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A Pilot Study of Individualized Adaptive Radiation Therapy for Hepatocellular Carcinoma

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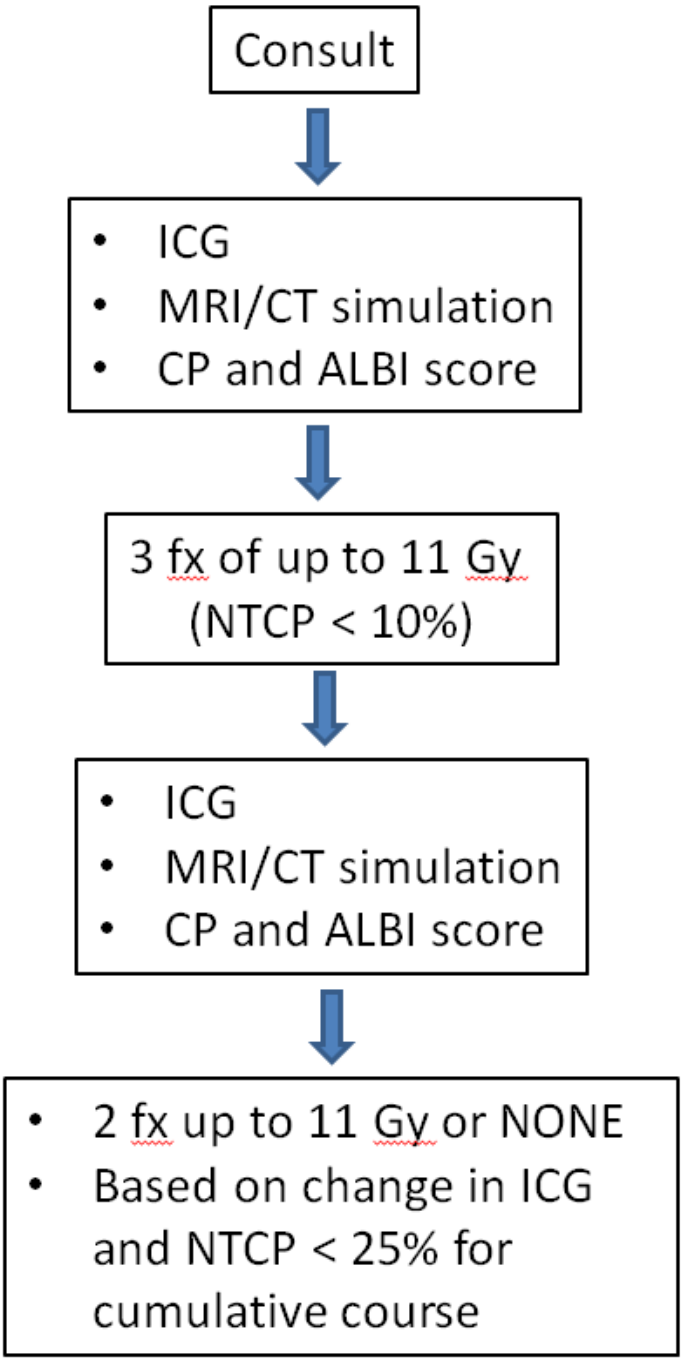
ABBREVIATIONS

AE	Adverse Event
ALB	Albumin
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CP	Child Pugh
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMR	Data and Safety Monitoring Report
GTV	Gross Tumor Volume
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IRB	Institutional Review Board
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NTCP	Normal Tissue Complication Probability
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PR	Partial Response
PRC	Protocol Review Committee
PTV	Planning Target Volume
QOL	Quality of Life
RT	Radiotherapy
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SD	Stable Disease
TBILI	Total Bilirubin
UaP	Unanticipated Problem
UMCCC	University of Michigan Comprehensive Cancer Center
WBC	White Blood Cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	A Pilot Study of Individualized Adaptive Radiation Therapy for Intrahepatic Cancer
Methodology	Single arm
Study Duration	2 years
Study Center(s)	Single-center
Objectives	Determine the safety and efficacy of individualized adaptive radiation therapy for intrahepatic cancer
Number of Subjects	80 evaluable patients
Inclusion Criteria	Patients who have hepatocellular carcinoma
Exclusion Criteria	Patients who have a known allergy to intravenous iodinated contrast agents or a contraindication to contrast-enhanced MRI
Study Product(s), Dose, Route, Regimen	Radiation dose and distribution within the liver adjusted based on function and tolerance of first phase of treatment. 3/5 of treatment delivered, followed by 1 month break, followed by the remaining 2/5 of treatment, with dose and spatial distribution adjusted based on biomarker and imaging tumor and normal tissue response.
Duration of Administration	3-5 treatments, depending on ICG, CP score, ALBI score and NTCP model
Statistical Methodology	This pilot study will establish the feasibility of this individualized adaptive radiation therapy. It will also provide preliminary estimates of the safety and efficacy of this treatment that will be used to plan a subsequent randomized controlled trial.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

1.1.1 Epidemiology and scope

Worldwide, primary liver cancer is a major health problem with more than 500,000 new cases diagnosed yearly. It is the fifth most common neoplasm, and the third most common cause of cancer-related death.[1] In some areas of Asia, HCC is the most common cause of death due to cancer. The American Cancer Society estimates that 33,190 people will be diagnosed with HCC or intrahepatic cholangiocarcinoma in the US in 2014[2]. The incidence has been increasing in Europe[3] [3] and in the US[2,4] and it is estimated that its incidence in the US will equal that currently reported in Japan within two decades.[5] Primary liver cancer is one of 4 cancer sites that has increased death rates between 1990 and 2004, and is the only cancer that has shown more than 10% increase (41% and 28% rate increases for males and females, respectively).[2] This disease is clearly a growing problem.

