative Oncology Group (ECOG) reported no benefit to chemoradiotherapy versus chemotherapy only. (Klaassen 1985) In the ECOG study, patients with unresectable, non-metastatic pancreatic or gastric adenocarcinoma were randomly assigned to receive either 5-FU chemotherapy alone or 40 Gy external beam RT with concurrent bolus 5-FU on week. Of the 91 pancreas patients, no survival difference was observed between the two groups (median survival, 8.2 vs. 8.3 months). (Klaassen 1985) The subsequent ECOG trial E4201, however, demonstrated a survival benefit for gemcitabine and concurrent radiation as compared to gemcitabine alone. (Loehrer 2008; Loehrer 2011)

Continuous-infusion 5-FU allows for increased cumulative drug dose and a more protracted radiosensitization relative to bolus 5-FU. Phase I and phase II trials have been performed in pancreatic cancer, showing that the use of infusional 5-FU is without excessive treatment-related toxicity and is effective. (Whittington 1995; Bo 2001; Osti 2001) Continuous oral dosing of capecitabine simulates a continuous 5-FU infusion. (Ben-Josef 2004; Vaishampayan 2002) Phase II studies of capecitabine/RT appear to have equivalent outcomes to continuous infusion 5-FU. (Dunst 2002).

The Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) retrospectively evaluated 128 patients with locally advanced pancreatic cancer who were prospectively enrolled on multiple clinical trials and had received chemotherapy for at least three months. In patients without disease progression, the investigator determined whether to continue chemotherapy or proceed with chemoradiation to 55 Gy with concurrent infusion 5-FU. The groups were

balanced for initial characteristics and induction chemotherapy. In the group receiving CRT vs. chemotherapy alone, the progression and median overall survival times were 10.8 vs. 7.4 months and 15.0 vs.11.7 months. (Huguet 2007)

**1.1.3** Induction Chemotherapy

Induction chemotherapy is favored prior to chemoradiation to provide early optimal systemic treatment and also to select patients most likely to benefit from chemoradiation. (Krishnan 2007; Huguet 2007) Previous RTOG studies, such as RTOG 0411, have shown no increase in toxicity during chemoradiation when induction chemotherapy is first administered.

Most induction chemotherapy for pancreatic cancer has consisted of gemcitabine-based regimens. (Krishnan 2007, Varadhachary 2008) The LAP 07 trial evaluated gemcitabine alone versus gemcitabine followed by radiation in patients with locally advanced pancreatic cancer. (Hammel, 2013) In this trial, 442 patients were first randomized to gemcitabine alone or gemcitabine plus erlotinib for four months. Patients without progression (60%) were then randomized to two additional months of chemotherapy or chemoradiation (54 Gy). There was no improvement in survival with the addition of radiation following gemcitabine for patients with locally advanced pancreatic cancer. Criticisms of this trial are that the radiation doses used were low in comparison to single institutional data. In contrast, a phase III trial by ECOG showed a survival advantage to the combination of radiotherapy and gemcitabine over gemcitabine alone. (Loehrer 2011) The study was closed early because of slow accrual; however, in the 74 patients enrolled, median survival improved from 9.2 to 11.1 months with the addition of radiation (p=0.017). These results, together with the John Hopkins University's rapid autopsy series revealing that uncontrolled local growth, rather than distant metastatic disease, is the cause of death in 30% of patients (Iacobuzio-Donahue 2009), confirm the premise that survival may be improved in select patients with unresectable pancreatic cancer with more intensified local therapy.

More recently, a phase III clinical trial has demonstrated that the aggressive multidrug regimen FOLFIRINOX (fluorouracil, oxaliplatin, leucovorin and irinotecan) was statistically significantly superior to gemcitabine with respect to response rate (31.6% vs. 9.4%), progression-free survival (6.4 months vs. 3.3 months), and overall survival (11.1 months vs. 6.8 months) (Conroy 2011). This drug combination is now used in the neoadjuvant setting for patients with resectable and borderline resectable pancreas cancer. (Christians 2014)

### 1.1.4 Dose Escalation in Pancreatic Cancer

Despite combinations of chemotherapy and radiation, local control, as well as distant control, continues to be a challenge for patients with locally advanced unresectable pancreatic cancer. Local progression occurred at the site of failure in 58% of the patients treated to 60 Gy in the GITSG study. (Moertel 1981) The Mayo Clinic has also demonstrated a high local failure rate of 70% in patients with unresectable pancreatic cancer treated to 40 to 60 Gy. (Roldan Cancer 1988)

A study at Thomas Jefferson University attempted to escalate the dose to 70 Gy with conventionally fractionated external beam irradiation with or without chemotherapy but there was still a high rate of local failure of 78%. This study, however, was done before the era of imaged-based technology for treatment planning and delivery. (Whittington 1984; Dobelbower 1980) Other studies have explored dose escalation for pancreatic cancer. (Hasard 2009; Brunner 2010; Gutt 2010; Ben-Josef 2012)

An analysis of recently published data was performed to assess the usefulness of dose escalation. (Moraru 2014) The results of trials with various dose fractionation schemes and several chemotherapeutic agents and schedules are summarized in Table 1. Patient participation required histologic/cytologic confirmation of unresectable pancreatic adenocarcinoma without distant metastases. Only results published after 1997 were included. Studies not reporting tumor response or those combining conventional radiation schedules with a large boost dose were excluded. Radiation treatment was usually combined with different chemotherapy treatments, yet due to the lack of sufficient studies for separate analysis, no distinction was made between the various agents.

In order to properly compare the data, a biologically equivalent dose (BED) was calculated for each trial based on the fractionation scheme and treatment duration, using estimates for the radiobiological parameters. (Qi 2006) Assessment of the median survival data as a function of the equivalent dose administered yielded no discernible correlation. This coincides with clinical experience that no treatment modality attempted thus far has proven distinctive in improving patient outcome.

Although the clinical results indicate no survival advantage with increasing the radiation dose, it is worthwhile to examine the response to treatment, since increased tumor control is

recognized as beneficial in terms of palliation and quality of life, even in the absence of a curative outcome. Some of these studies, however, may not have had optimal chemotherapy to control distant disease. Consequently, we analyzed the tumor response reported as a function of the radiation treatment, shown in Figure 1, where the clinical assessments were obtained from CT analysis or MRI in a few cases. These include the probability of complete responses (CR) and partial responses (PR). The former entails the disappearance of all target lesions, while the latter is defined according to the *WHO Handbook* (Miller 1981) and RECIST criteria. (Therasse 2000) For the analysis, we have differentiated tumor control as the fraction of all patients exhibiting CR, PR, and SD, while tumor response comprised of only those with CR and PR.

To quantify the added advantage for increasing dose, we utilized a modified linear quadratic (MLQ) model (Tai 2008) to perform a $\chi^2$ fit to the response data from conventional and high dose/fraction treatment. The extracted radiobiological parameters were used to calculate the BED. The results reveal that there is a benefit of increased tumor response with higher dose radiation, as illustrated in Figure 1. According to the fit, the standard fractionation of 50.4 Gy given in 28 fractions (1.8 Gy/fx) gives roughly a 10% tumor response. Using 2.25 Gy per fraction, a 37% response is expected for a total dose of 65.3 Gy administered in 29 fractions, 43% for 69.8 Gy in 31 fractions and 46% for 74.3 Gy in 33 fractions, pointing to good improvement in tumor response with dose escalation. For 70 Gy in 28 fractions (2.5 Gy/fx), a 54% tumor response is expected. Normal tissue complications, however, at these higher doses, need to be carefully considered.

| Study Group | Dose (Gy) | Dose/Fx (Gy) | No. of Patients | 1 Yr. Survival (%) | Response (%) | Chemotherapy Regimen |
|---|---|---|---|---|---|---|
| ***Conventional*** | | | | | | |
| Ishii, 1997 () | 50.4 | 1.8 | 20 | 41.8 | 10.0 | 5-FU |
| Ceha, 2000) | 72.0 | 2.0 | 44 | 47.0 | 27.0 | - |
| Andre, 2000 () | 45.0 | 1.8 | 32 | 31.0 | 16.0 | Cisplatin, 5-FU |
| Kornek, 2001 () | 45.0 | 1.8 | 15 | 13.3 | 6.0 | Mitomycin C, GEM |
| Boz, 2001 () | 59.4 | 1.8 | 42 | 26.0 | 23.0 | 5-FU |
| Ashamalla, 2003 () | 63.4 | 1.1 | 20 | 56.0 | 30.0 | Paclitaxel |
| Li, 2003 () | 52.4 | 1.8 | 34 | 43.5 | 31.3 | 5-FU, GEM |
| Okusaka, 2004 () | 50.4 | 1.8 | 42 | 28.0 | 21.0 | GEM |
| Morganti, 2004 (1) | 39.6 | 1.8 | 15 | | 6.7 | 5-FU |
| | 50.4 | 1.8 | 15 | 31.3* | 13.3 | 5-FU |
| | 59.4 | 1.8 | 20 | | 5.0 | 5-FU |
| Cohen, 2005 () | 59.4 | 1.8 | 104 | 20.0 | 8.0 | Mitomycin C, 5-FU |
| Tsujie, 2006 () | 45.0 | 1.5 | 20 | 40.0 | 35.0 | Cisplatin, 5-FU |
| Wilkowski, 2006 () | 45.0 | 1.8 | 32 | 67.2 | 62.6 | 5-FU, GEM |
| Murphy, 2007 () | 36.0 | 2.4 | 74 | 47.0 | 15.0 | GEM |
| Saif, 2007 () | 50.4 | 1.8 | 20 | 58.0 | 20.0 | Capecitabine |
| Small, 2008 () | 36.0 | 2.4 | 39 | 47.0 | 5.1 | GEM |
| Crane, 2009 ( | 50.4 | 1.8 | 82 | 47.0 | 26.0 | Bevacizumab, Capecitabine |

| Study Group | Dose (Gy) | Dose/Fx (Gy) | No. of Patients | 1 Yr. Survival (%) | Response (%) | Chemotherapy Regimen |
|---|---|---|---|---|---|---|
| Sudo, 2011 () | 50.4 | 1.8 | 34 | 70.6 | 12.0 | Oral S-1, GEM |
| | | | ***SBRT*** | | | |
| De Lange, 2002 () | 24.0 | 8.0 | 24 | 46.0 | 29.2 | GEM |
| Mahadevan,2010() | 29.3 | 9.8 | 36 | 50.0 | 61.0 | GEM |
| Polistina, 2010 (27) | 30.0 | 10.0 | 23 | 39.1 | 69.6 | GEM |

