Title: Phase I/II Study of Neoadjuvant Accelerated Short Course Radiation Therapy With Proton Beam and Capecitabine for Resectable Pancreatic Cancer

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Dana Farber / Harvard Cancer Center:
Massachusetts General Hospital, Dana Farber Cancer Institute

Phase I/II Study of Neoadjuvant Accelerated Short Course Radiation Therapy with Proton Beam and Capecitabine for Resectable Pancreatic Cancer

Study Treatment:
Proton Beam Radiotherapy
Capecitabine
Pancreatectomy

Support Provided By:
PO-1
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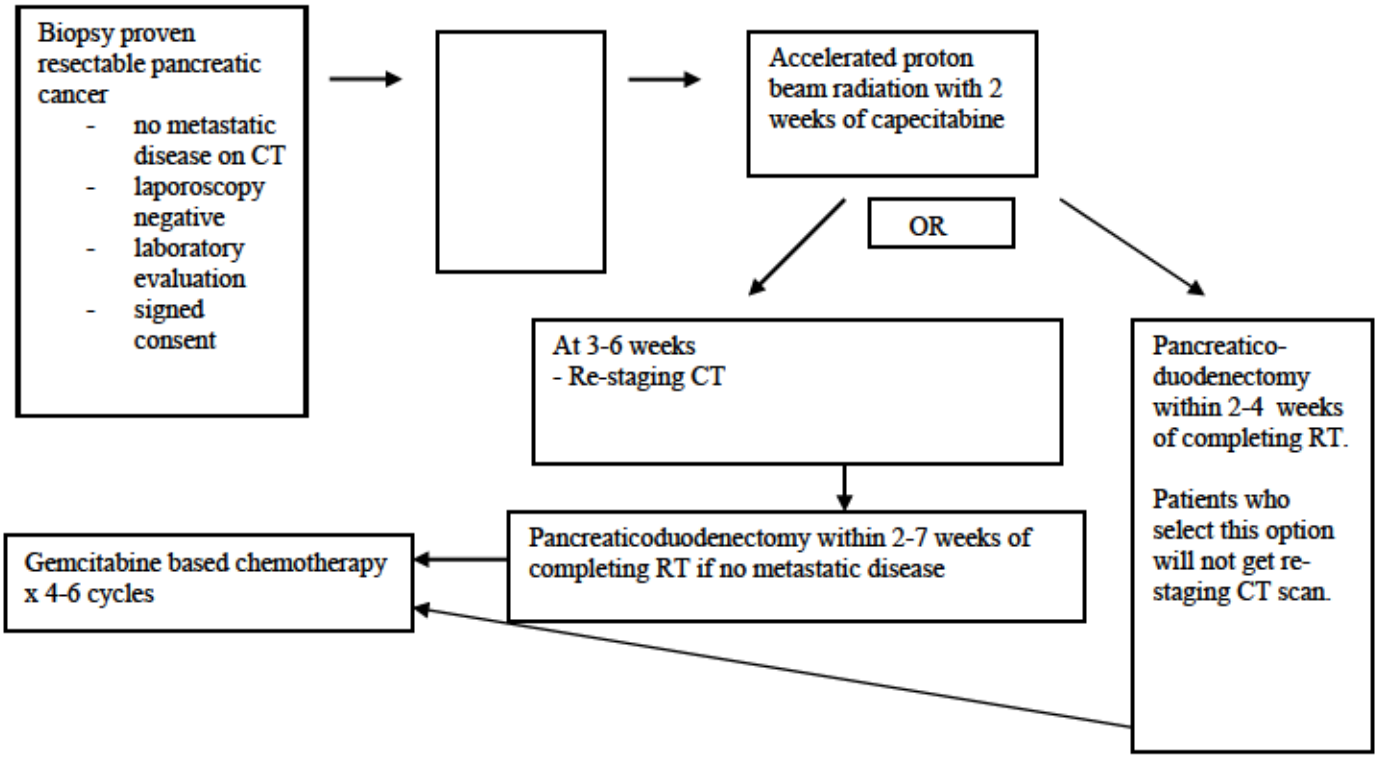
SCHEMA

Phase I/II Study of Neoadjuvant Accelerated Short Course Radiation Therapy with Proton Beam and Capecitabine for Resectable Pancreatic Cancer with 18F-labeled-fluorothymidine Positron Emission Tomography Bioimaging



Phase I: 3 patients per level, 6 patients at level 4
Phase II: 25 patients at MTD

Radiation Acceleration Schema (Dose Levels):
Days 1-14:
Proton Beam Radiation will be delivered in a progressively accelerated as below:

Dose Level	**Lead-in Phase**	**Dose/fraction**	**# Tx**	**Fractionation Schedule**	**Total Dose**	**Week 1 Schedule**	**Week 2 Schedule**	**Total Days**
1	1	3 CGE	10	QD	30	M T W Th Fri	M T W Th Fri	12
	Step 2	**Dose/fraction**	**# Tx**	**Fractionation Schedule**	**Total Dose**	**Week 1 Schedule**	**Week 2 Schedule**	**Total Days**
2	1	5 CGE	5	QD	25	M W F	T Th	11
3	2	5 CGE	5	QD	25	M T Th Fri	M	8
4	3	5 CGE	5	QD	25	M T W Th Fri	-	5

Capecitabine will be administered orally daily in two divided doses. The dose of capecitabine is fixed at 825 mg/m^2 PO BID for a total of 10 days (M-F) 2 weeks.

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1.0 Objectives

1.1 Primary

1.1.1 Phase I: To determine the feasibility and tolerability of radiation therapy delivered with proton beam in a one week accelerated schedule with concurrent capecitabine for pancreatic cancer.

1.1.2 Phase II: To demonstrate a grade 3 or greater (any) toxicity rate of less than 20%.

1.2 Secondary:

1.2.1 To determine the complete pathologic response rate of preoperative capecitabine and proton beam radiation therapy in patients undergoing pancreaticoduodenectomy.

1.2.2 To determine the progression-free survival in patients treated with preoperative capecitabine and proton beam radiation therapy.

1.2.3 To determine the toxicity of capecitabine and proton beam radiation therapy in patients with pancreatic cancer.

1.2.4 To determine the surgical morbidity in patients undergoing pancreaticoduodenectomy who received preoperative capecitabine and external beam radiation therapy.

1.2.5 To determine 30-day post-operative mortality after pancreaticoduodenectomy in patients who receive preoperative capecitabine and external beam radiation therapy.

2.0 Background

2..1 Neoadjuvant Therapy

Prospective and retrospective data suggest that compared with surgery alone, the combination of pancreaticoduodenectomy with postoperative fluorouracil (5-FU) and external-beam radiation therapy (EBRT) improves survival duration and local-regional control.[1,2] However, the morbidity and often prolonged recovery time associated with pancreaticoduodenectomy prevent the timely delivery of postoperative chemotherapy and EBRT in at least 20% of eligible patients.[3] The risk of delaying postoperative adjuvant chemoradiation has prompted investigators to assess the efficacy of chemotherapy and EBRT before pancreaticoduodenectomy in patients with potentially resectable adenocarcinoma of the pancreas. Several considerations support the use of preoperative chemotherapy and EBRT. First, positive gross or microscopic margins of resection along the right lateral border of superior mesenteric artery (SMA) are common following pancreaticoduodenectomy, suggesting that surgery alone may be an inadequate strategy for local tumor control.[4] Second, because chemoradiation is given before surgery, delayed postoperative recovery does not affect the delivery of multimodality therapy. Third, patients with disseminated disease evident on restaging studies after chemoradiation are not subjected to an unnecessary laparotomy as surgery would not benefit these individuals.

