LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #5

LCCC 0809:

AMENDMENT INCORPORATES:

_X_ Editorial, administrative changes
_X_ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
_X_ Eligibility Changes (IRB approval)
___ Other

AMENDMENT RATIONALE AND SUMMARY:

Editorial, Administrative Changes:

1. Typo corrected in section 4.1.
2. Minor revisions were made in sections 6 (Adverse Experiences) and Section 8 (Study Management) to reflect updated template language.

Scientific changes:

1. Section 5.5 was changed to indicate that follow-up of irradiated liver lesions will continue for up to 2 years even when disease progresses in non-irradiated lesions.
2. Section 5.6, Assessment of Response, was revised and re-titled to Assessment of Disease Status. The definition of what constitutes progressive disease was changed to reflect PI's intent, and is now based on a bi-dimensional measurement. Irradiated lesions will be assessed and documented separately from non-irradiated lesions.

Eligibility changes:

1. The PI's intent was to include patients with at least one and no >3 liver lesions. This had been written incorrectly as >1 and more than 3 lesions.

THE ATTACHED VERSION DATED 12/6/2011 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #4

LCCC 0809:

AMENDMENT INCORPORATES:

__X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
__X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)
___ Other

AMENDMENT RATIONALE AND SUMMARY:

Editorial, Administrative Changes:

3. "Childs-Pugh" revised throughout to read "Child-Pugh".
4. Section 6.0 pp. 19-21: Adverse Experienced revised for clarification and to conform to current LCCC protocol template.
5. Section 8.6.3 pp. 27-28 revised for clarification and to conform to current LCCC protocol template.

Therapy changes:

3. Clarified that both International Normalized Ratio (INR) and Prothrombin Time (PT) are collected and monitored, see Time and Events table, p15.
4. Addition of testing for circulating Tumor Markers: AFP (HCC) or CEA (CRC) to Time and Events table, p15.

THE ATTACHED VERSION DATED 10/21/2011 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #3

LCCC 0809:

AMENDMENT INCORPORATES:

__X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
__X_ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)
___ Other

AMENDMENT RATIONALE AND SUMMARY:

Editorial, Administrative Changes:

1. Title Page: Title revised to read: LCCC 0809: A Dose-Finding, Safety and Preliminary Efficacy Study of Stereotactic Radiosurgery for Hepato-Cellular Carcinoma and Other Metastatic Disease to the Liver. **Rationale:** Revised to reflect changes from Amendment 2 allowing liver metastases from other primary tumors.

2. Title Page: Revision history now includes amendment version and date.

Therapy changes:

1. Section 2.1 p.3 Primary Objective, now reads: Cohort 2: Patients with compromised liver function as defined by patients with Child-Pugh Class B. **Rationale:** Removed reference to central lesions.

2. Section 3.1 p.4 Schema, now reads: The second cohort is comprised of patients with Child-Pugh Class B lesions where liver tolerance is more likely to be a problem. **Rationale:** Removed reference to central lesions.

3. Section 3.2, pg. 5 Immobilization Cradle and Treatment Planning CT Imaging, now reads: **7**-10 days after fiducial placement (to enable resolution of any injury that may have occurred during fiducial placement and to allow for fiducial stabilization), subjects will return to the Radiation Oncology Clinic. **Rationale:** Increased minimum period between fiducial placement procedure and planning CT from 3 days to 7 days to allow longer healing period.

4. Section 3.2, pg. 5 The Stereotactic Radiosurgical Procedure: Now reads: The CyberKnife (CK) treatment will **generally** be initiated within 1 **to 2** weeks of the planning treatment CT. **Rationale:** To provide scheduling flexibility.

5. Section 3.2, pg. 6, Second Cohort (compromised liver function), now reads: The planned initial dose delivered to all patients with Child-Pugh Class B will be 700 cGy delivered to the prescription point for 5 fractions for a total of 3500 cGy if the dose-normal tissue constraints defined below can be met. **Rationale:** Removed reference to central lesions.

6. Section 3.2, pg. 6, now reads: ii) Second Cohort: Compromised liver function (as defined in primary objective). **Rationale:** Removed reference to central lesions.

7. Section 5.1. p.15, Time and Events Table, Liver Biopsy (if needed for diagnosis) revised to occur only during "Pre-study assessment period" (within 8 weeks prior to start of Cyberknife Radiation Therapy Treatment). **Rationale:** Restricted diagnostic biopsy to pre-study assessment period.

8. Section 5.1. p.15, Time and Events Table, Treatment Planning, now reads: [e]To be done 7-10 days following fiducial placement. Participants will be immobilized using Vac-Loc and Synchrony vest to facilitate in obtaining the treatment planning CT. **Rationale:** Increased minimum period between fiducial placement procedure and planning CT from 3 days to 7 days to allow longer healing period.

9. Section 5.2 p. 16, "Fiducial placement", now reads: CT planning in Radiation Oncology to be done **7**-10 days after fiducial placement. **Rationale:** Increased minimum period between fiducial placement procedure and planning CT from 3 days to 7 days to allow longer healing period.

THE ATTACHED VERSION DATED 04/18/2011 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #2

LCCC 0809:

AMENDMENT INCORPORATES:

__X_ Editorial, administrative changes
__ _ Scientific changes (IRB approval)
__X_ Therapy changes (IRB approval)
__ Eligibility Changes (IRB approval)
___ Other

AMENDMENT RATIONALE AND SUMMARY:
Editorial, Administrative Changes:

1. Title Page: David Morris title corrected from Assistant to Associate Professor. Suzanne Russo MD was removed as co-investigator, and Julian Rosenman MD was added. We removed the name of the UNC Study Coordinator from the protocol, leaving the contact phone number, in the event of staff changes (to avoid future amendments).

2. Signature page: This now includes the study title and Version date.

3. Section 1.1 Study Synopsis and Section 2.2 (Secondary Objective): Inclusion criteria and primary objective include patients with liver metastases from colorectal or other primary tumors. This was clarified up front in the study synopsis and in the secondary objective.

4. Section 5.4: Added clarification that patients need to be followed up to week 20 regardless of whether they have stopped treatment due to disease recurrence prior to this point.

5. Section 5.5: Clarified that if disease recurs after week 20, follow-up will crease other than follow-up of any unresolved treatment-related toxicity. Footnote c in the Time and Events table now refers to Section 5.5.

6. Section 6.4 (Safety Meetings) and Section 8.0 (Study Management): Revised to reflect updated standard language for these sections.

Therapy Changes:

1. Section 3.2 Treatment Dosage and Administration Dose-Volume Constraints First and Second Cohorts: The dose volume constraint was increased from 700 to 1500 cGy in each cohort. The mean target dose for the entire liver in each cohort was specified (≤1500 cGy in cohort one and ≤1300 cGy in cohort 2). We had already included the maximum dose to

>1cc of the esophagus, heart, stomach, and small bowel in the protocol. This current amendment now also addresses the maximum dose allowed to >1cc of the rib and chest wall. This same information was also revised in Tables 1 and 2, including the footnotes.

Rationale: Since the time this protocol was initially written additional information has become available that allows us to estimate better the tolerance of the normal liver to high dose radiation therapy delivered in a small number of fractions. Much of these data are summarized in the QUANTEC analysis that was published in 2010 (Pan CC, Kavanagh BD, Dawson LA et al. Int J Radiation Oncology Biol PHys.2010;76:S94-S100). This group has come out with formal recommendations for liver stereotactic radiation therapy as delivered here, based on the tolerance of normal liver. Most of these data are obtained with peripheral hepatic irradiation, so the question being asked in this protocol of tolerance of the portal structures (as well as of the hepatic parenchrma) is still a critically important issue. However, the overall tolerance of the hepatic parenchyma is less of a question for the patients with good pre-existing liver function. The data for the patients with poor baseline liver function is less well known, but should also build on the data for the patients with good function.