*TABLE 1: Recent clinical data on pancreatic cancer using combined modalities of radiation therapy and chemotherapy.*
*Note: Response includes reported complete responses (CR) + partial responses (PR).*
**- averaged over entire trial population.*

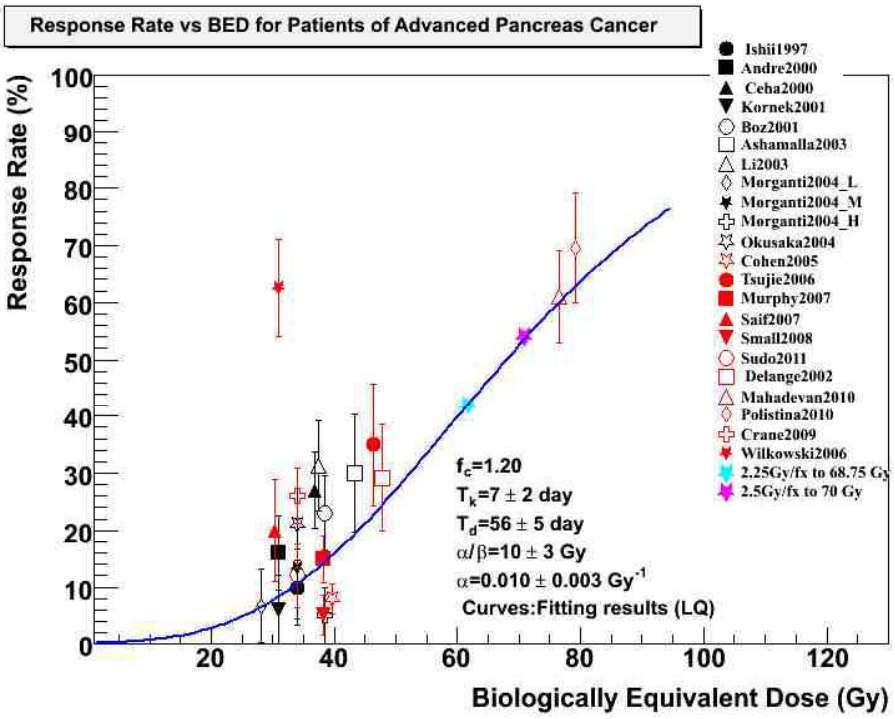


*FIGURE 1: Tumor response vs biologically equivalent dose for radiotherapy treatment of unresectable pancreatic cancer.*

### 1.1.5 IMRT for Unresectable Pancreatic Cancer

Intensity-modulated radiation therapy (IMRT) is a technique that allows for a very conformal dose distribution to established targets with favorable sparing of adjacent critical organs when compared to most 3D conformal plans. Studies in the literature confirm the feasibility of IMRT in the upper abdomen. (Ben-Josef 2004; Ben-Josef 2012; Fuss 2005; Milano 2004; Yovino 2011) The use of IMRT as a boost (Brown 2006) and throughout treatment has been described. Inherently, IMRT may be superior to 3D conformal radiation when delivering high doses to the designated targets while attempting to spare immediately adjacent critical organs, particularly if motion is minimized. Sparing of the GI tract is particularly important, especially in the setting of dose escalation. (Yovino 2011; Wood 2010). IMRT was used in a phase I/II trial (Ben-Josef 2012) at the University of Michigan, to escalate the dose from 50 to 60 Gy in 25

fractions delivered concurrently with full-dose gemcitabine (1000 mg/m$^2$ weekly on weeks 1, 2, 4, and 5 of radiotherapy). There was no elective lymph node irradiation and the Gross Tumor Volume (GTV), defined on CT, was expanded by 0.5 cm to form the Clinical Target Volume (CTV). The trial accrued 50 patients and established that high-dose radiotherapy (55 Gy in 25 fractions) can be delivered safely with concurrent full-dose gemcitabine, with the use of IMRT. The rate of severe toxicity (24%) observed at this dose compares favorably with toxicities reported with other contemporary regimens. The median and two-year survival in this trial (14.8 months and 30%, respectively) were significantly better than historical controls (11.2 months and 13%, respectively). (Murphy et al. 2007) High-dose radiotherapy also improved the two-year local control from 38% (historical controls, Murphy et al. 2007) to 59%. Additionally, 12 of 50 patients (24%) receiving high-dose radiotherapy were able to undergo resection with good outcomes; 10 patients (83%) had R0 resection and five patients (42%) had a major pathological response. The median survival in these patients was 32 months. The trial also confirmed that elective lymph node irradiation is not required in this setting.

Investigators at Washington University also reported a favorable progression-free and overall survival (13.9 and 23.1 months, respectively) for 25 patients with locally advanced disease and seven with borderline resectable disease following intensified radiation with 55 Gy in 25 fractions. (Badiyan, 2014) These trials demonstrate that intensification of local therapy with the use of high dose radiochemotherapy and highly conformal techniques can be delivered safely and results in encouraging local control rates and OS.

### **1.1.6** Respiration Motion and Gating

There is considerable respiratory-induced motion in the upper abdomen. This has been reported as a range of 2 mm to over 15 mm. (Minn 2009, Mori 2009, Song 2010, Goldstein 2010, Feng 2009, Liang 2010) Methods to control for motion can include immobilization devices as well as respiratory gating. Four-dimensional computed tomography (4DCT) is used to measure this motion and to plan gated treatment. (Tai 2010; van Der Geld 2008)

### **1.1.7** Image-guided Adaptive Radiation Therapy

During RT, the location and shape of the pancreas vary significantly from day to day due to daily setup variations and physiological changes. (Liu 2010, Singh 2006, Wysocka 2010, Langen 2001) Singh et al. (2006) reported that, due to the large interfraction anatomical changes, the day-to-day V80% (volume covered by 80% isodose line) for the duodenum and

non-duodenal small bowel varied in the ranges of 30% to100% and one to 20%, respectively.(Singh 2006) Image-guided RT (IGRT) based on soft-tissue registration can address setup error and these inter-fractional shifts. (Tai 2010) Furthermore, online adaptive RT (ART) has the potential to fully account for the interfraction variations, including organ deformation. (Peng 2010, Feng 2011) With the respiratory motion eliminated/reduced by a respiration management technique, such as gating, the PTV margin can be reduced from 1–2 cm to 0.3–0.5 cm by the use of IGRT and/or online ART. Because the PTV often overlaps with the duodenum and small bowel, such a drastic reduction in PTV margin would potentially reduce toxicities or allow RT doses to be escalated to eradicate the bulk of the tumor, (Bouchard 2009, Ogawa 2011, 2011a) and improve treatment outcome.

### 1.1.8 Imaging in Pancreatic Cancer

Pancreatic tumors are known to be hypoxic. (Kong IJROBP 2000) This may be due to hypoperfusion as these tumors have notoriously been resistant to antiangiogenesis agents. In fact, the dense fibrous stroma and relatively sparse vascularity of most pancreatic cancers may explain the resistance to treatment and is also the rationale for the imaging findings on contrast-enhanced MR and CT of pancreatic cancer. Normal pancreatic tissue typically demonstrates maximum enhancement in the early/arterial phase of contrast enhancement.

The relative hypoperfusion/non-enhancement of the pancreatic tumor in comparison to the normal pancreas makes it most conspicuous during the early phase of contrast enhancement. In addition, it is more feasible to perform multiphasic post contrast evaluation of pancreatic tumor perfusion with MR than CT because there is no associated ionizing radiation concern with MR.

The superior contrast resolution/ tissue differentiation of MRI typically makes it easier not only to detect pancreatic cancer but also to more accurately define the tumor volume in relation to the normal glandular tissue. (Gabata 1994, Semelka 1996) Not only is post contrast MR imaging superior to CT for defining the intra-glandular extent of pancreatic tumors, but there are other MR imaging sequences that are very helpful for distinguishing normal glandular tissue from tumor. The aqueous protein within the pancreatic acini is high signal on T1-weighted imaging; subsequently, T1-weighted imaging can be used to differentiate tumor from normal parenchyma. (Semelka 2006). In addition, fluid sensitive T2-weighted sequences allow for very high-resolution imaging of the pancreatic duct and the ductal disruption associated with pancreatic adenocarcinoma.

In the past several years, diffusion-weighted imaging (DWI) has become much more common in abdominal MRI. Initial experience with DWI of the pancreas has been very encouraging. Early investigations have yielded very high sensitivity and specificity for the detection of pancreatic cancer. (Ichikawa 2007) In addition, DWI appears to be very promising in predicting early progression of disease in chemotherapy-treated patients.(Ueno 2009) This may offer much more insight into treatment response than available with CT.

DWI is a very useful sequence for evaluating pancreatic cancer because it is very sensitive for detecting tissue that has relatively restricted diffusion in comparison with the adjacent normal tissue. (Semelka 1996) Pancreatic cancer has increased cellularity and a higher nucleus to cytoplasm ratio than normal pancreatic tumor. Therefore, the Brownian motion of water is significantly reduced compared to the adjacent normal pancreatic parenchyma. This results in higher signal in areas of the pancreas displaying restricted diffusion and DWI is subsequently quite sensitive for the detection of pancreatic cancer. (Ichikawa 2007) In addition, DWI appears to be quite promising for monitoring early treatment response/cell death prior to a change in tumor size. (Ueno 2009). Decreases in DWI signal can be correlated with treatment response/cell death prior to a reduction in tumor size and may be a more accurate way to assess response than simply a change in size as available with CT. Some of the seeming lack of response to treatment when using CT size criteria may in fact be a result of the shortcomings of CT in assessing response rather than the shortcoming of the treatment.

Post contrast MR perfusion imaging may also provide some prognostic information regarding treatment response. (Akisik 2010) In a recently published study, higher perfusion values for the rate of transfer of gadolinium-based contrast to and from the extracellular space ($K^{trans}$) in pancreatic tumors were correlated with better response to anti-angiogenic chemotherapy. Considering that tumor response to radiation therapy is dependent upon tissue oxygenation for the generation of the cytotoxic free radicals, measuring tumor perfusion may also yield important prognostic information prior to initiating radiation therapy.

The pancreatic cancer protocol abdominal MRI with and without intravenous contrast will be utilized to stage, assist in treatment planning, and monitor treatment response for the patients enrolled in this study. The three MR sequences that will typically be utilized for contouring the radiation targets are T2 (duodenal wall delineation), fat-suppressed T1 (normal gland

delineation), and late arterial phase post-contrast, fat-suppressed T1 (tumor boundary and lymph node delineation; e.g., tumor appears dark, lymph nodes appear bright) because these sequences offer the best contrast resolution between tumor and normal pancreatic parenchyma.

