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Feasibility of Hypofractionated Stereotactic Radiotherapy in Patients with Hepatocellular Carcinoma

Principal Investigator:
Chi Lin, MD, PhD, Radiation Oncology

Secondary Investigators:
Fedja Rochling, MB BCh
Margaret Kessinger, MD
Charles Enke, M.D

Participating Physicians/Healthcare Personnel:
Jean Grem, MD
Jue Wang, MD
Weining (Ken) Zhen, MD
Robert Thompson, MD
Andrew Wahl, M.D.
Aaron Sasson, MD
Quan P. Ly, MD
Chandrakanth Are, MD
Jean Botha, MB BS
Daniel Schafer, MD
Timothy McCashland, MD
Mark Mailliard, MD
Sandeep Mukherjee, MB BCH MPH
Michael Sorrell, MD

Research Coordinator:
Mary Mailliard, RN, BSN, OCN

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Index

Abstract		Page	3
Section 1.0	Objectives	Page	4
Section 2.0	Introduction	Page	4
Section 3.0	Eligibility Criteria	Page	10
Section 4.0	Registration Procedures	Page	12
Section 5.0	Research Design	Page	12
Section 6.0	Measurement of Effect	Page	16
Section 7.0	Study Parameters	Page	18
Section 8.0	Drug Formulation and Procurement	Page	19
Section 9.0	Toxicity Reporting Guidelines	Page	19
Section 10.0	Statistical Considerations	Page	22
Section 11.0	Record keeping	Page	24
Section 12.0	Patient Consent Form Statement	Page	24
Section 13.0	References	Page	24
Appendix I (Child Pugh Classification)		Page	28
Appendix II (Schedule of Activity)		Page	29
Appendix III (Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference)		Page	30
Appendix IV (Pain Assessment)		Page	33
Appendix V (Karnofsky Performance)		Page	34
Appendix VI (Eligibility checklist)		Page	35

ABSTRACT

Purpose: This is a phase I study to establish safety data of hypofractionated stereotactic radiotherapy (SRT) in patients with hepatocellular carcinoma.

Eligibility criteria: Patients must have pathologically confirmed hepatocellular carcinoma with at least one tumor with a maximum diameter of ≤ 8 cm and must have Karnofsky performance status ≥ 60% and a life expectancy of at least 12 weeks. Patients must be ≥ 19 years of age and able to give written informed consent prior to initiating treatment. Previous systemic chemotherapy or non-radiation local therapy (such as surgery, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation) is allowed.

Interventions: All patients who have had successful implantation of a liver marker will undergo a 4D CT scan for planning SRT. Following transfer to the treatment planning system, the CT scan may be correlated by imaging fusion with MRI for contouring integrated tumor volume (ITV). The planning target volume (PTV) will be defined as ITV plus individualized margins which are determined by a 4D CT scan. Novalis with 6MV photons will be used for imaging guided SRT. Cohorts of 3-6 patients will receive SRT at daily doses of 8, 10, 12, 14 Gy within 2 weeks. The starting daily dose level will be 10 Gy. The marker will be localized by orthogonal X-ray to ensure reproducibility. A continuous respiratory gating will be accomplished with ExacTrac Adaptive Gating system if the required planning target margin is larger than 1 cm based on the 4D CT data.

Evaluation:
1) Liver, right kidney and small bowel toxicity will be evaluated according to CTCAEv3.0
2) Tumor response will be accessed by tumor marker (AFP), CT and MRI scans

Follow-up: As part of standard of care, all patients will have a follow-up visit 1 month after SRT and every 3 months for 1 year and every 3 to 6 months indefinitely. The study follow-up will coincide with these visits. The last study follow-up visit will be 4 months after the completion of radiation therapy.

Section 1.0 Objectives

1.1 Primary Objective:
- 1.1.1 The safety of hypofractionated stereotactic radiotherapy in patients with advanced hepatocellular carcinoma.
  - 1.1.1.1 Record SRT related liver, right kidney, small bowel toxicity according CTCAEv3.0

1.2 Secondary Objective:
- 1.2.1 The maximum tolerable SRT dose.
- 1.2.2 Objective tumor response rate.
  - 1.2.2.1 Report the percentage of tumor size change on CT
  - 1.2.2.2 Report the percentage of intensity change on MRI
  - 1.2.2.3 Report the percentage of change in AFP
- 1.2.3 The value of 4D CT in liver cancer planning
  - 1.2.3.1 Report extent of liver motion three dimensionally
  - 1.2.3.2 Report the percentage of patients requiring breath gating because of the amplitude of organ motion exceeding 1 cm in any dimension.
- 1.2.4 The value of breath gating in liver cancer SRT
  - 1.2.4.1 Report the success rate of breath gating
  - 1.2.4.2 Report the percentage of treatment time prolongation secondary to the gating.

Section 2.0 Introduction

Hepatocellular Carcinoma and Cirrhosis - Review of Epidemiology

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm and the third most common cause of cancer-related death. Although there are more than 500,000 cases per year worldwide, there is a large geographical variation in both risk factors and incidence. Cirrhosis, most often due to viral and alcohol hepatitis, is the dominant risk factor for HCC. Geographical differences of tumor incidence are largely due to epidemiological variations in hepatitis B and C infection. In the United States, the incidence rate, which is approximately 3 per 100,000 persons, is increasing, mostly related to increasing rates of hepatitis C infection (HCV), with additional cases associated with cirrhosis due to alcohol, hemochromatosis and nonalcoholic fatty liver disease.

