A STUDY OF STEREOTACTIC BODY RADIATION THERAPY IN PATIENTS WITH UNRESECTED CARCINOMA OF THE PANCREAS OR AMPULLA

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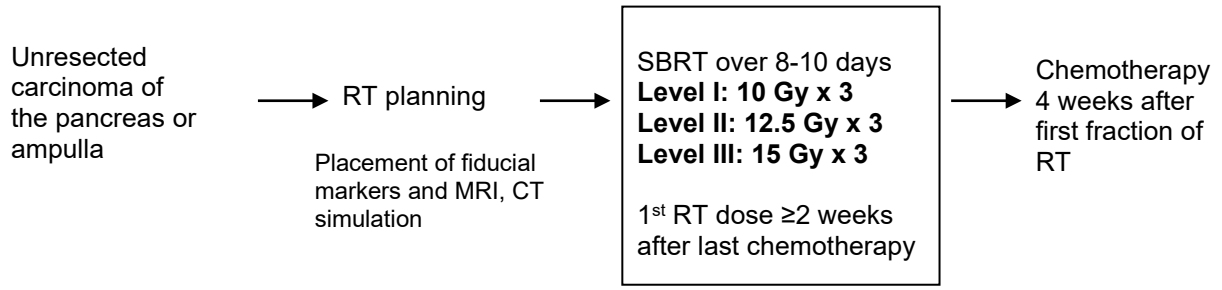

Patient Population: (see section 3.0 for complete eligibility)

- Biopsy-proven unresected cancer of the pancreas or ampulla
- No prior complete surgical resection
- ECOG performance status ≤2
- No prior history of radiation therapy to the abdominal area
- Primary tumor size ≤7.5 cm in largest diameter
- No duodenal invasion
- Patients with metastatic disease may be included if local symptoms are present

Required Sample Size: upto 24 patients, with 1-2 patients accrued per month

Study Center: University of Chicago Medical Center, Pritzker School of Medicine

Concept and Rationale: Cancers involving the upper gastrointestinal tract often present at advanced stages, and as such, are associated with an overall survival that may be less than one year after diagnosis. Because these cancers may progress both locally and distantly, a standard of care for unresected, non-metastatic disease is to administer both Radiation Therapy (RT) and systemic chemotherapy. Typically, radiation therapy is given concurrently with radiosensitizing chemotherapy using conventional fraction sizes (1.8-2 Gy/fraction), requiring 5-6 weeks of treatment.

In recent years, the ability to more precisely target and treat disease with RT has sparked interest in delivering larger fraction sizes (e.g., > 8 Gy/fraction), thereby reducing treatment time, and perhaps improving biologic effect. For other sites such as the lung and liver, this form of therapy (known as Stereotactic Body Radiation Therapy) has achieved high rates of local control, with no appreciable increase in toxicity of treatment in the observed time of follow-up.

From a practical standpoint, if there existed an effective and safe means to achieve local control and contract the length of RT into two weeks, patients would be more likely to tolerate aggressive systemic therapy. Meanwhile, with a positive initial experience in the unresectable setting, SBRT could be studied in the preoperative setting (e.g., for resectable or borderline resectable patients).

Primary Objective: To assess the maximum tolerated dose of delivering three fractions of SBRT and identify the appropriate dose for unresected carcinoma of the pancreas or ampulla

Secondary Objectives: To define toxicities, the post-treatment pain score, and quality of life, the rate of post-treatment resectability, and local control (as measured by CT or MRI and defined as lack of progressive disease by RECIST criteria).

Study Design:

- Dose escalation schema: Patients will be enrolled in a 3+3 dose escalation schema including doses of 10 Gy, 12.5 Gy, and 15 Gy. Once the MTD is reached, patients will be treated in an expanded cohort.
- Radiation therapy: The primary tumor will be treated with stereotactic body radiation therapy in three fractions over 10 days. Fiducial markers will be placed prior to therapy, when possible, to assist with localization. Respiratory gating will be used to help address movement of the target due to respiratory motion. Constraints to surrounding critical structures (duodenum, liver, kidneys, and spinal cord) will be observed.
- Chemotherapy: No concurrent chemotherapy will be administered with the RT. Patients will be allowed to receive chemotherapy prior to RT, although this is not required. Post-RT chemotherapy will be at the discretion of the treating physicians.
- Surgery: ability to achieve resection will be documented by completeness of resection (complete microscopic, incomplete microscopic, or gross residual). Re-evaluation for resectability will be at the discretion of the treating physician and not be a requirement of the study.

