A Phase I Study of Stereotactic Body Radiation Therapy (SBRT) for Liver Metastases (HCC 09-051)

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List of Abbreviations

3DCRT	3 Dimension Conformal External Beam Radiation Therapy
AE	Adverse Event
BED	Biologically Equivalent Dose
BSA	Body Surface Area
CAD	Coronary Artery Disease
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Treatment Volume
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
DVH	Dose Volume Histogram
ECOG	Eastern Cooperative Oncology Group
EDIT	Electronic Data Interface for Transplantation
EORTC	European Organisation for Research and Treatment of Cancer
FHSI	FACT-Hepatobiliary Symptom Index
Fx	Fraction
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GTV	Gross Tumor Volume
Gy	Gray
HCC	Hepatocellular Carcinoma
HPCS	Hepatobiliary Cancer Scale
HRQL	Health Related Quality of Life
INR	International Normalized Ratio
LINAC	Linear Accelerator
MID	Minimally Important Difference
MV	Mega Voltage
NCI	National Cancer Institute
NYHA	New York Heart Association
OTI	Outcome Index
PET/CT	Positron Emissions Tomography / Computer Tomography
PTV	Planning Target Volume
RILD	Radiation Induced Liver Disease
RPM	Real-time Position Management
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic Body Radiation Therapy
SUV	Standard Uptake Value

PROTOCOL SUMMARY

Title

A Phase I Study of Stereotactic Body Radiation Therapy (SBRT) for Liver Metastases

Objectives

The *primary* objectives of this study are:

1. To determine the maximum tolerated dose (MTD) and safety of SBRT for liver metastases using dose escalation.

The *secondary* objectives of this study are to:

1. To evaluate the local control associated with this local regional therapy.
2. To determine local response based on FDG-PET/CT compared to CT alone.
3. To evaluate the Health Related Quality of Life (HRQL) associated with this therapy

Patient population

In order to be eligible for this study, patients must have liver metastases intended for treatment with a combined volume no more than 100 cm^3 in size, $\leq$ 3 total lesions, or one lesion $\leq$ 6cm in greatest dimension. Patients will be required to have adequate pre-treatment baseline liver function, defined as total bilirubin $\leq$ 3mg/dl, albumin > 2.5mg/dl, and INR $\leq$ 2.3. Serum liver enzymes must be less than three times the upper limit of normal. Baseline renal function must be adequate with a creatinine < 1.8mg/dl or creatinine clearance > 50ml/min. Patients must be at least 18 years of age and able to give informed consent. They must have a Karnofsky Performance Status $\geq$ 70 and a life expectancy of at least 3 months. Eligible patients will have also had a FDG-PET/CT (or if insurance does not allow for a PET, then a contrast enhanced CT) scan performed at least 45 days prior to being enrolled in this study, with no chemotherapy within 4 weeks before SBRT and 2 weeks after.

Number of patients

18

Study design and methodology

This is a phase I dose escalation study. Dose escalation will be via the traditional "up and down" scheme detailed in the Statistical Considerations section 7.0.

Treatments administered

SBRT:
Patients will receive one of the following radiation regimens:

- 50 Gy in 5 fractions (10 Gy/fx) delivered over a 2-week period.
- 60 Gy in 5 fractions (12 Gy/fx) delivered over a 2-week period.
- 75 Gy in 5 fractions (15 Gy/fx) delivered over a 2-week period.

Efficacy data collected

The following evaluations will be performed to assess the efficacy of stereotactic body radiation therapy:

- Locoregional control
- Objective tumor response (by RECIST and EORTC 1999 criteria)
- Radiological assessment using FDG-PET/CT to evaluate local control compared to CT
- Quality of life assessment, FACT-HEP score, a validated measure of HRQL in hepatobiliary disease.

Safety data collected

The following evaluations will be conducted to assess the safety of radiosurgery:

- Recording of all toxicity data per NCI CTCAE version 4.0

1.0 Background

1.1 Liver Metastases

The liver is a common site of metastasis in patients with cancer. Autopsy studies estimate that 30-70% of people dying from cancer have liver metastases.[1] Surgical resection has been shown to be an effective palliative technique, and at times even curative for patients with isolated or limited disease in the liver. Studies examining outcome following resection of liver metastases have shown 5 year survival rates of 25-44%, with cure provided to 20-30% of patients.[2] Unfortunately, only an estimated 10-20% of patients with liver metastases are candidates for surgical resection.[3]

For those patients who are not eligible for surgery due to extent of disease, poor performance status, or advanced liver disease, treatment options include ablative therapy, chemoembolization, radiotherapeutic microspheres, and conformal or stereotactic body radiation therapy. Radiofrequency ablation uses high frequency alteration currents to induce ionic vibrations, heating, and subsequent coagulation necrosis of tumor tissue. Cryotherapy, also directly destroys tumor tissue, by lowering the temperature of the tumor to below -40^{o}C. These ablative therapies can produce local control rates of around 66 % with median survival times between 26-32 months.[4, 5] Chemoembolization uses selective intra-arterial chemotherapy with embolization agents to achieve high intra-tumor drug concentrations and destroy the surrounding vasculature to induce necrosis. Response rates to chemoembolization range from 15-55 %.[6] Similarly, Yttirum-90 microspheres can also be used and injected into the vascular supply of hepatic tumors, leading to selective radiation and necrosis of tumor tissue. Response rates can be as high as 90% on follow-up PET imaging, with a median survival of 10.5 months in those patients.[7] Three-dimensional conformal radiotherapy (3DCRT) has also been used concurrently with chemotherapy to treat liver metastases. In one study, 22 patients were treated with doses up to 72.6 Gy, producing a response rate of 50% and an overall median survival of 20 months.[8] A more recent study treated patients with unresectable liver disease with 3DCRT. Treatment consisted of twice daily fractions of 1.5 Gy to a total median dose of 60.75 Gy along with concurrent chemotherapy infused via the hepatic artery. Median survival was 17 months and the most important predictor of survival was radiation dose.[9]

1.3 SBRT for Liver Metastases

Hepatic metastasectomy in patients with a limited number of isolated liver metastases can result in 5-year relapse-free survival rates of 25-44 %.[2] However, in order to qualify for surgical resection patients must be medically-fit, have disease limited to the liver, and have adequate reserve of normal liver parenchyma. These criteria result in only a small fraction of patients being eligible for metastasectomy. Some of these patients who are poor surgical candidates could potentially benefit from non-surgical alternatives such as stereotactic body radiation therapy (SBRT).

