Moores UCSD Cancer Center
University of California, San Diego

Phase I Trial of Adaptive Stereotactic Body Radiotherapy (SBRT) Dose Escalation in Pancreatic Cancer

Version Date: 04/22/2014

PRINCIPAL INVESTIGATOR

James Murphy, M.D., M.S.
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0865
La Jolla, CA 92093-0865
Phone: (858)534-3508
Fax: (858)246-1505
E-mail: j2murphy@ucsd.edu

SUB-INVESTIGATORS

Radiation Oncology (UCSD)

James Murphy, M.D., M.S.
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0865
La Jolla, CA 92093-0865
Phone: (858) 534-3508
Fax: (858) 246-1505
E-mail: j2murphy@ucsd.edu

Jona Hattangadi-Gluth, M.D.
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0865
La Jolla, CA 92093-0865
Phone: (858) 534-1222
Fax: (858) 246-1505
E-mail: jhattangadi@ucsd.edu

John Einck, M.D.
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0865
La Jolla, CA 92093-0865
Phone: (858) 246--1506
Fax: (858) 246-1505
E-mail: jeinck@ucsd.edu

William Song, Ph.D.
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0865
La Jolla, CA 92093-0865
E-mail: wysong@ucsd.edu

Medical Oncology (UCSD)

Gregory Heestand, M.D.
University of California San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093
(858) 822-3115
gheestand@ucsd.edu

Paul Fanta, M.D.
University of California San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093
(858) 822-6185
pfanta@ucsd.edu

Surgical Oncology (UCSD)

Andrew Lowy, M.D.
University of California San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093
(858) 822-2124
alowy@ucsd.edu

Biostatistics (UCSD)

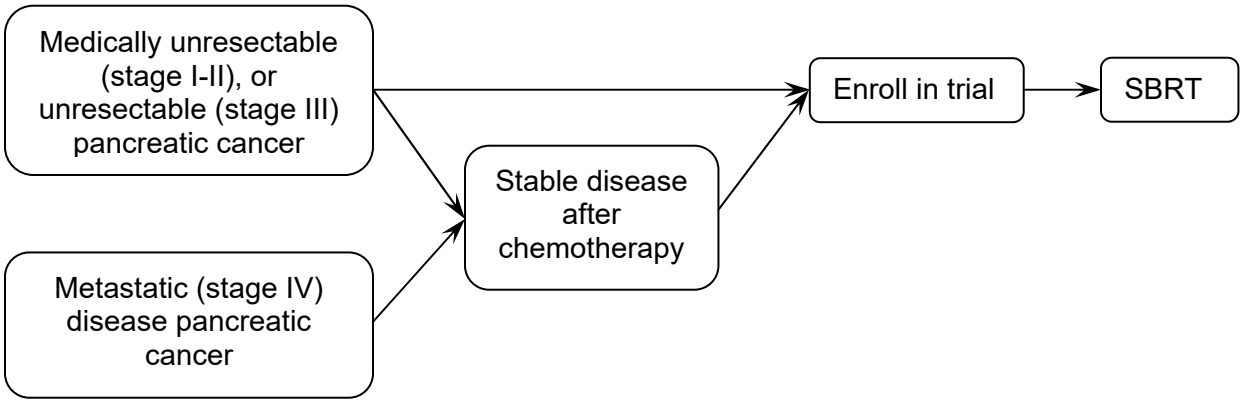
Ronghui (Lily) Xu, PHD
Division of Biostatistics and Bioinformatics
Department of Family and Preventive Medicine, and Department of Mathematics
Director, CTRI Biostatistics, Epidemiology, and Research Design
University of California, San Diego
9500 Gilman Drive, Mail Code 0112
La Jolla, CA 92093-0112

James Proudfoot, PhD
CTRI Biostatistics
University of California, San Diego
9500 Gilman Drive, Mail Code 0112
La Jolla, CA 92093-0112
jproudfoot@ucsd.edu

Table of Contents

EXPERIMENTAL DESIGN SCHEMA

SCHEMA



・Stereotactic body radiotherapy (SBRT)

Cohort	Dose level
1	*8 Gy x 5 fractions = 40 Gy*
2	*9 Gy x 5 fractions = 45 Gy*
3	*10 Gy x 5 fractions = 50 Gy*
4	*11 Gy x 5 fractions = 55 Gy*
5	*12 Gy x 5 fractions = 60 Gy*

Patient Population: Unresectable pancreatic adenocarcinoma.

Sample size: 30

1.0 INTRODUCTION

1.1 Pancreatic Cancer

Pancreatic cancer is the 10th most common cause of cancer, and the 4th most common cause of cancer-related death in the United States, with an annual incidence of 45,220 new diagnoses per year [1]. The only curative treatment for pancreatic cancer is surgery, yet approximately 75% of patients present with unresectable or metastatic disease. Of those patients with surgically resectable disease, the 5-year survival is around 20%. Among those with unresectable disease distant metastatic spread remains the primary problem, though up to 1/3 of patients will die from local tumor progression [2]. Additionally, local tumor progression leads to pain, gastrointestinal obstruction, or bleeding, all of which substantially decrease a patient's quality of life. Thus, local tumor control remains a crucial part of treatment for patients with pancreatic cancer who are not candidates for curative therapy.

1.2 Treatment options for locally advanced unresectable pancreatic cancer

The optimal treatment for locally advanced pancreatic cancer remains unclear, though current treatment often includes chemotherapy, or chemotherapy with radiotherapy. Unfortunately, patients with unresectable disease are not curable, and therefore chemotherapy is delivered with the intent of delaying disease progression, and lengthening life. Radiotherapy focuses on controlling the primary pancreatic tumor. Unfortunately, neither chemotherapy nor radiation has proven effective with unresectable pancreatic cancer, and the median overall survival for this disease is only around 10-12 months.