Statistical Methods: A 3+3 dose escalation design will be used. The maximum tolerated dose will be exceeded if 2 or more patients out of 6 (or a third or more) experience a dose limiting toxicity (DLT) at that dose. The dose immediately below will be recommended for further study. DLTs are defined as any acute toxicity of Grade 4 nausea, Grade 4 skin toxicity, Grade 3+ liver toxicity (metabolic or ascites), or Grade 3+ enteritis. Severe late toxicities of interest (occurring beyond the 4 week period of evaluation and up to 12 months after RT) will include any Grade 3+ gastrointestinal toxicity (such as small bowel ulcer, stricture, perforation, bleed, liver damage, pancreatitis, or cholecystitis). If the rate of any severe late toxicity of interest exceeds 25% (i.e., 7 or more patients in the expanded cohort of 18 treated at the MTD), the study committee will suspend accrual and determine whether further dose modifications are needed; the protocol will be amended accordingly.

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1. OBJECTIVES

1.1. Primary Objectives

The primary objective is to assess the Maximum Tolerated Dose (MTD) of delivering three fractions of Stereotactic Body Radiation Therapy (SBRT), and identify the appropriate dose for treatment of unresected carcinoma of the ampulla or pancreas.

1.2. Secondary Objectives

Secondary objectives include defining toxicities, effect on pain score, and quality of life, the rate of post-treatment resectability, and local control (as measured by CT or MRI and defined as lack of progressive disease by RECIST criteria).

2. BACKGROUND

2.1 Unresectable Carcinoma of the Pancreas

Cancers involving the upper gastrointestinal tract often present at advanced stages. While surgical resection offers some potential for long-term disease control, few patients present when disease can be addressed with a successful resection. As such, many patients with this disease have an overall survival that is less than one year after diagnosis. Because these cancers may progress both locally and distantly, and cause significant symptoms, patients are candidates to receive a combination of local Radiation Therapy (RT) and systemic chemotherapy. For patients with non-metastatic pancreatic cancer, data support the use of 5-Fluorouracil and RT as a means to favorably impact overall survival (Moertel, 1981). Typically, RT is given concurrently with radiosensitizing chemotherapy using conventional fraction sizes (1.8-2 Gy/fraction), over 5-6 weeks of treatment. Fewer data are available to support the use of RT for carcinoma of ampulla. However, it is known that these cancers are aggressive and have high rates of recurrence after surgical resection (Carter, 2008). In the unresectable setting, whether patients present with locally advanced or metastatic disease, lack of treatment may result in local symptoms including pain, gastrointestinal or biliary obstruction, bleeding, or perforation. For patients who are candidates to receive therapy, RT may be a useful adjunct to systemic chemotherapy to palliate patients of these symptoms (Boz, 2001).

2.2 Rationale

In recent years, the ability to more precisely target and treat disease with RT has sparked interest in delivering larger fraction sizes (e.g., > 8 Gy/fraction), thereby reducing treatment time, and perhaps improving biologic effect. For other sites such as the lung and liver, this form of therapy (known as Stereotactic Body Radiation Therapy) has achieved high rates of local control, with no appreciable increase in toxicity of treatment with limited follow-up (Timmerman, 2007; Kavanagh, 2006). In

the setting of unresectable pancreatic cancer, there are two published experiences using SBRT techniques (Hoyer, 2005; Koong, 2004). The experience from Stanford (Koong, 2004) with 15-25 Gy in one fraction has been favorable, with only 5 of 15 patients treated on this dose escalation protocol demonstrating grade 1-2 toxicity (nausea, diarrhea, abdominal pain) with no patient demonstrating grade 3+ toxicity on initial report. Meanwhile, all 6 patients treated to the highest dose of 25 Gy had local control of the disease. Longer term follow-up of 77 patients treated with 25 Gy demonstrated a local control rate of 84% at 1 year, with moderate late toxicity (Grade 2+) in 10 (13%) of patients (Chang, 2008). The nature of the toxicity was related to gastrointestinal function, including ulceration of the small bowel (n=3) or stomach (n=3), stricture of the duodenum (n=1) or biliary system (n=2), or perforation of the small bowel (n=1). Toxicity was increased for men who received prior external beam radiation therapy in addition to the single stereotactic dose of 25 Gy. The risk of severe toxicity (G3+) was approximately 10% in patients treated with SBRT alone. In contrast, a phase II study from Denmark (Hoyer, 2005) treated 22 patients with 45 Gy (15 Gy x 3 fractions) for unresectable pancreatic cancer and found lower rates of control. Local control was only 57% at 6 months. This lower rate of local control is consistent with the approximately 50% rates observed in other studies giving standard fractionation RT, including post-operative (Smeenk, 2007) and definitive settings (Moertel, 1981). Meanwhile, grade 2+ toxicity (defined in this study as performance status, nausea, diarrhea, or pain at day 14 assessment) was 79%. Of note, pretreatment evaluation revealed that patients had symptoms consistent with grade 2+ toxicity in approximately 63%, so the actual increase in toxicity over baseline is difficult to quantify given the grading schema used and the lack of follow-up past day 14. These discrepant reports of SBRT indicate a need for further trials to help identify the role of SBRT for unresectable pancreatic cancer. With the poor ability to achieve local control, it is of interest to note whether SBRT could be more effective than standard fractionation. Furthermore, as neither of these studies followed detailed gastrointestinal toxicity according to prospectively defined dosimetric planning criteria, it is important to better characterize the nature and frequency of such treatment.