Abdominal MR scans will therefore be performed prior to radiation and following radiation to help to monitor response in addition to screening for extra-pancreatic disease. MR simulation will be used for the radiation planning in addition to CT simulation. The necessary MR imaging for radiation planning, as well as the use of MR to evaluate response, will be key to this study.

PET imaging has also been explored in the staging of pancreatic tumors and is now an approved site for this test. PET imaging utilizes fluorodeoxyglucose (FDG), which is a glucose analog tagged with the fluorine 18 ($^{18}F$) isotope. FDG is preferentially taken up by cells with high metabolic activity, such as pancreatic adenocarcinoma. Changes in PET activity may correlate and be a means to assess tumor response after radiation. There is already precedent for utilization of PET for early evaluation of treatment response in other malignancies, e.g., chemotherapy response in lymphoma. (Hoekstra 1993; Romer 1998; Jerusalem 2000; Mikhaeel 2000 ; Kostakoglu 2002)

### 1.1.9 Considerations for Doses to Normal Structures

Duodenal toxicity is of concern when treating unresectable pancreatic cancer and has often restricted radiation dose escalation strategies due to this intimately related organ. Similar challenges exist for the stomach and other portions of the small bowel.

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review by Kavanagh et al. presents useful consensus guidelines on small bowel dose-volume effects for conventionally fractionated doses of the 45–50 Gy and suggest that the volume of the small bowel irradiated to 15 Gy, $V_{15}$, should be less than 120 cc. (Kavanagh 2010) However, delivering a dose of 60–70 Gy in 2 Gy per fraction that will minimize surrounding normal tissue toxicity is challenging given the lack of dose-response data in this high-dose regimen.

In a recent analysis, we performed modified linear quadratic (*MLQ*) (Guerrero and Li, 2004) based on iso-effective dose calculations using duodenum/small bowel dose-response data from reports whose fractionation schedules ranged from 1.5–25 Gy/fx (Prior 2014). Published

duodenum/small bowel dose-response data using a dose per fraction of 1.5–25 Gy were converted to MLQ equivalent dose in 2 Gy fractions ($MLQED_2$) using parameters obtained by modified Lyman model fitting. Furthermore, a method of converting dose-response data at one level of NTCP to another NTCP level was also presented. Our findings indicate that these converted dose-response data from conventionally fractionated radiotherapy (CFRT) and stereotactic body radiation therapy (SBRT) reports were reasonably consistent with one another in the range of 55–65 Gy.

There were three reports (Table 3) useful in determining duodenal planning constraints for the proposed dose escalation protocol. Two sets of iso-effective dose calculations are listed for each report: 1. Calculations of $MLQED_2$ as presented in our analysis mentioned above; and 2. *MLQ* equivalent dose in 2.2 Gy per fraction ($MLQED_{2.2}$) adjusted to an NTCP level of 15%. A brief summary of the reports useful in selecting planning constraints is given below.

*Murphy et al. (2010)*

A dosimetric model of NCI Common Terminology Criteria for Adverse Events (CTC) v3.0 duodenal toxicity had been developed by Murphy et al. using SBRT dose-volume data from 73 pancreatic cancer patients treated with CyberKnife. This study reported an association between 12-month actuarial estimates of grade $\geq$ 2 CTCAE duodenal toxicity (including ulceration, stricture, gastrointestinal (GI) hemorrhage, and perforation) and dose-volume parameters $V_{20}$, $V_{25}$, and the maximum dose to 1 cc of duodenum, $D_{1\,cc}$. According to $MLQED_2$ calculations, this single fraction of 23 Gy is equivalent to 55.6 Gy delivered in 2 Gy fractions. Similarly, the other dose-volume constraints $V_{20}$ and $V_{25}$, are equivalent to $V_{45.7}$ and $V_{62.5}$.

*Verma et al. (2013)*

The second report by Verma et al. reported on the duodenal toxicity of 112 women receiving IMRT to the para-aortic nodes for metastasis from various primary cancers (e.g., cervical, endometrial, ovarian, vaginal, vulvar, and others), receiving a dose of 45–66 Gy in 1.8–2.2 Gy per fraction. The authors found that the mean maximum dose of 63.3 Gy, dose to duodenum volume of 2cc, $D_{2cc}$, of 61.2 Gy and a $D_{5cc}$ of 59.1 Gy was found in eight patients experiencing grade $\geq$ 2 RTOG duodenal toxicity. Similar $MLQED_2$ calculations on the data from Verma et al. suggest that the risk of grade $\geq$ 2 duodenal toxicity could be limited to 7% if $D_{max} < 63.3$ Gy, $D_{2cc} < 61.2$ Gy, and $D_{5cc} < 59.1$ Gy.

*Huang et al. (2011)*

A third report by Huang *et al.* reported dosimetric predictors of GI toxicity in a group of 46 locally advanced pancreatic patients receiving 36 Gy in 2.4 Gy per fraction and concurrent gemcitabine. The authors report a 12 month GI toxicity rate of 8% provided the $V_{25} \leq 45\%$. $MLQED_2$ calculations found that $V_{24.2}$ and $V_{34}$ are equivalent to $V_{25}$ and $V_{35}$, respectively.

Dose-response SBRT data for the stomach and pyloric sphincter were found to be non-existent, making it difficult to perform a similar $MLQED_2$ analysis. Emami et al. (Emami 1991) state a $TD_{50}(1)$ (the dose corresponding to 50% complication probability for a uniformly irradiated whole organ) of 65 Gy, suggesting the stomach may be relatively more tolerant of higher doses than the duodenum. However, in light of the difficulty in performing a similar $MLQED_2$ analysis, the duodenum dose-volume constraints will be used for the stomach.

| Study | Primary Cancer | Number of Patients | Dose (Gy) | Dose/fx (Gy) | Dose-Volume Parameters | Toxicity (%) | $MLQED_2$-Volume Parameters | $MLQED_{2.2}$-Volume Parameters‡ | Clinical endpoint |
|---|---|---|---|---|---|---|---|---|---|
| Huang, 2011 | Locally advanced pancratic cancer | 46 | 36† | 2.4† | $V_{25} \leq 45\%$ | 8.0 | $V_{24.2} \leq 45\%$ | $V_{26.9} \leq 45\%$ | Grade ≥ 3 CTC4 GI Toxicity |
| | | | | | $V_{25} > 45\%$ | 48.0 | $V_{24.2} > 45\%$ | $V_{26.9} > 45\%$ | |
| Murphy 2010 | Locally advanced pancreatic cancer | 73 | 25 | 25 | $V_{20} < 3.3$ cc | 11.0 | $V_{48.3} < 3.3$ cc | $V_{48.8} < 3.3$ cc | CTC v3.0 Grade ≥ 2 duodenal toxicity (n=12)[a] |
| | | | | | $V_{20} \geq 3.3$ cc | 48.0 | $V_{48.3} \geq 3.3$ cc | $V_{48.8} \geq 3.3$ cc | |
| | | | | | $D_{1cc} < 23$ Gy | 12.0 | $D_{1cc} < 59.0$ Gy | $D_{1cc} < 59.5$ Gy | |
| | | | | | $D_{1cc} > 23$ Gy | 48.0 | $D_{1cc} > 59.0$ Gy | $D_{1cc} > 59.5$ Gy | |
| | | | | | $V_{25} < 0.21$ cc | 12.0 | $V_{66.3} < 0.21$ cc | $V_{66.9} < 0.21$ cc | |
| | | | | | $V_{25} \geq 0.21$ cc | 52.0 | $V_{66.3} \geq 0.21$ cc | $V_{66.9} \geq 0.21$ cc | |
| Verma, 2011 | Para-aortic nodel metastases | 112 | 45-66º | 1.8-2.2 | $D_{max} = 63.3$ Gy | 7.0 | $D_{max} = 63.3$ Gy | $D_{max} = 69.7$ Gy | Grade ≥ 2 RTOG duodenal toxicity |
| | | | | | $D_{2cc} = 61.2$ Gy | 7.0 | $D_{2cc} = 61.2$ Gy | $D_{2cc} = 67.4$ Gy | |
| | | | | | $D_{5cc} = 59.1$ Gy | 7.0 | $D_{5cc} = 59.1$ Gy | $D_{5cc} = 65.1$ Gy | |

‡ - MLQ based iso-effective doses in 2.2 Gy/fraction corresponding to an NTCP level of 15%.

[a] - Clinical endpoint consists of perforation, ulcer, stricture and GI hemorrhage

RTOG - RTOG late radiation morbidity scoring criteria

º - Prescription dose for patients who underwent resection was 45-50 Gy, while those having gross residual disease received 45-50 Gy to the nodal CTV and a boost of 60-66 Gy.

CTC - National Cancer Institute Common Criteria for Adverse Events version 3.0

CTC2 - National Cancer Institute Common Criteria for Adverse Events version 2.0

CTC4 - National Cancer Institute Common Criteria for Adverse Events version 4.0

† - median prescirption dose and dose per fraction

Table 3. Description of studies included in the analysis of radiation induced duodenal toxicity. The $MLQED_2$ and $MLQED_{2.2}$ are the doses in 2 and 2.2 Gy fractions, respectively, delivered uniformly to the whole organ volume. (Prior 2014)

**1.1.10** SMAD 4 expression

Smad4 (Dpc4) is a tumor suppressor gene that is inactivated in 53% of pancreatic cancer. It encodes a transcription factor that is involved in the regulation of expression of a broad set of genes; it has been implicated in the regulation of tumor microenvironment, and it has been correlated clinically with prognosis and the pattern of disease spread. (Crane 2011) Smad 4 immunostaining of diagnostic cytology specimens correlated with the pattern of disease progression in the series of Crane et al. Intact Smad4 expression had a local dominant pattern of disease progression and Smad4 loss had a distant dominant pattern of disease progression (p=0.016). (Crane 2011) The rapid autopsy series from Johns Hopkins University was the first to correlate Smad4 with the pattern of disease progression. (Iacobuzio-Donahue 2009) Together, these studies contradict the perception that all patients with pancreatic cancer will die because of disseminated disease and emphasize that complications of local tumor progression are a significant source of disease-related mortality. Testing of Smad4 expression prior to treatment (if tissue is available) may help to differentiate those patients in whom local therapy, in addition to systemic therapy, may alter their outcome and be a reasonable investment of their time and energy.