1.3 Radiation for locally advanced pancreatic cancer

Conventional radiotherapy in pancreatic cancer is given daily over 5-6 weeks with concurrent chemotherapy. The Gastrointestinal Tumor Study Group conducted a series of studies with chemoradiotherapy in pancreatic cancer defining its effectiveness. More recent series on chemoradiotherapy have yielded mixed results, with some reports of improved efficacy, and others without. A primarily limitation of chemoradiation relates to the side effects including nausea, vomiting, and fatigue, with a substantial fraction of patients experiencing grade 3-4 toxicity. Unfortunately, despite its efforts, conventional chemoradiation has low local control rates often in the range of 50% or lower. Additionally, this 5-6 week treatment duration occupies a significant time burden for patients and caregivers, plus this can delay much needed systemic chemotherapy. In an attempt to improve local control and reduce treatment time investigators have started to use shorter more intense courses of radiotherapy, specifically, stereotactic body radiotherapy (SBRT).

1.4 Stereotactic body radiotherapy (SBRT) in pancreatic cancer

SBRT in pancreatic cancer shows great promise with initial studies showing high rates of local control. The initial study from Stanford escalated the dose of single fraction radiotherapy from 15 Gy in a single fraction to 25 Gy in a single fraction [3]. A subsequent phase II study treated patients to 45 Gy in 25 fractions with conventionally fractionated radiation, followed by 25 Gy in a single fraction [4]. Two of the 16 patients in this trial (13%) had grade 3 toxicity. Additional data with 25 Gy in a single fraction found

high rates of local tumor control with a 1-year freedom from local progression rate of 84% [5]. Unfortunately, the Stanford group found increased risk of late toxicity with the 25 Gy in 1 fraction regimen [6]. The close proximity of the stomach and duodenum put these organs at risk in radiotherapy directed at the pancreas. Of 73 patients treated with 25 Gy in a single fraction, 12 had grade 2-4 duodenal toxicity [6].

More recently, Stanford has preliminarily reported on a phase II trial 5-day course of SBRT [7]. This 5 fraction schedule going to 33 Gy was safe, with one reported toxicity event, though the efficacy was lower with decreased rates of local control. The observation that 33 Gy in 5 fractions was safe but had lower local control suggests that there may be room for dose escalation. This current trial will determine the maximal tolerated dose of SBRT in 5 fractions, for which the efficacy will be tested in a subsequent phase II trial.

This trial will escalate the dose from 40 Gy in 5 fractions, to 60 Gy in 5 fractions, at 5 Gy intervals. Comparing different radiation fractionation schedules is complex, though the standard metric used is the biologic effective doses (BED), and the BED of multiple radiation fractionation schedules is provided below in Table 1. The selection of a dose range with this study was based on a number of factors. First, the starting dose level of 45 Gy has been found safe in recently reported hyporfactionated regimens in pancreatic cancer [8]. in five fractions is the natural extension beyond 33 Gy in five fractions found safe by the Stanford researchers. The final dose level of 60 Gy in five translates into a BED of 132 for tumor response, and 300 for late toxicity. This final dose level is similar to that used by Koong, et al. with 141 for tumor response, and 305 for late toxicity.

Table 1. Biologic effective dose of different radiation regimens in pancreatic cancer

		Biologic effective dose	
Radiation scheme	**Protocol**	**Tumor response ($\alpha/\beta = 10$)**	**Late toxicity ($\alpha/\beta = 3$)**
Conventional radiation			
50 Gy in 25 fractions		60	83
Completed SBRT protocols			
25 Gy in 1 fraction	Koong, et al [3]	88	233
33 Gy in 5 fractions	Herman, et al [7]	55	106
45 Gy in 25 fractions, then 25 Gy in 1 fraction	Koong, et al [4]	141	305
45 Gy in 6 fractions	Tozzi, et al [8]	79	158
Proposed SBRT protocol			
Cohort 1: 40 Gy in 5 fractions		72	147
Cohort 2: 45 Gy in 5 fractions (starting dose level)		86	180
Cohort 3: 50 Gy in 5 fractions		100	217
Cohort 4: 55 Gy in 5 fractions		116	257
Cohort 5: 60 Gy in 5 fractions		132	300

1.5 Primary study hypothesis

The purpose of this study is to determine the maximum tolerated dose of five fraction stereotactic radiotherapy (SBRT) in pancreatic cancer.

1.6 Imaging/treatment correlative study background

This trial is designed to find the maximum tolerated dose (MTD) under a fixed 5-fraction SBRT regimen. To do this, it is necessary to verify that the treatment accuracy remains consistent throughout, so as to not be a confounding factor in the outcome. Perhaps the biggest contributing uncertainties are the inter- and intra-fractional organ motion, principally driven by patients' respiration. Physiological changes may also impact organ motion during SBRT. To compensate for organ motion, generic margins are commonly applied to the CTV, such as ITV and PTV. In this trial, 2-3 mm PTV margin will be used and may be trimmed further depending on the location of the duodenum or stomach. For such a tight margin, along with highly hypofractionated dose, it becomes prudent to validate that the image guidance technologies used in this trial are adequate to meet the demanded accuracy. To do this, this trial will employ the following sequence of imaging: 1) kV/kV to bones, 2) CBCT to soft tissue and fiducial markers (4DCBCT if available), 3) fluoroscopy to fiducial markers during free-breathing, and 4) repeat CBCT to soft tissue and fiducial markers (4DCBCT if available) at the end of treatment. This sequence of imaging will help minimize the initial setup uncertainties due to inter-fractional motion (steps 1-3) as well as to monitor the intra-fractional motion (step 4). In addition to these primary objectives, the images will be further analyzed to determine 1) the minimum adequate margin in each principal direction per patient population, 2) identify anatomical motion surrogates for when fiducials are not available, and 3) potential for various adaptive RT strategies.