Studies from the MD Anderson Hospital first used a standard-fractionation treatment schema of preoperative chemoradiation and pancreaticoduodenectomy.[5-8] Radiation therapy was delivered 5 days/week over 5.5 weeks delivering a total dose of 50.4 Gy in 28 fractions. 5-FU was given concurrently by continuous infusion at a dosage of 300 mg/m2 per day, 5 days per week, through a central venous catheter. Thirty-eight patients were evaluable for analysis of patterns of treatment failure; 1 perioperative death occurred. Tumor recurrence was

documented in 29 patients: 8 recurrences (21%) were local-regional (in the pancreatic bed and/or peritoneal cavity), and 30 (79%) were distant (in the lung, liver, and/or bone). The liver was the most frequent site of tumor recurrence, and liver metastases were a component of failure in 53% of patients (69% of all patients who had recurrences). Isolated local or peritoneal recurrences were documented in only 4 patients (11%). In contrast, previous reports of pancreaticoduodenectomy alone for adenocarcinoma of the pancreas documented local recurrence in 50 to 85% of patients.[9, 10] The improvement in local-regional control with preoperative chemoradiation was seen even though 14 of 38 evaluable patients had undergone laparotomy with tumor manipulation and biopsy prior to referral for chemoradiation and reoperation. Excluding these 14 patients, local or peritoneal recurrence was a component of treatment failure in only 2 patients (8%). However, this 5.5-week chemoradiation program was associated with gastrointestinal toxicity (nausea, vomiting, and dehydration) that required hospital admission of one third of patients. Moreover, in an ECOG trial evaluating preoperative chemoradiation for pancreatic cancer patients, 51% of patients required hospital admission for toxicity of treatment during or within 4 weeks after completing chemoradiation.[11]

These findings prompted a change in the delivery of preoperative chemoradiation at the MD Anderson in favor of short course EBRT. In a series of prospective trials, investigators at MD Anderson treated 60 patients with either preoperative standard course RT at a total dose of 50.4 Gy (1.8 Gy/Fraction, 28 fractions, 5 days/week), short course RT at a total dose of 30 Gy (3 Gy/fraction, 10 fractions, 5 days/week), or postoperative standard course RT at a total dose of 50.4 Gy.[12] 5-FU was given concurrently by continuous infusion 5-FU at a dosage of 300 mg/m2 per day, 5 days/week. This short course chemoradiation program was designed to avoid the gastrointestinal toxicity seen with standard-fractionation chemoradiation (5.5 weeks) while attempting to maintain the excellent local tumor control achieved with multimodality therapy. As with other neoadjuvant treatment schemas, restaging with chest radiography and abdominal CT was performed 4 weeks following completion of chemoradiation in preparation for pancreaticoduodenectomy. The short course RT was associated with fewer grades 3 toxicity than standard course RT (7% vs 19%). No difference in efficacy could be ascertained as no patient treated with preoperative chemoradiation who underwent R0 resection experienced a local recurrence.

More recently, data from 132 consecutive patients who received preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas also supported the use of rapid-fractionation chemoradiation.[13] Forty-four patients received standard fractionation (45-50 Gy, 1.8 Gy/fraction/day) EBRT and 88 patients received short course EBRT (30 Gy, 3 Gy/fraction per day). The median overall survival from the time of tissue diagnosis was 21 months. Survival duration was not influenced by the dose of preoperative EBRT and chemotherapy used. The data suggested that short course chemoradiation (30 Gy in 2 weeks) combined with pancreaticoduodenectomy performed on accurately staged patients might be equivalent to standard-fractionation chemoradiation (45-50 Gy in 5-6 weeks).

2.2 Capecitabine and Radiation Therapy

Capecitabine is a rationally designed oral fluoropyrimidine.[14, 15] given its lack of a need for an implantable access device or portable infusion pump and patient convenience, it has become an attractive agent to be combined with radiation therapy. Capecitabine undergoes three steps of enzymatic activation before converting to the active

drug. It is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxyesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase . Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues. Capecitabine is rapidly and extensively absorbed with the peak plasma concentrations for the drug and its two main metabolites occurring shortly (0.5 - 1.5 hours) after administration. Then concentrations decline exponentially with a half-life of 0.5 - 1 hour. Plasma concentrations of the cytotoxic moiety 5-FU are very low.

Capecitabine is generally well tolerated. Major side effects include diarrhea, nausea, hand-and-foot syndrome, vomiting, fatigue, and stomatitis. The most frequent grade 3 or 4 laboratory abnormality was elevated total bilirubin and alkaline phosphatase, or abnormal liver function tests. Myelosuppression has been rarely reported (< 2%).

Its role as a radiosensitizer has been most studied in rectal cancer. Dunst et al reported the results of a phase I study using capecitabine in T3 and T4 rectal cancer.[16] Thirty-six patients with rectal cancer received treatment in the adjuvant, neoadjuvant, or palliative setting with a total radiation dose of 50.4 Gy. Capecitabine was administered at escalating doses from 250 to 1,250 mg/m^2 twice a day concurrently with radiation. They were able to escalate the capecitabine dose to 825 mg/m^2 twice a day. Dose-limiting grade 3 hand-and-foot syndrome was observed in two of six patients treated at 1,000 mg/m^2 bid. Other toxicities were generally rare and/or mild. One pathologic complete remission of a T3N1 tumor and nine partial remissions were observed in 10 patients treated in the neoadjuvant setting. In another study, capecitabine was administered concurrently with radiotherapy in locally advanced rectal cancer.[17] The treatment consisted of 2 cycles of 14-day oral capecitabine (825 mg/m^2 BID) and leucovorin (10 mg/m^2 BID), each of which was followed by a 7-day rest period. The overall downstaging rate, including both primary tumor and nodes, was 84%. A pathologic complete response was achieved in 31% of patients. Twenty-one patients had tumors located initially 5 cm or less from the anal verge; among the 18 treated with surgery, 72% received sphincter-preserving surgery. Grade 3 toxicities included hand-foot syndrome (7%), fatigue (4%), diarrhea (4%), and radiation dermatitis (2%). NSABP is planning a prospective randomized trial to compare capecitabine with infusional 5-FU in patients undergoing preoperative radiation therapy. Preliminary results from a trial combining capecitabine with radiation therapy in patients with locally advanced pancreatic cancer demonstrated the combination to be safe and tolerable at a dose of 825 mg/m2 twice daily.[18]

2.3 Proton Beam Radiation Therapy

There have been unprecedented efforts in radiation oncology to develop and use sophisticated, conformal photon techniques in order to improve the outcome for cancer patients. The aim of these new techniques is to concentrate the radiation dose distribution more completely on the disease target, thereby sparing critical normal tissues and increasing the target dose. Toward this end, many advances have been made and examples of new developments include Tomotherapy and intensity modulated photon therapy. At the same time, heavy, charged-particle programs, particularly those for proton therapy, have been developed. Proton therapy dose distributions are

superior to those of photon therapy and this provides the potential to further improve clinical outcomes. Several institutions have committed to build dedicated proton therapy centers such as the Francis H. Burr Proton Therapy Center (FHBPTC) at the Massachusetts General Hospital (MGH) and the Loma Linda University Medical Center proton therapy facility. Several more proton therapy centers are in the final planning stage.

2.3.1 The Advantages of Protons for Delivery of Conformal Therapy

Characteristics of Proton Beams

The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different (see Figure O-1). Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) - known as the Bragg peak (see the curve labeled "unmodulated proton beam" in Figure O-1). In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40 percent of the maximum dose.

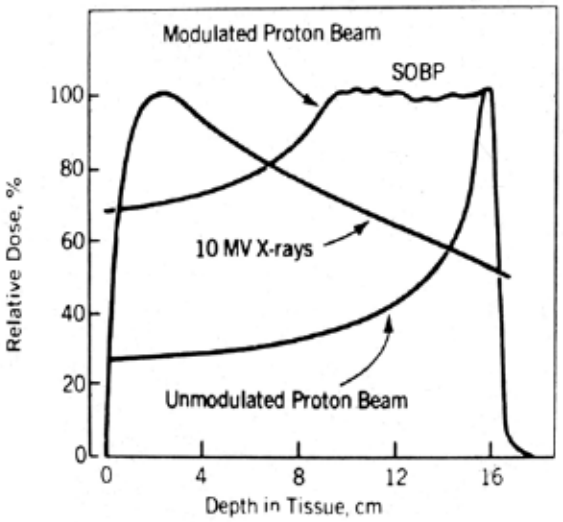


Figure O-1. Proton (Bragg peak and modulated Peak) and 10 MV depth dose curves.

The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated - several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peaks" (SOBP). This is shown in Figure O-1 as the “modulated proton beam”.