THE ATTACHED VERSION DATED 09/20/2010 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #1

LCCC 0809:

AMENDMENT INCORPORATES:

__X_ Editorial, administrative changes
__X_ Scientific changes (IRB approval)
__ _ Therapy changes (IRB approval)
__X Eligibility Changes (IRB approval)
___ Other

AMENDMENT RATIONALE AND SUMMARY:
Editorial, Administrative Changes:

7. Title Page and PI Signature page: Information on the UNC Study Coordinator, and Multi-center Research Coordinator added, text defining what PI signature signifies added onto signature page.

8. Section 1.1 Study Synopsis: Clarified that patients without cirrhosis may also be included in trial, and specified that patients have < 3 liver metastases (instead of generally <3). This change also reflected in eligibility (see eligibility changes below).
   Rationale: See rationale under eligibility changes

9. Section 3.2 Treatment Dosage and Administration: Description of First Cohort clarified that it includes patients with "no more than" Child-Pugh Class A cirrhosis.
   Rationale: Patients do not have to have cirrhosis of the liver to be included in the trial.

10. Section 5.1 Time and Events Table and Section 5.2 Pre-Study Assessments: Serum creatinine and pregnancy test added to baseline studies in T&E table and Pre-Study Assessments, and clarified that PET scan is optional. Added footnote regarding consideration of elective stent placement in patients who receive high dose irradiation to the main hepatic ducts. Footnote regarding treatment planning changed from 5-10 days following fiducials placement to 3-10 days following fiducials placement. Footnote added to baseline liver biopsy that must be done within 14 days pre-study. In Section 5.2, Fiducial placement revised from "Standard techniques will be used for biopsy, but…" to "Prior to CT planning" and "CT planning in Radiation Oncology to be done 3-10 days after fiducial placement" added to the end of this section. CT, PET or MRI of the liver performed at week 4 was removed from section 5.4. This was not in the T&E table, and not the PI's intent.
    Rationale: Changes made to enhance consistency between eligibility criteria, study assessments and T&E table.

11. Section 5.3-5.6 Study Assessments: Added history to treatment assessments, and toxicity assessments added to post-treatment and follow-up assessments.
    Rationale: Changes made to enhance consistency between eligibility criteria, study assessments and T&E table.

12. Sections 6.0 (Adverse Experiences) and Section 8.0 (Study Management): A number of changes made in these sections to direct affiliate sites in their interactions with UNC Cancer Network (UNCCN, new name for the multi-center group) Study Coordinator, and to reflect revised IRB SOPs regarding reporting of unexpected adverse experiences, and protocol deviations.

13. Section 6.2 Reporting: Case Report Forms changed to electronic Case Report Forms (eCRFs).

14. Section 7.3 Data Analysis (Safety and Efficacy): This section included the protocol template language for the data and safety monitoring plan. This was deleted, and a study specific data safety monitoring plan was drafted and titled "Safety Meetings". This section is now 6.4 Teleconferences were changed from monthly to bi-weekly given the complexity of the study design, but meetings will only be that frequent if patient accrual justifies this as determined by the PI. Section 8.3 Data Management and Monitoring is a new section, and clarifies this topic for multi-center trials that UNC is coordinating. Detailed information on protocol audits was removed as this information isn't essential for the protocol. However, protocol still includes (in section 8.3) that the trial will be audited every 6 months.

15. Section 8.9 Obligations of Investigators: The last sentence was removed from this section (partial sentence).

16. Appendices now in Section 10, instead of at the end of Section ((References)

Scientific Changes:

Primary Objective and Section 3.2 Treatment Dosage and Administration (i) and (ii): The primary objective of the trial was not revised, but the description of the cohorts to be included in the study (and that are initially defined in the primary objective) was clarified. Cohort 1 includes those with good liver function now defined as disease limited to peripheral lesions and if cirrhosis is present, no more than Child-Pugh Class A. Cohort 2 includes those with compromised liver function as defined by the presence of central lesions and/or those with Child-Pugh Class B. In (i) and (ii) of 3.2, First Cohort now defined as: "Good liver function (as defined in primary objective)" and Second Cohort now defined as "Compromised liver function (as defined in primary objective)".

Rationale: Study treatment and dose modifications differ by cohort. Cohorts are now fully described the first time they are mentioned, and are now consistently described throughout protocol.

Secondary Objective: "To develop preliminary data on response/control of HCC" was changed to "To develop preliminary data on **local** response/control of HCC".
Rationale: Revised objective now agrees with secondary study endpoint as written in statistical section, and as described in other sections of the protocol.

Section 3.2 Treatment Dosage and Administration **1)**: Several changes were made throughout this section:

.2 Dose-Volume Constraints for both first Cohort (defined in i.) and second cohort (defined in ii) expanded to include all dose constraints that were identified in Table 1.

.3 Text of protocol and tables differed in prescribed fractional dose reduction for doses that led to >1cc of esophagus, heart, stomach, and small bowel receiving >3000 cGy in cohort 2. Also, no mention was made regarding dose reduction for constraints in these particular organs for cohort 1 in the text, although it was in both Tables. Text and table now match; both call for 250cGy dose reduction if necessary for cohort 1, and 150 cGy if necessary for cohort 2. Text now included in protocol for cohort 1.

.4 Corrected Tables 1&2 regarding maximum dose to 50% of one kidney (now <14 Gy and not >14 Gy)

.5 Table 2 now includes all possible dose levels as defined in the text of the protocol. Title of Table 2 changed from "Dose Modification Schedule" to "Dose Levels by Cohort" as this is more accurate title.

.6 Footnoted Tables 1 and 2 to emphasize maximum # of dose reductions before patient considered ineligible and to clarify any escalations done separately by cohort

.7 The time course over which the primary endpoint will be evaluated (within the first 3 months from initiation of treatment) was added.

.8 The expected toxicities used to indicate the primary endpoint has been met are now referred to as "dose-limiting hepatic toxicities".

.9 Expanded and clarified definition of intolerable dose level. Incorporated Tables 3 and 4 to emphasize definitions. Removed reference to # of dose-limiting toxicities (DLTs) and focused on fraction of patients who experience DLTs instead.

.10 Protocol now explicitly states that if dose level 1 (full dose) found intolerable, subsequent patients eligible for full dose will enroll into dose level (-1). This was PI's intent all along.

Rationale: These changes were made to correct errors, improve clarity and consistency between text and tables, and to clarify definition of intolerable dose level. Text now more consistent with PIs original intent.

Treatment Dosage and Administration **2):** Several changes were made throughout this section:

.11 The rules for dose escalation in the face of >30% local failure were clarified. Instead of "If at this time-point there is evidence of a greater than 30% local failure rate, and if the tolerance parameters are acceptable, then dose escalation to a nominal prescription dose per fraction of 1750 cGy in the first cohort and 850 cGy will be undertaken", the text now reads "A minimum of 10 patients will be entered onto each dose cohort. However, if there are 4 local failures within a cohort at dose level 1 dose escalation may proceed provided the tolerance parameters are acceptable (that is, conditions in both Tables 5A and 5B are satisfied), and patients have been evaluated for toxicity for at least 3 months from the initiation of therapy. At that point, dose escalation to a nominal prescription dose per fraction of 1750 cGy in the first cohort, and 850 cGy in the second cohort, will be undertaken. Sentence added at end of dose escalation section emphasizing that no intra-patient dose escalation will be allowed.

.12 Tables 5A and 5B were incorporated into the protocol to clarify when dose escalation is appropriate and safe.

.13 The summarized goals have been revised to match the text of the protocol.

.14 Following goals, the following section was removed: "A minimum of 10 patients will be entered onto each dose cohort before dose escalation. There will be 10 patients at the actual planned research dose that achieves the planned total dose with no de-escalation for treatment planning parameters. So it is possible that there can be more than 20 subjects. For dose escalation, if the proposed dose for escalation is found to be too toxic, based on CTCAE, Version 3 and toxicities described in Section 3.3 below, the study will be stopped. A shorter follow-up prior to escalation will be allowed if the parameters prohibiting escalation cannot occur with additional follow-up" and replaced with the following: "For dose escalation, if the proposed dose for escalation is found to be too toxic, based on Tables 3 and 4, the study will be stopped. All patients in a cohort will be followed for 3 months from the time of initiation of therapy for evaluation of toxicity, prior to dose escalation in each cohort." This was moved up earlier in the protocol into the section describing dose escalation. This change was made to clarify that trial will stop if dose escalation levels too toxic. Change to 3 months was made due to definition of primary endpoint.