2.0 OBJECTIVES

2.1 Primary Aim

2.1.1 To determine the maximum tolerated dose (MTD) of stereotactic body radiotherapy (SBRT) in pancreatic cancer.

2.2 Secondary Aims

2.2.1 To estimate the rate of local tumor progression after SBRT.

2.2.2 To estimate the rate of distant disease progression after SBRT.

2.2.3 To measure overall survival after SBRT.

2.2.4 To estimate a dose-response between radiation dose and local control.

2.2.5 To measure longitudinal quality of life before and after SBRT.

2.2.6 To determine the correlation between quality of life, and disease progression after SBRT.

2.2.7 To determine if any dose-volume parameters predict grade ≥3 duodenal toxicity.

2.2.8 To determine if patients are able to receive additional chemotherapy after SBRT.

2.2.9 To identify natural anatomical surrogates that best correlate with the motion of the fiducial markers.

2.2.10 To determine if adaptive RT would be beneficial.

3.0 PATIENT SELECTION

The eligibility criteria listed below are interpreted literally and cannot be waived.

3.1 Inclusion Criteria

3.1.1 Diagnosis: Histologically-proven invasive adenocarcinoma of the pancreas.

3.1.2 Disease Status: Medically unresectable (stage I-II), or locally advanced (stage III). Patients with distant metastases (stage IV) must have stable disease or improved disease (partial response, or complete response) per Response Evaluation Criteria In Solid Tumors (RECIST) criteria as determined on serial imaging following a course of chemotherapy.

3.1.3 Tumor Location: Primary tumor may be located anywhere in the pancreas.

3.1.4 Treatment eligibility: The patient must be able to have fiducial markers implanted into the pancreatic tumor, and receive radiation regimen as specified in the protocol.

3.1.5 Performance Level: Karnofsky Performance Status ≥ 60 (see Appendix II)

3.1.6 Adequate Renal Function Defined As:
- Serum creatinine ≤ 1.5 x upper limit of normal

3.1.7 Age: Patients must be 18 years of age or older.

3.1.8 Informed Consent: All subjects must sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Pregnancy or Breast-Feeding: Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events. (Note: Serum Pregnancy tests must be obtained in women of child bearing potential). Sexually active females may not participate unless they have agreed to use an effective contraceptive method (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study.

3.2.2 Life expectancy < 6 months

3.2.3 The patient cannot have had prior radiation therapy to the thorax or upper abdomen.

3.2.4 Incarcerated individuals

3.2.5 Subjects unable to give informed consent

3.2.6 Subjects with uncontrolled distantly metastatic disease per RECIST criteria (progressive disease) on imaging following chemotherapy

4.0 PRETREATMENT EVALUATIONS

The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient's eligibility for this study, please contact Dr. James Murphy immediately (858) 534-3508.

4.1 Required Evaluations (In addition to the mandatory pre-testing for eligibility in Section 3.0)

4.1.1 History and physical examination including height, weight, and Karnofsky Performance Status (KPS).
4.1.2 CT of the abdomen, and pelvis.
4.1.3 Laboratory blood tests including CBC, comprehensive metabolic panel, and CA 19-9.

5.0 ENROLLMENT PROCEDURES

5.1 Recruitment

Subjects will be identified by study investigators and/or clinical research coordinators at participating centers. Information regarding the study will be included on the Moores UC San Diego Cancer Center Clinical Trials webpage and Clinicaltrials.gov.

5.2 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained.

5.3 Screening Procedures

Written informed consent will be provided prior to any study procedures. Documentation of informed consent will be maintained in the subject's research chart and medical

record. Studies or procedures that were performed for clinical indications or as standard of care (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

5.3 Placement of Fiducial Markers

Treatment on this protocol requires placement of 3-5 gold fiducials for targeting purposes. The fiducials will be used as surrogates for targeting the daily tumor position during treatment. The fiducials will be placed directly into the tumor, or surrounding normal pancreatic tissue under endoscopic ultrasound or CT guidance. Fiducials may be implanted prior to enrollment as this is an acceptable standard of care procedure for any patient receiving radiotherapy for locally advanced pancreatic cancer. Also, if a patient had an attempted surgical resection that was aborted, fiducials may have been implanted intraoperatively, which is also allowable prior to study enrollment.

Fiducial placement into pancreatic tumors carries a low risk of toxicity [9,10]. In one report of 50 patients who had fiducials implanted into the pancreas through endoscopy only one patient (2%) had minor bleeding without a significant drop in hemoglobin, and this event did not require hospitalization [10]. In another report of 61 patients who had fiducials implanted percutaneously under CT guidance only two patients (3.3%) had minor bleeding episodes [9].

6.0 RADIATION THERAPY

6.1 Pre-SBRT tests and procedures

6.1.0 Pre-SBRT tests

- Medical history and clinical examination.
- CBC, Chemistry Panel, CA19-9.
- Gold fiducial seed placement percutaneously, intraoperatively, or under endoscopic ultrasound guidance, which may be performed prior to enrollment.
- Signed informed consent document.

6.1 External Beam Radiation Therapy

6.1.0 Patient setup and simulation

6.1.0.1 Position
CT simulation will be done in the supine position with patient in an Alpha Cradle, or Vac-Lok for immobilization.