For comparison, Figure O -1 also shows the depth-dose curve for a 10 MV x-ray beam, an x-ray energy commonly used to treat deep seated tumors. Note that the x-ray beam dose rises to a maximum value at relatively shallow depths, then falls off exponentially to lower doses at the treatment depth. A clinical comparison of single-beam proton and photon beams is shown in Figure O-2 where a single posterior beam is used for the treatment of the spinal axis in the treatment of medulloblastoma. Note that, for the photon treatment, the heart, mediastinum, esophagus, lung and spinal cord are irradiated by the treatment beam whereas for the proton treatment, the beam stops abruptly distal to the target volume and there is no irradiation of the tissues and organs distal to the target volume.

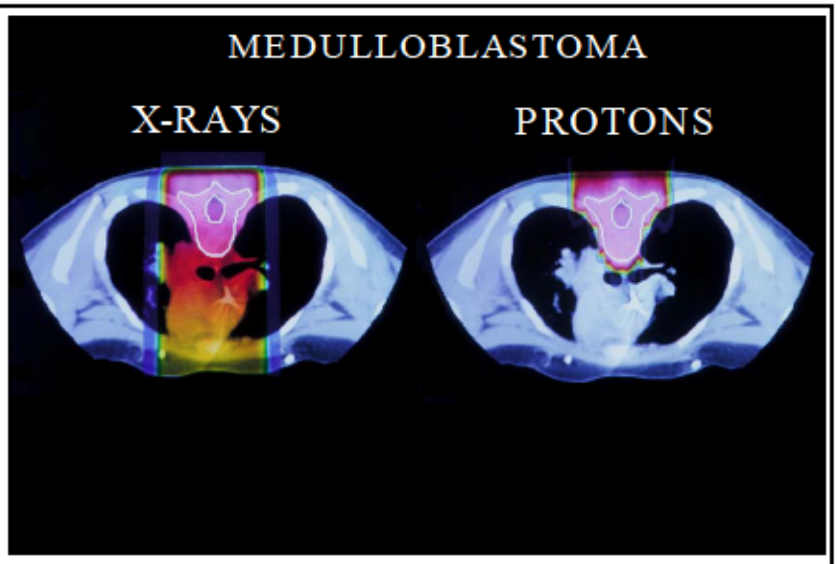


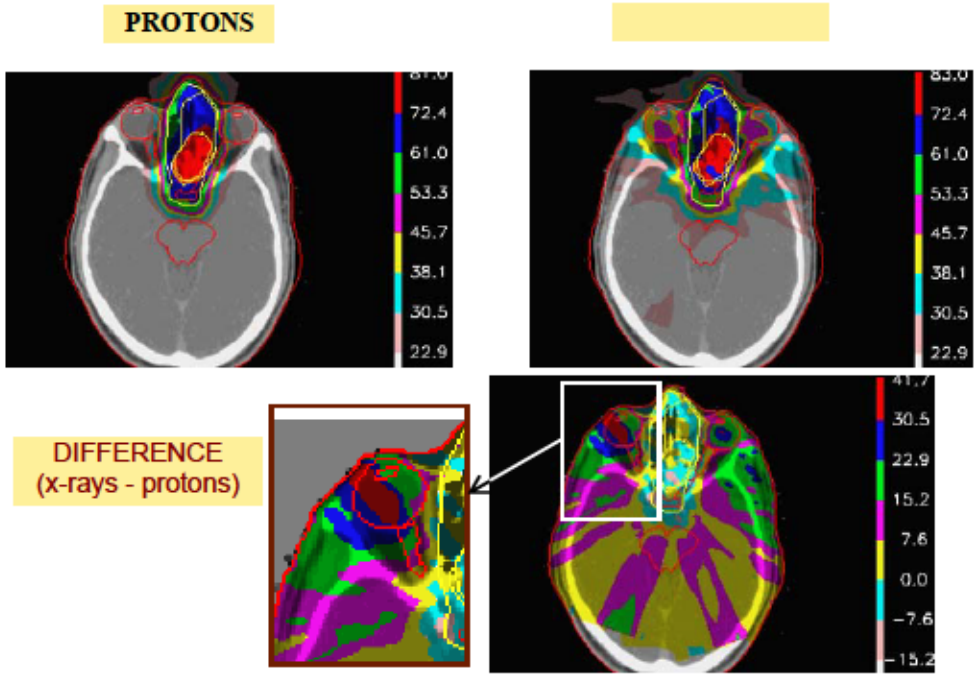
Figure O-2. Posterior, single-beam treatment of the spinal axis.

In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments. However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams or complex beam arrangements. In modern proton therapy facilities, which have isocentric gantries and sophisticated beam delivery and control systems, proton therapy capabilities are equivalent to those for state-of-the-art, conformal therapy using x-rays with respect to numbers of beams, beam directions and complex delivery techniques such as intensity modulation.

Intensity Modulated Radiation Therapy

Intensity-modulated x-ray therapy (IMXT) – the use of x-ray beams each of which is purposely made non-uniform over its cross-section – provides a new degree of freedom in treatment delivery and can lead to more conformal dose distributions. Protons, too, can be used in an intensity modulated mode (IMPT) similar to that for

Figure O-3: Paranasal sinus tumor treated with IMPT (left) and IMXT (right). Dose difference distribution below.



photons and, in an additional degree of freedom, are also made non-uniform in depth. The advantage that single beams of protons have over single beams of x-rays, which is maintained when multiple cross-firing beams of uniform intensity are employed, is similarly maintained when intensity modulation is employed.

In IMXT, the dose can be made to conform to the target volume while avoiding selected adjacent sensitive structures (although the dose uniformity within the target volume is strongly influenced by such selective avoidance and is often of undesirable magnitude). However, IMXT does not reduce the integrated dose delivered outside the target volume (as compared to standard conformal photon therapy); it only, in general, spreads that energy out over a larger volume. In our treatment planning intercomparisons (in nasopharynx, paranasal sinus, lung and Ewing's sarcoma) we have found that the integral dose for IMPT is a factor of two (on the average) less than for IMXT. Moreover, whatever improvement IMXT achieves over standard conformal x-ray therapy, a comparable improvement is achieved when IMPT is compared to standard conformal proton therapy.

Figure O-3 demonstrates the above points. It is a comparison of two IMRT plans, one with x-rays and one with protons, designed to treat a paranasal sinus tumor (with three target volumes receiving 76, 66, and 56 Gy, respectively). The two plans were subject to identical dose constraints on normal tissues. The proton dose distribution (left) is clearly excellent; the photon distribution on the right is also very good. However, the presentation of the dose in the top panels does not adequately reveal the significant differences between the two distributions. The lower panels show the dose difference between the plans. X-rays deliver an additional "bath" of from 5 to 15 Gy throughout the brain and, in the region of the right eye (which is magnified in the lower left), up to 40 Gy more than the protons. (The constraint on the right eye's retina was 50 Gy; had it been reduced, x-rays could certainly have reduced the dose in that region – but at the price of increased dose elsewhere and, perhaps, of greater non-uniformity of dose in the target volumes.)

Pancreatic tumors also have a number of normal structures in close proximity that have limited radiation tolerance including kidneys, liver, spinal cord and stomach. The lack of exit dose from proton beam radiation can allow for reduced dose to these and other normal tissues

2.4 Rationale for Short Course Radiation Therapy

2.4.1 Projected clinical efficacy

The role of neoadjuvant and adjuvant radiation therapy for resectable pancreatic cancer is to improve locoregional control by sterilizing microscopic disease that may not be removed with surgery. Hence, there may not be a clear benefit to higher doses of radiation therapy in this setting. This is supported by the MD Anderson experience (see 2.1), which suggest that short course chemoradiation (30 Gy in 2 weeks) combined with pancreaticoduodenectomy performed on accurately staged patients may be equivalent to standard-fractionation chemoradiation (45-50 Gy in 5-6 weeks). [13]

The schedule of 5 Gy x 5 has been extensively tested in rectal cancer in numerous randomized European clinical trials[19-21]. These trials demonstrated that the regimen is very tolerable with an associated improvement in local control. Bujko and colleagues formally compared 5 Gy x 5 vs. conventional chemoradiation to 50.4 Gy with 5-FU chemotherapy for low-lying rectal cancers in a randomized trial and did not find a difference in rates of sphincter preservation[21]. Local control was not reported in this early analysis.