From a practical standpoint, if there existed an effective and safe means to achieve local control and contract the length of RT into two weeks, patients would be more likely to tolerate aggressive systemic therapy. A recent phase III study randomizing patients with unresectable pancreatic cancer to gemcitabine chemotherapy with or without sandwich 5-FU, cisplatin, and concurrent RT found that the aggressive local therapy was associated with significant toxicity, which limited administration of systemic therapy and negatively impacted survival (Mornex, 2007). Meanwhile, "standard" administration of 5-FU with continuous course RT is also associated with a risk of severe toxicity. The RTOG 97-04 demonstrated a 59% risk of any Grade 3 non-hematologic toxicity in patients who received 5-FU/RT and adjuvant systemic therapy after pancreaticoduodenectomy (Regine, 2008). The hypothesis of any SBRT approach for locally advanced, non-metastatic pancreatic cancer is that this combination of dose-intense local therapy over 2 weeks will be relatively well tolerated, and not preclude further aggressive systemic therapy. It is possible that the proposed treatment will result in less quality of life decline than standard fractionation. Meanwhile, with a positive initial experience in the unresectable setting, SBRT could be studied in the preoperative setting (e.g., for borderline resectable patients). RT with

standard fractionation has been studied in the preoperative setting, with disappointing results. It is estimated that, after careful selection of borderline resectable patients and treatment with preoperative radiation therapy and chemotherapy, approximately 40% of these patients are able to then undergo resection (Katz, 2008). Resectability is the most important prognostic factor for success after treatment, and as such, is an important potential endpoint to evaluate.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed, unresected cancer of the pancreas or ampulla. The cancer may include any invasive histology (e.g. adenocarcinoma, neuroendocrine carcinoma). Patients with lymph node involvement or distant metastasis may be included if it is felt that local control of the primary site of disease would help reduce, or prevent the development of, local symptoms.

3.1.2 Patients must have measurable radiographic disease. Patients with previous complete resection are only eligible if there is measurable radiographic disease which is clearly felt to represent locally recurrent disease.

3.1.3 Patients may receive any number of cycles of chemotherapy prior to treatment with SBRT, but not within 2 weeks of the first fraction of RT. Patients are not required to receive any chemotherapy to be eligible for study enrollment.

3.1.4 Age $\geq$18 years. The effects of this therapy are unstudied in the pediatric population.

3.1.5 ECOG performance status $\leq$2 (Karnofsky $\geq$60%, see Appendix A).

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count (ANC) $\geq$ 1,800 cells/mm3
- Platelets $\geq$ 100,000 cells/mm3
- Hemoglobin $\geq$ 8.0 g/dl
- Creatinine $\leq$2 X institutional upper limit of normal
- total bilirubin $\leq$2.5 X institutional upper limit of normal
- AST(SGOT) or ALT(SGPT) $\leq$2.5 X institutional upper limit of normal

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 3.2.2 Concurrent investigational therapy delivered over the period of treatment or observation (28 days post-RT) for dose limiting toxicity.

3.2.3 Prior radiation therapy to the abdominal area which would overlap with the proposed area of treatment.

3.2.4 Pregnancy. Radiation therapy is known to have adverse effects on the fetus.

3.2.5 Primary disease >7.5 cm in largest diameter as measured by CT or MRI.

3.2.6 Gross extension of tumor into the lumen of the duodenum.

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Use of bevacizumab or vascular endothelial growth factor inhibitor chemotherapy within 3 months before RT or 6 months after RT.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1 Radiation Therapy Dose Escalation

Treatment will be administered on an outpatient basis. Details regarding planning and administration of RT are described in Section 6. Reported adverse events and potential risks are described in Section 7.