SBRT is an ideal approach to minimize radiation exposure to the normal liver while maximizing the dose to the tumor. A phase I trial tested dose escalation from 36 Gy (12 Gy/fx) to 60 Gy in 3

fractions (20 Gy/fx) with no dose limiting toxicities (defined as grade III liver, bowel, stomach, or spinal cord toxicity, or any grade IV toxicity). At the highest dose tier there was one episode of grade I dermatitis (erythema and mild desquamation), one patient with grade I fatigue, and one patient with grade I local pain.[13] A phase I/II trial found that liver metastases treated with 60.0 Gy in 3 fractions over 3 to 14 days was well tolerated with an actuarial local control rate of 93% at 18 months.[14] The authors updated this trial in 2009[24] with a total of 47 patients with 63 metastases. At the time of publication local control at 1 and 2 years was an impressive 95% and 92%. With the update, there was only one episode of grade 3 skin reaction and no grade 4 or 5 toxicity.

A similar phase I trial was conducted at the Princess Margaret Hospital[25] with escalating doses from 27.7 Gy to 60 Gy in six fractions in 70 patients with 143 tumors. The rate of grade III toxicity in this cohort was 10%, manifesting as liver enzyme elevation, thrombocytopenia, and abdominal pain. One paient developed a grade 5 small bowel obstruction. The one year local control was 71%. A study conducted in the Netherlands examined the use of SBRT in the treatment of 45 liver metastases and 11 hepatocellular carcinomas. Patients with metastases were treated to 37.5 Gy over 3 fractions. In the metastases group, the actuarial local control at 1 and 2 years was 100% and 86%, respectively. There were 2 episodes of grade III toxicity manifesting as an incease in GGT. Actuarial 2-year survival was 62% in the metastases group.[15] All of the above data suggest that SBRT is a safe, effective way to deliver non-invasive, local therapy to liver metastases.

2.0 Objectives

Primary

2.1 To determine the MTD and safety of using SBRT for liver metastases.

Secondary

2.2 To evaluate the local control associated with this local regional therapy.

2.3 To determine local response based on FDG-PET/CT compared to CT only.

2.4 To evaluate the HRQL associated with this therapy

3.0 Investigational Plan

3.1 Overall design and plan of study

Prior to registration all patients will be evaluated with a physical exam, review of pathology and laboratory values to confirm diagnosis, and baseline imaging studies.

3.2 Accelerator

Physicians will treat with a stereotactic radiosurgery system using 6MV photons to deliver stereotactic body radiotherapy.

3.3 Doses

Patients will receive a total dose ranging from 50-75 Gy in 5 fractions (10-15 Gy/fx). Dose escalation will be via the traditional "up and down" scheme detailed in the Statistical Considerations section 7.0.

In determining the radiation dose and fractionation scheme for this protocol, we used the linear-quadratic formalism for radiation cell killing to "equate" schemes that vary the dose/fraction and number of fractions. This concept of biologically equivalent dose (BED) states that the total effect is given by:

nd x (1 + d/□□ (α/β))

where n is the # of fractions and d is the dose/fraction. The "alpha-beta ratio" characterizes the radiation response of a particular tissue; a higher value is indicative of a tissue that responds acutely to the effects of radiation. Due to their highly proliferative nature, most tumors fall into this category.

This final dose scheme (total dose 75 Gy) is biologically equivalent to the previously studied doses in the literature (60 Gy in 3 fractions), meaning the first two sets of patients will be treated to a radiobiologically smaller (and likely safer) dose. We would favor treating in five fractions, as opposed to three, to allow more repair of normal tissue, reoxygenation of tumor cells, and redistribution of tumor cells to more radiosensitive parts of the cell cycle. Using a smaller fraction size, 10-15 Gy compared to 20 Gy, will also help reduce late effects of radiation therapy. SBRT treatment will be given on an every other day schedule, excluding weekends. The prescription dose will be prescribed to the isodose line best encompassing the planning target volume (PTV) depending on the volume of tumor (HCC).

3.4 Localization, immobilization, and simulation

Within 5 – 10 days after fiducial placement, patients will undergo 4D FDG-PET/CT simulation with the goal of evaluating tumor motion to allow for gated treatment when indicated. This goal will be accomplished by using the Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA) to create a retrospective 4D CT scan. Following the

institutional protocol, a helical CT scan and a 4D positron emission tomography (PET) scan with a patient with body immobilization device will be acquired. A patient will not eat or drink anything for four hours before the PET scan. Before the PET scan, blood sample will be taken from either a finger stick or a vein in the arm to check the sugar level. An injection of a small amount of a radioactive drug called FDG ([F18] fluorodeoxyglucose) which is a chemical similar to sugar will be administered into a vein in the arm or hand. Approximately 45 to 60 minutes after the injection of FDG, the patient will be asked to urinate (to empty the bladder).