## 2.0 OBJECTIVES

### 2.1 Primary Objective

To evaluate the efficacy of dose escalation to an MR-defined GTV of up to 69.75 Gy at 2.25 Gy per fraction for unresectable pancreatic cancer and to determine two-year and median survival rates measured from the date of diagnosis and from the end of treatment.

### 2.2 Secondary Objectives

**2.2.1** To evaluate local control based on imaging.

**2.2.2** To evaluate acute and late (> 3 months post treatment) radiation-induced toxicities for patients treated in this protocol.

**2.2.3** To evaluate radiographic and biochemical response for patients treated with the proposed dose escalation using pre- and post-treatment MR and PET scanning in addition to routine surveillance CT scans and CEA/ CA 19-9 levels.

**2.2.4** To evaluate SMAD 4 expression vs patterns of relapse.

## 3.0 PATIENT SELECTION

### 3.1 Conditions for Patient Eligibility

**3.1.1** Pathologically confirmed (histologic or cytologic), locally advanced, adenocarcinoma of the pancreas; patients must have unresectable disease based on institutional standardized criteria of unresectability or medical inoperability. Patients with bulky tumors (> 7cm on MRI), may not be eligible if the MR-defined SIB PTV volume is too large (> 400 cc).

**3.1.2** Patients with and without regional adenopathy are eligible.

**3.1.3** No convincing distant metastases, per PI discretion (for example, non-cancerous lung nodules, or equivocal lung or liver lesions that have been stable), based upon the following minimum diagnostic workup:

**3.1.3.1** History/physical examination, including collection of weight and vital signs, within 30 days prior to study entry;

**3.1.3.2** Diagnostic Abdominal/pelvic CT with IV contrast or Abdominopelvic MR scan with perfusion and diffusion-weighted sequences within 30 (+14) days prior to study entry. If the initial screening abdominal/pelvic CT falls out of window and a PET scan is subsequently performed, the PET can be used as the 30 day screening scan to confirm no metastatic disease in place of repeating the CT. The initial abdominal/pelvic CT would still serve as the comparator for subsequent abdominal/pelvic CT scans.

**3.1.3.3** Chest CT scan or X-ray within 30 (+14) days prior to study entry. This is optional if PET scan including chest has already been performed at this time point.

**3.1.4** Radiation treatment planning: abdominal MR with perfusion and diffusion-weighted sequences and abdominal CT. The abdominal MR will be done as a sim with interpretation. The CT sim will not be done with interpretation. PET scan is optional but encouraged (If PET is not allowed because of insurance or other issues, the patient is still eligible for the study). Ability to undergo abdominal MR scans for staging and radiation planning and follow up is mandatory.

**3.1.5** Zubrod performance status 0-1 within 30 days of study entry.

**3.1.6** Age ≥ 18.

**3.1.7** Heme Onc (Chem 24) and CA 19-9/CEA within 30 days prior to treatment, as follows:

**3.1.7.1** Absolute neutrophil count (ANC) ≥ 1,000 cells/$mm^3$;

**3.1.7.2** Platelets ≥100,000 cells/$mm^3$;

**3.1.7.3** Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);

**3.1.7.4** Serum creatinine ≤ 1.5 mg/dl;

**3.1.7.5** ALT or AST < 3 x upper limit of normal;

**3.1.7.6** Total bilirubin < 3.0 mg/dL;

**3.1.7.7** Alkaline phosphatase < 3 x upper limit of normal;

**3.1.7.8** Negative serum pregnancy test (if applicable).

**3.1.8** Ability to swallow oral medications.

**3.1.9** Patients must have had at least four months of prior systemic chemotherapy.

**3.1.10** Patient must provide study-specific informed consent prior to study entry.

**3.1.11** Women of childbearing potential and male participants who are sexually active must practice adequate contraception.

**3.2 Conditions for Patient Ineligibility**

**3.2.1** Distant metastatic disease, second malignancy or peritoneal seeding.

**3.2.2** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of three years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible).

**3.2.3** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.

**3.2.4** Any major surgery within 28 days prior to study entry (for example, insertion of a vascular access device, exploratory laparotomy and laparoscopy are not considered major surgery; biliary or gastric bypass is considered major surgery).

**3.2.5** Severe, active co-morbidity, defined as follows:

**3.2.5.1** Unstable angina and/or congestive heart failure requiring hospitalization within the last six months;

**3.2.5.2** Transmural myocardial infarction within three months prior to study entry;

**3.2.5.3** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;

**3.2.5.4** Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration;

**3.2.5.5** Uncontrolled malabsorption syndrome significantly affecting gastrointestinal function;

**3.2.5.6** Any unresolved bowel or bile duct obstruction;

**3.2.5.7** Major resection of the stomach or small bowel that could affect the absorption of capecitabine;

**3.2.5.8** Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because patients receiving antiretroviral therapy may experience possible pharmacokinetic interactions with capecitabine.

**3.2.6** Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during the course of the study and for women, for three months after the last study drug administration and for men, for six

months after the last study drug administration; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

**3.2.7** Women who are lactating at the time of registration and who plan to be lactating through three months after the last study drug administration.

**3.2.8** Prior allergic reaction to capecitabine or gemcitabine.

**3.2.9** Inability to undergo an MR of the abdomen/pelvis.

**3.2.10** Participation in another clinical treatment trial while on study.

## 4.0 REGISTRATION PROCEDURES

The eligibility criteria must be completed, and an IRB-approved consent form must be signed before a participant can be registered and receive a study case number. The research coordinator at Froedtert & the Medical College of Wisconsin will assign case numbers in numerical sequence, 1–45.

## 5.0 RADIATION THERAPY

Image-guided IMRT or three-dimensional conformal radiation therapy (3DCRT) with respiratory gating should be used. IMRT with simultaneously integrated boost is preferred due to the ability to decrease dose to the adjacent normal organs, including the stomach, duodenum, small and large bowels, kidneys, liver, and spinal cord. Rarely, insurance issues will prevent IMRT and then 3DCRT will be used (< 10% of patients). When 3D CRT is required, two 3DCRT plans, one for $PTV_{50.4}$ and one for $PTV_{boost}$, will be generated and delivered sequentially.

Protocol radiation treatment must begin no sooner than 14 days or at physician discretion, after the last chemotherapy dose. A 3D and 4D CT and MRI must be obtained for treatment planning. A mid-treatment (weeks 2–5) replanning CT/MRI or MR sim may occur if necessary.

### 5.1 Localization, Simulation, and Immobilization

Respiration correlated 3D and 4DI CT, MRI and optional PET will be acquired and fused for target and OAR delineation.

Patients will be simulated (and treated) supine with arms up. Immobilization is required. An alpha cradle or body vac fix is necessary.

**5.1.1** CT Simulation

Both intravenous and oral contrast must be used at the time of CT simulation acquisition, unless there is renal insufficiency or iodine allergy. CT slice thickness must be no greater than 3 mm. Approximately 10 ml of omnipaque will be mixed with 120 ml of water and True Orange drink mix for the CT simulation and two-thirds of this ingested approximately 30 minutes prior to simulation. The remaining third will be given after formation of the alpha-cradle or vac-fix immediately prior to scanning.

No abdominal compression can be used for gating. The CT at exhale (e.g., 50% phase) should be used for planning. The gating window should be selected such that the residual motion is less than 3 mm, for example, between 40% to 60% phases. The internal target volumes (ITV) should be obtained from the union of the target volumes delineated based on the selected-phase CTs, e.g., 40% and 60% phases. If there is very little motion between these phases, contouring on only the 50% phase is acceptable. All normal structures should be delineated based on the 50% phase CT.

**5.1.2** MR Simulation (Appendix V)

Patients not undergoing dialysis will be receiving gadolinium-based contrast during MR simulation. A glomerular filtration rate (GFR) greater than 30 must be confirmed within 45 days of the MR simulation for those patients identified with age greater than 60 years and/or history of hypertension, diabetes, or liver transplant. An IV should be placed in the antecubital vein for power injection of the contrast.

Patients must be set up in treatment position on an MR-compatible flat tabletop couch insert and be immobilized using the devices created during CT simulation. Phased-array receiver coils should be utilized to facilitate use of parallel imaging. A 1-mg injection of glucagon should be administered IM to suppress bowel motion. Images should be acquired in the transverse plane, using navigator-gating, based on the liver-diaphragm interface, whenever possible. The imaging protocol must include T2-weighted images, diffusion-weighted images (DWI), fat-suppressed T1-weighted images, and fat-suppressed, late arterial phase, post-contrast T1-weighted images. High order shimming over a reduced volume fully encompassing the patient is strongly recommended prior to any fat-suppressed T1-weighted imaging.

Upon completion of the MR simulation, and before transfer to a radiation treatment planning system, all images must be corrected for gradient nonlinearity-induced geometric distortion by applying a vendor-provided 3D distortion correction algorithm.

## 5.2 Target and Critical Structure Volumes for Treatment Planning

**5.2.1** Target Volume Definitions

**5.2.1.1** The ITV of the pancreatic head/body/tail and any suspicious lymph nodes is defined from the planning 4DCT. The GTV includes the primary tumor defined from the gated MRI (late arterial phase post contrast, T1 weighted and DWI and the optional PET, inside or adjacent to the pancreatic head or body or tail. The $PTV_{boost}$ is the GTV plus a 3–5 mm margin. The dose will vary depending on the normal tissue constraints as in Table 4. The adjacent luminal GTV should be excluded from the PTV boost. Use of a 3–5 mm PRV around the luminal GI structures can also be used to help exclude the adjacent GI structures from the boost PTV. This PTV will be labeled “PTV Eval.”

**5.2.1.2** The $CTV_{Low\ dose}$ is equal to the ITV (pancreatic head or body or tail including GTV), the adjacent vessels (SMA, celiac axis) and any suspicious lymph nodes.

**5.2.1.3** The $PTV_{Low\ dose}$ is defined as the $CTV_{low\ dose}$ plus a uniform 5–10 mm expansion in all directions.

**5.2.2** Critical Structures

The normal structures to be contoured are: stomach, duodenum, small bowel, large bowel, left and right kidneys, liver, and spinal cord. Contour the kidneys, liver, stomach, and duodenum in their entirety (See Appendix VI for stomach/duodenal anatomy) and any other small bowel or large bowel that is within 2 cm of the $PTV_{Low\ dose}$.