Hepatic function is an important parameter affecting the selection of therapy for HCC. The Child-Pugh score is widely used to assess risk in cirrhotic patients for surgical and other therapies. The score includes clinical manifestations of cirrhosis including encephalopathy and presence of ascites, as well as laboratory parameters reflecting hepatic synthetic, metabolic and cell function (albumin, prothrombin time [PT], and bilirubin) [1, 8].

Hepatocellular Carcinoma: Surgical Treatment Options

Surgical resection is considered a potentially curative modality for HCC. Five-year survival rates for patients with resectable lesions are 60-80%. Unfortunately, only about 15% of patients have resectable disease at initial diagnosis.

Localized HCC may still be unresectable due to tumor location or concomitant decompensate cirrhosis. Patients in this group may be considered candidates for liver transplantation. Post-transplant survival in several series has been reported as 60-75%. However, liver transplantation is an option only for patients who meet the Milan criteria [2]. Milan criteria are defined as the presence of a single lesion no larger than 5 cm in diameter or the presence of up to three lesions no larger than 3 cm with no extrahepatic disease. The model for end-stage liver disease (MELD) based organ allocation system in the United States provides for additional MELD score points for lesions size 2-5 cm in diameter.

Hepatocellular Carcinoma: Locoregional Treatment

Locoregional ablation therapy is the best treatment option for patients with early stage HCC who are not suitable for resection or transplantation. Destruction of tumor cells can be achieved by the injection of chemical substances (ethanol, acetic acid, and boiling saline) or by modifying the temperature (radiofrequency, microwave, laser, and cryotherapy). The results with ethanol injection show that it is highly effective for small HCC and has a low rate of adverse effects. Ethanol injection achieves necrosis rate of 90%-100% of the HCC smaller than 2 cm, but the necrosis rate is reduced to 70% in tumors between 2 and 3 cm and to 50% in HCC between 3 and 5 cm.[3] The best results obtained in series of HCC patients treated by percutaneous ethanol injection provide 5-year survival rates of 40-50%. The results for radiofrequency ablation (RFA) show that the efficacy of RFA in tumors <2 cm is similar to that of ethanol but requires fewer treatment sessions. The efficacy in tumors >2 cm is better than that of ethanol. Randomized controlled trials (RCT) have shown that RFA provides better local disease control. [4, 5 6 7] However, significant survival advantages have not been proved yet for RFA.

Transcatheter arterial chemoembolization (TACE) is widely used, since the majority of patients diagnosed in the West present with tumors at intermediate-advanced stages, when above percutaneous treatment options cannot be applied. There is a contraindication to TACE which is the presence of portal vein thrombosis. TACE has been shown to significantly delay tumor progression and vascular invasion. Overall modest survival benefits were identified in two RCTS[9, 10] and a metaanalysis[11]. However, it is currently the mainstay of treatment in only 10% of the HCC population. New trials are needed to refine the selection of target population and to establish the best chemotherapeutic agent and the optimal treatment schedule.

Hepatocellular Carcinoma: Systemic Therapy

Systemic Therapy with Doxorubicin is the most widely used, and is associated with at best an 11-15% response rate.[12] However, the recently published guidelines for HCC in Hepatology

discourage the use of doxorubicin in HCC [3]. There are multiple other treatment modalities such as octreotide, interferon, tamoxifen, or antiandrogenic therapy, but none have been shown to improve survival [3] .

Sorafenib (Sor) is a multikinase inhibitor with anti-angiogenic, pro-apoptotic and Raf kinase inhibitory activity, with clinical activity in a phase II HCC trial. Recently, a large, multicenter, randomized, placebo-controlled phase III trial[13] evaluated the efficacy and safety of Sor vs placebo (P) in 602 patients with advanced measurable HCC who had no prior systemic treatment, ECOG PS 0-2 and Child-Pugh status A. Median OS was 10.7 vs 7.9 mos (Sor vs P). Incidence of serious adverse events was similar for Sor vs P (52% vs 54%). It was concluded that Sorafenib was well tolerated and is the first agent to demonstrate a statistically significant improvement in OS for pts with advanced HCC. This effect is clinically meaningful and establishes sorafenib as first-line treatment for these patients.

Hepatocellular Carcinoma: Radiation Therapy

External beam radiotherapy has historically played a minor role in the primary treatment of hepatocellular carcinoma. Although there is evidence for tumor response to external beam radiotherapy and a radiation dose-response relationship has been established, the limited radiation tolerance of the adjacent normal liver has prohibited wider use of radiation therapy in this disease[21, 22]. In addition the adjacent liver may not be histological “normal” – i.e. cirrhotic as it is in more than 80% of cases of HCC in humans. Previous studies have shown that radiation-induced liver disease (RILD, defined as grade 3 or higher hepatic toxicity according to CTCAE v3.0[15]) is seen in 5-10% patients that receive 30-35 Gray to the entire liver and in 50% of patients who receive 40-50 Gray.[14] A recent study by Fox and Enke at UNMC (unpublished data) has shown that radiation treatment to the entire liver to a dose of 40 Gray or higher in 8 Gy or greater fractions over 5 days does not produce liver failure, but generates a cytokine syndrome. A second course of similar radiation treatment to the entire liver is also well tolerated, if given more than 6 months after the first course of radiation treatment. It can be concluded that focused radiation to a liver tumor with relatively small amounts of radiation dose to the remaining liver is extremely unlikely to generate significant loss of liver function. Robertson et al. from University of Michigan presented their experience with conformal radiotherapy in treating 11 patients with HCC and 11 with bile duct cancer, with concurrent intraarterial FdUrd infusion for radiation sensitization. They showed that overall progression-free survival within the liver was 50% in 2 years and the 4-year actuarial survival rate was 20%. No late hepatic toxicity was observed [23].