The patient will be set up in the PET/CT scanner using a vacuum cushion for immobilization in the supine position with feet tied and hands across the chest or above the head. There will also be a respiration-monitoring device called a marker block placed 5cm below the patient's xyphoid process. An infrared camera at the foot of the CT table will capture the images of the marker block and relay them to the RPM computer, which in turn will translate the images into a respiratory pattern. The audio coach (which instructs the patient in regulating breathing) will be calibrated to both patient comfort and time of expiration, inspiration, and full breathing cycle. The placing of the patient in a body immobilization device will take about 10-15 minutes. The patient will need to lie still for about 30 minutes before the completion of the 4D PET scan. The PET/CT scanner will then be programmed to acquire a retrospective 4D CT scan with a set of images for each phase of the breathing cycle. This scan will take place immediately after the PET scan. It will take around 5-10 minutes. The physician or physicist will then select the number of breathing phases to use while the software program selects the best image for each selected breathing phase.

The entire FDG-PET/CT scan procedure is expected to take about 2 hours.

3.5 Treatment Planning

Treatment planning will be carried out using the planning station for the radiosurgery equipment being used for treatment. The gross tumor volume (GTV) will be contoured on the fused image set. Two GTV volumes will be contoured; the gross tumor as seen on CT alone and the gross tumor corresponding to FDG avidity. No margins will be added for clinical target volume (CTV), but custom margins will be added for the planning target volume (PTV) based on the findings of the 4D FDG-PET/CT motion study assessment. The treatment will be prescribed to the isodose line that best covers the planning target volume, which will typically be the 80% isodose line.

3.6 Treatment Delivery

SBRT will take place within 14 days of the treatment planning scan. The planning data containing the coordinates of tumor isocenter, the external infrared markers, and the implanted markers are transferred to the appropriate platform depending on the treating machine. If the patient meets the criteria of gating technique then treatment delivery will be accomplished using the appropriate gating technology. Depending on the technology used external infrared markers attached to the patient's skin or a marker block placed on the patient's chest is used to determine the breathing pattern. The size of beam-on window will be determined based on the target

motion as detected by the 4D FDG-PET/CT scan. The threshold for gated treatment delivery is determined based upon the target motion due to respiration.

The daily initial positioning during treatment delivery will be performed using lasers and skin marks and infrared optical markers as appropriate. The target isocenter will be verified using daily imaging. Depending on the platform used, the moving target will be positioned within the beam under infrared and/or image guidance

3.7 Supportive Care

3.7.1 Prophylactic Anti-Emetic Premedication: 1 hr prior to radiation

- Granisetron 2 mg PO
- prochlorperazine 10 mg PO
- promethazine 12.5 mg PO
- or equivalent

3.7.2 Diarrhea

Patients will be instructed to begin taking loperamide after the first poorly formed or loose stool, or first episode of 2 or more bowel movements in one day.

Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then, 2 mg after every episode of diarrhea until reaching the daily maximum dose.

Loperamide should not be taken prophylactically

Patients must notify the research team as to when they initiated loperamide therapy. If diarrhea persists despite loperamide therapy, then the patient should be evaluated for the need for IV fluid & electrolyte replacement.
Alternative medications

Somatostatin analog (Octreotide7) 100 - 500 mcg SC/IV tid; maximum daily dose = 1500 mcg/day; alternatively, somatostatin analog may be given at 25-50 mcg/hour as a continuous IV infusion.

Atropine/diphenoxylate which is available as either a 0.025/2.5 tab, or 0.025/2.5 per 5 mL liquid. Patients should take 1-2 tabs PO tid or qid or 5-10 mL PO tid/qid.

Atropine/difenoxin (Motofen7) 0.025/1 tab; 2 tabs PO x 1, then 1 tab PO q 2-4 hr (max 8 tabs per day)

Paregoric: (an antidiarrheal opiate): 5 - 10 mL ORALLY 1-4 times daily: maximum 40 mL/day

OTC meds: bismuth subsalicylate 262 mg tabs: 2 tabs PO q 1 hr prn; maximum 4200 mg/24 hr

3.8.4 Blood Products

Blood product support will utilize packed red blood cells or platelets if clinically indicated.

3.8.5 Nutritional Supplementation

Patients will be encouraged to drink specialized cancer supplement between meals.

4.0 Patient Selection and Eligibility

4.1 Selection of Patients

Registration is defined as the day fiducials are placed.

4.2 Number of Patients

Up to 18 patients

4.3 Inclusion Criteria

All patients must meet the following criteria in order to be included in this study.

a. Male or female patients ≥ 18 years of age
b. A life expectancy of at least 6 months with a Karnofsky performance status of at least 70 (Appendix IV)
c. The target lesion(s) can be accurately measured in at least one dimension according to RECIST and must have a maximum tumor volume of $\leq 100\ cm^3$.
d. No prior radiotherapy to the upper abdomen.
e. Previous systemic chemotherapy or non-radiation local therapy (such as surgery, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation) is allowed. The lesion must however have shown criteria of progression based on RECIST. Local therapy must be completed at least 4 weeks prior to the baseline scan. This is to create a safer treatment environment and to help determine the effect of treatment by SBRT alone. Patients will be allowed to go onto appropriate systemic therapy, as determined by their medical oncologist, 2 weeks following delivery of SBRT.
f. Patients with resectable disease will be eligible for participation if, and only if, they have comorbidities precluding surgery or refuse to undergo an operation following a multi-disciplinary discussion involving surgical oncology, medical oncology, and radiation oncology. This discussion will actively involve the patient and reinforce that surgery is the current standard of care for such patients.
g. Cirrhotic status of Child-Pugh class A or B (Appendix I)
h. Patients can have extra-hepatic disease, provided the hepatic disease is the highest burden, the extra-hepatic disease is low burden and potentially treatable with surgery, ablative radiation therapy, or US Food and Drug Administration–approved first- or second-line systemic therapy regimens.
i. Patient's will have no evidence of gross vascular invasion.
j. Patients will have no more than 3 distinct lesions, all being ≤ 3cm in greatest dimension, OR 1 lesion ≤ 6cm in greatest dimension.
k. Platelet count $\geq 60 \times 10^9$/L, Hemoglobin ≥ 8.5 g/dL, WBC ≥ 2000/μL International normalized ratio (INR) must be ≤ 2.3. Patients who are being therapeutically anticoagulated with an agent such as Coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.

l. Other baseline labs must meet the following criteria: total bilirubin < 3mg/dl, albumin> 2.5mg/dl, and liver enzymes less than three times the upper limit of normal. Creatinine must also be < 1.8mg/dl or a creatinine clearance > 50ml/min.