6.1.0.2 Imaging
All subjects will undergo a 3-dimensional (3D) CT scan with intravenous contrast, and slice thickness ≤2.5 mm. This 3D scan should preferably be done during an expiratory breath hold phase. Following the 3D CT, a four-dimensional (4D) CT scan with respiratory gating will be done to account for tumor motion. CT scans should include T4/T5 to L5/S1.

6.1.0.3 Contrast
Intravenous contrast is used during the CT simulation scan. If a patient cannot

receive IV contrast then an MRI can be done and fused to the treatment planning CT scan. Oral contrast will consist of a cup of water that the patient will drink 30 minutes before the simulation.

6.1.1 Treatment planning

6.1.1.1 Planning CT scan

The treatment planning CT scan will be defined as the CT from simulation that most clearly shows the tumor and adjacent normal tissue, and can be any of the following:

1) Expiratory phase of the 4D CT scan (50%);
2) Expiratory 3D CT simulation scan
3) Average of select sequences from the 4D CT scan around expiration including 30%, 40%, 50% (end expiration), 60%, and 70%.

6.1.1.2 CT fusion

When available, a recent diagnostic pancreas protocol CT, PET/CT, or abdominal MRI should be fused with the planning CT scan, using fiducial-to-fiducial fusion if possible.

6.1.1.3 Tumor target delineation

The pancreas gross tumor volume (GTV) will be identified on the treatment planning CT scan. The internal target volume (ITV) will be defined by the attending radiation oncologist using the 4D CT scan to account for respiratory motion. The final planning target volume (PTV) will consist of a 2-3 mm expansion around the ITV. The PTV can be trimmed off of the duodenum or stomach at the treating physician's discretion. Elective nodal regions will not be irradiated.

6.1.1.4 Treatment planning

Treatment will consist of 6 MV or 15 MV photons directed at the PTV using 6-12 fields or a modulated arc technique. Intensity modulated radiation therapy (IMRT) techniques such as fixed-field IMRT, or volume modulated arc therapy (VMAT) can be used to reduce dose to surrounding normal tissues. The dose should be prescribed as follows:

1) 90-95% of the PTV (preferably 95%) should receive 100% of the prescription dose
2) No more than 1 cm^3 of the PTV can receive >120% of the prescription dose

6.1.1.5 Normal tissue constraints

Normal tissue dose should be minimized. Specific organ constraints are as follows.

1) **Duodenum**: no more than 1 cm^3 of duodenum may exceed the prescription dose.
2) **Stomach**: no more than 1 cm^3 of the stomach may exceed the prescription dose.
3) **Small bowel (excluding duodenum)**: no more than 1 cm^3 of small bowel may exceed the prescription dose.
4) **Large bowel**: no more than 1 cm^3 of large bowel may exceed the prescription dose.
5) **Liver**: 700 cm^3 of normal liver should receive less than a mean dose of 15

Gy.

6) **Kidneys (combined)**: combined volume should have 75% <12 Gy.
7) **Spinal cord**: no more than 1 cm^3 should exceed 8 Gy.
8) *If the above tumor and normal tissue constraints cannot be made then the prescription dose to the PTV can be reduced such that 100% of the GTV will receive the prescription dose. If this constraint cannot be met, then the patient should be removed from the protocol.*

6.1.1.6 Heterogeneity corrections
Heterogeneity corrections should be applied.

6.1.2 Treatment delivery
Patients will receive 5 fractions over a five day period. Treatment should start preferably on Monday, and extend through the following Friday, though it may extend over 2 weeks if scheduling issues arise.

Patient position will be verified daily before each treatment with the following
1) Orthogonal kV/kV imaging focusing on bone anatomic alignment.
2) Daily cone-beam CT before and after each treatment will be conducted to verify anatomic location and stability. 4DCBCT should be used if available.
3) Fluoroscopy will be used to confirm that the tumor fiducials fall within the respiratory gating window (aperture). The gating window or patient position should be adjusted to ensure precise positioning.

6.2 Radiation Adverse Events

Risks and side effects related to radiation include:

Likely (more than 10%)
- Tiredness
- Nausea
- Damage to the duodenum, stomach, or intestine including ulceration, bleeding, or perforation which may require surgery or hospitalization.

Less Likely (3-9%)
- Redness and skin irritation in the treatment area
- Vomiting or dehydration

Rare, but serious (less than 2%)
- Development of an abnormal pathway or connection between organs (fistulae) including the duodenum, stomach, and blood vessels in the abdomen such as the aorta which may require hospitalization or surgery
- Damage to the liver causing liver failure
- Damage to the kidney causing kidney failure
- Damage to the spinal cord resulting in paralysis

7.0 DRUG THERAPY

7.1 Chemotherapy

Chemotherapy is not specified per protocol. Prior to enrollment, or after completion of SBRT patients may receive standard chemotherapy, or other investigational agents at the discretion of their treating oncologist. Patients may not receive chemotherapy during or within 7 days (before or after) pancreas SBRT.

8.0 OTHER THERAPY

8.1 Permitted Supportive Therapy/Procedures:

8.1.1 Antiemetic Agents
Standard antiemetic agents are allowed at the discretion of the treating physician.

8.1.2 Antidiarrheal Agents
Standard antidiarrheal agents are allowed at the discretion of the treating physician.

8.1.3 Analgesics
Standard analgesics, both narcotic and non-narcotics, are allowed at the discretion of the treating physician.

8.1.4 Nutritional supplementation
Nutritional supplementation, both by mouth and by enteric feeding tube, is allowed at the discretion of the treating physician.

9.0 PATHOLOGY

All patients will have pathologically confirmed pancreatic adenocarcinoma. Central review of pathology is not required.