A schedule of 25 Gy in 5 fractions of 5 Gy has a similar anticipated efficacy to the 30 Gy schedule mentioned above. Using linear-quadratic formulation[22], the tumor effect of the 25 Gy should be almost equivalent to the 30 Gy schedule.

Table 1 Efficacy Comparison of conventional, MD Anderson Short Course, and proposed schedule

Schedule	Dose/fraction	# Tx	Total Dose	*B.E.D (Gy) (no time correction)	**N.T.D (Gy) (no time correction)	*B.E.D. (Gy) (time correction)	**N.T.D. (Gy) (time correction)
Conventional	1.8 Gy	28	50.4	50.4	59.5	46.8	39
MDACC	3 Gy	10	30	39	32.5	39	32.5
MGH Proton	5 CGE***	5	25	37.5	31.3	37.5	31.3

*B.E.D. – Biologically equivalent dose
**N.T.D. – Normalized Total Dose, or equivalent physical dose if delivered in 2 Gy fractions.
*** CGE – Cobalt Gray Equivalent, assuming a Relative Biological Effectiveness of 1.1.

No repopulation (no time correction):

$B.E.D = nd(1+d/\alpha/\beta)$

With repopulation (time correction):

$B.E.D = nd(1+d/\alpha/\beta) - (T-T_k)(\ln 2/(\alpha T_{pot}))$

Where:

n = number of fractions
d = dose per fraction
nd = total dose
T = total time of treatment in days
T_k = time after start of treatment repopulation begins
T_{pot} = potential doubling time

Assuming:

$\alpha/\beta = 10$
$\alpha = 0.35$ T = assuming treatment starts on a Monday with no breaks during treatment
T_k = 28 d
T_{pot} = 5 days

$N.T.D. = B.E.D./ (1+2/\alpha/\beta)$

As can be seen in Table 1, the reason for similar clinical outcomes between a conventional schedule and the MD Anderson 30 Gy short course may be due to both the larger fraction size and shorter treatment time. Similarly, in looking at the 25 Gy schedule, one would expect very similar clinical efficacy.

2.4.2 Projected clinical toxicity

With alteration of a radiation schedule, there is always concern that the toxicity of treatment may increase. However, when investigators at MD Anderson moved from a conventional schedule to a short course, the clinical tolerability in fact improved. Furthermore, with larger fraction sizes, there is also a concern for increased late effects. Using linear-quadratic formulation, the risk for late effects appears to be lower for late effects than with a conventional schedule.

Table 2

Late Effect Comparison of conventional, MD Anderson Short Course, and proposed schedule ($\alpha/\beta = 3$)

§Schedule	Dose/fraction	# Tx	Total Dose	B.E.D (Gy)	**N.T.D. (Gy)
Conventional	1.8 Gy	28	50.4	80.6	48.4
MDACC	3 Gy	10	30	60	36
MGH Proton	5 CGE	5	25	66.7	40

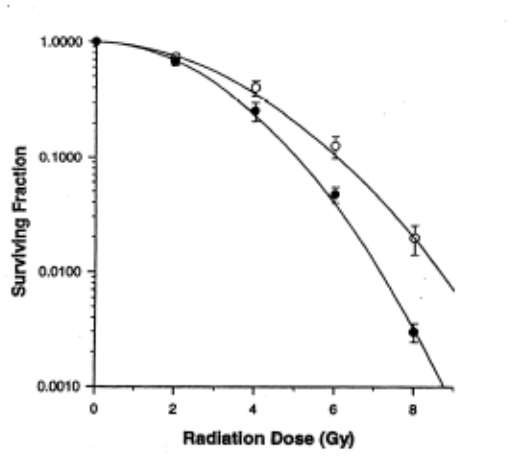
For the above mentioned randomized trial for low-lying rectal cancers comparing conventional fraction with 5 Gy x 5, an analysis of perioperative complications was also performed[23]. There were no differences in the rates of complications or in severe complications. These results suggest that there should not be an increase in surgical complications with this schedule.

Recommended dose limits for both acute and late effects can be adjusted for the accelerated schedule. However, the fewer number of fractions render the constraints significantly more stringent. With protons, greater dose conformality can be achieved. It is the goal of this protocol to demonstrate the feasibility and tolerability of the 5 CGE x 5 regimen for pancreatic cancer.

2.4.3 Hypofractionation and radiosensitization with capecitabine

Radiation therapy has been conventionally in 1.8-2 Gy fractions. However, for a wide variety of putative radiosensitizers and cell lines, radiosensitization is not seen until larger fraction sizes. For example, as study from MD Anderson cancer center assessing the 5-FU-radiation interactions in human colon adenocarcinoma cells did not show significant radiosensitization at 2 Gy/fraction but did at 4 and 6 Gy/fractions[24].

Figure O-4 Increased radiosensitization with larger fraction sizes with 5-FU



From Buchholz DJ (ref 24) Radiation survival curves for plateau phase Clone A cells irradiated on ice with between 2 and 8 Gy with x-rays with (solid circles) or without (empty circles) 5 FU.

Others have generated similar survival curves demonstrating greater radiosensitization with larger fraction size with 5-FU[25, 26] . This phenomenon has also been demonstrated with other radiosensitizers including but not limited to cetuximab[27] and HDAC inhibitors[28]. The 5 Gy fraction size is particularly of interest when used with capecitabine in light of the study by Sawada and colleagues[29]. In this study, 5 Gy of x-ray irradiation in several human cancer xenografts produced upregulation of thymidine phosphorylase, the key enzyme in converting the capecitabine to 5-FU in tumors. These investigators correspondingly found that 5 Gy combined with capecitabine had greater anti-tumor effect than even 5 Gy with 5-FU. Figure O-5 below summarizes their results.

Figure 5

Antitumor activity of the combination of X-ray irradiation and fluoropyrimidines on the growth of WiDr human colon cancer xenograft in nude mice[29].

Drug mg/kg/day (mmol/kg/day)		Radiation	Efficacy after 3 weeks of treatment (on day 21) Tumor volume change (mm^3), Mean ± SD	% of tumor growth inhibition	Carcass body weight (g) Mean ± SD	$T_{2.5}$ (day)	Growth delay[a] (day)
Vehicle		−	700 ± 147	−	22.3 ± 1.7	12.6	−
Capecitabine	539 (1.5)	−	391 ± 176[b]	44	21.2 ± 2.8	21.4	8.8
5'-dFUrd	185 (0.75)	−	567 ± 95[c]	19	21.0 ± 1.2	14.8	2.2
5-FUrn	19.5 (0.15)	−	568 ± 100[c]	19	21.6 ± 1.6	14.6	2.0
Vehicle		+ 5 Gy	300 ± 103[b]	57	23.3 ± 3.0	23.8	−
Capecitabine	539 (1.5)	+ 5 Gy	−77 ± 47[b–d]	111	22.1 ± 1.6	>42.0	>18.2
5'-dFUrd	185 (0.75)	+ 5 Gy	53 ± 55[b,d]	92	20.2 ± 2.2[b]	39.7	15.9
5-FUrn	19.5 (0.15)	+ 5 Gy	247 ± 139[b,d]	65	20.1 ± 2.1	26.3	2.5

[a] Difference in the $T_{2.5}$ day between each fluoropyrimidine-treated group and its respective vehicle control.
[b] Significantly different from the vehicle group; $P < 0.05$ by the Mann-Whitney U test.
[c] Significantly different from the group treated with radiation alone; $P < 0.05$ by the Mann-Whitney U test.
[d] Significantly different from the group treated with fluoropyrimidine alone; $P < 0.05$ by the Mann-Whitney U test.

It remains unknown if this increased radiosensitization with larger fraction sizes will be seen in patients with pancreatic cancer. However, it is unlikely to be less than seen with conventional fractionation.

2.4.4 Patient and societal cost with short course proton beam therapy.

With the application of any new technology, patient and societal costs must be considered. The benefit to the patient is simple- fewer visits for radiation therapy. As long as the side effect profile is not greater than with conventional therapy, the patient will spend less time traveling for radiation therapy and subsequently greater quality

of life in that time not directly related to cancer care. This decrease of treatment time by over a month is important for a group of patients who has a median survival of only 20 months.