Dose-Escalation Schedule	
Dose Level	
Level -1	7.5 Gy x 3
Level 1	10 Gy x 3
Level 2	12.5 Gy x 3
Level 3	15 Gy x 3

4.2 Measuring Health Related Quality of Life

Patient reported outcome measures will include the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) questionnaire, a 45-item self-reported instrument designed to measure health-related quality of life (HRQOL) in patients with hepatobiliary cancers including pancreatic cancers. The FACT-Hep consists of the 27-item FACT-G, which assesses generic HRQOL concerns including physical, emotional, social and functional well being, and the newly validated 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues (see Appendix D). The questionnaire will be administered to all patients on trial at baseline, post treatment at follow up exams at 1,2,4,6,9 and 12 months from the start of SBRT. The questionnaire will be completed in writing by the patients, and after 12 months from the start of radiation therapy it will not be required.

4.3 Definition of Dose-Limiting Toxicity

The evaluation period of acute toxicity will be defined by the period of 28 days following the first fraction of RT. Dose Limiting Toxicity (DLT) will be defined according to Common Toxicity Criteria version 3.0 (See Appendix B) and includes the following acute toxicities:

- Grade 4 nausea (life-threatening consequences)
- Grade 4 skin toxicity (necrosis or ulceration of full thickness dermis, spontaneous bleeding from involved site)
- Grade 3+ liver toxicity including symptomatic ascites requiring invasive procedure, or total bilirubin >3 x ULN, or AST >5 x ULN, or ALT >5 x ULN that persists until day 28, and is attributable to radiation therapy.
- Grade 3+ enteritis (abdominal pain, fever, change in bowel habits with ileus, peritoneal signs) that is attributable to radiation therapy.

Patients must have a minimum of 3 weeks of follow-up after RT start for patient data to contribute enough follow-up for consideration of dose-limiting toxicity. However, any DLT that occurs with shorter follow-up will count towards the dose escalation rules. In addition, any grade 5 toxicity (i.e., death) considered possibly, probably or likely related to RT will be considered a DLT.

Any late toxicity that occurs beyond the 4 week period of evaluation will be closely followed and documented as a toxicity of interest. Included are the following severe late toxicities of RT:

- Grade 3+ gastrointestinal ulcer, fistula, stricture, or perforation (symptomatic and severely altered GI function, IV fluids or TPN ≥24 hrs, intervention indicated)
- Grade 3+ gastrointestinal mucositis (confluent ulcerations or pseudomembranes, bleeding with minor trauma)
- Grade 3+ gastrointestinal bleed (transfusion, interventional radiology or endoscopic or operative intervention)
- Grade 3+ gastrointestinal necrosis (inability to aliment adequately by GI tract, interventional radiology, intervention indicated)
- Grade 3+ liver toxicity including symptomatic ascites requiring invasive procedure, or total bilirubin >3 x ULN, or AST >5 x ULN, or ALT >5 x ULN, or asterixis, that is attributable to radiation therapy.

- Grade 3+ enteritis (abdominal pain, fever, change in bowel habits with ileus, peritoneal signs) that is attributable to radiation therapy.
- Grade 3+ pancreatitis (interventional radiology or operative intervention indicated)
- Grade 3+ cholecystitis (interventional radiology or operative intervention indicated)

These severe, late toxicities will be evaluated between 1 and 12 months of therapy. There is no minimum follow-up time after RT start required for patient data to contribute enough follow-up for toxicities of interest.

Enrollment of 12 additional toxicity-evaluable patients at the MTD will provide a cohort of 18 patients at the putative MTD. If six or fewer of the 18 patients experience a toxicity of interest during the evaluation period, the combination will be considered tolerable. If 7 or more patients experience a toxicity of interest, the study committee will suspend accrual and determine whether further dose modifications are needed; the protocol will be amended accordingly. If the true probability of DLT at the MTD is 50%, the combination will be identified as too toxic with probability 0.88. If the true probability of DLT at the MTD is 25%, the combination will be identified as having an acceptable toxicity profile with probability 0.86.