10.0 PATIENT ASSESSMENTS

10.1 Study Parameters

Table 2

Study Procedures	Pre-Treatment	Week 1	Post-Treatment [b]
Informed Consent	X		
History and Physical	X		
Physical Exam with Vital Signs	X	X	1,3,6,9, 12 months, and every 6 months thereafter
CBC with differential, and comprehensive metabolic panel [a]	X		

CA 19-9	X		3, 6, 12, and every 6 months thereafter, or until disease progression
CT Abdomen, and Pelvis	X		3, 6, 12, and every 6 months thereafter, or until disease progression
Treatment: SBRT		D1-5	
Clinical evaluation for Toxicity	X	X	1,3,6,9, 12 months, and every 6 months thereafter
EORTC QLQ C-30/PAN26 questionnaire[c]	X		1,3,6,9, 12 months, and every 6 months thereafter

[a] Electrolytes including Creatinine, Bilirubin, SGOT, and SGPT
[b] Visit should occur at timepoints above +/- 28 days
[c] See appendix for details on questionnaire

10.2 Adverse Events (AEs)

Adverse event information will be documented on appropriate case report forms (CRF) which will include timing, severity and perceived causation of the events and followed until they either stabilize or resolve.

This study will utilize the Common Terminology Criteria for adverse events (CTCAE) of the National Cancer Institute for reporting of adverse events within 90 days after completion of radiation therapy. A copy of the current version of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). Adverse events after 90 days after completion of radiation therapy will be scored with the RTOG/EORTC Late Radiation Morbidity Scoring Schema. A copy of the current version of the RTOG/EORTC scale is available on the RTOG home page (http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx).

Definition of an AE: any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Serious Adverse Events (SAEs)
A serious adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in death.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is life-threatening.**
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**

- **Is a congenital anomaly/birth defect**
- **Is an important medical event**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

10.3 Steps to Determine If Expedited Reporting for an Adverse Event is Indicated

Step 1: Identify the type of adverse event using the CTCAE v4. The CTCAE v4 provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE v4 can be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). Additionally, if assistance is needed, the NCI has an Index to the CTCAE v4 that provides help for classifying and locating terms.

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
Unrelated, Unlikely Related, Possibly Related, Probably Related, and Definitely Related.
Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions above.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the investigator's brochure or the drug package insert

Step 5: Review Section 10.6 to determine if:
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

10.4 Reporting Requirements for Adverse Events

Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study.
- The UCSD Human Research Protections Program (HRPP) and the Moores Cancer Center Data and Safety Monitoring Board (DSMB) must be notified

within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

Routine Reporting

- The UCSD HRPP will be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- The FDA will be notified of all other adverse events that do not meet the criteria for expedited reporting at the time of the IND Annual Report.

10.5 Criteria for Removal from Protocol Therapy

a) Adverse Events requiring removal from study.
b) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
c) Physician determines it is in the subject’s best interest.

10.6 Criteria for Removal from Study

a) Loss to follow-up.
b) Withdrawal of consent for any further data submission.

11.0 DATA COLLECTION

11.1 Data and Safety Monitoring Plan

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by the clinical trials office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board to provide oversight in the event that this treatment approach leads to unforeseen toxicities. The DSMB will review data from this study semi-annually.

Data from this study will be reported semi-annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients
6) a summary of any recent literature that may affect the ethics of the study.

11.2 Confidentiality Procedures

Recruitment procedures will involve the review of patient records by designated study personnel (e.g., investigators and/or study coordinators) in order to identify potentially eligible patients. Since Protected Health Information (PHI) will be accessed via the hospital's medical record database and scheduling system (e.g., CPRS) prior to contacting the potential subject about the research study, we are requesting a partial waiver of HIPAA authorization for access to PHI for purposes of prescreening only. Standard HIPAA authorization to collect research data from the subject's medical record will be obtained at the time of informed consent.

Protected health information (PHI) will be maintained in the subjects' medical charts and thus confidentiality is protected via routine procedures. Data specific to this study will be kept in an electronic database to which only the principal investigator and involved study personnel will have access. The database will be de-identified by removing subjects' names and assigning a unique identifier to each subject. The database will be maintained on a protected disk drive in the radiation oncology department.

12.0 STATISTICAL CONSIDERATIONS

12.1 Statistical Analysis

12.1.1 Primary Endpoint: The purpose of this study is to determine the maximum tolerated dose (MTD) of five fraction SBRT in pancreatic cancer. The MTD will be defined from dose limiting toxicity, which will represent grade ≥3 gastrointestinal (GI) toxicity. GI toxicity from SBRT can occur anywhere from 6 weeks to 1 year after SBRT, with the median time to a toxic event being 6 months [6]. Because of the long "window" for toxicity a classic phase I 3+3 dose-escalation trial design would require a substantial amount of time between enrolled subjects to observe for toxic events. Therefore, to improve efficiency this study will use a time to event continual reassessment method (TITE-CRM) trial design [11], described in more detail below.

12.1.2 Secondary Endpoints

12.1.2.1 Local control. The cumulative incidence of local failure will be determined for all patients treating distant progression or death as a competing

risk. Local progression will be defined as a ≥20% increase in size on CT compared with CT prior to SBRT.

12.1.2.2 Distant metastatic progression rate. The cumulative incidence of distant metastatic failure will be determined for all patients treating death as a competing risk. In patients initially presenting with locally advanced disease, distant disease progression will be defined as the appearance of new metastatic lesions. In patients presenting with metastatic disease, distant progression will be defined as a ≥20% increase in size on CT of the previously noted metastatic lesions.

12.1.2.3 Overall survival. Overall survival will be measured from the date of diagnosis through death of any cause. Survival will also be reported from the date of SBRT for comparisons to other trials in the literature. Finally, survival will be stratified by those with locally advanced disease, and those with metastatic disease on presentation.