Even with the use of proton beam, the proposed schedule appears to be cost effective. To assess this issue, we accumulated radiation-related reimbursement for patients with pancreatic cancer based on the 2006 Medicare Fee schedule. 4 IMRT and 5 3D patients were averaged for their respective columns. Estimated proton schedule was based on patients treated on the proton accelerated partial breast protocol. These findings are summarized in Table 3.

Table 3

Summary of professional and technical costs for three radiation treatment regimens based on the 2006 Medicare Fee Schedule.

	CPT Code	3D-CRT 50.4 Gy	IMRT 50.4 Gy	Proton 25 Gy
Professional Costs				
Clinical	77263	1	1	1
IMRT Plan	77301		1	
Simulation:	77280	1	1	1
Therapeutic	77295	1		1
Basic radiation	77300	7	9	2
Isodose plan:	77315	1		
Treatment	77332			1
Treatment	77334	6	9	4
Weekly	77427	6	6	1
Special treatment	77470		1	
Consult:	99245	1	1	1
Total Professional		$2,600	$3,100	$1,200

	CPT Code	3D-CRT 50.4 Gy	IMRT 50.4 Gy	Proton 25 Gy
Technical Costs				
CT guidance for	76370	1	1	1
Simulation:	77280	1	1	1
Therapeutic	77295	1		1
Basic radiation	77300	7	9	2
IMRT plan	77301		1	
Isodose plan:	77315	1		
Treatment	77332			1
Treatment	77334	6	9	4
Radiation	77336	5	6	1
Radiation	77414	28		
IMRT treatment	77418		28	
Port film	77417	5	5	1
Special treatment	77470		1	
Proton treatment:	77523			5
Consult:	99245	1	1	1
Total Technical		$7,500	$13,700	$8,000
Overall Cost		$10,000	$16,700	$9,200

Comments: 4 IMRT and 5 3D patients averaged. Simulations will need to be clarified (only one complex sim was coded and IMRT patients did not have a 77295 coded – do not know if sim is included in a 77301) Blood collection from VAD and flu vaccination not considered. All patients assumed to have a level 5 initial consultation though this was routinely not coded. Also, cannot find fee for CPT code 99211 (weekly technical e & m). Weekly port films for IMRT patients averaged 3 (and were therefore undercoded) – for comparison, 5 has been used.

This cost analysts suggests that the proposed proton shortened schedule is at least as cost-effective as a conventional course of adjuvant radiation therapy.

2.5 Summary of Phase I Results and Determination of Phase II Dosing

The Phase I portion of this Phase I/II study completed accrual in September, 2008. All subjects enrolled in Phase I (n=15) have completed study treatment. Preliminary analysis of acute toxicity data demonstrates the most common toxicities were fatigue and nausea (both reported by 80% of subjects; all nausea events were grade 1; all fatigue events were grade 1 or 2). Pain was reported by 60% of the Phase I subjects, followed by anorexia reported by 47%. Other toxicities reported by 20% or more of the subjects included vomiting (33%), indigestion (27%) and diarrhea (20%). All of the above events were grade 1 or 2. There were six grade 3 events reported in the Phase I, occurring in four of the subjects. All grade 3 events were unrelated or unlikely related to study treatment. Grade 3 events included blocked biliary stents (2 events), elevated bilirubin (2 events), infection (1 event) and positional shoulder pain (1 event). There were no related adverse events or grade 4 or 5 toxicities.

The final dose level (level 4; 5Gy x 5 in 5 days) was achieved in the Phase I portion of the study without any dose limiting toxicities. Thus, this will be the planned dose level for the Phase II portion of the study.

2.5.1 Correlative Studies Background

The search for new biomarkers of response to short course neoadjuvant radiation will involve an examination of the molecular and genetic characteristics of tumor specimens. This analysis will begin with the primary tumor after the course of treatment and may also include analysis of the initial biopsy specimens. To characterize the tumors at the genetic level, mutational analysis of the treated tumor will be performed using a customized SNAPSHOT platform that examines the tumor for approximately 100 specific genetic mutations. We will also analyze DPC4, SDF1, CXCR4, IL-6, c-MET and SHH status of the tumor specimens. Tumor analysis studies will be conducted on the pancreaticoduodenectomy specimens and may also be conducted on the initial biopsy specimens.

In addition to tumor analysis, blood samples will also be evaluated to screen biomarkers in order to assess what effects radiation has in the blood. Blood will be obtained via venipuncture within two weeks prior to the start of chemo-radiotherapy and prior to surgery during routine clinical monitoring. Blood samples (approximately 1 teaspoon) will be collected in plasma EDTA (purple top) vacutainers. Plasma will be prepared in standard method by Steele Lab personnel under the supervision of Dan G. Duda, D.M.D., PhD and stored at -78 degrees Celsius until analysis. Following complete patient accrual, VEGF, PlGF, sVEGFR2, sVEGFR1, bFGF, SDF1α, IL-1, IL-6, IL-8, TNF-α, sICAM1, collagen IV and sVCAM1 levels will be measured.

3.0 Patient Eligibility.

3.1 Inclusion Criteria:

1 Cytologic of histologic proof pancreatic ductal carcinoma is required prior to treatment.

2. No evidence of metastatic disease as determined by chest CT scan, abdominal CT scan (or MRI with gadolinium and/or manganese), staging laparoscopy and all patients must be staged with a physical exam, chest CT, abdominal CT with intravenous contrast (or Abd MRI with gadolinium and/or manganese) and laparoscopy. Only potentially resectable patients are eligible. Potentially resectable is defined as: a). no extrapancreatic disease, b) no evidence (on CT) of involvement of the celiac axis or SMA, c) no evidence (CT or MRI) of occlusion of the SMV or SMPV confluence, and d)no evidence of distant metastases on staging laparoscopy.

3. Patients must be 18 years old or older. There will be no upper age restriction; patients with ECOG-4.Performance Status of 0 or 1 are eligible.

5. Women of childbearing potential must agree to practice adequate contraception and to refrain from breast feeding, as specified in the informed consent from time of study entry until 30 days after last chemotherapy. Female patients must have a negative pregnancy test within 7 days of treatment or be categorized as not of child-bearing potential. WOCP must agree to use adequate contraception and to refrain from breast feeding until 30 days after last chemotherapy.

6. Patients must sign a study-specific consent form, which is attached to this protocol.

7. Lab Values
ANC ≥ 1500 cells/mm3

Platelet count at least 100,000 cells/mm3.
AST and ALT ≤ 2.5 x upper limit of normal

Total Bilirubin ≤ 2.5 x upper limit of normal if patient is s/p biliary stenting

Total Bilirubin ≤ 1.5 x upper limit of normal if no biliary stenting was done

Serum Creatinine within normal range (0.6-1.5mg/dl)
Creatinine Clearance ≥ 30ml/min (as estimated by Cockroft Gault Equation):

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

3.1 Exclusion Criteria:

Patients who fulfill any of the following criteria will be excluded:

1. Tumors in the body or tail of the pancreas (to the left of the portal-SMV confluence) are not eligible. Location at the portal –SMV confluence is allowed.

2. Patients cannot have hepatic or peritoneal metastases detected by imaging or laparoscopy prior to chemoradiation. Patients with positive peritoneal cytology (from washings at the time of laparoscopy) will not be eligible.

3. Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator), such as significant cardiac or pulmonary morbidity, ongoing infection as manifested by fever.

4. Pregnant or lactating woman. Woman of childbearing potential with either a positive or no pregnancy test (serum or urine) at baseline. Woman / men of childbearing potential not using a reliable and appropriate contraceptive method. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential). Patients will agree to continue contraception for 30 days from the date of the last study drug administration

5. Life expectancy < 3 months.

6. Serious, uncontrolled, concurrent infection(s).

7. Any prior chemotherapy or radiation for treatment of the patient's pancreatic tumor.

8. Treatment for other carcinomas within the last five years, except cured non-melanoma skin and treated in-situ cervical cancer.
9. Clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months.
10. Other serious uncontrolled medical conditions that the investigator feels might compromise study participation.
11. Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome.
12. Known, existing uncontrolled coagulopathy.
13. Unwillingness to participate or inability to comply with the protocol for the duration of the study.
14. Any prior fluoropyrimidine therapy (unless given in an adjuvant setting and completed at least 6 months earlier).
15. Prior unanticipated severe reaction to fluoropyrimidine therapy, or known hypersensitivity to 5-fluorouracil or known DPD deficiency.
16. Participation in any investigational drug study within 4 weeks preceding the start of study treatment.
17. History of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance or oral drug intake.
18. Major surgery, excluding laporoscopy, within 4 weeks of the start of study treatment, without complete recovery.
19. Patients should not be on cimetidine as it can decrease the clearance of 5-FU. Another H2-blocker or proton pump inhibitor may be substituted before study entry.