Treatment with Conformal Radiotherapy (CRT) and Intensity Modulated Radiotherapy (IMRT)

Intensity-modulated radiation therapy, image-guided radiation therapy, and stereotactic body radiation therapy are recent technological and conceptual developments in the field of radiation therapy, which have the potential to improve radiation treatments by conforming the delivered radiation dose distribution tightly to the tumor or target volume outline while sparing normal liver tissue from high-dose radiation. Image guidance allows for a reduction of added (tumor unaffected tissue) safety margins designed to account for interfraction patient and target setup

variability. Stereotactic targeting will further reduce residual target setup uncertainty. Combining improvements in tumor targeting with normal tissue sparing, radiation dose delivery will enable clinically effective and safe radiation delivery for liver tumors such as hepatocellular carcinoma[14].

The clinical paradigm underscoring the potential success of such an approach proposed is that of stereotactic radiosurgery (SRS). When small beams of radiation are directed from many angles, a highly focal distribution of radiation dose is created which decreases rapidly within millimeters from the intended target. The resultant sparing of surrounding dose-limiting structures enables a higher dose of radiation to be safely delivered to the target, in turn increasing the probability of tumor control and ultimately cure. Stereotactic radiosurgery has been used for over a decade in the focal treatment of cranial neoplasms; SRS has become the standard of care in the treatment of brain metastases. The success of radiosurgery has given rise to speculation by a number of authors, however, that similar success of a highly focused single fraction or hypo-fractionated approach may be possible in extra-cranial solid tumors [16-20].

Early studies from the international arena [16 19 24] demonstrated that a high probability of local tumor control and a low likelihood of late normal tissue toxicity can be accomplished using focused radiotherapy techniques. More recently, Schefter et al have presented results from a phase I study of stereotactic body radiotherapy for the treatment of liver metastases [25]. The dose was escalated from 36 to 60 Gy delivered in three fractions, with three patients in each dose regimen. Dose-volume constraints were specified such that a minimum of 700 ml of unaffected liver could receive no more than 15 Gy (over three fractions). Additional dosimetric constraints were placed on the total kidney volume (no more than 5 Gy per fraction to no less than 35% of the total volume), and on the spinal cord, stomach, and small intestine (maximum doses of 18 Gy, 30 Gy and 30 Gy respectively). No dose-limiting toxicity was observed at any dose level.

Following the methodology of Schefter et al [25], one can apply 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) says that the total effect is given by:

$$(nd)\left\{1+d\Big/\frac{\alpha}{\beta}\right\}$$

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. Because prolonging the treatment time introduces a sparing (repair) effect in acutely responding tissues, there is significant motivation to deliver radiation in larger fractions over a shorter time.

While the dose-fractionation scheme employed by Schefter et al resulted in no significant morbidity, we propose a slightly more conservative dose escalation study as follows:

Dose Level	# Patients	# Fractions	Dose/fraction	Total Dose	Equivalent dose in 2 Gy/fractions
I	3-6	5	8 Gy	40 Gy	60.0 Gy
II*	3-6	5	10 Gy	50 Gy	83.3 Gy
III	3-6	5	12 Gy	60 Gy	110.0 Gy
IV	3-6	5	14 Gy	70 Gy	140.0 Gy

*Starting dose level is Dose Level II.

For comparison, the 3 x 12 Gy arm in the Schefter study is equivalent to a total dose of 66 Gy in 2 Gy fractions, while the 3 x 20 Gy arm is equivalent to 150 Gy. All calculations assume an alpha/beta ratio of 10.

Likewise, this study will follow the dose-volume constraints used by Schefter et al [25]. Using the Novalis to deliver radiation, and excluding patients with a maximum tumor diameter of ≥ 8 cm, these criteria are easily achievable.

Data [26-30] have shown that radiological response rates to modern partial external radiotherapy of HCC are of the order of 50-70%. Single center studies show a strong dose-response relationship when doses >50 Gray are given [26-31].

An autopsy series of patients who received 50-70 Gray showed evidence of tumor regression, but not eradication of HCC [32] It suggests that higher dose is required to eradicate HCC.

Recently, a study[50] (the abstract is published in the July volume of the 2007 ASCO annual meeting) evaluated the effect of Cyberknife stereotactic radiosurgery (SRS) for both small primary non-resectable HCC (23 lesions in 22 patients), and advanced HCC with portal vein tumor thrombosis (PVTT) (9 lesions in 9 patients). The total SRS doses treated were 30-39 Gy (median, 36 Gy) to the 70-85%, 3 fractions and the target volume was of 3.6-57.3 cc (median, 25.2 cc). After median follow up of 10.5 months, a complete response (CR) was achieved in 10 lesions, a partial response (PR) in 13 lesions (CR+PR was 71.9%), stable disease in 6 lesions, and disease progression in 3 lesions. The level of serum alpha-fetoprotein after the treatment was decreased significantly in 17 patients (54.8%) Complications greater than grade 3 were observed in two patients. These results suggest that Cyberknife SRS could be considered as an effective and safe treatment for primary HCC. For PVTT, Cyberknife SRS as the only curative tool, and produced acceptable local control in this study.

The issue of respiratory motion has long been recognized as a major limitation in the management of radiotherapy patients. The limitations are manifest both in conventional

imaging for target localization, and in the delivery of radiotherapy itself. Respiratory motion during computed tomography (CT) scanning causes artifacts that distort the size, shape, and density of objects within in the image, and introduce uncertainty in their location [33-36]. Larger radiation fields are therefore required to ensure adequate coverage of the target anatomy. As a consequence, greater volumes of normal tissue are irradiated, which subsequently limits the therapeutic dose that can be delivered.