12.1.2.4 Dose response. An exploratory analysis evaluating for a correlation between radiation dose response and local control will be done with a competing risk analysis, dividing patients into two groups stratified by the median dose..

12.1.2.5 Longitudinal quality of life. We will track longitudinal quality of life using the European Organization for Research and Treatment in Cancer (EORTC) quality of life core cancer questionnaire with the pancreatic cancer module (EORTC QLQ C-30/ PAN26) (see appendix). The questionnaire will be given prior to treatment, and periodically during follow-up visits after treatment has concluded. Trends will be assessed with a linear mixed effects model.

12.1.2.6 Correlation between quality of life and disease progression. Disease progression is a commonly used surrogate endpoint in clinical trial with pancreas cancer, however its relationship with quality of life has not clearly been demonstrated. Therefore, we will assess for correlation between quality of life and local or distant disease progression.

12.1.2.7 Dose-volume relationship with duodenal/gastric toxicity. We will plan to use logistic regression models to determine the relationship between grade ≥3 duodenal or gastric toxicity and dose to these structures. The dose to the duodenum will be extracted from our treatment planning system.

12.1.2.8 Ability to receive additional chemotherapy. We will determine the fraction of patients who are able to receive additional chemotherapy among those whose initial intent was to do so. After consultation with an oncologist, but prior to treatment, we will record whether patients wish to receive additional chemotherapy after the course of chemo-radiotherapy delivered with this study. Possible responses include: yes, no, or undecided. We will then record who receives subsequent chemotherapy after completing treatment in our protocol.

12.1.2.9 Surrogate target discovery. We will determine the natural anatomical surrogates that best correlate with the motion of the fiducial markers. Potential surrogates include the superior mesenteric vessels, aorta, portal vein, and soft-tissue border of the pancreas. This information will help treat pancreas cancer

patients using image guidance technologies who could not have the markers placed.

12.1.2.10 Adaptive RT strategies. We will conduct a study to determine the best adaptive RT strategies that maximize the therapeutic ratio based on analyzing the information contained in the daily imaging studies to be performed on the patients.

12.2 Trial Design, Sample Size, and Study Duration

12.2.1 Trial Design: We will use a time to event continual reassessment method (TITE-CRM) trial design [11] to enroll a maximum of 30 patients onto this protocol.

The primary goal of this trial will be to determine the SBRT dose associated with a dose-limiting toxicity (DLT) in 20% of patients. DLT will be defined as grade ≥3 gastrointestinal toxicity (defined further below).

The TITE-CRM extends the original CRM by weighting each patient's contribution to the likelihood function described below. To determine the recommended dose for a newly enrolled patient, model parameters are estimated via the weighted likelihood. All previously enrolled patients who had either experienced toxicity or had completed the 12-month observation period without toxicity are assigned weights of 1; otherwise they are assigned weights equal to the proportion of the observation period they have completed.

The first patient in this study will enroll at dose level #2. Dose de-escalation can occur at anytime, though dose escalation will be restricted to 1 level between sequential patients. Additionally, before escalating the dose to the next level two conditions must be met: 1) the sum of the observation periods for all patients at the current dose level must be at least 12 months; and 2) at least one patient must have been under observation for at least 6 month at the current dose level. The rationale for these two conditions is mainly due to the short life expectancy of this patient population, which has a median survival of 8.25 months.

A two-parameter logistic regression model will be used to estimate the probability of toxicity at each dose level after each patient has been enrolled, which will inform the decision as to whether we should dose-escalate the patient in question. A final two-parameter logistic model will be fitted using follow-up data from 6 months after accrual of the last patient

Table 3. A priori toxicity estimation

Dose level	Probability of dose limiting toxicity
1	0.01
2	0.05
3	0.10
4	0.20
5	0.30

12.2.2 Dose Limiting Toxicity: The only toxicity observed thus far in pancreas SBRT has been related to nearby normal gastrointestinal organs, namely the duodenum and

stomach. Dose limiting toxicity in this study will be defined as any grade 3-5 gastrointestinal toxicity as measured by the Common Terminology for Adverse Events, version 4.0 (see appendix).

12.2.3 Maximum Sample Size: 30

12.2.4 Study duration: We anticipate accruing 12 patients per year, and will follow the last patient for a minimum of 6 months.

12.2.5 Interim analysis: This TITE-CRM trial design will de-escalate the radiation dose rapidly according to the observed dose-limiting toxicity. In addition to this built-in dose de-escalation we plan to conduct interim safety analysis after enrollment of every patient. We will stop the trial early if either of the following three conditions are met:

Condition 1 for early trial stoppage: more than 50% of patients at any dose level experience a dose-limiting toxicity.

Condition 2 for early trial stoppage: more than 34% of patients at dose level #1 experience a dose-limiting toxicity.

12.2.6 Operating Characteristics of the design: We used simulation to investigate the operating characteristics of our TITE-CRM configuration. We set the prior probability of toxicity at dose levels as in the table above, and investigate four different scenarios for the true underlying probabilities of toxicity:

- Scenario 1: Toxicity probabilities (.01, .05, .10, .20, .30) for dose 1-5, respectively (Prior Probability = True Probability)
- Scenario 2: Toxicity probabilities (.01, .05, .07, .10, .15) for dose 1-5, respectively (Prior Probability > True Probability)
- Scenario 3: Toxicity probabilities (.01, .05, .07, .10, .25) for dose 1-5, respectively (Prior Probability > True Probability)
- Scenario 4: Toxicity probabilities (.05, .10, .20, .30, .50) for dose 1-5, respectively (Prior Probability < True Probability)

We set our target rate of toxicity at the MTD to be .20, and set a vague normal prior with mean 0 and variance 1.34 (9). When a simulated patient enters the study, they are assigned to the dose chosen by the 'titecrm' function in the R library **dfcrm** (10), following the rules for dose escalation above. The incoming patient experiences a toxicity with probability given by the true underlying rate of toxicity for their assigned dose level, with toxicity time occurring uniformly between 0 and 12 months. Potential drop out (i.e. death) times are drawn randomly (with replacement) from the literature [5]. We set the number of simulations for each scenario at 5000.