Management associated with the above adverse events is outlined in Section 7.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

4.4 General Concomitant Medication and Supportive Care Guidelines

There is no restriction towards the use of any non-chemotherapeutic agent during administration of RT as specified for the symptom management.

A proton pump inhibitor is recommended one week prior and for three months following RT. Ondansetron 8 mg will be administered prior to each radiation treatment. It is optional for patients to receive corticosteroid premedication (e.g. dexamethasone 4 mg p.o. in a single dose) 15-60 minutes prior to each of three treatments. Analgesic premedication to avoid general discomfort during long radiation planning or treatment durations is also recommended when appropriate. Antiemetics will be ordered at the discretion of the attending physician. Mucositis/esophagitis may be treated with sulcrafate or a GI cocktail (e.g. Tylenol #3 suspension, benadryl elixir, Maalox, viscous lidocaine). Intravenous hydration is recommended in patients with inadequate oral intake. Treatment-related diarrhea may be managed with loperamide. The recommended dose of loperamide is 4 mg initially (two capsules) then 2 mg after each loose stool, not to exceed 16 mg daily.

Administration of chemotherapy concurrent with RT is not allowed. Chemotherapeutic agents given before or after RT are at the discretion of the treating physician, with exclusion of bevacizumab or vascular endothelial growth factor inhibitor, given concern for RT-related wound healing issues particularly regarding small bowel.

4.5 Duration of Therapy

Duration of SBRT is to occur within a 10 day time period. Completion of the three fractions of RT will be delayed or foregone if:

- Intercurrent illness that prevents further administration of treatment,
- Further treatment is felt to be likely to result in severe and permanent impairment, or death (life-threatening toxicity),
- The patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

The use of chemotherapy after RT will be at the discretion of the treating physician.

4.6 Duration of Follow Up

Patients will be followed on protocol for 12 months after initiation of RT or until death, whichever occurs first. Patients removed from protocol therapy for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.7 Criteria for Removal from Study

Patients will be removed from study (but followed for potential of toxicity) when any of the criteria listed in Section 4.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5. Radiation Therapy Guidelines

5.1 Treatment Related Planning Procedures

5.1.1. All patients will be evaluated prior to simulation for placement of fiducial markers (by endoscopic approach or interventional radiology) in or around the primary tumor, for purposes of stereotactic localization prior to SBRT. Marker placement is preferred but not required.

5.1.2. When done, the ideal timing of MRI will be ≥2 days after placement of fiducial markers.

5.1.3. All patients will undergo CT simulation ≥2 days after placement of markers, and prior to the first treatment using appropriate immobilization**.** Patients should have no food 2 hours prior to undergoing simulation. However, medications may be taken with liquid.

5.1.4. Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment.

5.1.5. Simulation with respiratory gating and acquisition of a 4D CT scan for retrospective respiration phase-based imaged sorting is highly preferred but not required.

5.2 RT Planning Parameters

5.2.1. The definition of volumes will be in accordance with the ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy. (ICRU, 1999)

5.2.1.1. A gross tumor volume (GTV) will be entered for each lesion, based on available imaging data.

5.2.1.2. In the absence of respiratory gating, an internal target volume (ITV) will be defined as the volume that accounts for intrafraction target motion.

5.2.1.3. A clinical target volume (CTV) will be defined as the GTV or ITV (when available) plus a margin for microscopic extension.

5.2.1.4. A planning target volume (PTV) will be determined which will correspond to CTV plus appropriate margin for tumor motion and set-up uncertainty.

5.2.2. 3D coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose volume histogram of the PTV and normal structures. 3D “forward” planning or “inverse” planning with beamlet intensity modulated treatment planning are allowed.

5.2.3. Treatment is to be delivered using a linear accelerator and photon energies ≥ 6 MV.

5.2.4. Corrections will be made to account for tissue heterogeneity.

5.2.5. RT is to be delivered to each site in 3 fractions over a period of up to 10 total days.

5.2.6. RT Dose: A phase I escalation of doses will be performed in order to determine in MTD in Gy. Doses of radiation will start at Level 1 and increase as follows in order to determine the MTD in Gy:

Level 1: 10 Gy/ fraction x 3 fractions = 30 Gy

Level 2: 12.5 Gy/fraction x 3 fractions = 37.5 Gy
Level 3: 15 Gy/fraction x 3 fractions = 45 Gy
If DLT is met at Level 1, dose will be de-escalated to Level -1: 7.5 Gy x 3 fractions = 22. 5 Gy

5.2.7. Doses will be prescribed to the PTV. The PTV may be covered by a lower isodose line than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-100%. Ideally, the prescription dose will cover >90% of the GTV (V100 GTV > 90%, and V95PTV > 90%). A lower coverage goal (with no minimum requirement of PTV coverage) will be acceptable if necessary to meet normal tissue constraints, which will be assigned priority over tumor coverage.