Minimizing the impact of respiratory motion is essential in order to achieve further gains in the treatment of hepatic disease. In this study, we will apply advanced imaging and delivery technology to provide added confidence in imaging and targeting. First, all patients will undergo a planning CT that uses a respiratory correlation technique [37-42 43]. Briefly, patients' respiration will be monitored using a commercial strain gauge (ANZAI Medical Co. Ltd., Tokyo, Japan) device placed inside an elastic belt and positioned about the patient's abdomen. Patients will subsequently undergo a low pitch, over-sampled CT scan. By retrospectively correlating the CT data with the respiration signal obtained using the ANZAI device, CT images will be reconstructed into four bins as a function of respiratory phase: end exhale, mid exhale, mid inhale and full inhale. End exhale images will be used for planning purposes, as this has been shown to be the most reproducible phase of respiration and that with the longest duration.

The Novalis accelerator (BrainLAB AG, Heimstetten, Germany) incorporates stereotactic x-ray capabilities for verifying target position. This consists of two floor mounted x-ray tubes and two opposing amorphous silicon (aSi) flat panel detectors mounted to the ceiling. Each x-ray tube/detector pair is configured to image through the linac isocenter with a coronal field of view of approximately 18cm in both the superior-inferior (S-I) and left-right (L-R) directions at isocenter. For soft tissue targets the system is designed to be used with radio-opaque fiducial markers implanted near the target. These markers are implanted prior to CT imaging and treatment planning, and should be placed close enough to the target anatomy so that they can be observed within the field of view of the x-ray localization system at the time of treatment.

Markers are placed by introducing a small coil (VISICOIL™, RadioMed Corp., Tyngsboro, MA) percutaneously through a coaxial needle (18 to 22 gauge) in or near the target. This is performed under fluoroscopic guidance in a manner analogous to a biopsy or radiofrequency ablation. The extended and coiled-wire structure of the VISICOIL is designed to minimize migration and movement, providing stability of the marker in tissue. VISICOIL needles are delivered with preloaded coils of an appropriate length and sterilized ready for use. The use of implanted makers for radiotherapy localization has been described for a number of tumor sites, including prostate[44 45], liver[46], and lung[47, 48]. An excellent primer on the percutaneous placement of helical coils in lung tumors has been presented by de Mey et al [48].

Based on specific patient motion characteristics determined during 4D CT, an appropriate course of radiotherapy will be determined. This may include the use of gated deliver, which is, turning the beam on only at a specified phase of respiration. This "freezes" target motion and allows reduction of beam margins, thereby reducing the amount of irradiated normal tissue (in this case, normal liver). The Novalis system is well suited to gated delivery and has been

evaluated extensively by Tenn et al [49]. The following is a brief procedural summary from that work which will be incorporated into this study:

The patient is set up in the treatment room and IR reflective markers with adhesive bases are attached to their anterior surface so that breathing motion can be monitored. A second set of IR reflective markers is rigidly attached to the treatment couch and used as a reference against which the movement of patient markers is measured. These rigidly mounted reflectors are also used to track couch location during the patient positioning process. The 3D movement of the patient's anterior surface is tracked via the IR markers and the anterior-posterior (A-P) component of this trajectory is used to monitor breathing motion. The system plots breathing motion versus time and a reference level is specified on this breathing trace. This designates the point in the breathing trace at which the verification x-ray images will be triggered. The two images are obtained sequentially at the instant the breathing trace crosses this level during exhale phase. Because the patient is localized based on these images, the gating level is set at the same phase in the breathing cycle at which the planning CT data was obtained. Within each image the user locates the positions of the implanted markers. From these positions the system reconstructs the 3D geometry of the implanted markers and determines the shifts necessary to bring them into alignment with the planning CT. The patient is subsequently positioned according to the calculated shifts. Finally, a gating window (beam-on region) during which the linac beam will be delivered is selected about the reference level. The system can gate the beam in both inhale and exhale phases of the breathing cycle. Subsequent x-ray images verifying the location of the implanted markers locations are obtained at the gating level continuously during treatment. If marker positions remain within tolerance limits the target position may also be assumed to be correctly positioned. If they are outside the limit the newly obtained images can be used to reposition the patient and maintain treatment accuracy.

In summary, for the majority of HCC patients, surgery is precluded. Percutaneous ethanol injection and RFA showed relative good results for early stage HCC only. TACE has shown to provide modest survival advantages and is currently the mainstay of treatment in only 10% of the whole HCC population. Systemic chemotherapy is ineffective for HCC patients. Although targeted therapy has been shown survival advantage, it is only on HCC patients with Child-Pugh status A. The effectiveness of high dose radiation therapy on both early and advanced HCC without dose limiting toxicity suggested the importance of the further investigation of newer conformal radiation technology, i.e. IMRT, IGRT, SRT, for treatment of HCC.

Section 3.0 Eligibility Criteria

3.1 Inclusion Criteria:

Patients must meet all the following criteria

- 3.1.1 Male or female patients ≥ 19 years of age
- 3.1.2 A life expectancy of at least 12 weeks with a Karnofsky performance status ≥ 60% (Appendix V)
- 3.1.3 Histologically or cytologically documented HCC
- 3.1.4 The target lesion can be accurately measured in at least one dimension according to RECIST and must have a maximum tumor diameter of ≤ 8 cm

3.1.5 Previous systemic chemotherapy or non-radiation local therapy (such as surgery, hepatic arterial therapy, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation) is allowed. Local therapy must be completed at least 6 weeks prior to the baseline scan.