4.4 Exclusion Criteria

a. Renal failure requiring hemo- or peritoneal dialysis
b. Uncontrolled inter-current illness including, but not limited to ongoing or active infection (> grade 2 National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] version 4.0), congestive heart failure (> New York Heart Association (NYHA) class 2), active coronary artery disease (CAD), cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin), uncontrolled hypertension and any condition which could jeopardize the safety of the patient and his/her compliance in the study . Myocardial infarction more than 6 months prior to screening is permitted.
c. A history of variceal bleeding where the varices have not been eradicated or decompressed by shunt placement.
d. History of an active connective tissue disorder.
e. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
f. Pregnant or breast-feeding patients are excluded from this study because abdominal radiation therapy has potential for teratogenic and/or abortifacient effects.
g. Portal vein occlusion.
h. Extensive liver tumor burden, defined as more than 75% of the liver.
i. Patients with primary tumor histology of lymphoma, leukemia, or germ cell tumor.
j. Patients with hepatocellular carcinoma will be excluded from this study.

5.0 TREATMENT EVALUATION, ADMINISTRATION, AND MODIFICATION

5.1 Prior Radiation Therapy History

Details of prior chemotherapy and/or radiotherapy plans including port and simulation films (when available) must be submitted for review and verification of RT to ensure that no normal structures exceed dose limitations for patients with prior abdominal or thoracic irradiation.

5.1.1 Tissue constraints

Treatment shall be delivered via linear accelerator (LINAC) commissioned and equipped to deliver stereotactic radiosurgery. Normal tissues and sensitive critical structures (e.g. spinal cord, normal liver, kidneys, stomach, etc) shall be contoured and the dose to these organs limited. Normal tissue constraints are outlined below.

a. A typical estimate of normal liver size is 2000 cm^3. At least one-third of the liver should be spared from receiving a dose likely to cause notable hepatic dysfunction, meaning that 700 cm^3 should receive a total SBRT dose of less than 15 Gy over 3 fractions and 25 Gy over 5 fractions.
b. Two-thirds of the right kidney cannot receive a dose of more than 15 Gy in 3 fractions or 25 Gy in 5 fractions.
c. The percent of total kidney volume receiving a dose of 15 Gy in 3 fractions or 25 Gy in 5 fractions must be less than 35% of the total kidney volume
d. The maximum dose to any point within the spinal cord can not exceed 18 Gy total in 3 fractions or 20 Gy total in 5 fractions.
e. The maximum point dose to the stomach can not exceed 30 Gy in 3 fractions or 35 Gy in 5 fractions.

Normal Tissue Constraints		
Organ	**Maximum Dose in 3 Fractions**	**Maximum Dose in 5 Fractions**
Liver (700 cm^3)	15 Gy	25 Gy
Right Kidney (2/3 volume)	15 Gy	25 Gy
35% of Total (left & right) Kidney Volume	15 Gy	25 Gy
Spinal Cord	18 Gy	20 Gy
Stomach	30 Gy	35 Gy

5.1.2 Dose Specification, Homogeneity Considerations & Plan Evaluation

The treatment plan used shall be based on the assessment of the dose-volume histogram (DVH) with attention to coverage of the planning tumor volume (PTV) and critical normal structures.

The prescription dose is the isodose cloud that encompasses at least 80% of the PTV.
No more than 20% of any PTV shall receive doses >110% of its prescribed dose.
No more than 2% of any PTV shall receive <93% of its prescribed dose.
No more than 5% of any normal tissue shall receive doses in excess of 110% of the primary PTV dose.

5.2 On-Treatment and post-treatment toxicity evaluation

All patients will be seen prior to each fraction of stereotactic body radiotherapy and their toxicity evaluated by physical examination. Subsequently, patients will be evaluated for toxicity one month later and then every 3 months. Toxicities will be scored by the NCI CTCAE version 4.0. Also see Section 6.0.

5.2.1 Stereotactic Body Radiation Therapy Related-Toxicity

Implantation of a liver marker: The side effects of implantation will be similar to the needle biopsy of liver tumor and stent placement. These include but are not limited to tumor seeding, foreign body, infection, bleeding, pain at local area, and dislocation of the marker.

SBRT: Short-term side effects include but not limited to skin reaction, local hair loss, fatigue, abdominal pain, nausea, vomiting, diarrhea, increasing liver function abnormality, GI bleeding or perforation which may require surgical intervention. Long term side effects are less likely to occur but if they do occur are more likely to be permanent. They include local hair loss, liver function abnormality, diarrhea, small bowel obstruction which may require surgical intervention, spinal cord injury which could result in paralysis, and kidney function abnormality.

5.2.2 CT and FDG-PET/CT
The subject will be exposed to radiation associated with the FDG-PET/CT and/or CT scans performed to assess the liver metastases and their response to therapy. FDG-PET/CT and CT scans are routinely performed as standard-of-care for tumor staging and to monitor response to therapy, and the radiation dose associated with these diagnostic scans are felt to represent minimal risk.

Adverse reactions to the administration of the FDG being used for the PET/CT scans are not expected. However, as with the administration of any drug, the possibility of an adverse event cannot be totally excluded. The subject will be monitored for adverse events, and a physician and emergency drugs and equipment will be available in the scanning area should a reaction occur.

Claustrophobia: Possible anxiety, claustrophobia, and/or temporary discomfort may occur as a result of being placed in the scanning devices. Subjects will be monitored and removed from the scanner if required

6.0 STUDY EVALUATIONS

6.1 Pretreatment Evaluation

The following tests/procedures will be performed in order to ascertain subject eligibility within 28 days prior to registration unless otherwise specified. Some of the standard of care testing may be performed before the research consenting process and if in the window, results will be used for screening, but no testing exclusively ordered for research will be done before the consent is signed.