5.2.7.1. Any dose > 110% must be within the PTV.

5.2.8. Dose/volume constraints: The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and are listed as total over 3 fractions and per fraction. In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms (DVHs) can be generated.

Organ	Volume	Dose
Spinal cord	Any point	21 Gy (7 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Stomach	<2 cc	24 Gy (8 Gy per fraction)
	Any point	30 Gy (10 Gy per fraction)
Heart/pericardium	Any point	30 Gy (10 Gy per fraction)
Liver	700 cc	17 Gy (5.66 Gy per fraction)
Duodenum	<2 cc	24 Gy (8 Gy per fraction)
	Any point	30 Gy (10 Gy per fraction)
Jejunum/ileum	<2 cc	24 Gy (8 Gy per fraction)
	Any point	30 Gy (10 Gy per fraction)
Total kidney	200 cc	15 Gy (5 Gy per fraction)
Skin	Any point	24 Gy (8 Gy per fraction)

5.2.9. Contouring of normal tissue structures

- Spinal cord. The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.
- Esophagus. The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.
- Stomach. The outer wall of the stomach will be contoured to include the cardia of the stomach to the pylorus.
- Heart/pericardium. The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

- Liver. The normal liver is defined as that portion of liver not radiographically involved by gross tumor (Normal liver volume minus GTV).
- Duodenum. The outer wall of the duodenum will be contoured from the edge of the pylorus of the stomach to the start of the jejunum, and include four segments of the duodenum.
- Jejunum/ileum. The jejunum and ileum will be contoured to include the outer wall of the small bowel distal to the duodenum to the end of the ileum, and also include the mesentery and vessels anterior to the aorta.
- Total kidney. Kidneys will be contoured to include the renal capsule and parenchyma up to the hilum.
- Skin. The skin will be defined as the outer 0.3 cm of the body surface. As such it is a rind of uniform thickness (0.3 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

5.3 RT Treatment

5.3.1. The first fraction of RT should occur no earlier than 2 weeks after administration of the last dose of chemotherapy.

5.3.2. Patients should have no food 2 hours prior to receiving treatment. However, medications may be taken with liquid.

5.3.2. Orthogonal portal films (imaging to visualize fiducial markers) or cone beam CT must be obtained and approved by the radiation oncologist prior to each treatment. Treatment will preferably be administered with respiratory gating.

6. ADVERSE EVENTS

Adverse event (AE) monitoring and reporting will be performed.

- Radiation side effects are limited to the area involved in the treatment field. Acute and late toxicity related to radiation therapy may include fatigue, nausea and vomiting, skin erythema, subcutaneous fibrosis, esophagitis, pericarditis, diarrhea, myelitis, damage to the small bowel (including stricture or obstruction, bleed, fistula formation, or perforation), liver dysfunction, kidney damage, and radiation enteritis.

- Acute toxicity including Grade 4 nausea, Grade 4 skin toxicity, and Grade 3 liver toxicity will be referred to as dose limiting toxicities (DLT).

- Late toxicity including any Grade 3+ GI toxicity (small bowel damage including stricture or obstruction, bleed, fistula formation, or perforation; liver damage including ascites but not including abnormal lab values only; pancreatitis, cholecystitis) will be considered a toxicity of interest.

- All life-threatening Grade 4 and all fatal toxicities (Grade 5) must be reported immediately and evaluated.

- Acute toxicity: Acute side effects are considered as occurring ≤ 28 days from the start of radiation therapy. They will be documented using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (A copy can be downloaded from http://ctep.info.nih.gov). The relevant sections are included in the appendix.

- Late toxicity: Late side effects are considered as occurring > 28 days from the start of radiation therapy through a 12 month total evaluation period. They will also be documented using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The relevant sections are included in the appendix.

- University of Chicago Reporting Guidelines

  - If the reaction requires reporting, the Research Nurse or MD reports the adverse reaction to the Cancer Clinical Trials Office (CCTO) at 773-702-5149 by the end of the business day when he/she becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12 pm (noon) the next business day.