.15 Same changes made throughout Section 7.1 Study Design.

Rationale: All of these changes were made to clarify the investigator's original intent.

Section 3.3 Toxicities and Dose Modifications: The title of this section was changed to Expected Toxicities as this is a more accurate title.

Eligibility Changes:

1. Inclusion Criteria (#1): Specified that patients can have no more than 3 liver lesions for eligibility. This was also changed in the study synopsis on page 1. Also clarified that patients must have more than one measurable liver lesion.
   Rationale: Local therapy considered appropriate option for patients with ≤3 lesions. Measurable added to match response assessment criteria in section 7, which specifies measurable disease.

2. Exclusion Criteria: (#4) Patients with a myocardial infarction within 12 months was changed to 6 months. Deleted #9 (history of myocardial infarction or unstable angina within 6 months).
   Rationale: Redundant exclusion criteria. MI "within 6 months" reflects investigator's original intent.

THE ATTACHED VERSION DATED 07/29/09 INCORPORATES THE ABOVE REVISIONS

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LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC 0809: A DOSE-FINDING, SAFETY AND PRELIMINARY EFFICACY STUDY OF STEREOTACTIC RADIOSURGERY FOR HEPATO-CELLULAR CARCINOMA AND METASTATIC DISEASE TO THE LIVER.

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Sponsor: UNC, Lineberger Comprehensive Cancer Center
Date: January 6, 2009
Revised: Amendment 1 dated 21 December 2009; Amendment 2 dated September 20, 2010; Amendment 3 dated April 18, 2011; Amendment 4 dated 10/21/11; Amendment 5 dated 12/06/11

LCCC 0809: A DOSE-FINDING, SAFETY AND PRELIMINARY EFFICACY STUDY OF STEREOTACTIC RADIOSURGERY FOR HEPATO-CELLULAR CARCINOMA AND OTHER METASTATIC DISEASE TO THE LIVER.

Signature Page

The signatures below constitute the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

PI Signature: _____

Date: _____

Version: Amendment 5 dated 12/06/11

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

The study will include patients with hepatocellular carcinoma (HCC) who are not appropriate for surgical resection or radiofrequency ablation (RFA) as a bridge to transplant, or with positive margins after surgical resection, with no cirrhosis, or Child-Pugh A or B. In addition, patients with limited liver metastases (≤3) from colon or rectal cancer or other cancers for whom local therapy to the liver is deemed appropriate, but who are not amenable for curative therapy with surgical resection or radio frequency ablation would also be eligible.

Patients will be irradiated with radiation doses using the CyberKnife system in 3-5 radiation fractions using guidance from fiducials placed by interventional radiology. Tolerance algorithms from conventional radiation therapy will be modified based on the data generated to determine hepatic tolerance at large dose per fraction radiation for each patient, while preliminary dose-control information would be determined on the same patient subsets. These data would be used to help expand the utility of radiotherapeutic ablative approaches for HCC patients and for treatment of liver metastases.

Implications: This study would define the parameters necessary for further expansion of the use of stereotactic radiosurgery for HCC and liver metastases (primarily colorectal cancer) and determining the best approaches for further studies on the incorporation of radiosurgery into the treatment algorithms in these diseases.

1.2 Disease Background and Rationale

The best outcomes from the treatment of HCC are when the primary tumor can be resected or ablated. Some patients can be treated with partial hepatectomy or total hepatectomy with liver transplant. However, non-transplant treatments are limited by both the extent of the tumor and pre-existing liver disease related to viral infection or other causes. Ablative therapies can be limited by the location of the tumor, as tumors near major vasculature may undergo ablation secondary to the "heat sink" effect from the adjacent vessels producing inadequate heating. Thus, an adequate resection cannot be obtained purely because of tumor location. Patients with HCC can also be treated with trans-arterial chemoembolization as well as infusion of radioactive substances into the liver, but these are not locally curative approaches.

Patients with limited metastatic disease to the liver from a variety of malignancies, but especially colon or rectal cancer are routinely treated with surgical resection or radiofrequency ablation in order to destroy the liver tumor. Approximately 25% of patients can obtain long term cure of their disease with these local approaches. However, as is true for HCC, many patients have tumors that are not technically amenable to therapy with these modalities. In addition, other patients are found to have areas at high risk of residual disease after surgery or RFA, or are thought likely to have residual disease with these techniques.

External beam radiation therapy has rarely been used in the treatment of HCC or colorectal liver metastases[1-3] for a number of reasons, including risk of exacerbating existing liver disease or producing unacceptable liver damage from the radiation, relative insensitivity of the tumors to conventional radiation doses, and inability to compensate for tumor motion secondary to respiratory movement[4,5]. Stereotactic radiosurgery (SRS) enables the selective delivery of an intense dose of high energy radiation to destroy a tumor with precision targeting. It is distinguished from other forms of radiation treatment by its improved accuracy. This accuracy is achieved by very precise spatial localization of the tumor and the delivery of multiple cross-fired beams of precisely directed radiation to converge upon the tumor, minimizing the injury to the surrounding healthy tissue. This selective radiation delivery capability also enables the delivery of very high radiation dose treatment to a tumor in close proximity to critical structures (situations in which the patient is at increased risk during surgery).

UNC has recently acquired a robotic driven linear accelerator (CyberKnife) that can deliver high doses of radiation therapy to small well-defined volumes while tracking the respiratory driven tumor motion [6]. This allows for delivery of radiation to hepatic tumors that cannot otherwise be resected or ablated [7], as the large vessels are relatively insensitive to high dose radiation therapy.

In the present study, SRS will be delivered using the CyberKnife® Stereotactic Radiosurgery System, a non-invasive, 100% frameless radiosurgery system that can ablate tumors and other lesions anywhere in the body. Treatment can be administered in single or staged (typically 2-5) sessions and the system is capable of monitoring internal reference points in the anatomy (skeletal landmarks or small implanted markers) to correct for patient movement.

The CyberKnife system has been cleared by the U.S. Food and Drug Administration (FDA) to treat lesions, tumors and conditions anywhere in the body when radiation treatment is indicated. In order to treat tumors during the respiratory cycle (vs. increasing the margin of treatment around the tumor to compensate for movement or requiring the patient to breath hold during the delivery of each beam), the Synchrony™ option, a system option that enables dynamic radiosurgery during respiration, will be used.

The Synchrony option enables the delivery of dynamic radiosurgery to tumors that move with respiration. The Synchrony option precisely tracks tumors in or near the target organ as they move, enabling the highly focused beams of radiation to destroy the tumors with minimal injury to adjacent normal tissue. The Synchrony option records the breathing movements of a patient's chest and combines that information with sequential x-ray pictures of tiny markers inserted inside or in the proximity of the tumor to enable precise delivery of radiation during any point in the respiration cycle. The CyberKnife system with the Synchrony option enables reduced normal tissue exposure by using smaller treatment margins and increased accuracy.

1.3 Rationale

There are reasonably good data on liver tolerance to radiation therapy with conventional external beam therapy, [4, 5] and there are some data on the use of high dose per fraction radiation therapy for patients with liver metastases. However, the location of the tumor in these studies has not been well defined and good data do not exist on radiation tolerance[8] in the context of pre-existing cirrhosis or using the high doses per fraction that are used with stereotactic radiation therapy such as with the CyberKnife for centrally located tumors. There are also minimal dose-local control data for HCC either with conventional radiation therapy or with high dose per fraction stereotactic radiation therapy [9-13]. This proposal, using existing data from conventional radiation therapy as a base line, would help define these tolerance doses and also provide preliminary tumor control data [14].