Operating characteristics of the TITE-CRM simulation under different scenarios are included in the table below. 'Power' is defined as the simulated probability that the algorithm will recommend the correct MTD, defined in our simulation as the dose whose true toxicity probability is closest to, but not great than, the target (dose 4, 5, 4, and 3 for each of the four scenarios, respectively) at the trials conclusion. Trial duration is the amount of time (in months) from the first patients' enrollment to the end of the final patients observation period. Total Obs. is the cumulative observation time (in months) on all 30 patients. Pr(Tox.) is the simulated probability of toxicity in that configuration, and Pr(Tox. Above MTD) is the simulated probability of a subject having toxicity at a dose above the MTD.

Table 4. Operating characteristics

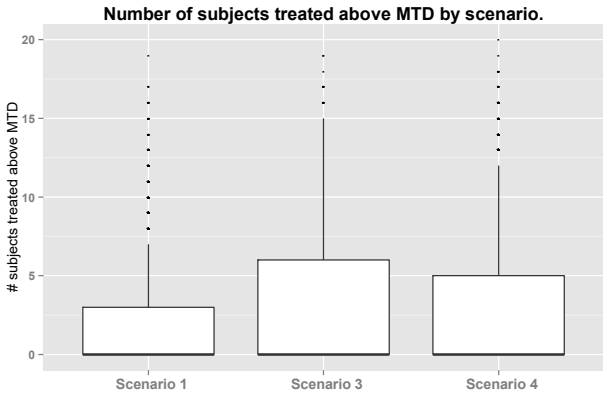
	'Power'	Trial Duration	Total Obs. Time	Pr(Tox.)	Pr(Tox. Above MTD)
Scenario 1	0.341	39.4	237.0	0.091	0.016
Scenario 2	0.436	39.4	240.5	0.062	0.014
Scenario 3	0.369	39.5	239.1	0.071	0.022
Scenario 4	0.334	39.5	233.9	0.116	0.029

The probability of recommending each dose as the MTD by scenario is included in the table below.

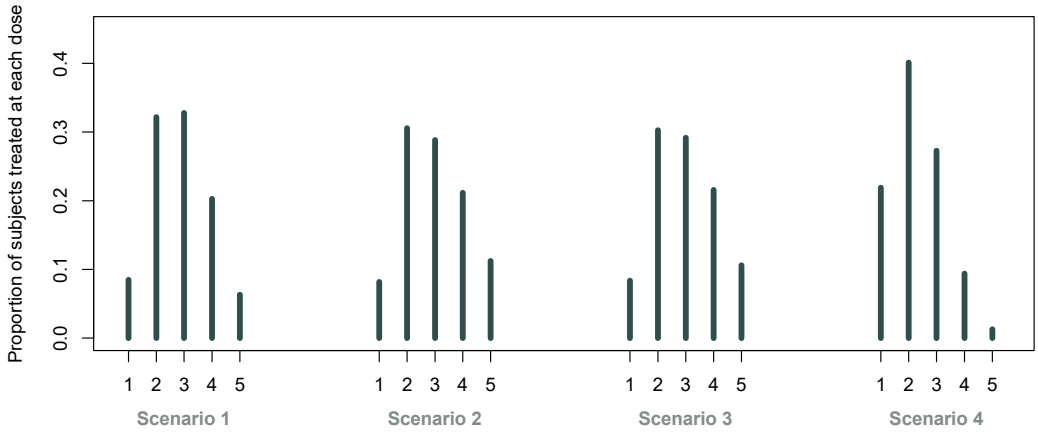
Table 5. Probability of recommending each dose as the MTD

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	MTD and (MTD - 1)
Scenario 1	0.000	0.123	0.386	0.341	0.150	0.727
Scenario 2	0.001	0.068	0.195	0.299	0.436	0.736
Scenario 3	0.003	0.069	0.204	0.369	0.356	0.573
Scenario 4	0.062	0.500	0.334	0.094	0.011	0.834

A boxplot of the number of patients treated above the MTD (treated above dose 4, 4, and 3, respectively) in scenarios 1, 3 and 4 is below.



A barplot of the average number of patients treated at each dose level with each scenario is below.


Proportion of subjects treated at each dose
0.0
0.1
0.2
0.3
0.4
1 2 3 4 5
Scenario 1
1 2 3 4 5
Scenario 2
1 2 3 4 5
Scenario 3
1 2 3 4 5
Scenario 4

REFERENCES

1. Siegel R, Naishadham D Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11-30.
2. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009;27:1806-1813.
3. Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1017-1021.
4. Koong AC, Christofferson E, Le QT, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005;63:320-323.
5. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009;115:665-672.
6. Murphy JD, Christman-Skieller C, Kim J, et al. A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:1420-1426.
7. Herman JM. A Phase II Multi-Center Study to Evaluate Gemcitabine and Fractionated Stereotactic Body Radiotherapy for Locally Advanced Pancreatic Adenocarcinoma. *Proceedings of the 55th Annual ASTRO Meeting* September 2013.
8. Tozzi A, Comito T, Alongi F, et al. SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. *Radiat Oncol* 2013;8:148.
9. Kothary N, Heit JJ, Louie JD, et al. Safety and efficacy of percutaneous fiducial marker implantation for image-guided radiation therapy. *J Vasc Interv Radiol* 2009;20:235-239.
10. Park WG, Yan BM, Schellenberg D, et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. *Gastrointest Endosc* 2010;71:513-518.
11. Normolle D Lawrence T. Designing dose-escalation trials with late-onset toxicities using the time-to-event continual reassessment method. *J Clin Oncol* 2006;24:4426-4433.