4.0 Treatment

4.1 Capecitabine:

4.1.1 Description:

Capecitabine (Xeloda) is a commercially available fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine and has a molecular weight of 359.35.

Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20° C. Capecitabine is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg of capecitabine and each peach-colored tablet contains 500 mg of capecitabine. The inactive ingredients in capecitabine include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate, and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

4.1.2 Drug Administration:

The dose of capecitabine will be given orally 825 mg/m2 BID (total 1650 mg/m^2 per day) for a total of 10 days (M-F) 2 weeks. The first dose of capecitabine will start on the first day of radiation therapy. The dose of capecitabine will be fixed unless there are dose level reductions. The daily dose will be administered in two divided doses approximately 12 hours apart. The medication should be given within 30 minutes after the end of a meal or snack and swallowed with about 8 oz. of water. The dose of capecitabine will be calculated on the basis of milligrams of drug per square meter of body surface area (BSA).

Doses will be rounded to the nearest multiple of whole tablets. Capecitabine tablets are either 150 or 500 mg in size, so the dose given will be rounded to the nearest 150 mg tablet. The BSA will be rounded to the nearest tenth and the investigator will prescribe capecitabine according to the following chart. The dose of capecitabine will not exceed 2000mg po bid.
A drug diary will be provided to document appropriate administration.

Does Modifications: See section 8.2.

Table 4

Treatment with capecitabine will be given for a total of 10 days (M-F) 2 weeks.

BSA (m^2)	Dose BID (Total mg per dose)	500 mg tabs	150 mg tabs
1.0	800	1	2
1.1	1000	2	0
1.2	1000	2	0
1.3	1000	2	0
1.4	1150	2	1
1.5	1300	2	2
1.6	1300	2	2
1.7	1500	3	0
1.8	1500	3	0
1.9	1500	3	0
2.0	1650	3	1
2.1	1800	3	2
2.2	1800	3	2
2.3	2000	4	0
2.4	2000	4	0
2.5	2000	4	0

4.1.3 Storage and Stability:

Store at 25° C (77° F); excursions permitted to 15° to 30° C (59° to 86° F), keep bottles or storage devices tightly closed.

4.1.4 Ancillary Therapy:

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 on the flow sheets. Erythropoietin is allowed. Myeloid growth factors should not be used prophylactically but may be utilized to treat grade 4 neutropenia (ANC < 500) with or without fever.

4.1.5 Concomitant Medications:

Patients may receive all concomitant therapy deemed necessary to provide adequate support. No other cytotoxic therapy or radiotherapy may be used during therapy.

Capecitabine and some of its metabolites are converted principally by liver enzymes (carboxylesterase and cytidine deaminase and TP in tumor tissues). At present, it is unknown whether this metabolism is likely to be influenced by other treatments or alcohol, which either induce or inhibit certain liver enzymes.

Allopurinol: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

Sorivudine and Brivudine: A metabolite of the above two investigational antiviral agents, 5-bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Patients should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine. If a patient has received prior sorivudine or brivudine, then at least four weeks must elapse before the patient receives capecitabine therapy

Anticoagulants: See Warnings and Precautions Section 6.9 In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin: Increased phenytoin plasma concentrations have been reported during concomitant use of Xeloda® with phenytoin, suggesting a potential interaction. Patients taking phenytoin concomitantly with Xeloda® should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Laxatives: The use of drugs with laxative properties should be avoided.

4.1.6 Warnings and Precautions:

Renal Insufficiency: Patients with moderate renal impairment as measured by serum creatinine (> 1.3) **at baseline** require dose reduction. Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse events. Prompt interruption of therapy with subsequent dose adjustments will be made if a patient develops a grade 2 to 4 adverse event. Capecitabine is contraindicated in patients with a calculated creatinine clearance of < 30 ml/min. Creatinine level will be checked and creatinine clearance calculated on Study Day 8 for all subjects to ensure safety of continued administration of capecitabine.

Pregnancy/Nursing: Capecitabine may cause fetal harm when given to a pregnant woman. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. Because of the potential for serious adverse reactions in nursing infants from capecitabine, the patient will be instructed that nursing must be discontinued when receiving capecitabine therapy.

Coagulopathy: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important Capecitabine-Warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including **death**, have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time capecitabine was introduced. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Cardiotoxicity: The cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse events may be more common in patients with a prior history of coronary artery disease.

This treatment is foreseen as a self-administered out-patient treatment, and in certain circumstances adverse events that could occur, such as diarrhea, or hand-foot syndrome can rapidly become serious. In the case where a patient experiences any toxicity between scheduled visits, the patient will be instructed to contact the clinic as soon as possible, for further directions, discontinuation of study medication, and/or treatment.

4.2 Radiation Therapy.

TREATMENT PLAN

4.2.1 Simulation and Planning

Tumor volume will be defined on the basis of CT and MRI imaging findings and operative notes and findings. Position of stents and surgical clips, if any, and cholangiography may also be utilized. Specifically, a clip

will be placed at the second portion of the duodenum for image guidance. The primary tumor and any clinically enlarged lymph nodes will be treated with a margin of 2 cm to include peripancreatic nodes. The porta hepatis, celiac axis, superior mesenteric artery (SMA) root, and the pancreaticoduodenal nodes will also be treated. In step 1 (dose level –1), total dose will be prescribed to the 95% isodose and will be 30 CGE in 10 fractions (3 Gy/day) with multifield techniques. In step 2, total dose will be prescribed to the 95% isodose and will be 25 CGE in 5 fractions (5 Gy/day) with multifield techniques.

Patients will be simulated supine. Intravenous and oral contrast will be administered per standard department protocol. If tolerated, the BodyFix system will be used. The BodyFix system is an FDA approved system. With this system preliminary experience demonstrates that chest wall motion is limited to approximately 2 mm in the AP direction. If the BodyFix is not feasible, no restrictive device will be used. 4-D planning CT will be obtained for treatment planning to ascertain the extent of tumor motion.

The Gross Tumor Volume (GTV) is defined as the gross primary tumor and any lymph nodes enlarged over 1 cm during simulation using contrast given during CT or MRI. The clinical target volume (CTV) will also include the following at-risk nodal basins: porta hepatis, celiac axis, superior mesenteric artery, and pancreaticoduodenal nodes as defined by the inner-third of the duodenum. Planning target volume (PTV): Because daily localization and gating and/or BodyFix Immobilization will be used, a 1 cm margin in the in all directions except 0.5 cm posteriorly. The PTV must be digitized or drawn on the planning CT scan DRRs.

Computerized dosimetry is required if more than two fields are used. All fields must be simulated using a machine that duplicates the geometry of the actual treatment machine. Patient contours and isodose plots are required. Isodose plots must account for the effect of all treated fields, including any blocking used.

Radiation therapy will begin on Day 1. Treatment must begin on a Monday.

In step 1, fields will receive a total dose of 30 CGE at 3 CGE per fraction 5 days per week over 2 weeks. In step 2, fields will receive a total dose of 25 CGE at 5 CGE per fraction as outlined below.

Table 5
Radiation Dose Schedule

)ose Level	**tep 1 ead-in hase**	**Dose/fraction**	**# Tx**	**Fractionation Schedule**	**Total Dose**	**Week 1 Schedule**	**Week 2 Schedule**	**Total Days**
1	1	3 CGE	10	QD	30	M T W Th Fri	M T W Th Fri	12
	Step 2	**Dose/fraction**	**# Tx**	**Fractionation Schedule**	**Total Dose**	**Week 1 Schedule**	**Week 2 Schedule**	**Total Days**
2	1	5 CGE	5	QD	25	M W F	T Th	11
3	2	5 CGE	5	QD	25	M T Th Fri	M	9
4	3	5 CGE	5	QD	25	M T W Th Fri	-	5

4.2.2 Treatment

All charged particle treatment will be given with the patient at the Francis H. Burr Proton Therapy Center. Film or digital images will be taken prior to each treatment in accordance with the proton center's standard practice for all patients. These images are used to verify the position of the patient and the aperture. These digital images are permanently stored electronically for each patient.