6.1.1 Signed informed consent
6.1.2 Medical history
6.1.3 Physical examination, including Karnofsky Performance Status or ECOG performance status and vital signs.
6.1.4 Subject body weight and height taken within 14 days of the registration.
6.1.6 Histologic and/morphologic confirmation of diagnosis, and disease status/staging at entry.
6.1.7 CBC including: WBC with complete differential, platelets, RBC, hemoglobin, hematocrit, within 30 days prior to registration.
6.1.8 Blood chemistries including BUN, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, calcium, phosphorus, chloride, magnesium within 30 days of registration.
6.1.9 Urine or blood HCG test for female subjects of child-bearing potential (women who are not at least 1 year post-menopause or who have not undergone a surgical sterilization procedure) within 14 days prior to registration. Female subjects of child-bearing potential will be instructed to use contraception from the time of the screening pregnancy test until study completion.
6.1.10 FDG-PET/CT (or if insurance does not allow for a PET, then a contrast enhanced CT) of the abdomen and pelvis within 45 days prior to registration.
6.1.11 Patient will be discussed by a multi-disciplinary team involving surgical oncology, medical oncology, and radiation oncology to reinforce that surgery is the current standard of care for such patients

6.2 Evaluation during treatment

The patient will be carefully followed while on active treatment and post-treatment for 16 months, or until death. Evaluation during treatment will consist of the following activities:

6.2.1 Administration of stereotactic body radiation therapy.
6.2.2 Interim medical history and physical examination at baseline and prior to each radiation therapy treatment.

6.3 Follow up Interval

The patient will be followed post-treatment for 16 months, or until death unless otherwise indicated. Evaluation during the follow up interval will consist of the following activities:

6.3.1 Physical exam and vital signs at one, two, and three months post SBRT, five months post SBRT, and then every three months thereafter.
6.3.2 Monthly blood work to be done at a local laboratory starting 2 weeks following SBRT - CBC, Diff with platelets, basic electrolytes, BUN, creatinine, t-bili, ALT, AST, GGTP, calcium, magnesium, and phosphorus. Bloodwork to be completed for at least the first six months.
6.3.3 CT or FDG-PET/CT scans (for consistency procedure done at screening/planning will continue in follow-up) at 8 weeks post-treatment and every 12 weeks thereafter for 12 months for assessment of response to therapy and monitoring.
6.3.4 Patients will follow up with their treating medical oncologist after SBRT, and if deemed appropriate, will be able to start systemic therapy 2 weeks after treatment.

6.4 Study procedures

6.4.1 PET/CT Imaging

Patients will be required to fast for at least 4 to 6 hours prior to the FDG-PET/CT imaging procedure. Prior to injection of [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG), a 1 ml blood sample (1/3 teaspoonful) will be taken to measure the patient's blood glucose level. After the injection of 10-15 mCi of [^{18}F]-FDG and an approximate 45 minute wait allowing for tracer incorporation, a CT scan will be performed for attenuation correction and anatomical correlation on the General Electric Discovery ST PET/CT (GE Medical Systems, Waukesha, WI) scanner. The CT scanner portion of the GE ST consists of a multi-detector spiral CT scanner. CT scans will be acquired as diagnostic quality CT, after the patient receives 900 ml Gastroview orally and 125 ml Optiray 350 intravenously (I.V.) through an automated injector. This will be followed by a whole body emission PET scan. The [^{18}F]-FDG is being used in this study in accordance with the current FDA regulations addressing radioactive drugs for use in PET procedures. The total scan duration, including a spiral CT scan of the same axial extent as the FDG-PET, will not exceed 60 min. A CT scan will be acquired over the same axial length as the FDG-PET scan.

6.5 Objective criteria for defining response

6.5.1 Definition of Response

6.5.1.1 Clinical Benefit Response

Clinical benefit response is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change.
A patient is considered a clinical benefit responder if either:
a. The patient shows a $\geq$ 50% reduction in pain intensity or analgesic consumption
OR

b. Improvement in performance status (Appendix IV) of ≥ 20 points for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters (sustained worsening was defined as four consecutive weeks with either any increase in pain intensity or analgesic consumption or a ≥ 20 point decline in performance status

OR

c. The patient is stable on all of the aforementioned parameters, and shows a marked, sustained weight gain (≥ 7% increase maintained for ≥ 4 weeks) not due to fluid accumulation

6.5.1.2 Tumor Response on CT (RECIST)

Measurable Disease Response: CTEP's RECIST guidelines will be followed. A quick reference to the RECIST guidelines can be downloaded at the following URL: http://ctep.info.nih.gov/Policies/WordDocs/RCSTF.PH2TEMPF.doc. (Appendix II) Patients enrolled in this study must have a measurable liver metastasis which is defined as lesions that can be accurately measured in at least one dimension: [longest diameter to be recorded] on the CT scan.
The same method of assessment and the same technique should be used to characterize each identified & reported lesion at baseline & during follow-up.

Parameters to Measure Response Outcome:	
1	Clinical examination
2	CT scan
3	FDG-PET/CT scan

Taking into account the measurement of the longest diameter only for those lesions with size response, response criteria are defined as:

1. Complete Response (CR): the disappearance of a lesion.
2. Near Complete Response (NCR): at least an 80% decrease in the longest diameter of a lesion, taking as reference the longest diameter recorded since the treatment started.
3. Partial Response (PR): at least a 30% decrease in the longest diameter of a lesion, taking as reference the longest diameter recorded since the treatment started.
4. Progressive Disease (PD): at least a 25% increase in the longest diameter of a lesion, taking as reference the longest diameter recorded since the treatment started.
5. Stable Disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the longest diameter since the treatment started.