APPENDICES

APPENDIX I
AJCC CANCER STAGING SYSTEM, PANCREAS
(AJCC, 2010, 7th Edition)

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

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 II
KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III
QUALITY OF LIFE QUESTIONNAIRE

ENGLISH

EORTC QLQ-C30 (version 3)

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

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

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

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

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

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

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH/US

EORTC QLQ - PAN26

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

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

Please go to the next page

ENGLISH/US

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

APPENDIX IV
COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

CTCAE v4.0 Term	CTCAE v4.0 AE Term Definition	Grade 3	Grade 4	Grade 5
Colitis	A disorder characterized by inflammation of the colon.	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Colonic fistula	A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site.	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Colonic hemorrhage	A disorder characterized by bleeding from the colon.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Colonic obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Colonic perforation	A disorder characterized by a rupture in the colonic wall.	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Colonic stenosis	A disorder characterized by a narrowing of the lumen of the colon.	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Colonic ulcer	A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the colon.	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Diarrhea	A disorder characterized by frequent and watery bowel movements.	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Duodenal fistula	A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site.	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Duodenal hemorrhage	A disorder characterized by bleeding from the duodenum.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

| CTCAE v4.0 Term | CTCAE v4.0 AE Term Definition | Grade 3 | Grade 4 | Grade 5 |

Duodenal obstruction	A disorder characterized by blockage of the normal flow of stomach contents through the duodenum.	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Duodenal perforation	A disorder characterized by a rupture in the duodenal wall.	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Duodenal stenosis	A disorder characterized by a narrowing of the lumen of the duodenum.	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Duodenal ulcer	A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Dyspepsia	A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.	Severe symptoms; surgical intervention indicated	-	-
Enterocolitis	A disorder characterized by inflammation of the small and large intestines.	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Gastric fistula	A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric hemorrhage	A disorder characterized by bleeding from the gastric wall.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastric necrosis	A disorder characterized by a necrotic process occurring in the gastric wall.	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric perforation	A disorder characterized by a rupture in the stomach wall.	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric stenosis	A disorder characterized by a narrowing of the lumen of the stomach.	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

CTCAE v4.0 Term	CTCAE v4.0 AE Term Definition	Grade 3	Grade 4	Grade 5

Gastric ulcer	A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Gastritis	A disorder characterized by inflammation of the stomach.	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastroesophageal reflux disease	A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.	Severe symptoms; surgical intervention indicated	-	-
Gastrointestinal fistula	A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal pain	A disorder characterized by a sensation of marked discomfort in the gastrointestinal region.	Severe pain; limiting self care ADL	-	-
Ileal fistula	A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site.	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Ileal hemorrhage	A disorder characterized by bleeding from the ileal wall.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Ileal obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum.	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Ileal perforation	A disorder characterized by a rupture in the ileal wall.	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Ileal stenosis	A disorder characterized by a narrowing of the lumen of the ileum.	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Ileal ulcer	A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Ileus	A disorder characterized by failure of the ileum to transport intestinal contents.	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death

CTCAE v4.0 Term	CTCAE v4.0 AE Term Definition	Grade 3	Grade 4	Grade 5

Intra-abdominal hemorrhage	A disorder characterized by bleeding in the abdominal cavity.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Jejunal fistula	A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site.	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Jejunal hemorrhage	A disorder characterized by bleeding from the jejunal wall.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Jejunal obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum.	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Jejunal perforation	A disorder characterized by a rupture in the jejunal wall.	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Jejunal stenosis	A disorder characterized by a narrowing of the lumen of the jejunum.	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Jejunal ulcer	A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Lower gastrointestinal hemorrhage	A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus).	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Nausea	A disorder characterized by a queasy sensation and/or the urge to vomit.	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Obstruction gastric	A disorder characterized by blockage of the normal flow of the contents in the stomach.	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Pancreatic duct stenosis	A disorder characterized by a narrowing of the lumen of the pancreatic duct.	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Pancreatic fistula	A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site.	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

CTCAE v4.0 Term	CTCAE v4.0 AE Term Definition	Grade 3	Grade 4	Grade 5

Pancreatic hemorrhage	A disorder characterized by bleeding from the pancreas.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pancreatic necrosis	A disorder characterized by a necrotic process occurring in the pancreas.	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Pancreatitis	A disorder characterized by inflammation of the pancreas.	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Peritoneal necrosis	A disorder characterized by a necrotic process occurring in the peritoneum.	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Retroperitoneal hemorrhage	A disorder characterized by bleeding from the retroperitoneal area.	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Small intestinal mucositis	A disorder characterized by inflammation of the mucous membrane of the small intestine.	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Small intestinal obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents.	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Upper gastrointestinal hemorrhage	A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Vomiting	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders - Other, specify		Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Bile duct stenosis	A disorder characterized by a narrowing of the lumen of the bile duct.	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Biliary fistula	A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site.	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

CTCAE v4.0 Term	CTCAE v4.0 AE Term Definition	Grade 3	Grade 4	Grade 5

Hepatic failure	A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
Hepatic hemorrhage	A disorder characterized by bleeding from the liver.	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hepatic necrosis	A disorder characterized by a necrotic process occurring in the hepatic parenchyma.	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Hepatic pain	A disorder characterized by a sensation of marked discomfort in the liver region.	Severe pain; limiting self care ADL	-	-
Perforation bile duct	A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death