## 5.3 Dose Specifications and Dose Volume Constraints

The recommended treatment plan for this protocol is an IMRT plan due the ability to spare the adjacent normal organs **Treatment planning will be done to achieve the highest dose plan (31 fractions) if the normal tissue dose constraints can be met. If the normal tissue dose constraints are not met, the dose will be adjusted down incrementally from 31 to 30 to 29 to 28 fractions until those dose constraints are met.** At least five fields are required. 3DCRT is only acceptable if there are insurance issues which occur in <10% of patients. Photon beams of at least 6 MV should be used.

**5.3.1** Target Dose Specifications

The prescription dose to the $PTV_{boost}$ will be in 2.25 Gy daily fractions with number of fractions of 28, 29, 30, or 31, subject to the dose-volume constraints for the duodenum, stomach, colon, and small bowel. When possible, the prescription dose will cover ≥ 90–95% of the $PTV_{boost}$. This coverage can be lowered as needed to meet the luminal GI constraints. The PTV boost is defined by MR+/-CT.

A minimum dose equivalent of 50.4 Gy in 28 fractions will be prescribed to give ≥95 coverage of the $PTV_{low\ dose}$. The minimum dose within the PTVs must not fall below 95% of the prescribed dose. The PTV low dose will include the entire pancreatic head, body or tail, the MR-defined tumor, the associated blood vessels (SMA, celiac axis) and any suspicious lymph nodes.

**Table 4: Target prescription doses**

| **Target** | 28 fractions | **29 fractions** | **30 fractions** | **31 fractions** |
|---|---|---|---|---|
| **$PTV_{50.4}$** | 28 x 1.80 Gy 50.4 Gy | **29 x 1.75Gy 50.75Gy** | **30 x 1.70Gy 51Gy** | **31 x 1.65Gy 51.15Gy** |
| **$PTV_{boost(SIB)}$** | 28 x 2.25 Gy 63 Gy | **29 x 2.25Gy 65.25Gy** | **30 x 2.25Gy 67.5Gy** | **31 x 2.25Gy 69.75Gy** |

***Note that the PTV boost dose (SIB) per fraction stays the same for all the dose levels but the PTV 50.4 dose per fraction varies.**

**5.3.2** Normal Tissue Dose-Volume Constraints

| Structure | Constraints |
|---|---|
| Kidney (L & R) | Not more than 30% of the total volume can receive ≥ 18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥ 18 Gy. |
| duodenum, Stomach, /small bowel and large bowel | Max dose is the PTV boost dose(< 0.03 cc)<br>V56 < 5 cc (duodenum)<br>V45<30 cc (duodenum)<br>V45<75 cc (stomach)<br>V45< 135 cc (small bowel) |
| Liver | Mean dose < 28 Gy ; V30 < 30% |
| Spinal cord | Max dose to a volume of at least 0.03 cc must be ≤ 45 Gy |

## 5.4 Treatment Delivery

### 5.4.1 Patient Positioning with IGRT

Patient should be positioned as in the simulation. Respiration-gated kVCT(CT on rails) should be acquired at every fraction prior to the delivery of treatment and will be registered with the planning CT based on soft-tissue. If necessary, patient should be repositioned according to the shifts calculated from the registration (MV CT and KV cone beam CT are not allowed as they cannot be gated).

### 5.4.2 Respiration Gated Delivery

Treatment should be delivered with respiration gating using the gating window consistent with that used for the plan unless there is < 8 mm of superior/inferior motion measured on 4D CT. Real-time monitoring of patient respiration should be carried out during the delivery. Treatment should be interrupted if a significant change is observed in respiration.

### 5.4.3 Online ART (optional)

Patients should be treated with IGRT (Section 6.4.1). The pancreatic head (or body) should be delineated from the daily CTs for the first five fractions. Deformation of the pancreatic head or pancreas should be reviewed. If the deformation is found to be severe (i.e., the 5-mm margin expansion is not sufficient to cover the pancreatic head), the online ART process should be carried out on two days per week (e.g., Monday and Thursday) and at the last day of the treatment. On the other three days, the patient will undergo regular IGRT (Section 6.4.1). On the treatment days with the online ART, these steps will be followed: (1) set up the patient using laser maker alignment in the same way as for regular IGRT; (2) image the patient with the CT-on-rails in the same way as for regular IGRT, and transfer the images into the RealART system; (3) perform auto-segmentation with manual editing to obtain contours of the pancreatic head and duodenum; (4) replan based on the newly generated contours using the plan generated with the offline adaptive optimization (Section 6.4.4) or, for the first application of the online ART, using the original plan; (5) reconstruct the repositioning plan based on the new contours assuming the patient to be treated with the standard IGRT and compare with adaptive plan; (6) transfer the adaptive plan to the R & V system; (7) perform the independent monitor unit (MU) check and data transfer check using a quality assurance (QA) software tool; and (8) deliver the adaptive plan without the patient repositioning. Under rare situations, if the adaptive plan is not superior to the repositioning plan, the patient will be treated with standard regular IGRT.

**5.4.4** Offline Adaptive Optimization (Optional)

Before each treatment with the online replanning (Section 6.4.3) to be performed, the offline adaptive optimization procedure should be performed following these steps: (1) reconstruct dose for each of the repositioning fractions after the previous online replanning fraction, using the CT of the day and taking into account the couch shifts; (2) register all daily CT images acquired at and after the previous online replanning fraction based on deformable registration; (3) accumulate dose delivered up to the latest fraction based on the deformable registration in previous step; (4) generate the desired plan (gold standard) by performing a full-scope optimization based on the CT of the latest fraction using the same dosimetric objectives as for the original plan; (5) calculate the residual imperfection by subtracting the accumulated dose from the desired dose; and (6) generate the adaptive optimization plan taking into account the residual imperfection. The adaptive plan will be used as the initial plan for the subsequent online replanning.

## 5.5 Documentation Requirements

**5.5.1** Quality Assurance Documentation Stored in the Department of Radiation Oncology via MIM and Mosaic

The following documentation must be saved and available for review:

The CT, MRI, PET images used for planning;

The target and critical structure contours and the treatment plan;

The results of patient specific IMRT QA;

The detailed patient setup and treatment delivery record;

The daily treatment CTs and screen captures with daily shift data;

The online adaptive plans, if applicable;

The patient respiration signals during the daily delivery;

The follow-up images (CT and MRI) and follow-up notes.

**5.5.2** Treatment Interruptions

Treatment interruptions should be clearly documented in the patient's treatment record. If the sum total exceeds 14 break days, the treatment will be considered deviation unacceptable.

## 5.6 Compliance Criteria

**5.6.1** Volume Definitions

**5.6.1.1** Variation acceptable

- Minimum dose within the PTV is less than 95% of the prescribed dose, but does not fall below 60% of this dose.
- Maximum dose within the PTV is greater than 110% of the prescribed dose, but does not exceed 115% of this dose.

**5.6.1.2** Deviation Unacceptable

- Minimum dose within the PTV falls below 60% of the prescribed dose.
- Maximum dose goes above 115% of the prescribed dose.
- Incomplete contouring of the entire GTV or PTV.
- Use of different margins than specified in Section 5.2 for the CTV and PTV.
- Over contouring of the GTV by > 30 cc.

**5.6.1.3** Elapsed Days

- Per Protocol – No break days.
- Variation Acceptable – Up to nine break days.
- Deviation Unacceptable – More than 14 break days.

| **Evaluation** | **Total Dose** | **Elapsed Days** |
|---|---|---|
| Per Protocol | ≤ 5% | 38-45 |
| Variation Acceptable | > 5%≤10% | 47-54 |
| Deviation Unacceptable | >10% | > 55 |

**5.6.2** Compliance Criteria for Critical Structures

The compliance criteria for the critical structures identified for this protocol are based on the planning constraints presented in Section 5.3.

**5.6.2.1** Kidneys:

Per protocol: the requirements in Section 5.3.2 are fulfilled.

Variation Acceptable: If two kidneys are functional, >20% but < 30% of total kidney volume receives ≥ 18 Gy. If one kidney is functional, >10% but < 20% of total kidney volume receives ≥ 18 Gy.

- Deviation Unacceptable: If two kidneys are functional, **≥** 30% of total kidney volume receives ≥ 18 Gy. If one kidney is functional, **≥** 20% of total kidney volume receives ≥ 18 Gy.

**5.6.2.2** Spinal cord:

- Per protocol: the requirements in Section 5.3 are fulfilled.
- Variation Acceptable : None.
- Deviation Unacceptable: Max dose > 45 Gy to a volume that is at least 0.03 cc.

**5.6.2.3** Liver:

- Per protocol: the requirements in Section 5.3 are fulfilled.
- Variation Acceptable: None.
- Deviation Unacceptable : The mean liver dose exceeds 28 Gy.

## 5.7 Radiation Therapy QA and Reviews

After the first 10 patients are treated at Froedtert & the Medical College of Wisconsin, consideration will be given to opening the study up to other select institutions. Institutions interested in participating in this protocol should submit the following document for review by the physics study chair:

(1) Description of MR simulation (scanner details, sequences, positioning, coils).
(2) Description of IMRT planning, QA and delivery process and technology.
(3) Description of IGRT process and technology.
(4) Description of motion management method.

The necessary technologies required in this protocol include: 4DCT, MRI, IMRT, respiration gating or equivalent motion management technology, soft-tissue based patient positioning using diagnostic-quality CT.

The first case enrolled by each radiation oncology facility will undergo a rapid review by Drs. Erickson and Li. In this process, the treatment plan is submitted immediately (within 24 hours) after it is finalized. The case may proceed to treatment following planning without waiting for review and approval. The case will be reviewed in a timely manner with feedback given to the submitting radiation oncology facility. Corrections and resubmission of data will be requested for cases that do not meet contouring, dose-volume and quality assurance criteria.

All cases enrolled on trial will be reviewed. Corrections and resubmission of data will be requested for cases that do not meet contouring, dose-volume and quality assurance criteria.

## 5.8 Radiation Therapy Adverse Events

5.8.1 Adverse Event (AE)

Radiation therapy would stop early if the patient has significant grade 3 toxicities.

| Toxicity | Parameters | Agent | Modification |
|---|---|---|---|
| Hematologic | Grade 4 neutropenia or ≥ grade 3 platelets | RT | Dose modification per investigator discretion. |
| Clinically significant treatment-related nonhematologic toxicity | ≥ grade 3 | RT | Dose modification per investigator discretion. |
| GI | Grade 3 Intractable abdominal pain, nausea, vomiting, gastritis, gastric ulcer, duodenal ulcer, duodenitis; dyspepsia, colitis, diarrhea ≥ 7 stools over baseline or IVF > 24 hr. Hospitalization needed. | RT | Dose modification per investigator discretion. |

## 5.9 Radiation Therapy Adverse Event Reporting

See Section 6.4 for adverse event reporting.