  - The following information is required when calling in the event:

    - Caller's Name and Telephone Number
    - Patient Initials
    - Patient Medical Record Number
    - IRB Protocol Number
    - PI of Study
    - Attending Physician
    - Date of Event
    - Description of Event (including grade of the event and attribution of the event and if the event required hospitalization)

  - E-mail is sent to the research nurse, attending physician and PI of the study informing them that adverse reaction notification has been received.

  - The University of Chicago's IRB Serious Adverse Event Form must be sent to the CCTO within **5 calendar days of event occurrence**. The UC IRB Serious Adverse Event form is available on-line at: http://ors.bsd.uchicago.edu/HS/newirbforms. This form must be typed. Once the forms are completed, the original is forwarded to the study PI to review and sign. The signed report is delivered to the QA Coordinator. A weekly report of delinquent or pending documents will be forwarded to the applicable person who reported the event. All delinquent reporting (greater than 10 days from event occurrence) must include documentation of reason for delinquency and may require implementation of an action plan.
  - Once the appropriate AE documents have been received, the CCTO forwards these to the IRB. A copy will be forwarded to the appropriate Research Nurse.

- Data Safety and Monitoring

- Data Safety and Monitoring will occur at the weekly University of Chicago GI oncology phase I/II conference meetings, which are lead by senior level medical oncologists. At each meeting, all active studies will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be completed for each protocol and signed by either the Principal Investigator, the Chairman of the Department or by his designate if the Chairman is not available.

7. STUDY CALENDAR

Baseline evaluations (including pain score, performance status, and medications) are to be conducted within 21 days prior to start of protocol therapy. Scans must be done within 28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of therapy.

	Pre-treatment	Week 1 of RT	Week 2 of RT	Post-treatment
Inclusion/exclusion	X			
Informed consent	X			
Pathology confirming cancer	X			
History and physical	X	X	X	X[f]
Vital signs	X	X	X	X[f]
Performance status and pain score	X	X	X	X[f]
Documentation of current medicines	X	X	X	X[f]
CT or MRI of abdomen[a]	X			X[a]
Hematology[b]	X	X	X	X[f]
Chemistry[c]	X	X	X	X[f]
β-HCG[d]	X			
Patient QOL Questionnaire	X			X[f]
Toxicity assessment[e]		X[e]	X[e]	X[f]

a = Imaging will be done within 28 days of RT start, and in follow up at 3-5 weeks after completion of RT. Further abdominal imaging will be performed every 6 months for the first year after RT.
b = CBC with differential, platelet count
c = comprehensive metabolic profile (glucose, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, calcium, total bilirubin, alkaline phosphatase, AST, ALT). CA19-9 will be measured at months 1, 6, 12 from the start of radiation therapy, then every 6 months indefinitely (off protocol).
d = for women of child bearing potential, serum beta-hCG
e = prior to each radiation treatment after the first fraction, and with all other post-treatment clinic visits
f = From the start of radiation therapy, visits will be q2 weeks for the first month; then at months 2, 4, 6, 9, and 12; then every 6 months indefinitely (off protocol).

8. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated with CT or MRI of the abdomen at 3-5 weeks after RT, and every 6 months for the first year.

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Therasse, 2000). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

8.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with RT.

Evaluable for objective response. Only those patients who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

8.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT or MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease.

Target lesions. The primary lesion (with immediately adjacent lesions) that will be treated with RT should be identified as the **target lesion(s)** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

8.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

CT and MRI These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously.

8.1.4 **Response Criteria**

8.1.4.1 **Evaluation of Target Lesions**

Complete Response (CR):Disappearance of the primary target lesion(s)

Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The study is a phase I/II study that will escalate dose according to determination of dose limiting toxicities, in a 3+3 design as outlined in section 5.2. The MTD will be exceeded if 2 or more patients out of 6 (or a third or more) experience a DLT at that dose. The dose immediately below will be recommended for further study. . The phase II portion of the study will continue accrual at the maximum tolerated dose and measure the efficacy and health related quality of life after SBRT.

9.2 Sample Size/Accrual Rate

The study will accrue 18 patients at the putatitive maximum tolerated dose, giving a sample size of up to 24 patients. Accrual will likely be 1-2 patients per month. Toxicities of interest that occur within the 1-12 month time frame after RT start will be documented. For further detail regarding modification of enrollment or dose escalation based on late toxicities of interest, see section 5.2.

9.3 Analysis of Secondary Endpoints

Secondary endpoints will include post-treatment surgical resectability, and local control. Patients who are able to undergo surgical resection will be documented as having a microscopically complete (R0), microscopically incomplete (R1), or gross incomplete (R2) resection.