. All patients will be treated with respiratory gating to account for respiratory excursion if tumor motion is > 5mm. Treatment must start on a Monday

4.2.3 Normal tissue volume and dose considerations

Normal tissue guidelines are as outlined below. In step 1 (lead-in phase), the 10 fraction constraints will be used. In step 2, the 5 fraction constraints will be used.

Table 6
Planning Goals - Normal tissue constraints

ORGAN	Threshold Dose Conventional 28 fraction Schedule	Normalized Total Dose (2 Gy equivalents)	Threshold Dose- Step 1- 10 fraction schedule (CGE)	Threshold Dose- Step 2- 5 fraction schedule (CGE)	% Above threshold
Liver	30 Gy	23.0 Gy_2	22	17.5	30%
Kidney	20 Gy	14.8 Gy_3	16	13	30%
Spinal Cord	45 Gy	40.6 Gy_2	31	24	0%
Stomach	40 Gy	38 Gy_{10}	18*	7	10%

Assumed α/β in subscripts

- * If possible - Stomach dose threshold is to prevent nausea, an acute effect. No established guidelines exist. However, in the preliminary MGH IMRT experience, the above dose threshold is associated with ~ 10% rate of ANY anti-emetic use. The daily NTD of the conventional schedule is 1.36 Gy. This means that that the threshold dose (NTD) for a five fraction schedule is 6.8 Gy (2 Gy equivalents) and correlates with the listed dose threshold.

Treatment planning should be adjusted for decreased renal function based on an elevated serum creatinine, a history of unilateral or bilateral renal disease, and abnormalities in baseline laboratory or radiographic studies. Additional studies to assess renal function will be performed as needed.

4.3 Surgery

4.3.1 Surgery will be performed 2-7 weeks after radiation therapy if no metastatic disease on re-staging. Patients who receive surgery 2-4 weeks after completing RT will not be restaged prior to surgery.

4.3.2 At laparotomy, the liver and pancreas will be examined by palpation and inspection.

4.3.3 In the absence of metastases, tumor mobilization and surgical resection will be performed. A pancreaticoduodenectomy (Whipple procedure) with standard lymphadenectomy will be done. This involves dissection up to the superior mesenteric artery, with skeletonization of the right lateral and anterior aspects of the vessels.

4.34 Feeding jejunostomy and gastrostomy tubes may be placed at the discretion of the operating surgeon.

4.4 Pathology

Processing the specimen and pathology will be reported according to the AJCC Cancer Staging Manual, 6th Edition. Pancreatic transection margin, and the bile duct margin will be evaluated on frozen section. Recorded on permanent section will be: tumor size, degree of differentiation (well, moderate, poor), lymph node status, margin status, and degree of treatment effect.

4.4.1 Biomarkers of Response

The search for new biomarkers of response to short course neoadjuvant radiation will involve an examination of the molecular and genetic characteristics of the tumor specimens. This analysis will begin with the primary tumor after the course of treatment and may also include analysis of the initial biopsy specimen. To characterize the tumors at the genetic level, mutational analysis of the specimens will be performed using a customized SNAPSHOT platform that examines the tumor for approximately 100 specific genetic mutations. Findings from the molecular and genetic studies will be analyzed in the context of changes appreciated in the histological and immunohistochemical changes found in tumor tissue sections in order to validate known markers of radiation sensitivity and define new biomarkers of treatment response. All correlative studies are optional.

5.0 Pre-treatment, On-Study, and Post Treatment Evaluations

5.1 Prior to Study Enrollment: Prior to study enrollment patients must undergo the following evaluations:

Within 42 days of enrollment: laparoscopy, Chest CT, Abdominal-pelvic CT (or MRI),

Within 28 days of enrollment: Signed informed consent,

Within 7 days of enrollment: Physical exam, Lab studies (CBC with diff, Na, K, BUN, Cr, Glucose, Phosphorous, Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase, CA19-9, CEA, and a urine or serum HCG for women of childbearing potential).

5.2 Evaluation During Study: On treatment days 8 and 15, the patients will be assessed as follows:

a) Complete blood count (CBC: hemoglobin, hematocrit, red blood cells, WBC, platelets, and differential blood counts) weekly.

b) Blood chemistries (Na, K, BUN, Cr, Glucose, , Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase)

c) History, physical exam, and vital signs

d) After completion of capecitabine and radiation therapy, patients will have a 3 to 6 week rest period followed by a restaging Chest CT, Abd CT (or MRI), CEA, CA19-9Surgery will be performed 4 to 7 weeks after completion of neoadjuvant therapy.

5.3 Post Treatment evaluation

After completion of therapy and surgery, patients will be followed for 30-day morbidity and mortality evaluation. It is recommended (although not mandated) that patients undergoing R0 resections should receive adjuvant treatment with 4 cycles of gemcitabine-based therapy. Patients should be contacted either by telephone or clinic visit every 6 months for 5 years after surgery in order to follow progression-free and overall survival status.

6.0 Required Data (also see sections 5.1 – 5.3)

Table 7
Required Data Table

Tests and Observation	Prior to Study	Days 1,8,15	Preop**	Post-op F/U
Signed informed consent	A			
History	X			
Physical Examination	X	X	X	
Vital Signs and performance status	X		X	
Height/Weight/Surface Area	X			
Drug Toxicity		X	X	
Laboratory*: (within 7 days of enrollment)				
CBC/plts/diff	X	X	X	
Serum chemistries (Na, K, BUN, Cr, Glucose, , Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase)	X	X	X	
Creatinine clearance calculation (Cockroft Gault)	X	X (days 1 and 8 only)		
CA19-9	X		X	
CEA	X		X	
Pregnancy test*	A			
Optional Research Blood	G		G	
Staging:				
Chest CT Abd-pelvic CT (or MRI)	A		X, F	D
Laparoscopy	B			
Radiation Planning	A			
Adjuvant therapy				C

*Laboratory values need to be obtained within 7 days of study entry

** Preop evaluations should take place 3-6 weeks after completing XRT and capecitabine

A: Staging CT or MRIs need to be obtained with 42 days of study entry
B: Laparoscopy needs to be obtained within 42 days of study entry. Clip will be placed in second portion of duodenum.
C: It is recommended that all patients who undergo R0 resections receive 4 cycles of gemcitabine-based therapy. Clinic visits and/or phone calls are required every 6 months for 5 years after Whipple or until death.

D. CT scans will be performed at least every 6 mo for the first 2 years and yearly for years 3-5.

F. Patients receiving surgery 2-4 weeks after completing RT will not have pre-op scans.

G. Optional research blood samples will be obtained at baseline and prior to surgery. Please refer to section 2.5.1 for specific instructions.

7.0 Determination of MTD and DLTs:

7.1 Phase I Determination of MTD

The Maximum Tolerated Dose (MTD) will be determined as follows. The dose limiting toxicities (DLT) are defined in 7.2 within three weeks of the start of radiation therapy. Patients will be evaluable for DLT whether or not they undergo surgery following the neoadjuvant therapy. Beginning at level 1 of the lead-in step 1, 3 patients will be treated initially according to each of the accelerated dose schedules in 4.2, Table 5. If no DLT were observed, the protocol will proceed to the next level of dose schedule. If at least 2 of them were to experience DLT, the previous level will considered the maximally tolerated dose (MTD) schedule. If 2 patients at dose level 1 are observed to have DLTs, the study will be closed. If exactly 1 of the initial 3 patients were to have DLT at a given level, 3 more patients will be treated using the same dose schedule. If no further DLT were to occur, the next level of dose schedule will begin enrollment. If 1 or more of the additional 3 patients were to experience DLT, the previous level will be considered the MTD schedule. If none of the first 3 patients treated at level 4 or only 1 of 6 patients were to have DLT, level 4 will be declared as the MTD schedule.