6.5.1.3 Tumor Response on ^{18}F-FDG-PET/CT

The most recent consensus recommendations by the NCI on assessing PET response indicate semiquantitative SUV (standard uptake value) analysis based on lean body mass and/or body surface area be used in determining ^{18}F-FDG uptake.[17] The SUV is calculated using the tumor radiotracer concentration (Q [MBq/l]), body surface area (BSA [m^2] and injected activity (Q_{inj} [MBq]):

$SUV_{BSA} = (Q \times BSA)/ Q_{inj}$

The subject's body surface area is calculated using weight (W [kg]) and height (H [cm]):

$BSA = W^{0.425} \times H^{0.725} \times 0.00718$

We will use the EORTC 1999 criteria for defining ^{18}F-FDG response[18].

1. Progressive Metabolic Disease (PMD): An increase in ^{18}F-FDG tumor SUV of greater than 25% within the tumor region defined on baseline scan, visible increase in the extent of ^{18}F-FDG tumor uptake (> 20% in the longest dimension) or the appearance of new ^{18}F-FDG uptake in metastatic lesions.

2. Stable Metabolic Disease (SMD): An increase in tumor SUV of < 25% or a decrease < 15% and no visible increase in extent of ^{18}F-FDG tumor uptake (> 20% in the longest dimension).

3. Partial Metabolic Response (PMR): A reduction of a minimum of 25% in tumor ^{18}F-FDG SUV uptake. A reduction in the extent of tumor ^{18}F-FDG is not required to be classified as a PMR.

4. Complete Metabolic Response (CMR): Complete resolution of ^{18}F-FDG uptake within the tumor volume so that it is indistinguishable from surrounding normal tissue.

For those patients with non-FDG avid tumors, their response to therapy will be assessed by CT scan as detailed in 6.5.1.2.

6.5.1.5 Definition of local control

Local control will be defined as sustained stable disease, partial response, or complete response in the target lesion(s) at one year post-treatment.

Local Response Rate is defined as stable disease, partial response, or complete response per RECIST at any point in the first year of follow-up.

Local failure will be defined as any progression of disease within the target volume.

Regional failure will be defined as development of new liver metastases outside of the treated lesions.

Distant failure will be defined as development of new metastatic lesions outside of the liver (brain, bone, etc).

6.5.1.6 Quality of life assessment

6.5.1.6.1 Disease-specific information:

Disease specific information will be obtained by the data manager through the use of Electronic Data Interface for Transplantation (EDIT). EDIT is a computer application designed specifically for the Starzl Transplantation Institute at the University of Pittsburgh, which the LCC is affiliated. It provides the ability to track patients through the disease and treatment process. EDIT works in conjunction with other medical record systems that stores information regarding the patients' medical history (e.g., Medical Archive Record System). The data will be extracted from EDIT and summarized using Microsoft ACCESS 2000 and then transferred to SPSS.X for statistical analysis. Variables that will be extracted from EDIT will include: (1) stage of cancer, (2) tumor size, (3) lobar distribution of tumor, (4) suspected number of lesions, (5) grade of vascular invasion, (6) Child's-Pugh class, (7) presence of fibrosis or cirrhosis, (8) pathology of tumor, (9) capsulation of tumor, (10) ascites, (11) treatment type, (12) comorbid medical conditions, (13) medications; as well as lab values such as (14) prothrombin Time/Partial Thromboplastin Time PT/PTT), (15) electrolytes, (16) SGOT, (17) BUN, (18) SGPT, (19) creatinine, (20) LDH, (21) glucose, (22) alkaline phosphatase, (23) albumin, (24) total bilirubin. The disease-specific information will be analyzed to determine if there are baseline differences on any of these variables or contribute to a significant amount of the variance on any of the outcome variables (e.g., survival, disease progression, and HRQL). If any of the disease-specific variables are found to be different at baseline between the two treatment groups or are significantly related the outcomes at baseline, the variable will be covaried in later analyses.

6.5.1.6.2 Health-Related Quality of Life

Health related quality of life will be assessed using the Functional Assessment of Cancer Therapy-Hepatobiliary [FACT-Hep; Appendix V]. The FACT-Hep is part of the Functional Assessment of Chronic Illness Therapy (FACIT; 13) measurement system and includes the FACT-General (FACT-G) and an 18-item module specifically designed for patients diagnosed with hepatobiliary carcinomas. The FACT-G is a multidimensional 27-item self-report instrument that measures four dimensions of quality of life including physical well being, social/family well-being, emotional well-being, functional well-being, and overall HRQL. In addition, the FACT-Hep includes a module with 18 additional items specific for patients with hepatobiliary carcinoma. The module includes questions that pertain to symptoms of the disease as well as side effects of the treatment. The FACT-Hep has been demonstrated to be reliable and valid.[19] The internal consistency of the FACT-Hepatobiliary as measured by

Cronbach's alphas was found to be adequate (0.72-0.94) and test-retest reliability ranged between 0.84 to 0.91.[19] Convergent and divergent validity were demonstrated by examining the FACT subscales with scales measuring mood (POMS), social support (ISEL), and social desirability (Marlowe-Crowne Social Desirability Scale).[20] This FACT-Hep will be administered at the following time points:

- screening
- the initial radiation therapy session
- after completing the final radiation treatment
- two months following radiation
- every three months thereafter

6.5.1.6.3 Data Management

The clinical psychologist will manage the prospective data collection and database for the psychosocial data collected at the UPMC Liver Cancer Center. The FACT-Hepatobiliary questionnaire will be administered to patients by telephone interviews. The interviews will be conducted by a trained interviewer with education and training in social sciences. The interviewer will be supervised by a clinical psychologist (Jennifer Steel). The interviews will take approximately 15-20 minutes to complete at each time point. The interviewer will enter the patients' responses on a secure study website that has been designed specifically to evaluate patient health-related quality of life as part of clinical trials. The data from this website will be imported into SPSS.x".