Since the time this protocol was initially written additional information has become available that allows us to estimate better the tolerance of the normal liver to high dose radiation therapy delivered in a small number of fractions. Much of these data are summarized in the QUANTEC analysis that was published in 2010[15]. This group has come out with formal recommendations for liver stereotactic radiation therapy as delivered here, based on the tolerance of normal liver. Most of these data are obtained with peripheral hepatic irradiation, so the question being asked in this protocol of tolerance of the portal structures (as well as of the hepatic parenchyma) is still a critically important issue. However, the overall tolerance of the hepatic parenchyma is less of a question for the patients with good pre-existing liver function. The data for the patients with poor baseline liver function is less well known, but should also build on the data for the patients with good function.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To determine a tolerable dose of radiation delivered by the CyberKnife in two cohorts of patients who have hepatocellular carcinoma or liver metastases from colorectal cancer or other tumors:

Cohort 1: Patients with good liver function as defined by, no more than Child-Pugh Class A if cirrhosis is present and disease limited to peripheral lesions

Cohort 2: Patients with compromised liver function as defined by patients with Child-Pugh Class B.

2.2 Secondary Objectives

To develop preliminary data on local response/control of HCC, colorectal liver metastases, and liver metastases from other primary sites to these radiation doses.

3.0 TREATMENT PLAN

3.1 Schema

After initial evaluation for eligibility and signing of the informed consent, fiducial markers will be placed via percutaneous approach by interventional radiology.

CT scans will be obtained, and when necessary, CT scans will be registered with MRI scans. The gross tumor volume (GTV) as well as the location of the GTV will be defined based on placement of the fiducial markers. The fiducial placement will be carried out by interventional radiology. For treatment planning, the GTV will be expanded by 5 mm in all directions except for supero-inferior where the expansion will be 8 mm. This expansion will account for both clinical target volume (CTV) expansion and motion. Treatment planning software will be used to plan radiation delivery schemes that will best meet the dose criteria defined above. The prescription dose will be modified as necessary as per section 3.3 to meet the defined liver tolerance dose.

Because of the difference in anatomy and expected normal tissue tolerance based on hepatic function, there are two well defined patient cohorts. The first cohort comprises of patients with good liver functions and peripheral lesions. The second cohort is comprised ofpatients with Child-Pugh Class B lesions where liver tolerance is more likely to be a problem.

Treatments will be delivered with standard CyberKnife procedures and the Synchrony™ option to account for respiratory motion and set up variations. The fiducial location will be the prime determinant of the delivery site and respiratory motion.

3.2. Treatment Dosage and Administration

Fiducial placement:

Standard techniques will be used as for biopsy, but gold seed markers compliant with the CyberKnife software will be placed in the vicinity (within 6 cm) of the tumor. At least 3, but generally 4-5, markers will be placed in such a manner as to not be co-linear, and as widely spaced as possible. Markers can be placed within the tumor mass, but some of the markers should be placed in the normal liver surrounding the tumor. It is recommended that at least 1 gold fiducial should be implanted inside the gross tumor. The fiducials may be placed via percutaneous needle placement under imaged guidance and local anesthesia or utilizing endoscopic ultrasound techniques in the standard fashion. Similar to fine needle biopsy, it is possible that placement of the fiducials may result in inflammation, bleeding, infection, pneumothorax or bile leak.

Immobilization Cradle and Treatment Planning CT Imaging
At least 6 days after fiducial placement (to enable resolution of any injury that may have occurred during fiducial placement and to allow for fiducial stabilization), subjects will return to the Radiation Oncology Clinic. If fiducials have been placed surgically, then the planning CT should be done as soon after 6 days as deemed clinically appropriate.

Prior to or at this visit, a radiation therapy immobilization device (i.e. Alpha Cradle) will be custom made for each subject to position them during the treatment.

While positioned in the immobilization device, a treatment planning CT scan with and without IV contrast will be taken. Patients with allergies to the contrast agent will be premedicated per institutional protocol. The CT scans taken for treatment planning will be taken with a breath hold with the tumor located approximately midway axially of the slices required. This imaging set will be downloaded to the CyberKnife treatment planning system to develop the radiosurgery treatment plan.

A radiosurgical treatment plan will be developed based on tumor geometry and proximity to vital structures. The treating surgeon and or the treating radiation oncologist will contour the tumor as well as all dose-limiting structures. Briefly, the lesion representing the gross tumor volume (GTV) will be outlined on sequential axial computed tomography images utilizing soft tissue/liver windowing. Planning target volume (PTV) is created by expanding GTV by 0.5-0.8 cm in all directions. The dose will be prescribed to the minimal isodose line that covers (>95%) the PTV. All vital structures close to the irradiated target, potentially including the heart, esophagus, aorta, spinal cord, and stomach will be contoured for the purpose of limiting incidental radiation to these structures and for the development of dose volume histograms (DVH).

The Stereotactic Radiosurgical Procedure
The CyberKnife (CK) treatment will generally be initiated within 1to 2 weeks of the planning treatment CT. On the day of CK treatment, the subject will be taken into the CK treatment room and the applicable LED (light emitting diode) monitors will be attached. The LEDs will assist the system to track the tumor throughout the respiratory cycle. The subject then will be set up in their immobilization cradle on the CyberKnife couch. X-rays will be taken with the CyberKnife System to ensure that the tumor is aligned in a manner consistent with the position in which the treatment plan CT image was taken. Fiducial locations in the images will be extracted and compared to the fiducial locations in the CT scans to estimate tumor movements. Once the tumor is properly aligned, SRS will be initiated. During the course of SRS, x-rays will continue to be taken periodically to ensure correct tumor alignment. The SRS treatment will be administered in three to five fractions, given over 3-15 days.

First Cohort (good liver function):
The planned initial dose to all patients with peripheral lesions and no more than Child-Pugh Class A will be 1500 cGy delivered to the prescription point for 3 fractions for a total of 4500 cGy if the dose-normal tissue constraints as defined below can be met. Treatments are delivered

≥ 48 hrs apart and should be completed within 2 weeks depending on routine scheduling or maintenance related issues with the CyberKnife. No treatment should be completed in less than 5 days (i.e., M, W, F is most common).

Second Cohort (compromised liver function):
The planned initial dose delivered to all patients with Child-Pugh Class B will be 700 cGy delivered to the prescription point for 5 fractions for a total of 3500 cGy if the dose-normal tissue constraints defined below can be met. Treatments will generally be given over approximately 2 weeks with ≥ 48 hrs between the fractions.

For both cohorts, the dose will generally be quoted at the 70-80% isodose line and this should encompass the entire planning target volume (PTV). Higher isodose lines can be used for prescription purposes if that isodose line encompasses the PTV. Lower isodose lines should not be used if the fields can be modified appropriately. If lower isodose lines are required, they should not be less than 60%. The 100% isodose line is defined as the maximum dose in the tumor.

Dose-Volume Constraints- Liver Tolerance Parameters
i). First Cohort: Good liver function (as defined in primary objective) and peripheral lesions:
Full radiation doses will be used if the dose to 35% of the liver can be kept below a total dose of 1500 cGy, the dose to 50% of one kidney can be kept below 1400 cGy, and/or the maximum point dose to the spinal cord can be kept to ≤ 1500 cGy. In addition, the total volume of liver kept below 1500 cGy should be at least 700 cm^3. If these normal tissue dose constraints cannot be met, then the dose/fraction should be lowered by a 250 cGy increment to meet this dose constraint (i.e., 1250 x 3, 1000 x 3). Tumor size per se will not be a factor that will affect radiation dose, although it will affect the ability to meet the liver tolerance parameter. Tumor volumes will be recorded based on diagnostic imaging studies. Attempts will be made to minimize the dose to 35% of the liver, and not just meet the dose constraint. If dose constraints cannot be met after two decrements in dose per fraction as described above, the patient will not be eligible for study. See Tables 1 and 2..