3.1.6 Cirrhotic status of Child-Pugh class A and B (Appendix I)

3.1.7 Platelet count ≥ 60 x 10^9/L, Hemoglobin ≥ 8.5 g/dL, WBC ≥ 2000/μL

3.1.8 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 (PT, PTT,INR) exists.

3.1.9 Must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks and discomforts.

3.2 Exclusion Criteria:

3.2.1 Previous (within 3 years) or concurrent cancer that is distinct in its primary site or histology from HCC, EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors (Ta, Tis & T1). Any cancer curatively treated > 3 years prior to entry is permitted.

3.2.2 Renal failure requiring hemo- or peritoneal dialysis

3.2.3 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 3.0), 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 study entry is permitted.

3.2.4 Known Central Nervous System tumors including metastatic brain disease

3.2.5 A history of variceal bleeding where the varices have not been eradicated or decompressed by shunt placement.

3.2.6 Any conditions that would prevent the patient from undergoing maker implantation.

3.2.7 Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results

3.2.8 Pregnant or breast-feeding patients are excluded from this study because abdominal radiation therapy has potential for teratogenic or abortifacient effects.

3.2.9 Prior radiotherapy to the liver.

Section 4.0 Registration Procedures

4.1 Eligible patients will be identified from our institutional patient base or referred from community oncologists. All patients with HCC or suspicious HCC referred to the UNMC are evaluated in a multidisciplinary team conference. On initial presentation, a history and physical examination are performed, laboratory data obtained, and performance status is assessed. Imaging studies obtained include a high-resolution multi-detector computed tomography (CT) of the abdomen and pelvis as well as a chest radiograph (two views). Further imaging studies will be obtained as clinically indicated. Any pathologic specimens obtained at referring institutions are reviewed for accuracy. Patients with suspicious HCC will require liver biopsy for confirmation of malignancy.

4.2 Patient's cirrhotic status will be evaluated according to Childs-Pugh scale (Appendix I)

4.3 Assessment of medication intake

4.4 Patients will be consented once eligibility has been confirmed by participating hepatologists, medical oncologists and radiation oncologists. Eligible patients will be counseled about the study with special emphasis on the risks involved in a trial. Patients and their families who are interested in pursuing experimental therapy can be counseled in a group by the principal investigator. After an appropriate waiting time, a second opportunity for conference will be offered to answer remaining questions. Informed consent will be obtained from all patients.

4.5 The standard of care outside a clinical trials setting for patients with locally advanced HCC is localregional ablative therapy including percutaneous ethanol injection and RFA, TACE, palliative chemotherapy with or without palliative radiation therapy. Targeted therapy may be offered in the future.

4.6 Study schedule of activity (Appendix II)

Section 5.0 Research Design

5.1 Liver marker implantation: Under CT or ultrasound guidance, a marker will be implanted into the liver tumor in a fashion similar to liver tumor biopsy and a stent placement. Prophylactic antibiotics will be given to prevent infection. The marker position and geometry will be documented on the simulation CT scan for planning SRT.

5.2 SRT:

5.2.1 Machine: Novalis with 6 MV photons will be used for imaging guided SRT.
5.2.2 Doses: Doses of 40, 50, 60 or 70 Gy (daily doses of 8, 10, 12 or 14 Gy in 2 weeks) will be prescribed to 90% isodose line. The prescription isodose volume should encompass the entire PTV. The subjects will be divided into groups of 5

to receive escalating doses of the SRT. The first group will receive a daily dose of 10Gy (Dose Level II). The next group will be enrolled only after the first group has been observed for 4 weeks following the SRT to document any side effects. The observation period will be used for every increase in dose level. Each subject will only receive one dose level of the SRT.

5.2.3 Localization, Immobilization and Simulation: A body-fix bag will be used for treatment simulation and delivery. Infrared markers will be attached to the patient's chest and abdomen in suitable positions to yield a good breathing signal. A 4D CT scan of abdomen will be performed for treatment planning. Treatment Planning: Following transfer to the treatment planning system, the CT scan may be correlated by imaging fusion with a MRI scan for contouring tumor volume. Integrated tumor volume (ITV) will be generated. The planning target volume (PTV) is defined as ITV plus individualized margins, which will be determined by a 4D CT scan. The uniformity requirement will be +10% -5% of the total dose at the prescription point within the tumor volume. The IMRT may be used if there is a benefit of decreasing tissue complications. The dose to the kidney will require careful monitoring and kidney volumes must be defined on simulation fields. The percent of total kidney volume (defined as the sum of the left and right kidney volume) receiving 15 Gy (3 Gy per fraction) should be required to be less than 35% of the total kidney volume. The maximum dose to any point within the spinal cord should not exceed 15 Gy (3 Gy per fraction). At least 700 ml or 35% of normal liver (entire liver minus cumulative GTV) should receive at total dose less than 15 Gy (3 Gy per fraction). The maximum point dose to the stomach or small bowel except duodenum should not exceed 80% of prescription dose. An isodose distribution of the treatment at the central axis indicating the position of kidneys, liver and spinal cord is required. The treatment plans should be optimized using dose volume histograms of any irradiated vital organ.

5.2.4 Treatment Delivery: The planning data containing the coordinates of tumor isocenter, the external infrared markers, and the implanted marker are transferred to the ExacTrac Adaptive Gating platform. The daily initial positioning will be performed using lasers and skin marks. The target isocenter will be verified on daily x-rays. If the patient meets the criteria of breath gating, treatment delivery is accomplished using the ExacTrac Adaptive Gating in combination with Novalis. External infrared markers attached to the patient's skin are used to determine the breathing pattern. The respiratory moving target is positioned, under infrared and x-ray guidance to a defined point within the patients' end expiratory breathing cycle. The gating reference level will be defined to evaluate target motion due to respiration. The size of beam-on window will be determined based on the target motion as detected by the 4D CT scan.