7.2 Dose Limiting Toxicities (DLTs). DLT will be defined as occurring within 3 weeks of the start of radiation therapy:

a) Any grade 3 non-hematologic or hematologic toxicity requiring a greater than 7 day interruption in therapy (excluding alopecia and nausea/vomiting not controlled by optimal supportive care or
b) Any grade 4 non-hematologic toxicity or
c) Any grade 4 neutropenia or thrombocytopenia as defined by NCI CTCv3.0. (See section 7.2.1 for dose modifications).

Toxicities not due to chemoradiation, such as cholangitis from a blocked biliary stent, or symptoms thought to be from tumor progression such as pain or bowel obstruction, will not be classified as DLTs.

Any DLT should be reported to the principle investigator or the study data manager within 72 hours.

7.3 Phase II Dosing

As described in Section 2.5, above, there were no DLTs observed in the Phase I study subjects. The MTD reached was dose level 4 (5Gy x 5 in 5 days). Thus, this will be the planned dose level for the Phase II portion of the study.

8.0 Toxicities and Dose Modifications

8. 1 Capecitabine and Radiation Therapy

8.1.1. General Toxicities:

The most common toxicities of capecitabine and radiation therapy are fatigue, nausea, abdominal pain, diarrhea, indigestion, vomiting, weight loss and anorexia. Other toxicities may include neutropenia, thrombocytopenia, anemia, cutaneous eruptions, alopecia, fever, flu-like symptoms, and urticarial reactions. Much less common toxicities could include anaphylactic reactions, peripheral neuropathy, arrhythmia, gastrointestinal bleeding and bowel obstruction.

8.2 Dose Modifications:

8.2.1 Hematologic and Non-Hematologic Toxicity

Capecitabine and radiation therapy will be held for any Grade 3 or 4 toxicity (except for alopecia and nausea/vomiting which is controlled with anti-emetic therapy). After toxicity resolves to < grade 2, capecitabine will be resumed at 600 mg/m2 BID to complete the 10 weekdays of therapy. Capecitabine can be held a maximum of 7 days. If further grade 3 or 4 toxicity is noted at the reduced dose level, after toxicity resolves to < grade 2, capecitabine will be resumed at 500 mg/m2 BID to complete two weeks of therapy. If the second dose reduction is not tolerated, capecitabine will be stopped. Patients will keep a capecitabine diary and will record the number of capecitabine tablets and the time that they will take the tablets. Note that patients can potentially have no combination therapy for up to 3 days without being considered a DLT as no therapy is planned for day 11 and combination of chemoradiation does not exceed 10 days. Radiation therapy will be held for Grade 3 or 4 nausea until nausea resolves to Gr 2 or less.

9.0 Adverse Events

9.1 Adverse Event and Reporting Definitions

In the event of an adverse event the first concern will be for the safety of the subject.

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

9.2 Reporting of Serious Treatment Emergent Adverse Events

All treatment emergent SAEs should be recorded and faxed to:

Study Coordination Center/Principal Investigator
Contact Information and fax #
Theodore S. Hong, MD
[redacted]
AND:(TBD)
IRB Contact information and fax #

10.0 EVALUATION OF RESPONSE

10.1 Response Criteria

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1 Radiographic Response

Definition of Response: Overall tumor response will be based on an integration of the evaluation of target, non-target, and new lesions, as described below:

Evaluation of target lesions (pancreatic mass):

Complete Response (CR): Disappearance of all clinical and radiological evidence of target lesions.

Partial Response (PR): A 30% or greater decreased in the sum of LD of all lesions in reference to the baseline sum LD.

Stable Disease (SD): Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR.

Progressive Disease (PD): A 20% or greater increase in the sum of LD of all target lesions, taking as reference the smallest sum LD recorded since baseline.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat evaluations which should be performed no less than 4 weeks after the criteria for response are first met.
Evaluation of non-target lesions:

Progressive Disease (PD): the development of new lesion(s).

Evaluation of new lesions:

No: There are no new lesions.

Yes: New lesions are present. Note: If new lesions are present, the patient is considered to have progressive disease overall.

Overall Response:

Overall response will be determined as tabulated below, based on the evaluation of target, non-target, and new lesions:

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Every effort should be made to document tumor measurements and extent of disease, even after discontinuation of therapy, in order to classify patients for overall response as described above. Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered as non-responders, will be included in the denominator for the response rate, and will be classified into one of the following categories:

- death attributed to disease progression
- deterioration attributed to disease progression
- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

10.2 Pathological Response

All patients will undergo a full pathological review of their pancreaticoduodenectomy specimen according to the AJCC Staging Classification, 6th. Initial gross evaluation and identification of resection margins will be performed jointly by the surgeon and the pathologist. Pathological complete response will be defined as the absence of any viable tumor cells within the pathologic specimen.

10.3 Time to tumor progression

Time from date of protocol entry to first objective documentation of progressive disease or death. Patients who die without a reported prior progression will be considered to have progressed on the day of their death.

10.4 Time to death

Time from date of protocol entry to date of death

10.5 Time to local recurrence

A local recurrence will be defined as any evidence of tumor recurrence within the radiation field. The time to local recurrence will be from the date of protocol entry to the first objective documentation of a local recurrence.

11.0 STATISTICAL CONSIDERATIONS

11.1 Phase 1

The dose limiting toxicities (DLT) are defined in 6.2 within three weeks of the start of radiation therapy. Patients will be evaluable for DLT whether or not they undergo surgery following the neoadjuvant therapy. Beginning at level 1 of the lead-in step 1, 3 patients will be treated initially according to each of the accelerated dose schedules in 4.2, Table 5. If no DLT were observed, the protocol will proceed to the next level of dose schedule. If at least 2 of them were to experience DLT, the previous level will considered the maximally tolerated dose (MTD) schedule. If exactly 1 of the initial 3 patients were to have DLT at a given level, 3 more patients will be treated using the same dose schedule. If no further DLT were to occur, the next level of dose schedule will begin enrollment. If 1 or more of the additional 3 patients were to experience DLT, the previous level will considered the MTD schedule. If none of the first 3 patients treated at level 4 or only 1 of 6 patients were to have DLT, level 4 will be declared as the MTD schedule.

Following the escalation algorithm, the probability of progressing to the next level of dose schedule is given below under a range of the true DLT rate. For example, if a dose schedule were associated with an underlying DLT rate of 50%, the probability of escalating is 17% so that the protocol is unlikely to proceed to the next level. As 3-6 patients will be enrolled at each level of progressively accelerated dose schedule, accrual to the escalation phase may be up to 24 patients.

True DLT rate	Probability of escalation
10%	91%
20%	71%
30%	49%
40%	31%
50%	17%
60%	8%

11.1 Phase 2

Accrual will be expanded so that another 25 patients will be treated at the MTD level in order to determine the rate of any grade 3 or greater toxicity associated with the accelerated dose and to investigate the secondary endpoints. Toxicity will be defined according to the NCI Common Terminology Criteria (version 3). The MD Anderson data demonstrated 19% grade 3 toxicity using the standard course of preoperative radiation at a total dose

of 50.4 Gy concurrently with continuous infusion 5-FU. If grade 3 or greater toxicity were observed among at least 3 of 25 patients, the exact 90% one-sided upper bound will exceed 20%. If the underlying rate of grade 3 or greater toxicity related to the MTD schedule were 6% that is comparable to the MDA short-course schedule, the decision rule is associated with 81% probability of ruling out rates higher than 20% at a one-sided significance level of 10%.

A sample size of 25 patients treated at the MTD schedule will provide an exact 90% confidence interval of width no more than +/- 0.18 for the estimation of toxicity, surgical morbidity and pathologic complete response. Patients who do not undergo surgery will be considered as failures in the estimation of pathological complete response. Historically, pathologic complete responses are rarely observed with neoadjuvant radiation and concurrent 5-FU. Thus any pathologic complete response will be deemed as significant. Progression-free survival will be estimated using the Kaplan-Meier method. Accrual is projected to take about 18 months for each phase. If a patient is found to be ineligible once registered and therefore taken off study and excluded from analysis, an additional patient may be enrolled and included in analysis.

12.0 RETENTION OF RECORDS

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be retained for at least 2 years after the investigation is completed.

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