Once the raw data has been transferred into SPSS.X, the FACT-Hepatobiliary will be scored according to the manual for the Functional Assessment of Chronic Illness Therapy (FACIT; 13). All scales of the FACT are scored so that a high score is good. All negatively phrased questions are reverse scores, and then the items are summed. Items with missing data are prorated using the average of the other response to items on the same scale. Prorated scores can only be calculated if less than 50% of the data is missing (e.g., 3 of 7 items) for a particular subscale or greater than 80% of the data is available for the overall all HRQL score. The FACT-G score (overall HRQL) is the sum of the individual subscale scores (physical, social/family, emotional, and functional well-being). Total scores for the disease-, treatment, and condition-specific subscales are obtained by summing all subscale scores (physical, social/family, emotional, functional, and additional concerns). To calculate a Trial Outcome Index (TOI), the sum of the physical and functional well-being subscales and the additional concerns subscale is calculated. The TOI is a commonly used endpoint in clinical trials because it is responsive to change, whereas the social/family and emotional well-being subscale scores do not change as quickly over time or have as great of change subsequent to pharmacological treatment. The Functional Assessment of Cancer Therapy-Hepatobiliary Index which consists of 8 items from the FACT-Hepatobiliary will also be calculated.

Minimally Important Difference (MID) scores for all the scales of the FACT have been documented.[20] Combined results from distribution-based analyses and cross-sectional anchor-based methods suggest that clinically meaningful changes are estimated as follows for the FACT-Hepatobiliary: Cancer-specific subscale=2-3; FACT-General=6-7; Hepatobiliary Cancer Scale (HPCS)=5-6; FACT-Hep=8-9; Trial Outcome Index (TOI)=7-8; and FACT-Hepatobiliary Symptom Index (FHSI)=2-3 points.[25]

6.6 Study Schema

		SBRT						Follow-up interval: months post therapy												
Assessment	**Pre-entry**	**Fx 1[8]**	**Fx 2**	**Fx 3**	**Fx 4**	**Fx 5**	**2 W**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**11**	**13**	**14**	**16**
History	X	X	X	X	X	X		X	X	X		X			X		X		X	
Physical exam, vital signs	X	X	X	X	X	X		X	X	X		X			X		X		X	
Karnofsky or ECOG Status	X																			
Height, weight	X																			
CBC, platelets	X[7]						X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]							
Chemistries, CMP	X[7]						X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]							
Magnesium,Phosphorus	X[7]						X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]							
Urine or Blood HCG[6]	X																			
Fiducial Placement	X[1]																			
4D FDG-PET/CT Sim	X[5]																			
FDG-PET/CT or CT	X[2]								X[4]			X[4]			X[4]		X[4]			
FACT-HEP Questionnaire	X	X				X			X			X			X		X[4]			

1. After patient is deemed eligible this will be performed within 2 to 3 weeks after screening
2. FDG-PET/CT will be performed within 45 days of registration
3. Can be done at local lab
4. ± 1 week
5. 5 - 10 days post fiducial placement
6. Within 14 days prior to registration
7. Within 30 days prior to registration
8. Within 14 days of 4D FDG-PET/CT

7.0 Statistical Considerations

7.1 Study Design/Endpoints

The primary objective of this study is to determine the Maximum Tolerated Dose (MTD) and safety of SBRT for liver metastasis using dose escalation. Dose escalation will be via the traditional "up and down" scheme indicated in the two tables below. The traditional up and down study design is a rule-based design which recruits up to 6 patients at each of the 3 dose levels. Patients in cohort(s) of 3 will be entered and the first cohort will be given the lowest dose. The detailed decision rule is in the two Tables below, where there are decisions corresponding to one or more dose limiting toxicities at any given dose level.
The three dose levels are:

- 50 Gy in 5 fractions (10 Gy/fx) delivered over a 2-week period.
- 60 Gy in 5 fractions (12 Gy/fx) delivered over a 2-week period.
- 75 Gy in 5 fractions (15 Gy/fx) delivered over a 2-week period.

Dose limiting toxicity (DLT) will be defined as any grade III stomach, bowel, liver, or spinal cord toxicity, or any grade IV toxicity as defined by the Radiation Therapy Oncology Group (RTOG).[21] The monitoring and evaluation for dose escalation is referenced below in section 7.3.1. Cohorts of three patients each will be treated at a dose level. Only toxicities observed prior to 7 months after the last fraction of radiation will affect dose escalation.

DECISION RULES FOR DOSE LEVEL ESCALATION

Number of patients with DLTs at this dose level	Number of patients treated at this dose level	Action
0	3	Treat 3 patients at the next higher dose level (or add 3 patients if at the highest dose level).
1	3	Treat 3 additional patients at this dose level.
1	6	Treat 3 patients at the next higher dose level.
>1	3 or 6	Stop dose escalation. Begin de-escalation, or stop the trial if at the lowest dose level.

After escalation has stopped, de-escalation will begin at one dose level below the maximum achieved during escalation, and will be carried out according to the table below. The action taken depends on the number of patients previously treated at a dose level. If 3 patients have previously been treated, 3 patients are added; if 6 patients have previously been treated, this level will be declared to be the MTD. The MTD is defined to be the highest dose level at which no more than 1 of 6 treated patient experiences a DLT.

DECISION RULES FOR DOSE LEVEL DE-ESCALATION

Number of patients with DLTs at this dose level	No. of patients treated at this dose level	Action
0	3	Treat 3 additional patients at this dose level.
1	3	Treat 3 additional patients at this dose level.
0 or 1	6	Stop de-escalation. The dose at this level is the MTD.
>1	3 or 6	De-escalate one dose level, or stop trial if at lowest level.

Patients within a cohort need not be accrued or treated at the same time; thus, accrual at a dose level should stop as soon as 2 patients at a dose level have experienced DLT at that level.