All patients included in the study will be assessed for response to treatment. Patients who do not demonstrate any local progression (patients with CR+PR+SD) at the primary site (using RECIST criteria by CT or MRI) will be considered to be locally controlled. Duration of local control (TLC) will be defined to be the time from the start of RT until clinical or RECIST progression, death from treatment toxicity, or last patient follow-up. Patients who experience clinical or RECIST progression, or death from treatment toxicity will be considered to have experienced a local control event; otherwise patients will be considered censored at last contact. The probability of LC as a function of time since RT will be quantified by the method of Kaplan and Meier (Kalbfleisch, 2002). The relative hazard for LC event according to assigned RT level will be calculated using the relative risk regression model of Cox, but formal statistical conclusions will not be drawn from this analysis.

10. CONFIDENTIALITY

10.1 Patient Confidentiality Issues

Study records that identify patients will be kept confidential. Study records will contain patients' name, address, and medical history number and will be available to the study doctor, research nurse, and data coordinator. Data collected in this study will be maintained on a password protected computer that only the primary investigator, co-investigators, research nurse, and data coordinator will be able to access. Study records will be secured in locked offices in the Department of Radiation and Cellular Oncology. Neither patient's name nor other personally identifying information will be used in any publication resulting from the research study.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

TOXICITY

Acute toxicity

	Grade				
Adverse event	1	2	3	4	5
Skin, dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening Consequences	Death
AST (SGPT) or ALT (SGOT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Total bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	-
Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening Consequences	Death
Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death

Late toxicity

	Grade				
Adverse event	1	2	3	4	5
Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening Consequences	Death
Enteritis	Asymptomatic, pathologic or radiographic	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel	Life-threatening consequences (e.g.,	Death

	findings only		habits with ileus; peritoneal signs	perforation, bleeding, ischemia, necrosis)	
Fistula	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening Consequences	Death
Mucositis	Erythema of the mucosa	Patchy ulcerations or Pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Necrosis	-	-	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Obstruction	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 Hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Perforation	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening Consequences	Death
Stricture/stenosis	Asymptomatic radiographic	Symptomatic; altered GI	Symptomatic and severely altered GI	Life-threatening consequences;	Death

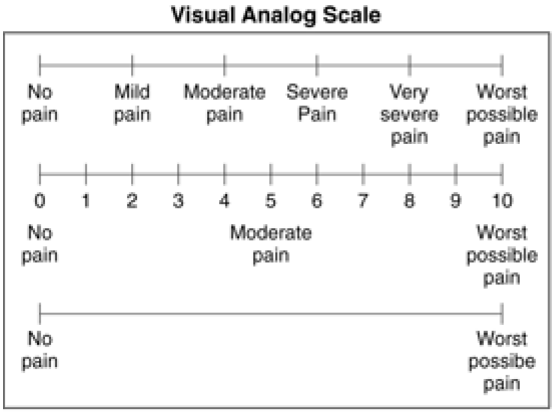
	findings only	function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	operative intervention requiring complete organ resection (e.g., total colectomy)	
Ulcer	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening Consequences	Death
Hemorrhage, GI	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
Liver dysfunction	-	Jaundice	Asterixis	Encephalopathy or coma	Death
Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
AST (SGPT) or ALT (SGOT)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Total bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	-

APPENDIX C

Pain score (report numerical scale only)

FACT-**Hep (Version 4)**

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.



Not at all	A little **bit**	Some-**what**	Quite **a bit**	Very **much**

APPENDIX D

PHYSICAL WELL-BEING

GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed.....	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Ouite a bit	Verv much
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1 *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*

GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7						

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6						
Hep1 CNS 7	I have a good appetite	0	1	2	3	4
Cx6	I am unhappy about a change in my appearance	0	1	2	3	4
H17	I have pain in my back	0	1	2	3	4
An7	I am bothered by constipation	0	1	2	3	4
Hep2	I feel fatigued	0	1	2	3	4
Hep3	I am able to do my usual activities	0	1	2	3	4
Hep4	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep5	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep6	I have had itching	0	1	2	3	4
HN2	I have had a change in the way food tastes	0	1	2	3	4
Hep8	I am content with the quality of my life right now	0	1	2	3	4
	I have had chills	0	1	2	3	4
	My mouth is dry	0	1	2	3	4
	I have discomfort or pain in my stomach area	0	1	2	3	4