Maximum dose to greater than 1 cc of the esophagus, heart, stomach, and small bowel (including duodenum) must be kept below a total of 3000 cGy. The maximum dose to greater than 1 cc of the rib and chest wall must be kept below 4000 cGy. The prescription dose will be decreased in 250 cGy per fraction increments to meet this constraint.

ii). Second Cohort: Compromised liver function (as defined in primary objective):
Full radiation doses will be used if the dose to 50% of the liver can be kept below a total dose of 1500 cGy, the dose to 50% of one kidney can be kept below 1400 cGy, and/or the maximum point dose to the spinal cord can be kept to ≤ 1500 cGy. In addition, the total volume of liver kept below 1500 cGY should be at least 700 cm^3. If these normal tissue dose constraints cannot be met, then the dose/fraction should be lowered by 150 cGy increments to meet this dose constraint (i.e., 550 x 5, then 400 x 5). Tumor size per se will not be a factor that will affect

radiation dose, although it will affect the ability to meet the liver tolerance parameter. Tumor volumes will be recorded based on diagnostic imaging studies. Attempts will be made to minimize the dose to 35-50% of the liver, and not just maintain the dose constraint. If dose constraints cannot be met after two decrements in dose per fraction as described above, the patient will not be eligible for study. The expectation is that patients with Child-Pugh Class B will have lower doses because of these dose constraints. See Tables 1 and 2. The target mean liver dose in this cohort is ≤1300 cGy.

Maximum dose to greater than 1 cc of the esophagus, heart, stomach, and small bowel (including duodenum) must be kept below a total of 3000 cGy. The maximum dose to greater than 1 cc of the rib and chest wall must be kept below 4000 cGy. The prescription dose will be decreased in 150 cGy per fraction increments to meet this constraint. Fractional dose reduction for both cohorts will be carried out as described in the following table:

Table 1: Fractional Dose Reduction Criteria

Max of Single Liver Lesion	**Number of Fractions**	**Fractional Dose**	**Total Dose**	**Constraints and Fractional Dose Reduction**[1]
Cohort 1 (Good liver function)	3	15 Gy	45 Gy	Reduce fractional dose by 250cGy until all the following 5 parameters have been met: **1.** V_{15} of liver is < 35% of liver **2.** 700cc of liver < 15 Gy **3.** Max dose to > 1 cc of esophagus, heart, stomach, small bowel < 30 Gy, and max dose to >1 cc of rib and chest wall <40 Gy **4**.50% of one kidney <14 Gy **5.** Max point dose to spinal cord of 15 Gy
Cohort 2 (Compromised liver function)	5	7Gy	35 Gy	Reduce fractional dose by 150cGy until all the following parameters have been met: **1.** V_{15} of liver is < 50% of liver **2.** 700cc of liver < 15Gy **3.** Max dose to > 1 cc of esophagus, heart, stomach, small bowel < 30 Gy, and max dose to >1 cc of rib and chest wall <40 Gy **4**.50% of one kidney <14 Gy **5.** Max point dose to spinal cord of 15 Gy

[1] If the dose constraints cannot be achieved with two dose reductions (e.g., 15 Gy reduced to 10 Gy fraction still results in 700 cc of liver receiving >15 Gy for Cohort 1) then the patient is not evaluable for toxicity or local control, and should be removed from the study.

Table 2: Dose Levels by Cohort

Max of single Liver lesion	Number of Fractions	Fractional Dose	Number of subject	Total Dose	Constraints and Fractional Dose Reduction[2]
Cohort 1[1] (Good liver function)	3	Dose Level -2 10.0 Gy Dose level -1: 12.5 Gy Dose level 1: 15 Gy Dose level 2: 17.5 Gy Dose level 3: 20.0 Gy	10 10 10 10 10	Dose Level -2: 30.0 Gy Dose level-1: 37.5Gy Dose Level 1: 45 Gy Dose Level 2 52.5 Gy Dose Level 3: 60.0 Gy	Reduce fractional dose by 250cGy until all the following **5** parameters have been met: **1.** V_{15} of liver is < 35% of liver **2.** 700cc of liver < 15 Gy **3.** Max dose to > 1 cc of esophagus, heart, stomach, small bowel < 30 Gy, and max dose to >1 cc of rib and chest wall <40 Gy **4**.50% of one kidney < 14 Gy **5.** Max point dose to spinal cord of 15 Gy
Cohort 2 [1] (Compromised liver function)	5	Dose Level -2 4.0 Gy Dose Level-1: 5.5 Gy Dose Level 1: 7 Gy Dose Level 2: 8.5 Gy Dose Level 3: 10 Gy	10 10 10 10 10	Dose Level -2 20.0 Gy Dose Level-1: 27.5 Gy Dose Level 1: 35 Gy Dose Level 2: 42.5 Gy Dose Level 3: 50 Gy	Reduce fractional dose by 150cGy until all the following parameters have been met: **1.** V_{15} of liver is < 50% of liver **2.** 700cc of liver < 15 Gy **3.** Max dose to > 1 cc of esophagus, heart, stomach, small bowel < 30 Gy, and max dose to >1 cc of rib and chest wall <40 Gy **4**.50% of one kidney <14 Gy **5.** Max point dose to spinal cord of 15 Gy

[1] Escalation of the two cohorts will be done separately as their tolerance might be substantially different. No intra-patient dose escalation is allowed.
[2] If the dose constraints cannot be achieved with two dose reductions (e.g., 15 Gy reduced to 10 Gy fraction still results in 700 cc of liver not receiving < 15 Gy) then the patient is not evaluable for toxicity or local control, and should be removed from the study.

* Escalation of the two cohorts will be done separately as their tolerance might be substantially different.

Table 2 displays dose levels considered for the study.

1). The primary end-point will be the development of radiation induced liver disease as measured by the > 2-fold worsening of liver functional parameters, clinically apparent worsening of portal hypertension, new or worsening bleeding esophageal varices, or worsening ascites within the first 3 months from initiation of treatment. These will be considered dose-limiting hepatic toxicities. Increases in hepatic enzymes by less than 2-fold alone will not be considered a dose-limiting radiation induced hepatic toxicity if they are not accompanied by other signs of deteriorating liver function as any irradiation of normal liver would be expected to elevate enzymes.

The two patient cohorts will be evaluated separately for determination of toxicity. Deteriorating liver function that can be explained by tumor progression or other non-treatment related events will not be considered a treatment toxicity for the purpose of this analysis.

A dose level will be considered beyond tolerance depending on the fraction of patients who experience a dose-limiting radiation induced hepatic toxicity. See Table 3. Once this happens, enrollment to that dose level will be halted. If this happens at dose level 1, subsequent patients eligible for full dose therapy will enroll into dose level -1. If dose level -1 is found intolerable in patients eligible for full dose therapy, the trial will be stopped.

Patients will also be evaluated for other unexpected toxicities according to the NCI CTCAE, Version 3.0. Unexpected Grade 3 toxicities thought to be due to therapy will be scored as 1 and unexpected Grade 4 toxicities thought to be due to therapy will be scored as 2. A patient with both unexpected Grade 3 and Grade 4 toxicities will be counted as a patient with unexpected Grade 4 toxicity. If the total score exceeds 3 in the first 3, 4, or 5 patients, or exceeds 4 at any point within a dose level, enrollment to that dose level will be halted and that dose will be considered beyond tolerance. See Table 4. If this happens at dose level 1, subsequent patients eligible for full dose therapy will enroll into dose level -1. If dose level -1 is found intolerable in patients eligible for full dose therapy, the trial will be stopped.

Table 3:

# of patients with a DLT	Total # patients in cohort	Action
≥3	3, 4, 5	Stop dose-cohort[1]
≥4	6, 7, 8, 9, 10	Stop dose-cohort[1]
[1]If this occurs within Dose level 1, enter the next group of patients eligible for full dose to Dose level -1. If dose level -1 is found intolerable in patients eligible for full dose therapy, the trial will be stopped.		

Table 4:

# of patients with unexpected Grade 3[1]	# of patients with unexpected Grade 4	Total # patients in cohort	Action
≥0 ≥4	≥2 ≥0	3, 4, 5	Stop dose-cohort[2]
≥0 ≥1 ≥5	≥3 ≥2 ≥0	6, 7, 8, 9, 10	Stop dose-cohort[2]

[1]A patient with both unexpected Grade 3 and Grade 4 toxicities is counted as a patient with unexpected Grade 4 toxicity

[2]If this occurs within Dose level 1, enter the next group of patients eligible for full dose to Dose level -1. If patients eligible for full dose cannot tolerate dose level -1, the trial will be stopped.