5.3 The study follow-up will coincide with the standard of care follow-up visits which will be 1 and 3 months after the completion of SRT. None of the tests or procedures is

performed more frequently than would be considered clinically standard. No procedures would be done exclusively for research purposes.

5.4 Toxicity:

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

5.4.2 SRT: 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, kidney function abnormality.

5.5 Dose Modifications:

Radiation therapy will be held if the AGC is < 500/μL and/or the platelets are < 50,000/μL. Upon recovery of the AGC to ≥ 500/μL and platelets to > 50,000/μL, radiation therapy will resume at the full planned daily dose.

5.5 Supportive Care:

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

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

5.5.2 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

5.5.3 Treatment of Fever & Neutropenia

Subjects developing a fever of 100.5º C or higher will have a CBC with WBC differential obtained along with a history & physical examination to look for signs of infection.

If the ANC is < 500/µL, the patient will be treated with empiric antibiotic therapy as an inpatient & undergo appropriate radiographic & laboratory investigation for sources of infection, & development of a specific treatment plan. Fever & neutropenia occurring during a treatment cycle will require interruption of chemotherapy. The patient may resume chemotherapy at the start of the next scheduled cycle if therapy for infection has been completed & the patient meets other criteria for starting a new cycle

If the ANC is between 500-1000/µL, antibiotic therapy will be instituted if there is clinical suspicion of an infection. Daily CBCs with differentials will be obtained if the patient remains febrile.

If the ANC is > 1000/µL, & there is no clinical evidence of an infection, then therapy may resume.

5.5.4 Blood Products

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

5.5.5 Nutritional Supplementation

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

5.6 Criteria for removal of patients from study

5.6.1 Disease progression
5.6.2 Study closure
5.6.3 Any dose limiting toxicity (defined at section 10.1)
5.6.4 Patient decision to withdraw from the study, or

In the judgment of the investigator, further treatment would not be in the best interest of the patient.

Section 6.0 Measurement of Effect

6.1 Toxicity criteria

The NCI Common Toxicity Criteria Adverse Events version 3 will be used to grade toxicity; it is available at the following internet site: http://ctep.cancer.gov/forms/CTCAEv3.pdf.

6.2 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:

6.2.1 The patient shows a ≥50% reduction in pain intensity or analgesic consumption (Appendix IV: Pain assessment)

OR

6.2.2 Improvement in performance status (Appendix V) 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

6.2.3 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

6.3 Tumor Response

6.3.1 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 III)

Patients enrolled in this study must have a measurable HCC which is defined as lesions that can be accurately measured in at least one dimension: [longest diameter to be recorded] on the CT scan or MRI scan.

The same method of assessment & 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	MRI scan
4	AFP

6.3.2 Response criteria

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

Complete Response (CR): the disappearance of a lesion.

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.

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.

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.

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.

6.3.2.2 The criteria used to determine the objective tumor response for those lesions without size response:

Complete Response (CR): the normalization of AFP level.

Partial Response (PR): at least a 25% decrease in the AFP level.

Progressive Disease (PD): the maintenance of AFP level above the normal limits

In some circumstances, it may be difficult to distinguish residual disease from the radiation induced necrotic tissue. When the evaluation of complete response depends on the normalization of AFP level, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status.)

Section 7.0 Study Parameters

7.1 Laboratory/imaging Studies:

Parameter	**Baseline**	**Pre- and post-SRT therapy**	**Post-Treatment Follow-up**
History	X	X [b]	a
Physical examination	X	X [b]	a
Weight	X	X	a
Vital signs	X	X	a
Performance status (Karnofsky)	X	X	a
CBC, differential, platelet count	X	X Post- SRT	a
Comprehensive metabolic panel (including bilirubin, alk phos, AST, ALT,)	X	X Post- SRT	a

Fill out pain assessment card	X	X Post-SRT	a
AFP	X	X post-SRT	a
PT, PTT, INR	X	X Post-SRT	a
CT	X	X simulation	
MRI	X	X Post-SRT	a
Serum pregnancy test	prn		

a - *will be done at one month and 3 months after the completion of SRT*
b – A brief physical exam and history will be performed

7.2 Monitoring of peri- and post-marker implantation morbidity

The liver marker position and geometry will be documented on simulation CT images. Information regarding the development of infectious complications, bleeding, and any implantation associated adverse events will be recorded.

Section 8.0 Drug Formulation and Procurement

No drugs are used in this study.

Section 9.0 Toxicity Reporting Guidelines

9.1 Adverse Events that will be reported to UNMC's IRB

9.1.1 Unexpected serious adverse events
9.1.2 Any death, which occurs while the subject is being treated on protocol or occurs within 30 days of completing research related interventions
9.1.3 Toxic deaths will be reported to the UNMC IRB within 24 hours following PI knowledge of the event via e-mail notification to irbora@unmc.edu

The IRB only requires submission of internal AE reports when the event is unexpected. Internal adverse events occurring on a study which satisfy this criterion must be submitted to the IRB within two business days following the time it becomes known. Any death must be reported immediately. One original of the Internal AE Report form (or Internal Fatal Event form), and one copy of the current IRB approved consent form must be submitted, along with any other relevant information, to the IRB:

The contact information is: Institutional Review Board, University of Nebraska Medical Center, 987830 Nebraska Medical Center, Omaha, NE 68198-7830; Tel: 559-6463; FAX: 559-3300; e-mail: irbora@unmc.edu

9.2 Reporting of Adverse Events to the Scientific Review Committee of the UNMC Eppley Cancer Center

The SRC defines an adverse event as any undesirable experience associated with the use of the protocol treatment in a patient. The event is considered to be SERIOUS and should be reported when the patient outcome is:

9.2.1 Death: Report if the patient's death is suspected as being a direct outcome of the adverse event.

9.2.2 Life-threatening: Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use of the SRT would result in the patient's death.