# 6.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines.

Protocol drug treatment must begin within 30 days from study entry. The screening weight is used to calculate the BSA unless changed by > 10%.

## 6.1 Treatment

Patients will receive either gemcitabine or capecitabine at the discretion of the medical oncologists. Gemcitabine will be given once per week on Monday, Tuesday or Wednesday and capecitabine will be given orally twice per day. Drug dose adjustments can occur at the start of treatment at the discretion of the treating oncologist using guidelines in Section 7.5.1.1

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**6.1.1** Gemcitabine 400 mg 1m$^2$ IV weekly x six doses. Administer over 30 to 40 minutes

**6.1.2** Capecitabine 825 mg/m$^2$ po bid. Monday – Friday on days of radiation use 500 mg tablets, round to the nearest 500 mg dose. If there is an uneven number of pills, give the extra dose with the evening administration (e.g., three in AM and four in PM). Take 30 to 60 minutes after eating. For patients with GFR 30 – 50: 75% dose, GFR <30: hold drug (per up to date).

## 6.2 Gemcitabine (HCl) Agent Information

See package insert for comprehensive information.

**6.2.1** Formulation

Gemcitabine is an antineoplastic agent that is structurally related to cytarabine. It is a pyrimidine analogue that is cell-cycle specific. Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.

**6.2.2** Mechanism of Action

Gemcitabine is cytotoxic to cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S- phase boundary. Gemcitabine is converted intracellularly to gemcitabine-5'-triphosphate, its active form. Steady-state plasma levels of gemcitabine occur within 15 minutes after starting the infusion. The elimination half-life of gemcitabine ranges from 32 to 638 minutes, depending on the age and gender of the patient and the rate of administration of gemcitabine.

**6.2.3** Preparation

Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL. The concentration for 200-mg and 1-g vials should be no greater than 40 mg/mL.

**6.2.4** Administration

An appropriate amount of drug will be prepared with normal saline and administered as a 30- to 40-minute intravenous infusion.

**6.2.5** Adverse Events

The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, nausea, diarrhea, itchy skin rash, myalgia, and anorexia. Other side effects have included fatigue, peripheral edema, and proteinuria. Less likely side effects include abnormal renal and liver function tests, vomiting, constipation, malaise, and anorexia. Rare side effects include Stevens-Johnson syndrome (severe skin reaction) and shortness of breath, cough, inflammation or scarring of the lung. Rare side effects have included hemolytic

uremic syndrome/renal failure and liver failure, which have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

**6.2.6** Storage and Stability

The lyophilized product should be stored at controlled room temperature (20–25°C or 68–79° F). Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours. The manufacturer recommends solutions of gemcitabine not be refrigerated as crystallization may occur.

**6.2.7** Supply

Gemcitabine is commercially available.

**6.3 <u>Capecitabine Agent Information</u>**

See package insert for comprehensive information.

**6.3.1** Formulation

Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration. Approximately 500 mg tablets will be utilized in this study. Dosages will be rounded to the nearest 500 mg.

**6.3.2** Mechanism of Action

Capecitabine is an oral prodrug of 5-fluorouracil. Metabolized in the liver to 5'-deoxy-fluorocytidine, subsequently converted to 5'-deoxy-5-fluorouridine which is then hydrolyzed to 5-fluorouracil (active). Peak plasma levels occur in 90 minutes, and elimination half-life is 45 minutes.

**6.3.3** Preparation

This is an oral agent. Food delays the time to peak plasma level by about 90 minutes, and reduces the peak plasma concentration about 60%. Despite the effects of food on capecitabine pharmacokinetics, the manufacturer recommends giving the drug at the end of a meal because established safety and efficacy data are based on administration with food.

**6.3.4** Administration

The capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Dosages will be based on the dosing guidelines in 7.1.2; the tablets should be taken with water.

**6.3.5** Potential Drug Interactions

**6.3.5.1** Antacids

The administration of 20 mL of an antacid containing aluminum hydroxide and magnesium hydroxide may result in an increase in the area under the concentration-time curve (AUC) and

maximum concentration ($C_{max}$) of capecitabine of 16% and 35%, respectively. These changes were not considered clinically significant.

**6.3.5.2** Oral Anticoagulants

Altered coagulation parameters and/or bleeding, including death, have been reported in patients receiving capecitabine and coumarin-derivative anticoagulants. Post-marketing reports have revealed clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants when capecitabine was initiated. These events occurred within several days to several months after concurrent therapy was initiated. Patients receiving capecitabine and an oral anticoagulant should be closely and regularly monitored.

**6.3.5.3** Phenytoin

Some patients receiving capecitabine and phenytoin may experience phenytoin toxicity as a result of increased phenytoin plasma levels. Phenytoin levels should be closely monitored in patients taking concomitant phenytoin and capecitabine. The dose of phenytoin may need to be reduced.

## 6.4 Adverse Events

Only toxicities related to treatment require dose modifications. For patients experiencing adverse events unrelated to treatment (such as deep venous thrombosis, pulmonary embolus or non-neutropenic infection), when treatment is resumed after recovery from these adverse events, no dose modifications are required.

Common side effects from capecitabine include diarrhea (which may be severe), dermatologic effects (hand-and-foot syndrome referred to as palmar-plantar erythrodysesthesia), hematologic effects (neutropenia, thrombocytopenia, anemia, and lymphopenia), weight gain, and gastrointestinal effects (diarrhea, nausea, vomiting stomatitis, abdominal pain, and constipation). Uncommon side effects include hepatotoxicity (hyperbilirubinemia). Rare side effects may include cardiovascular effects (myocardial infarction, dysrhythmias, and cardiomyopathy).

**6.4.1** Storage and Stability

Tablets should be stored at controlled room temperature (25°C) in tightly closed containers with excursions to 15–30°C permitted.

**6.4.2** Supply

Capecitabine is commercially available.

## 6.5 Dose Modifications

Dose modifications will be made according to the greatest degree of toxicity. Adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) (per Section 7.7).

- Use NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for assessment of toxicity.
- If multiple toxicities are seen, the dose reduction should be based on the most severe toxicity experienced.
- Dose reduction is not permanent and may be adjusted week to week at treating physician's discretion.
- If chemotherapy is held due to a grade 2 toxicity, radiation therapy should continue.

If the patient develops a non-hematologic grade 3 toxicity related to chemotherapy, the chemotherapy must be held until the toxicity has resolved to grade 1. If the toxicity has not resolved after two weeks, protocol therapy should be discontinued, and the patient treated at the discretion of the investigator.

### 6.5.1 Hematologic Toxicity

Dose modifications according to blood counts the day of treatment are at the investigator's discretion using the following as a guideline. The investigator may make adjustments per their discretion for patient safety purposes or other circumstances (e.g., anticoagulation or on Plavix®, history of infection, etc.).

**Gemcitabine Dose Modifications**

ANC > 1,000 and platelets ≥100,000 100%

ANC 750–999 or platelets 75,000–99,000 75%

ANC 500–749 or platelets 50,000–74,000 50%

ANC < 500 or platelets < 50,000 hold

**Capecitabine Dose Modifications**

ANC > 1000 and platelets ≥ 100,000 100%

ANC 750–999 or platelets 75,000–99,000 ↓Reduce by 500 mg per day

ANC 500–749 or platelets 50,000–74,000 Reduce by ↓1000 mg per day

ANC < 500 or platelets < 50,000 hold until recovery

### 6.5.2 Non-hematologic Toxicity

Patients with adverse events not related to treatment, such as cholangitis from blocked biliary stents or pulmonary embolus from hypercoagulable state, after recovery from these adverse events, on resumption of treatment, do not require dose reductions when treatment is resumed.

## 6.6 Adverse Events

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading all adverse events.

### 6.6.1 Adverse Events (AEs)

Adverse events and serious adverse events will be submitted to the MCW IRB following their reporting criteria. Please refer to the DSMB Section 10.3.2 for the AE/SAEs that will be collected and reported for this protocol.

**Adverse Event:** For data collection and analysis, all unexpected grade 3, and all grade 4 and 5 adverse events will be captured for up to two years post treatment, death, or initiation of a new therapy, whichever occurs first.

**Serious adverse event:** For data collection and analysis, serious adverse events will be captured from first treatment date for up to 30 days post treatment, death, or initiation of a new therapy, whichever occurs first.

# 7.0 OTHER THERAPY

## 7.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded in the institution's source documentation.

### 7.1.1 Prophylaxis for Gastric Ulceration during Chemoradiation

It is recommended that patients be on a proton pump inhibitor during and for one month after radiation. If any new epigastric pain develops, ulceration should be expected and Gaviscon® liquid should be started. Upper endoscopy may be performed as clinically directed.

**7.1.2** Anticoagulants: Caution Concerning Co-administration of Warfarin and Capecitabine
A significant interaction occurs with co-administration of capecitabine and warfarin that can result in severe prolongation of the prothrombin time and resultant increased risk of severe bleeding. Patients requiring warfarin should have their prothrombin time monitored carefully according to institutional guidelines. Low molecular weight heparin does not interact with warfarin or capecitabine and is the preferred agent for patients requiring anticoagulation.

**7.1.3** Hematopoietic Growth Factors

**7.1.3.1** Erythropoietin is allowed.

**7.1.3.2** Myeloid growth factors may be utilized to treat CTCAE grade 3–4 ANC.

**7.2 Non-Permitted Supportive Therapy**

**7.2.1** Other investigational chemotherapeutic agents.

**7.2.2** Other chemotherapeutic agents.

**7.2.3** Other monoclonal antibody.

**7.2.4** Sorivudine or brivudine A.

**7.2.5** Cimetidine.

## 8.0 PATIENT ASSESSMENTS

**8.1 Study Parameters**: See Appendix II.

**8.2 Evaluation During Treatment**

**8.2.1** In all clinic visits and weekly during each cycle, sites will question patients regarding compliance with study instructions.

**8.3 Measurement of Response**

Response will be evaluated in this study using the international criteria proposed in the Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 (*Eur J Cancer*. 2009;45:228–247.)
See https://ctep.cancer.gov/protocoldevelopment/. CA 19-9 and CEA levels will also be followed.