The development of any Gr. 5 toxicity thought related to therapy will result in temporary suspension of the trial for full evaluation. If specific toxicity related to an irradiated organ is found, alteration of the dose parameters for that tissue will be modified, although not necessarily a reduction in the planned tumor dose.

2). The secondary study end-point will be local tumor response and control. Our expectation is that a dose of 1500 cGy per fraction for 3 fractions (4500 cGy total) will be adequate for control of irradiated lesions of moderate size, but higher doses may be needed. In the second cohort the optimal dose is less clear, and dose escalation will likely be desired. Patients will be evaluated for local control at 5-6 months after irradiation. A minimum of 10 patients will be entered onto each dose cohort. However, if there are 4 local failures within a cohort at dose level 1 dose escalation may proceed provided the tolerance parameters are acceptable (that is, conditions in both Tables 5A and 5B are satisfied), and patients have been evaluated for toxicity for at least 3 months from the initiation of therapy. At that point, dose escalation to a nominal prescription dose per fraction of 1750 cGy in the first cohort, and 850 cGy in the second cohort, will be undertaken. A second dose escalation with the same increase in dose/fraction could occur based on the same parameters as above. Escalation of the two cohorts will be done separately as their tolerance might be different. No intra-patient dose escalation will be allowed. For dose escalation, if the proposed dose for escalation is found to be too toxic, based on Tables 3 and 4, the study will be stopped. All patients in a cohort will be followed for 3 months from the time of initiation of therapy for evaluation of toxicity, prior to dose escalation in each cohort.

Table 5A

# of patients with a DLT	Total # patients in cohort	Action
0	5, 6, 7, 8	DLT rate warrants escalation to next dose level for subsequent patients[1]
≤ 1	9, 10	DLT rate warrants escalation to next dose level for subsequent patients[1]
[1] Dose escalation will only occur in patients eligible for full dose, see text of protocol		

Table 5B

# of patients with unexpected Grade 3[1]	# of patients with unexpected Grade 4	Total # patients in cohort	Action
≤ 1	0	5, 6, 7, 8	Rate of unexpected toxicities warrants escalation
≤ 2 ≤ 0	0 1	9, 10	Rate of unexpected toxicities warrants escalation
[1]A patient with both unexpected Grade 3 and Grade 4 toxicities is counted as a patient with unexpected Grade 4 toxicity			

To summarize, the goal is to find a dose such that:
1). The rate of dose limiting hepatic toxicity at that dose does not exceed 0.33.
2). The rate of unexpected Grade 3 plus double the rate of Grade 4 toxicities does not exceed 0.4.;
3). The rate of the local tumor control at that dose is at least 70%.

3.3 Expected Toxicities

There are a few specific toxicities that are of concern in the irradiation of tumors in the liver. The first concerns the overall maintenance of good hepatic function. From the data in the literature [4,5], this appears to be strongly related to the amount of liver in the radiation field treated to moderate dose. The data from liver resection surgery has shown that with a proliferative response, the liver can regenerate itself after removal of ½ or more of the liver. This regeneration will likely not occur if the remaining liver has received a significant amount of radiation, although the dose that would prevent regeneration is not known.

Secondly, the primary biliary radicals could be damaged by the radiation. This would likely be a late response, although initial edema could produce an acute temporary obstruction that would likely be minimized by the use of steroids. Long term, fibrosis could occur producing biliary obstruction.

Third, there can be vascular injury producing a veno-occlusive picture with hepatomegaly and other signs of liver failure that can occur about 3 months after irradiation. In addition, as the liver is in close proximity to multiple normal structures, the tolerance of these structures (liver, lung, esophagus, duodenum) must also be considered as ulceration and necrosis could occur if those structures are irradiated to high dose. Toxicity from structures distant to the radiation beam is very unlikely. Doses to all the above mentioned normal tissues can be calculated during the planning phase of the therapy to allow us to estimate high-risk sites.

These toxicities described above are primarily captured in the CTCAE, Version 3.0 formulation as hepatic and biliary tract related, and they will be measured accordingly. We would not expect toxicities in other organs other than liver, stomach, bowel, or lung. However, all toxicities that are not clearly ascribable to other unrelated causes or to tumor progression will count for the toxicity evaluation.

Dose modifications for individual patients will be based on dosimetric information as described above. As all treatments will be delivered over approximately one to two weeks, there is no expectation that acute toxicities will occur. However, acute toxicities (defined as within one week of the delivery of the radiation therapy) that are possible include toxicity related to the gastrointestinal, cardiac and pulmonary systems. Any acute Grade 3 or greater toxicity as defined by the CTCAE, Version 3.0 will be assessed regarding the organ of origin and the dose-volume relationship in that organ evaluated.

4.0 PATIENT ELIGIBILITY

Each patient must meet all of the following eligibility criteria to be enrolled in the study:

4.1 Inclusion Criteria

1. Hepatocellular carcinoma (as defined by biopsy or alpha-fetoprotein (AFP) greater than 1000ng/dL with appropriate imaging) or liver metastases from colorectal cancer or other tumor (as defined by biopsy or elevated CEA or a positive PET scan in conjunction with a mass on CT or MRI in a patient with previously resected cancer). Patients with at least one measurable liver lesion and no more than 3 lesions are eligible if they meet all other eligibility criteria including the dose constraints on the composite plan.
2. ECOG Performance Status 0-1.
3. Patients who are not candidates for definitive surgical resection because of tumor location, hepatic function, or other medical or personal reasons.
4. Patients with HCC who are being considered for liver transplant may be entered as a bridge to transplant if it is considered by the transplant team that an ablative therapy would be of value while awaiting transplant.
5. If cirrhosis is present, patients will have Child's-Pugh score of A or B (Appendix A).
6. Patients will have tumors not optimally treated with radio-frequency ablation by interventional radiology, or by GI/transplant surgery. This could be for reasons of size, tumor location, or other reasons.

7. Ability to place fiducial markers in the vicinity of the tumor to allow for radiographic tracking of respiratory motion and tumor localization. Fiducial placement will generally be done by interventional radiology.
8. Estimates of hepatic tolerance must meet the criteria as defined in Section 3.2 (Dose-Volume Constraints – Liver Tolerance Parameters)
9. Adequate bone marrow and renal function as assessed by the following:
   - Absolute neutrophil count (ANC) $\geq$ 1000/mm^3
   - Platelet count $\geq$ 80,000/mm^3
   - Creatinine $\leq$ 2.0 mg/dL OR Creatinine clearance $\geq$ 45 mL/min based on Cockcroft-Gault formula).
10. Patients with extrahepatic metastatic disease are eligible if it is the opinion of the treating physician that local therapy to the liver may produce worthwhile clinical benefits
11. Patient is able to understand fully the potential risks and benefits of this approach and signs an appropriate informed consent.
12. Male and female of >18 years of age. Male or female patients capable of reproduction must agree to use medically acceptable methods of contraception, such as an intra-uterine device, diaphragm, with spermicide, condom with spermicide or abstinence. Inclusion of females of childbearing potential requires a negative pregnancy test within 14 days prior to study initiation

4.2 Exclusion Criteria

1. Child-Pugh Class C cirrhosis
2. Patients with clinically apparent CNS disease.
3. Medical or psychiatric illness that would not allow the patient to tolerate the proposed treatment including inability to lie flat for an extended period of time, severe claustrophobia or other reasons.
4. Uncontrolled or significant cardiovascular disease including: myocardial infarction within 6 months, uncontrolled angina within 6 months, Class III-IV New York Heart Association (NYHA) congestive heart failure, grade 3 cardiac valve dysfunction.
5. Evidence of decompensated liver disease as evidenced by: clinically significant ascites (refractory to diuretic therapy), evidence of hepatic encephalopathy, coagulopathy not corrected by conservative measures.
6. A history of CTCAE Grade 3 bleeding esophageal or gastric varices within the past 2 months. Prior variceal bleed permitted if patient has undergone banding or sclerotherapy and there has been no evidence of bleeding for 2 months. Patients at risk for varices (based on the following: known history of esophageal or gastric varices; evidence of hepatic cirrhosis and/or portal hypertension including biopsy-proven cirrhosis, hypersplenism, or radiographic findings of varices) will be screened for esophageal varices. If varices are identified that require intervention (banding), patient will not be eligible until varices adequately treated.
7. Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.
8. Uncontrolled intercurrent illness.