9.2.3 Hospitalization (initial or prolonged): Report if the patient requires admission to the hospital for 24 hours or more or prolongation of a hospital stay results because of the adverse event.

9.2.4 Disability. Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.

9.2.5 Requires intervention to prevent permanent impairment or damage. Report if you suspect that the use of the protocol treatment may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

Copies of the adverse event report will be submitted to the IRB (when required), to the UNMC Eppley Cancer Data and Safety Monitoring Committee (DSMC).

9.3 Data and Safety Monitoring Plan

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC/Eppley Cancer Center Data Monitoring Plan. All research data will be stored in the case report forms in a locked file cabinet. These forms are available only to the investigators, his/her designee (i.e., the study coordinator), the UNMC Eppley Cancer Center Scientific Review Committee (SRC), and representatives of the Institutional Review Board at the University of Nebraska Medical Center. Any information obtained during this study which could identify the subject will be kept strictly confidential and will be identified by code numbers rather than the patient's name. The data safety plan also includes: Weekly review of all patients on study by the investigators. All adverse events will be reported to the PRMS Internal Audit Committee for audit by a clinician not involved with the clinical trial.

All patients will be closely followed for toxicity. Toxicity will be assessed using the revised NCI Common Toxicity Criteria (version 3.0) retrieved from the National Cancer Institute, Cancer Therapy Evaluation Program web site: (ctepcancer.gov/forms/CTCAEv3.pdf). Therapy will be discontinued at any time due to the development of unacceptable toxicity. If a Grade 1 or 2 or 3 toxicity develops, the investigator may elect to continue the treatment with careful monitoring. Any grade 4 or greater toxicity according to CTCAE v3 will constitute a DLT. 1) SRT dose escalation will be stopped if 2 patients at a given dose level experience a DLT. If one patient has a DLT, then an additional five patients will be evaluated at the same dose level. 2) Implantation of a liver marker will be stopped if 2 patients experience implant-related-adverse events which do not response to medical or surgical management.

Therapy will be discontinued at any time due to the development of unacceptable toxicity. If, at any time, the data suggest a significant hazard to further dose escalation, regardless of whether the formal stopping rules are satisfied, dose escalation will be halted pending a review of all data. There will be a four week waiting period after the last patient in each cohort completes radiation therapy for toxicity evaluation between dose levels.

Adverse events will be assessed by reports from patients of any adverse events to their physician-investigators and by physical examinations. The following information will be recorded for all adverse events: date of onset, date of resolution, severity, action taken, relationship to study medication and patient outcome. The worsening of a concurrent disease or the development of a new concurrent disease will be regarded as an adverse event and information regarding the event will be added to the adverse event page of the case record book.

The plan also includes the following: the status of all patients participating in this protocol will be reviewed by the principal investigator with the research nurse on the weekly visit during the SRT and on each follow-up visit. During this meeting, the clinical toxicities experienced by the patients will be discussed, and plans will be made for any modification, and whether any changes need to be made to the protocol through an amendment. Any logistical or social issues for the patients will also be addressed at this meeting. The research nurse will be in contact with each patient by either telephone or e-mail. Laboratory studies done at outside facilities are faxed to the research nurse on a real-time basis. Any abnormalities are brought to the attention of the principal investigator or designee.

Patients may continue on concurrent medications for symptom relief on an as needed basis. The need for additional or more potent concurrent medication after the start of the study may constitute an adverse event, and information regarding such an experience will be added to the appropriate page of the case record form. The details of all concurrent medications, including vitamins, blood and blood products, will be recorded on the case record forms.

Section 10.0 Statistical considerations

10.1 Trial Design

This phase I trial will determine safety, dose-limiting toxicities (DLT) and maximum tolerable dose (MTD) of SRT for HCC. Although unacceptable toxicity is unlikely, four dose levels (40, 50, 60, 70 Gy in 5 fractions) will be evaluated in a cohort escalation design of 3-6 patients. At the MTD, 10 additional patients will be enrolled to generate pilot data on radiologic response and to evaluate further toxicity. Patients will start at dose level II (50 Gy at 5 fractions).

Endpoints

Toxicity will be graded by NCI Common Toxicity Criteria (CTC Version 3.0). Due to delayed toxicities attributable to radiotherapy, all toxicities observed within 1 month after SRT will be scored. DLT is defined as any of following toxicities, that is possibly, probably or definitely related to SRT occurring within 30 days from the start of treatment:

a) grade 4 or 5 hepatic
b) grade 4 or 5 gastrointestinal
c) grade 4 or 5 thrombocytopenia
d) grade 4 hepatic liver enzyme elevations persisting for ≥ 5 days
e) any adverse event requiring interruption of therapy by ≥ 2 weeks (14 calendar days). This does not include patient desire to discontinue therapy. It does include failure for thrombocytopenia to improve to a level of 80 requiring interruption of therapy.
f) Any grade 5 treatment-related adverse event

The MTD of SRT is defined as the highest dose level at which no greater than 2 DLT is observed in 6 patients.