7.2 Sample Size/Accrual Rate

The number of patients accrued to the study will depend on the MTD. No more than 18 evaluable patients will be treated in the trial. Based on previous efforts in recruiting patients at the University of Pittsburgh Cancer Institute, it is anticipated that at least 6 patients per year will be enrolled in the protocol and the accrual will be completed within 3 years. An evaluable patient is defined as one who either a) completes the five fractions and has no DLT until one month after the last fraction, or b) a patient who receives at least one fraction and suffers DLT. Patients who are not evaluable will be replaced.

7.3 Data Analysis

Data analysis will be done mostly by dose group and will be exploratory due to the small sample size.

7.3.1 Analysis of the primary endpoints

Baseline descriptive statistics on all evaluable patients will be provided for demographic variables (age, sex, race/ethnicity), ECOG performance status, disease stage and status at the screening and treatment regimens previously used.

The NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) will be used to evaluate toxicity. We will consider a toxicity to be an adverse event that is possibly, probably or definitely related to treatment. The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. We will describe all DLTs and other serious (≥ Grade 3) adverse events on a patient-by-patient basis; descriptions will include dose level and any relevant baseline data. The monitoring and follow-up procedures are listed in detail in section 6.3.1 and 6.3.2. Specifically, patients will be seen at one, two, and three months post SBRT, five months post SBRT, and then every three months thereafter. They will undergo a comprehensive physical exam at each of

these visits. Monthly blood work will also be completed starting 2 weeks following SBRT - CBC, Diff with platelets, basic electrolytes, BUN, creatinine, t-bili, ALT, AST, GGTP, calcium, magnesium, and phosphorus. Bloodwork will be completed and reviewed for at least the first six months. All toxicity data gathered from these visits will be graded according to CTCAE v4.0. Statistics on the radiation dose and number of fractions received by patients will be tabulated.

7.3.2 Analysis of Secondary Endpoints

Local control, local failure, regional failure and distant failure of patients, defined in Section 6.5.1.5, will be summarized in tables. Their rate will be calculated along with their exact 95% confidence intervals. The local response rates with FDG-PET/CT will be compared to those with CT using McNemar's test. The HRQL data analysis will be mostly descriptive and performed according to Section 6.5.1.6.

8.0 Data Safety and Recording

8.1 Data safety monitoring plan

All patient data will be collected by the University of Pittsburgh Cancer Institute's Protocol Office. All data will be secured in a password protected file with observance of all applicable HIPAA regulation. A data safety monitoring board will meet monthly to evaluate toxicity for this trial along with dose escalation and de-escalation. Patients/adverse events will be discussed at these monthly disease center meetings. Unexpected serious adverse events will be reported to the IRB and DSMC, and minutes of the monthly disease center meetings will be reviewed at the DSMC meetings.

8.1.1 Subject Removal Criteria

1. Disease progression
2. Development of a serious medical illness
3. Evidence of dose-limiting toxicity
4. Voluntary withdrawal
5. Protocol violation
6. Discretion of the principal investigator in conjunction with a multi-disciplinary team
7. Development of grade 4 toxicity related to experimental therapeutic

8.2 Safety Reporting

8.2.1 Acute Adverse Events

The CTCAE (described below) will be used to grade acute toxicity during this trial.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas will have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication.

Exacerbation of a pre-existing illness should be considered when a subject requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the study. Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect should not be recorded as an adverse event. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

In addition, abnormal objective test findings (e.g., electrocardiogram changes, abnormal laboratory test results) that can result in a change in study drug dosage or in discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the patient, should also be recorded as adverse events. Clinically significant changes in physical examination findings should also be recorded as adverse events. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to UPCI or its designated representative.

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

Attribution of the AE:
Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality, (i.e., study drug or other illness). Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse events that continue, or emerge within 30 days, after the patient's discontinuation or completion of the study will be followed until the events resolve, are considered stable, or can be ascribed to causes other than study treatment.

All serious AE shall be reported meeting criteria for reporting can be found on the University of Pittsburgh Institutional Review Board's website at http://www.irb.pitt.edu. In the event of such adverse event, the investigator must report the event(s) via phone within 24 hours and a written report filed within 24 hours to the Principal Investigator, or the UPCI's Clinical Research Office.

8.2.2 Late Adverse Events

The SOMA/LENT grading system will be used to evaluate late toxicity.[22, 23.] Radiation induced liver disease (RILD) will be defined as, anicteric ascites and elevation of alkaline

phosphatase levels to at least two fold increase above the pretreatment values in absence of tumor progression (classic), or hepatic toxicity grade 3 or higher according to the CTCAE also in absence of tumor progression (nonclassic).

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Appendix I

Criteria for Child-Pugh Classification

Score ____

Grade A = 5-6 Grade B = 7-9 Grade C = 10-15

Clinical and Biochemical Measurements		Points Scored for Increasing Abnormality		
		1	2	3
Hepatic encephalopathy (grade)*	○ 1 ○ 2 ○ 3	None	1 and 2	3 and 4
Ascites	○ 1 ○ 2 ○ 3	Absent	Mild	Moderate
Total bilirubin (mg/dl)	○ 1 ○ 2 ○ 3	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	○ 1 ○ 2 ○ 3	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time (sec. prolonged) or Prothrombin time INR**	○ 1 ○ 2 ○ 3	< 4 or < 1.7	4 - 6 or 1.7 - 2.3	> 6 or >2.3

*According to grading of Trey, Burns, and Saunders (1996).

Appendix II

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- **Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.**

Measurable disease **- the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- 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.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted

to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** 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.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the 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

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

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

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is

objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- **All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).**
- **All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.**
- **All conclusions should be based on all eligible patients.**
- **Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.**
- **The 95% confidence intervals should be provided.**

Appendix III

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix IV

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
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**	**Quite a bit**	**Very 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 check 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)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	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	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	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	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4