9. Inability to comply with study and/or follow-up procedures.
10. A patient with Child-Pugh Class A will not be eligible for study if the liver dose constraint described in Section 3.2 cannot be met after two decrements in dose per fraction as described above.
11. A patient with Child-Pugh Class B will not be eligible for study if the liver dose constraint described in Section 3.2 cannot be met after two decrements in dose per fraction as described above.

5.0 EVALUATIONS AND ASSESSMENTS

5.1. Time and Events Table

Assessments	**Pre-Study[a]**	**Cyberknife RT Delivery[b]**	**Post RT Week 1[h]**	**Post RT Week 4**	**Post RT Week 8**	**Post RT Week 20**	**Follow-up q 3 Months[c] x 2 Years**
Informed Consent	X						
History and PE	X	X		X	X	X	X
Performance Status	X			X	X	X	X
Chest x-ray	X						
CBC	X		X	X	X	X	
Liver function tests (T Bili, INR, PT for Child-Pugh score, AST, ALT, LDH, Alk Phosphatase, Albumin)	X		X	X	X	X	X
Serum Creatinine	X						
Circulating Tumor Markers : AFP (HCC) or CEA (CRC)	X				X	X	X
CT and/or MRI of liver, PET scan is optional	X				X	X	X
Fiducial Placement[d]	X						
Liver Biopsy (if needed for diagnosis confirmation)	X[g]						
Treatment Planning[e]	X						
Toxicity Assessment		X	X	X	X	X	X
Pregnancy Test	X[g]						

[a] Pre-study assessments to be completed within 8 weeks prior to start of Cyberknife Radiation Therapy Treatment.

[b]CyberKinfe radiation therapy (RT) will be completed within 2 weeks depending on routine scheduling or maintenance related issues with the CyberKnife. No treatment should be completed in less than 5 days.

[C] Every three months following week 20. See section 5.5 for additional details.

[d]This would be done after study entry but prior to radiation therapy (RT).

[e]To be done at least 6 days following fiducials placement. Participants will be immobilized using Vac-Loc and Synchrony vest to facilitate in obtaining the treatment planning CT.

[g] Within 14 days pre-study, and only if clinically appropriate

[h] Patients in whom high dose irradiation is delivered to the main hepatic ducts or common bile duct will be considered for elective stent placement within the first 4 weeks after completion of radiation therapy to prevent biliary obstruction.

5.2 Pre-study Assessments

- Informed Consent
- History and physical examination
- Performance status
- Chest x-ray
- Laboratory studies including: CBC, LFT, Serum creatinine
- CT and/or MRI of the liver; PET scan is optional
- Pregnancy test within 14 days pre-study, and only if clinically appropriate

Fiducial placement: Prior to CT planning gold seed markers compliant with the CyberKnife software will be placed in the vicinity (within 6 cm) of the tumor as described in Section 3.2. CT planning in Radiation Oncology to be done at least 6 days after fiducial placement.

Liver biopsy: Tumor biopsies should occur pre-study (within 14 days of study entry), although earlier biopsies can be acceptable with the approval of the Principle Investigator (PI) if sufficient diagnostic information has been obtained. Tumor biopsies will be performed by qualified radiology/interventional radiology personnel under CT or US guidance (presumably at the time of fiducial placement) of the tumor site deemed least likely to produce patient discomfort or complications. Patients should be monitored per the site standard of care after the procedure and any complications graded and reported utilizing the criteria for toxicity reporting described in section 6. Up to three passes should be made if safe in the judgment of the physician performing the procedure. A 14-20 FG needle will be used, at the discretion of the interventional radiologist.

5.3 Treatment Assessments

- Toxicity Assessment
- Physical examination and history

5.4 Post-treatment Assessments (Up to week 20 after RT Treatment)

- History and physical examination
- Performance status
- Laboratory studies including CBC, and liver function tests
- CT, PET or MRI of the liver will be performed at, 8 and 20 weeks after the completion of radiation therapy and then at regular intervals per Section 5.1.
- Toxicity assessment (NOTE: this should occur up to week 20 regardless of whether disease recurs prior to this point or not).

5.5 Follow-up Assessments:

Follow-up will be done every three months for two years, or until disease progresses in an irradiated liver lesion. If disease progresses in a non-irradiated lesion only, follow-up will continue until disease progresses in one of the irradiated liver lesions. Once disease progresses in an irradiated liver lesion, protocol follow-up will cease other than follow-up of any unresolved treatment-related toxicity. Follow-up assessments will include:

- History and physical examination
- Performance status
- Laboratory studies for liver function tests
- CT, PET or MRI of the liver.
- Toxicity assessment

Patients in whom high dose irradiation is delivered to the main hepatic ducts or common bile duct will be considered for elective stent placement within the first 4 weeks after completion of radiation therapy to prevent biliary obstruction.

5.6 Assessment of Disease Status

Criteria for response evaluation in patients with measurable disease:
Patients eligible for this trial must have at least one measurable liver lesion and no more than 3 liver lesions. Any of these measurable liver lesions irradiated under this protocol will be separately evaluated for progression/response. These measurable irradiated lesions must be accurately measured in at least two dimensions.

Progression in any non-irradiated liver lesion or distant site (including non-measurable disease e.g.,ascites, malignant pleural/pericardial effusion, bone lesions, or marrow involvement) will be evaluated separately. These non-irradiated lesions will be followed up for progression only.

It is a known and expected effect from radiosurgery for there to be peri-lesional enhancement up to 2.5 cm surrounding the target lesion that will not be considered as part of the response criteria or as tumor progression. Therefore, specifically for the irradiated liver lesions, the 8 weeks post treatment tumor assessment will be considered baseline for evaluation of progression/response.

5.6.1 Response evaluation (Evaluation of Irradiated Liver Lesions)

Complete Response (CR): Disappearance of all target lesions. Lack of any PET activity will also be measured as an indicator of response, but will not be used in the formal evaluation of CR.

Partial Response (PR): Regression of measurable disease and no new sites.

Stable Disease (SD): Does not qualify for CR or PR, and does not fulfill criteria for progressive disease.

Progressive Disease (PD): Increase by ≥50% in the product of two perpendicular diameters of a previously irradiated lesion

5.6.2 Evaluation of Progression in non-irradiated Lesions

Progressive Disease: The appearance of one or more new lesion(s) and/or unequivocal progression of existing non-irradiated lesions. If there is any question regarding whether a non-irradiated lesion meets the criteria for progression, please check with the study PI, Dr. Joel Tepper.

6.0 Adverse Experiences

6.1 Definitions

6.1.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse experience or event (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.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

The NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 will be used to identify the type and to grade the severity of unanticipated adverse events in patients participating on this study.

6.1.2 Unexpected AE

An unexpected adverse event is considered unexpected if the specificity or severity of which is not consistent with the risk information described in the general investigational plan.

For this study, machine malfunction that affects delivery of treatment as defined as the inability to complete a fractional dose will be recorded and reported as unexpected.

6.1.3 Serious AE

An AE is considered serious if in the view of the investigator or sponsor, it in any of the following outcomes:

- Death

- A life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization*
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

6.2 Documentation of non-serious AEs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

For all adverse events reported or observed, the information should be recorded in the electronic Case Report Forms (eCRFs) for that patient. Please include a full description of the event, its severity or toxicity grade, the relationship to the study drug, and the treatment, outcome and sequelae of the event. Documentation should occur at least monthly.