Abdominal CT imaging with IV contrast using 5-mm maximum slice thickness is recommended for evaluation of the primary tumor. CT will be obtained within 30 days prior to starting radiation and will be obtained 30 days post treatment to assess for response to

treatment as well as resectability. Abdominal MR is required prior to radiation for radiation planning and at three months following completion of the radiation. Additional MR scans every six months for the first two years should be obtained and alternated with CT scans every six months. This will result in a diagnostic scan every three months. After two years, alternating abdominal MR and abdominal CT scans will be obtained every 12 months until year 5. This will result in a diagnostic scan every six months. After year 5, a CT abdomen scan will be obtained annually. Changes in perfusion ($K^{trans}$) and diffusion (ADC) with respect to the pretreatment MR will be documented in addition to changes in tumor size.

A PET scan should be performed three months post treatment and on an as-needed basis thereafter. (PET scan is optional but encouraged; if the patient cannot tolerate it or if it is not approved by insurance, the patient can still participate in the study.)

- **Measurable disease**: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest X-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
- **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

**Response Criteria: Evaluation of Target Lesions**

| | |
|---|---|
| Complete Response (CR): | Disappearance of all target lesions; Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. |

| | |
|---|---|
| Progressive Disease (PD): | At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). |
| Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. |

## 8.4 Criteria for Discontinuation of Protocol Treatment

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease.
- Adverse events, as described in Sections 6.8.1 and 7.5.
- Delays in protocol treatment greater than four weeks.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

## 8.5 Summary of Dosimetry Digital Data (will only be needed if protocol open to other institutions with an amendment)

**Item**

**Preliminary Dosimetry Information (DD)**

Digital Data:

- CT and MR data, critical normal structures, all GTV, CTV, and PTV contours.
- Digital beam geometry for initial and boost beam sets.
- Doses for initial and boost sets of concurrently treated beams.

- Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan **(DV).**

## 9.0 TISSUE/SPECIMEN ANALYSIS

### SMAD 4 TISSUE ANAYSIS

SMAD 4 testing will be done on specimens from prior biopsy tissue pretreatment if possible. SMAD 4 immunostaining should be performed on the biopsy specimens if possible from the original biopsy material, or any biopsy material. Testing will be done at the Medical College of Wisconsin laboratories. SMAD 4 test results will be included in the patient's research chart. SMAD 4 testing can be repeated post treatment if the patient is undergoing surgery.

The PI will contact the clinical research coordinator (CRC) with a list of subjects for SMAD 4 testing. The CRC will notify the CTO lab staff to request tissue and deliver tissue to the Genomic Science Precision Medicine Center. One to two blocks of tissue will be requested for SMAD 4 analysis.

## 10.0 STATISTICAL CONSIDERATIONS

### 10.1 Study Endpoints

#### 10.1.1 Primary Endpoint

Two-year survival probability and median survival time starting diagnosis.

#### 10.1.2 Secondary Endpoints

Local control as defined by imaging.

Acute and late (> 3 months post-treatment) toxicities (CT CAE).

Adverse events at any time.

Imaging/Marker Response (MR/CT +/- PET; CA 19-9/CEA).

SMAD 4 Expression vs. patterns of relapse.

### 10.2 Sample Size

The historical value of median survival time, taken as the average value from reported studies for unresectable pancreatic cancer treated with radiation and chemotherapy, is approximately 15 months starting from the end of treatment. Assuming survival time has an exponential distribution, this value leads to two-year survival probability of around 33%. We assumed that more patients will be eligible for the study when this protocol opens. We plan to accrue 23 patients in three years, accruing seven, eight and eight patients for first, second and third years, respectively. The study will be closed at end of the fourth year. We expect the median

survival time will be double to around 30 months and lead to a two-year survival probability of around 59%. Based on exponential distribution and on a one-sided test with a significance level of 5%, we will have 80% power to detect at least a 15-month increase in median survival time. Allowing 5% subjects to withdraw, we plan to accrue 23 patients, accruing seven, eight and eight patients in the first, second and third years, in the final study.

**Analysis Plan**

Kaplan-Meier method will be used to estimate the two-year survival probability and median survival time with 95% confidence interval. Fitting an exponential distribution and one-side test for the null hypothesis of median = 15 month versus alternative of median > 15 month will be tested.

Descriptive statistics and survival analysis methods will be used to analyze the secondary endpoints presented in Section 11.1.2.

**10.2.1** Evaluation of Adverse Events for MTD

Adverse events will be scored according to the NCI CTCAE version 4 criteria. Dose-limiting toxicity (DLT) is defined as any of the following occurring during chemoradiation or within 21 days from the completion of chemoradiation and being reported as definitely related to treatment:

- Grade 4 non-hematologic toxicity except grade 4 hyperglycemia unless associated with acidosis (pH < 7.3), hyperosmolar state (serum osmolality > 310 mOsm/kg), or ICU hospitalization.
- Grade 4 thrombocytopenia or neutropenia toxicity lasting > 7 days.
- Grade 3 toxicity due to chemoradiation, preventing treatment for > 7 days or causing bleeding, ulceration, perforation, fistula formation or obstruction of the duodenum, stomach or small or large bowel and the study re-evaluated for reconsideration of dose to the PTV boost and to these organs at risk.
- Elevation of ALT or AST > 10 x upper limit of normal for > 7 days (and not due to blocked stent or disease progression) also will be considered a DLT.
- Any grade 5 AE.
- We will evaluate and monitor grade 4 and 5 GI toxicity after the first 10, 15, and 20 patients enrolled the study. A 10% incidence of grade 4 and 5 GI toxicity occurring in the enrolled patients will trigger stopping enrollment so that the protocol can be

reviewed. A Pocock-type boundary with the lower limit of 95% confidence interval will be used for monitoring toxicity. At planned interim monitoring points, if no more than four, five, or six GI toxicities occur, the study will continue to its full enrollment of 23.

**10.2.2** Dose Escalation

Dose escalation will be based on meeting the recommended dose constraints for the normal tissues. The highest dose will be attempted first and the PTV 50.4 and PTV boost doses will be decreased until the normal tissue constraints can be met. Treatment planning will be done to achieve the highest dose plan (31 fractions) if the normal tissue dose constraints can be met. If the normal tissue dose constraints are not met, the dose will be adjusted down incrementally from 31 to 30 to 29 to 28 fractions until those dose constraints are met.

**10.2.3** Patient Accrual

Patient accrual is projected to be 23 patients in three years, accruing seven, eight and eight patients for the first, second and third years, respectively.

## 10.3 Analysis Plan

**10.3.1** Interim Reporting

Interim reports with statistical analyses are prepared every six months and reported to the IRB annually until the primary endpoint results have been presented. In general, the interim reports will contain information about:

- The patient accrual rate with projected completion date,
- Institutional accrual,
- Pretreatment characteristics,
- Compliance rates of treatment delivery with respect to the protocol prescription,
- The frequency and severity of adverse events due to protocol therapy. A safety review will be done after completing treatment of the first three patients.
- The protocol will report any grade 3 duodenal small or large bowel or stomach toxicities to include bleeding, ulceration, perforation, fistula formation, or obstruction of the stomach, duodenum, small or large bowel.
- The protocol will be temporarily closed to accrual for any unexpected non-hematologic grade 4 or 5 toxicities and the study will be re-evaluated.

**10.3.2** Data Safety Monitoring Board (DSMB) Review

To monitor the safety of this study, the Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (MCW CC DSMC) Cancer Center will review this study twice per year or for every five patients entered until all participants have completed treatment.

A summary of the MCW CC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 and 5 events must be reported to the DSMC within five calendar days of study staff's knowledge.)
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

A copy of the MCW CC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary. Any available DSMC letters will be submitted to the IRB of record as required.

**10.3.3** Analysis for Reporting the Initial Treatment Results

**10.3.3.1** Local control/ Treatment response

RECIST criteria for MR and CT and biochemical marker response

Local control - if local progression was not first progression, local progression will be determined by two consecutive imaging reports showing primary tumor growth and confirmed as progression by investigator; median survival and 1 year overall survival

Acute and late toxicity assessment

SMAD4 vs. Pattern of relapse

**10.3.3.2** Efficacy Endpoints

This analysis will be limited to the patients who completed treatment when these patients have potentially been followed for one year. Overall survival will be estimated with the Kaplan-Meier method (Kaplan 1958).

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**Appendix I NCCN Criteria**

## CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

- No distant metastases
- No radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement
- Clear fat planes around the celiac axis, hepatic artery, and SMA.

Tumors considered borderline resectable include the following:

- No distant metastases
- Venous involvement of the SMV/portal vein demonstrating tumor abutment with impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.

Adapted from: Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable demonstrate the following:

- HEAD
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- BODY
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- TAIL
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

## APPENDIX II STUDY PARAMETER TABLE

| **Trial Period:** | Screening | On Treatment | Follow-Up | | | |
|---|---|---|---|---|---|---|
| Scheduling Window: | Within 30 days prior to concurrent treatment | Assessed every 5 radiation treatments or at investigator discretion | 30 days (+/- 7 days) | Every 3 months until 2 years (+/- 1 month) | Every 6 months' years 2-5 (+/- 1 month) | Annually after year 5 (+/- 1 month) |
| **PHYSICAL** | | | | | | |
| History | X | X | X | X | X | X |
| Physical with Weight and Vital Signs | X | X | X | X | X | X |
| Response Assessment | X | | X | X | X | X |
| Performance Status | X | | X | X | X | X |
| **PATHOLOGY** | | | | | | |
| Pathologically Confirmed Disease | X (prior to study entry) | | | | | |
| **LABORATORY** | | | | | | |
| CBC w/ diff; platelets, ANC | X | X | X[7] | X[7] | X[7] | X[7] |
| Creatinine, ALT or AST, Total Bilirubin, Alkaline Phosphate | X | X | X[7] | X[7] | X[7] | X[7] |
| NA, K, Cl, Mg, $CO_2$ | X | X | X[7] | X[7] | X[7] | X[7] |
| CA19-9 & CEA | X | | | | | |
| Serum Pregnancy Test (if applicable) | X (Before radiation simulation) | | | | | |
| **IMAGING** | | | | | | |
| CT Abdomen & Pelvis (within 30 (+ 14) days for screening scan)[2] | X | | X | X[1] (Months: 6, 12, 18, 24) | X[1] (Months: 36, 48, 60) | X[1] |
| MR Abdomen | X | | | X[1] (Months: 3, 9, 15, 21) | X[1] (Months: 30, 42, 54) | |
| PET Scan (Not Mandatory)[2] | X | | | X | | |
| Chest CT or CXR (within 30 (+ 14) days for screening scan)[2] | X[5] | | | X[1,3] | X[1,3] | X[1,3] |
| CT sim Abdomen **and/or** MR sim Abdomen for Radiation Planning | X | X[6] (weeks 2-5 if necessary) | | | | |
| **OTHER** | | | | | | |
| Adverse Event Evaluation (And as needed based on reporting requirements) | | X | X | X | | |
| Tissue for SMAD 4 Testing[4] | | X | X | | | |

1.Follow-up Imaging: CT Chest or CXR to be completed until disease progression. MR Abdomen and CT Abdomen and Pelvis are to be completed until disease progression. After disease progression, if CT Abdomen and Pelvis or MR Abdomen are still obtained as part of SOC, data will continue to be collected as available but is not required.