Dose-escalation Rules

A standard cohort escalation design will be employed to evaluate 3 dose levels of SRT. Three patients will initially be treated at each dose level. A minimum of 1 month of observation after surgery is required in all 3 patients before escalation is initiated.

At the second dose level, 3 patients are entered. If:

0/3 have DLT	then the third dose level is investigated.
2/3 have DLT	then the MTD is exceeded at the second dose level. De-escalation of SRT to the first dose level will be considered.
1/3 have DLT	then 3 additional patients are entered. If none of the additional patients develop DLT, then the third dose will be investigated. Otherwise, the MTD is exceeded at the second dose level. De-escalation of SRT will be considered.

At the third dose level, 3 patients are entered. If:

0/3 have DLT	then the fourth dose level is investigated.
2/3 have DLT	then the MTD is exceeded at the third dose level. The second dose level will be expanded to a total of 6 patients (if only 3 patients had been treated).
1/3 have DLT	then 3 additional patients are entered. If none of the additional patients develop DLT, then the fourth dose will be investigated. Otherwise, the MTD is exceeded at the third dose level.

At the fourth dose level, 3 patients are entered. If:

0-1/3 have DLT	then 3 additional patients are entered. If at most 1 of 6 patients develops DLT, then the fourth dose will be declared the MTD. Otherwise, the MTD is exceeded and the third dose level will be expanded to a total of 6 patients (if only 3 patients had been treated).
2/3 have DLT	then the MTD is exceeded and the third dose level will be expanded to a total of 6 patients (if only 3 patients had been treated).

10.2 Plans for Expansion at the MTD

Once the MTD has been defined, 10 additional patients will be enrolled, to provide preliminary efficacy data. One month of observation after SRT will not be required between groups of patients during the expansion phase, but monitoring DLT will be performed, as described in the next section.

10.3 Monitoring Dose-Limiting Toxicity

With 6 evaluable patients, the probability of not escalating when the true DLT rate is 35% or higher is at least 68%. If the true DLT rate is 20%, the probability that the dose will be escalated is 66%.

10.4 Plans for Data Analysis

Toxicity will be graded and tabled by dose level. At the MTD, the rates of radiological complete and partial responses and 90% exact binomial confidence intervals will be calculated.

10.5 Sample Size

The number of evaluable patients that will be needed depends on the number of times the dose is escalated or possibly de-escalated. If the escalation continues up through Dose Level IV, 18 evaluable patients will be required. If the dose is de-escalated after Dose Level II, then a maximum of 12 evaluable patients will be required. Since 10 additional patients will be enrolled once the MTD has been defined, a maximum of 28 patients will be enrolled on the trial.

Section 11.0 Records to be kept

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. Serious adverse events, when noted, will be recorded on site via the standard serious adverse effects form.

Section 12.0 Patient consent form statement

See attached consent form.

Section 13.0 References

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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

Schedule of Activity

	Screening/Baseline	Liver Marker Implant Procedure	1-7 Days Post Implant	SRT planning,	Start SRT	End SRT	1 month Post SRT	3 Months Post SRT
History & Physical	x		x	x	x	x	x	x
CT abdomen/pelvis	x	x		x				
MRI abdomen/pelvis	x			x				x
biopsy	x							
Inclusion/Exclusion	x							
Informed consent	x							
CT or U/S guided marker implant		x						
AFP	x			x			x	x
CBC with diff	x		x	x			x	x
INR	x							
complete chemistry pannel	x		x	x			x	x
Chest X-ray or Chest CT	x							
Record adverse events		x	x	x	x	x	x	x

Appendix III

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 IV

Pain Intensity Assessment

UNMC IRB protocol # _____ Date: ____ ____ 200____
Day Month year

Subject Initials: ____ ____ ____ Subject ID: _____

Visit: ☐ Baseline (prior to study treatment)
☐ End of treatment
☐ 1-month follow up
☐ 3-month follow up

This form is to be completed by study subject.
Please make a mark on the pain scale line with a black-ink pen.

0 _____ **10**

least possible pain — worst possible pain

Subject Initials

Appendix V

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 VI
Eligibility Checklist

IRB# _____

MR# _____

SEX Male female

AGE _____, ≥ 19 years of age	YES	NO
life expectancy of at least 12 weeks	YES	NO
Karnofsky performance status ≥ 60%	YES	NO
Histologically or cytologically documented HCC	YES	NO
The target lesion can be accurately measured in at least one dimension according to RECIST	YES	NO
Maximum tumor diameter of ≤ 8 cm	YES	NO
No prior radiotherapy to the liver	YES	NO
Local therapy was completed at least 6 weeks prior to the baseline scan	YES	NO
Cirrhotic status of Child-Pugh class A and B	YES	NO
Platelet count ≥ 60 x 10^9/L	YES	NO
Hemoglobin ≥ 8.5 g/DL	YES	NO
WBC ≥ 2000/MI	YES	NO
International normalized ratio (INR) ≤ 2.3	YES	NO
Informed consent signed	YES	NO
Liver marker implanted	YES	NO
AFP tested	YES	NO
CT/MRI scans available	YES	NO

Complete chemistry panel, PT,PTT,INR	YES	NO
For patient with history of cancer: It is cervical carcinoma in situ or treated basal cell carcinoma or superficial bladder tumors (Ta, Tis & T1) or Any cancer curatively treated > 3 years	YES	NO
Renal failure requiring hemo- or peritoneal dialysis	YES	NO
Uncontrolled inter-current illness	YES	NO
Central Nervous System tumors	YES	NO
Varices NOT eradicated or decompressed by shunt placement	YES	NO
Substance abuse or medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results	YES	NO
Pregnant or breast-feeding	YES	NO