6.3 SAEs

6.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Documentation and Notification

These events must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. For Affiliate sites, an email must also be sent to the NCCN Study Coordinator indicating that an SAE has been entered into Oncore (email contact will be provided at study start-up).

6.3.2 Reporting

IRB Reporting Requirements:

UNC**:**

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 8.6.3) within 7 days of the Investigator becoming aware of the problem. .

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Study Coordinator using the IRB's web-based reporting system (see section 8.6.3) within 7 days of the Investigator becoming aware of the problem.

6.4 Data and Safety Monitoring Plan

The Principle Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

As this will be a multi-center study, the following approach will be used to ensure proper data and safety monitoring:

Bi-weekly teleconferences will be held provided patient accrual warrants this schedule, which will include the principal investigators from the participating site (or a designated co-investigator if a PI is unavailable), as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. Subject accrual, toxicity assessments, dose modification, protocol adherence, data entry, validity, integrity, and completeness, and management issues will be discussed at the meetings.

The team will produce summaries or minutes of these meetings.. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a semi-annual basis. The UNC PI will be responsible for submitting the following information for review: 1) accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

7.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

7.1 Study Design

The primary end-point of this study will be hepatic tolerance to the radiation treatment. This will be complicated by patients who could have progressive disease in the liver that could result in worsening liver function studies. Damage secondary to radiation therapy should appear within 3 months, so that will be the primary time for evaluation. Liver tolerance will be determined by the following:

1). The primary end-point will be the development of radiation induced liver disease as measured by the > 2-fold worsening of liver functional parameters, clinically apparent worsening of portal hypertension, new or worsening bleeding esophageal varices, or worsening ascites within the first 3 months from initiation of treatment. These will be considered dose-limiting hepatic toxicities. Increase in hepatic enzymes by less than 2-fold alone will not be considered a dose-limiting radiation induced toxicity if they are not accompanied by other signs of deteriorating liver function as any irradiation of normal liver would be expected to elevate enzymes.. The two patient cohorts will be evaluated separately for determination of toxicity. Deteriorating liver function that can be explained by tumor progression or other non-treatment related events will not be considered a treatment toxicity for the purpose of this analysis.

A dose level will be considered beyond tolerance depending on the fraction of patients who experience a dose-limiting radiation induced hepatic toxicity. See Table 3. Once this happens, enrollment to that dose level will be halted. If this happens at dose level 1, subsequent patients eligible for full dose therapy will enroll into dose level -1. If dose level -1 is found intolerable in patients eligible for full dose therapy, the trial will be stopped.

Patients will also be evaluated for other unexpected toxicities according to the NCI CTCAE, Version 3.0.. Unexpected Grade 3 toxicities thought to be due to therapy will be scored as 1 and unexpected Grade 4 toxicities thought to be due to therapy will be scored as 2. A patient with both unexpected Grade 3 and Grade 4 toxicities will be counted as a patient with unexpected Grade 4 toxicity. If the total score exceeds 3 in the first 3, 4, or 5 patients, or exceeds 4 at any point within a dose level, enrollment to that dose-level will be halted and that dose will be considered beyond tolerance. See Table 4.

If this happens at dose level 1, subsequent patients eligible for full dose therapy will enroll into dose level -1. If dose level -1 is found intolerable in patients eligible for full dose therapy, the trial will be stopped.

The development of any Gr. 5 toxicity thought related to therapy will result in temporary suspension of the trial for full evaluation. If specific toxicity related to an irradiated organ is found, alteration of the dose parameters for that tissue will be modified, although not necessarily a reduction in the planned tumor dose.

2). The secondary study end-point will be local tumor response and control. Our expectation is that a dose of 1500 cGy per fraction for 3 fractions (4500 cGy total) will be adequate for control of irradiated lesions of moderate size, but higher doses may be needed. In the second cohort the optimal dose is less clear, and dose escalation will likely be desired. Patients will be evaluated for local control at 5-6 months after irradiation A minimum of 10 patients will be entered onto each dose cohort. However, if there are 4 local failures within a cohort at dose level 1 dose escalation may proceed provided the tolerance parameters are acceptable (that is, conditions in both Tables 5A and 5B are satisfied), and patients have been evaluated for toxicity for at least 3 months from the initiation of therapy. At that point, dose escalation to a nominal prescription dose per fraction of 1750 cGy in the first cohort, and 850 cGy in the second cohort, will be undertaken. A second dose escalation with the same increase in dose/fraction could occur based on the same parameters as above. Escalation of the two cohorts will be done separately as their tolerance might be different.

To summarize, the goal is to find a dose such that:
1). The rate of hepatic toxicity at that dose does not exceed 0.33;
2). The rate of unexpected Grade 3 plus double the rate of Grade 4 toxicities does not exceed 0.4.;
3). The rate of the local tumor control at that dose is at least 70%

7.2 Sample Size

It is estimated that the initial dose/volume parameters will be safe based on historical data with low dose per fraction. In order to assure safety, 10 patients will be entered on the study at each dose level, unless as specified in 3.2 and 7.1 there is evidence of >30% local failure rate with acceptable toxicity in the full radiation dose levels of each cohort. We would not expect a different tumor control related to liver function, but tolerance is likely to differ. We might need one dose escalation in the first cohort and likely one dose escalation for the second cohort. Although we do not expect toxicity at these doses for the second cohort, a dose escalation may not be possible as it may not be possible to continue to meet normal tissue constraints with the dose escalation. However, dose escalation will proceed if possible. We, thus, expect approximately 40-60 patients, with 40 evaluable patients on study, with an accrual time of 3 years. To clarify, there will be no intra-patient dose escalation. De-escalation to a lower dose level for subsequent patients enrolled may be necessary as outlined in Table 2, section 3.2.

7.3 Data Analysis (Safety and Efficacy)

Safety and efficacy will be evaluated as per Section. 7.1

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient or the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.

8.2 Registration Procedures

The informed consent must be signed by the patient, or his/her legally authorized representative, before participating in the study and prior to any protocol procedure that is not part of the individual patient's routine medical care.

The patient's medical record should document the Informed Consent process and subsequent signing of the consent. A copy of the executed informed consent documents must be given to the patient and a copy of placed in the patient's medical record. The original consent will be kept with the research files.

All patients must be registered with the Oncology Protocol Office at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM.

For Affiliate patients, please contact the UNCCN Study Coordinator to ensure there is an

opening available on the study for the potential subject (direct line 919-966-7359), Monday through Friday, 9:00AM-5:00PM. To register a patient, please fax registration forms and eligibility documents to 919-966-4300.

8.3 Data Management and Monitoring

The CPO of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow the monitor to review all source documents supporting data entered into OnCore®. The UNCCN CRA can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six months.

8.4 Removal of Patients from Protocol Therapy

Removal of patients from protocol therapy can occur for the following reasons:

- Extraordinary Medical Circumstances

  If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, remove the patient from protocol therapy. In this event:

  -Notify the Principal Investigator
  -Document the reason(s) for withdrawal on the e-CRF
  -Follow the patient as per protocol
  -Notify the Institutional Review Board

- Voluntary Withdrawal

  Unacceptable Adverse Event

- Investigator's Judgment

8.5 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Oncology Protocol Office at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list

- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification and institution lab normal values
- Executed clinical research contract

8.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.6.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:

For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

8.6.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

8.6.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria::

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Study Coordinator with 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the

data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:

Affiliate Sites:

Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Study Coordinator. The UNCCN Study Coordinator will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

8.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. The written amendment will be sent to investigators and must be submitted to the IRB at the investigator's site for approval. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

8.8 Record Retention

Study documentation includes all eCRFs , data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment

of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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10.0 APPENDICES

Appendix A: Child-Pugh Class

Parameters	**Points**		
	1	**2**	**3**
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec. prolonged above ULN)	<4	4-6	>6
Encephalopathy (grade)	None	1-2	3-4*
Ascites	None	Mild	Severe

CHILD-PUGH Class:

A 5-6 points

B 7-9 points

C >9 points

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