2.PET Scan: Not mandatory but suggested one month prior and 3 months' post. If the initial screening abdominal/pelvic CT falls out of window and a PET scan is subsequently performed, the PET can be used as the 30-day screening scan to confirm no metastatic disease in place of repeating the CT. Screening chest CT or CXR is optional if PET scan including chest has already been performed at this time point.

3.Follow-up Chest CT or CXR: Alternated every 3 months, however a CT is preferred. After year 5 the Chest CT or CXR is to be completed annually with the CT abdomen and pelvis.

4.SMAD 4 Testing: If possible- Pre-treatment and Post-treatment specimens obtained (if post-treatment surgery performed)

5.Optional if: PET scan including chest was already performed for this timepoint

6.CT/MRI SIM or MR SIM abdomen as clinical indicated, per MD discretion

**7.** Laboratory tests will be performed at the investigator discretion

## APPENDIX III

## ZUBROD PERFORMANCE SCALE

| | |
|---|---|
| **0** | **Fully active, able to carry on all predisease activities without restriction** |
| **1** | **Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work** |
| **2** | **Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours** |
| **3** | **Capable of only limited self-care, confined to bed or chair 50% or more of waking hours** |
| **4** | **Completely disabled. Cannot carry on self-care. Totally confined to bed** |
| **5** | **Death** |

**APPENDIX IV**

**AJCC STAGING SYSTEM**

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

**EXOCRINE AND ENDOCRINE PANCREAS**

**Primary Tumor (T)**

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ**
T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3 **Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery**
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification.

**Regional Lymph Nodes (N)**

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

**Distant Metastasis (M)**

M0 No distant metastasis
M1 Distant metastasis
*This also includes the "PanInIII" classification

## *Stage Grouping*

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage III | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

## APPENDIX V

### Dual Phase Pancreatic Imaging Protocol

Dual phase pancreas CT protocol using iodinated intravenous contrast will be obtained at 2.5- or 3-mm slice thickness and, if possible, reconstructed to 1.25- or 0.625 mm slice thickness in addition to the 2.5-mm sections or 1.5- and 0.75-mm slice thickness in addition to the 3-mm sections. The two phases are during the phase of peak pancreatic enhancement and during portal venous enhancement and will be obtained of the entire abdomen. If CT cannot be obtained because of allergy to iodinated contrast, gadolinium-enhanced MRI will be utilized of the entire abdomen utilizing T1-, T2- and dynamically obtained T1-weighted sequences at a slice thickness of maximally 7 mm. If patient has history renal insufficiency or renal failure, and calculated GFR within 14 days prior to CT or MRI is < 30, non-contrast MRI will be utilized with T1- and T2-weighted sequences with a slice thickness not to exceed 7 mm. If MRI cannot be obtained (i.e., implanted electronic devices), unenhanced 2.5- or 3-mm sections of the abdomen will be obtained by CT without intravenous contrast.

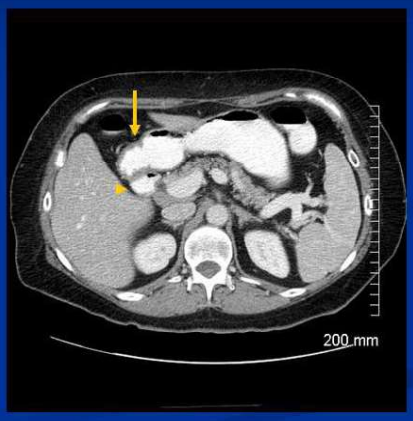
**The timing of imaging after contrast administration**: **Bolus Tracking Technique**
The timing varies between the 16 and 64 detector scanners. For example, imaging of the entire abdomen during the pancreatic parenchymal phase, in a normal patient with normal cardiac circulation time, on a 16 would approximately begin at 36 seconds after the start of contrast injection and finish at 46 seconds. On the 64, it would begin at 40 seconds, and end at 45 seconds. (The pancreas is imaged during the same time period for both — note both terminate at 45–46 seconds). The second phase is at 60 seconds after the start of injection depending on the scanner (60 for 16) in a normal patient.

A standard commercially available intravenous bolus tracking technique **is recommended for use** to control for variations in cardiac circulation time to ensure that images are obtained during the correct phases of contrast enhancement. As is standard practice, a cursor is placed in the aorta at the level of the origin of the celiac axis and is used to detect when contrast arrives in the abdominal aorta and raises the density value to 100 Hounsfield units. The 16 detector row scanner is instructed to begin scanning 16 seconds after that level is reached. Scanning of the abdomen is completed within 10 seconds, and after a subsequent 14 second delay, the abdomen is imaged again during the portal venous phase. In a normal patient, scanning of the abdomen during the first phase would begin 36 seconds after the start of contrast injection, and scanning of the second phase would begin 60 seconds after contrast injection.

In contrast, the 64 detector row scanner is instructed to begin 20 seconds after the 100 HU threshold is reached. Scanning of the abdomen is completed within five seconds, and after a subsequent delay of 15 seconds, the abdomen is imaged again during the portal venous phase. In a normal patient, scanning of the abdomen during the first phase would begin 40 seconds after the start of contrast injection, and scanning of the second phase would begin 60 seconds after contrast injection. The differences in timing between the 16 and 64 detector scanner are designed so that imaging of the pancreas during the first phase is finished at approximately 45–46 seconds after the start of contrast injection.

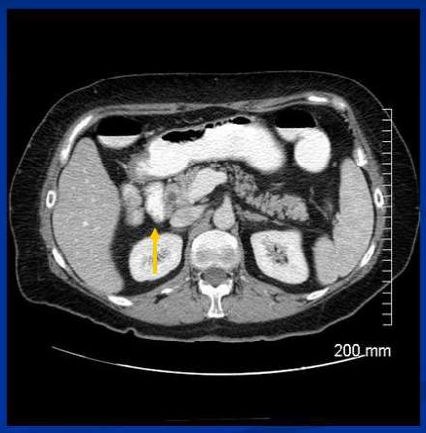
## Duodenal Anatomy

- The thin wall of the duodenal bulb (arrow head) can readily be distinguished from the much thicker gastric wall in the region of the pylorus (arrow).



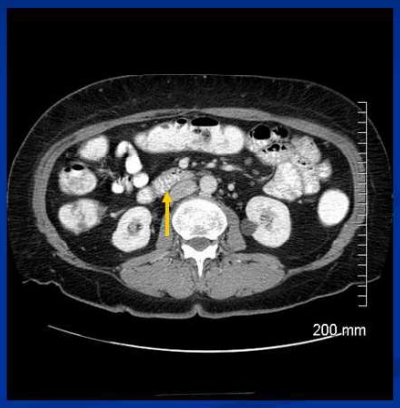

## Duodenal Anatomy

- The second portion of the duodenum then descends inferiorly (arrow).



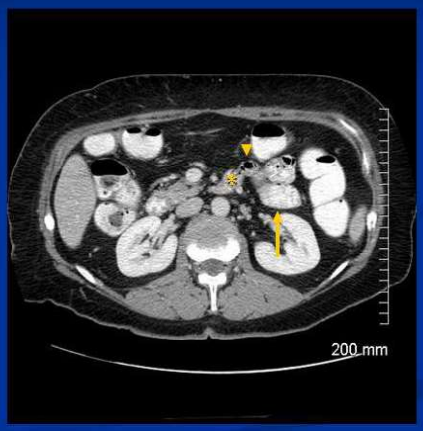
## Duodenal Anatomy

- The third portion of the duodenum (arrow) crosses midline posterior to the superior mesenteric artery and vein.




## Duodenal Anatomy

- The fourth portion of the duodenum (asterisk) ascends to the ligament of Treitz (arrow) and becomes the jejunum (arrow head).



## Appendix VII-Glossary of Terms

($MLQED_2$)-MLQ equivalent dose in 2 Gy fractions
3DCRT-Three-dimensional conformal radiation therapy
4DCT-Four-dimensional computed tomography
5FU-5- fluorouracil
ADC-apparent diffusion coefficient
AE-adverse events
AIDS-acquired immune deficiency syndrome
ART-adaptive radiation therapy
BED-biologically equivalent dose
CFRT-conventionally fractionated radiation therapy
cGy-centigray
CPR-continuing progress report
CR-complete responses
CRT-chemoradiation
CTC AE-Common Terminology Criteria for Adverse Events
CT-computed tomography
CTV-Clinical target volume
DLT-dose-limiting toxicity
DSMB -Data Safety Monitoring Board
DWI-diffusion-weighted imaging
ECOG-Eastern Cooperative Oncology Group
FOLFIRINOX- FOL (folinic acid), F (fluorouracil) (5-FU), IRIN ( irinotecan) OX (oxaliplatin)
GERCOR-Groupe Coopérateur Multidisciplinaire en Oncologie
GFR-glomerular filtration rate
GITSG-GI tumor study group
GTV-gross tumor volume
Gy-Gray
IGRT-image-guided radiation therapy
IMRT- intensity-modulated radiation therapy
IRB-internal review board
ITV-internal target volumes
KV conebeam CT-kilovoltage CAT scan
MLQ-modified linear quadratic equation
MRI-magnetic resonance imaging
MU-monitor unit
MV CT-megavoltage CT
NTCP-normal tissue complication probability
PET –Positron Emission Tomography
PR-partial responses
PTV-Planning Target Volume
QUANTEC-Quantitative Analysis of Normal Tissue Effects in the Clinic
R&V system-record and verify system
RECIST- Revised Response Evaluation Criteria in Solid Tumors
RTOG-Radiation Therapy Oncology Group
RT-radiation therapy
SBRT-stereotactic body radiation therapy
SD-stable disease
SAE-serious adverse events
SIB-simultaneous integrated boost
SMA-superior mesenteric artery
SMF -Streptozocin, Mitomycin, and 5-FU
SMV-superior mesenteric vein
$TD_{50}$-the dose corresponding to 50% complication probability for a uniformly irradiated whole organ