1.1.2 Current Therapies for unresectable intrahepatic cancer

Complete resection is the most effective therapy for HCC. Unfortunately, curative surgery cannot be offered to most patients. Many patients are inoperable due to co-morbidity, and others present with disease extent that requires resections that would not leave sufficient residual functional liver parenchyma. For instance, Abdalla et al. reported the M.D. Anderson experience with hepatic resection.[6] Of 418 patients who were deemed resectable and were explored, only 190 patients (45%) underwent complete resection. Three major therapies have been used for these unresectable patients.

1.1.2.1 Radiofrequency Ablation (RFA)

In a prospective trial by Lencioni and colleagues[7], 10% of 206 patients initially evaluated for RFA had contraindications based on tumor location. After these patients were excluded, 20% had an inadequate response to RFA (viable tumor remaining after 1 month). Of the patients who had an inadequate response to RFA, only approximately half of the patients were controlled by a second RFA. Finally, 10% of patients who were thought to be controlled recurred locally within 3 years. In a systematic review of the use of RFA for HCC, local failures over a 3 year period tend to average from 10 - 29%, and failure elsewhere in the liver approximately 50%.[8] In the case of metastases from colorectal cancer, recurrences after RFA range from 2-39%, with other liver failures from 14-58%.[8] In all series, local failure increases with tumor size > 3-4 cm. Our experience at the University of Michigan suggests a similar or somewhat higher local failure rate.[9] In this proposal, we anticipate focusing on patients who have recurred after RFA or have tumors that are not amenable to RFA, such as tumors greater than 3.5 cm in size, as well as those abutting vasculature, lung, or bile duct.

1.1.2.2 Transcatheter Arterial ChemoEmbolization (TACE)

Although some trials and an initial randomized trial showed no difference between chemoembolization and best supportive care[1011]more recent studies have begun to suggest that chemoembolization can improve survival of a subset of patients with hepatocellular carcinoma.[12,13]A systematic review of all modern randomized trials suggests that TACE modestly prolongs survival (from approximately 16 months to 20 months), compared to best supportive case, for patients with tumors < 6 cm who have excellent performance status and do not have portal vein thrombosis[14,15].However, TACE is not a curative therapy and tumors typically recur even after multiple TACE administrations,

suggesting that additional therapies are required.

1.1.2.3 **Radiation Therapy**

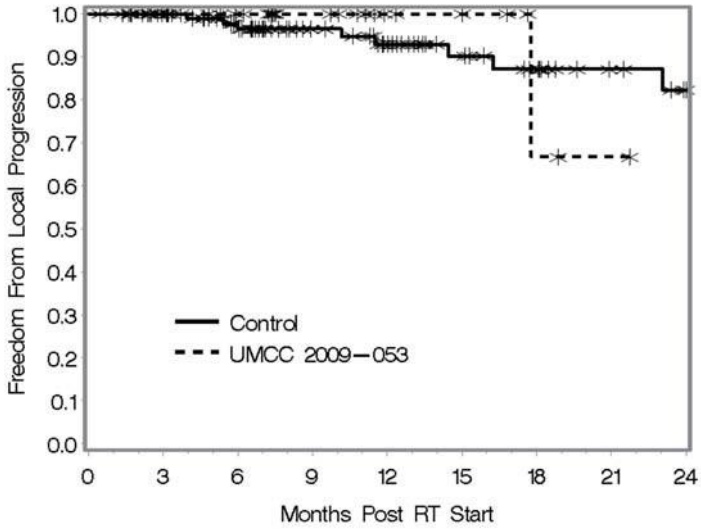
In our previous series of prospective clinical trials,[16,17] we found improved survival with higher radiotherapy dose. Further, dose delivered was the most important predictive factor for survival. Indeed, approximately 20% of patients receiving >75 Gy using 1.5 Gy BID are alive 4 years after treatment; historically that number would be very close to 0%. These data are proof of principle that focused radiation can control intrahepatic cancer, and that we are experienced in these techniques.[18] Since the mid 2000s,stereotactic body radiotherapy (SBRT) has gained in popularity, due to the improvement in convenience, with 5, rather than 30 or more treatments. We have recently published our results, which are in line with other experiences. In the immediately preceding study, we used stereotactic body radiotherapy to successfully and safely treat liver tumors, with 97% 1 year local control and no significant liver toxicity.[19] High efficacy and safety were obtained by individualizing treatment based on not only pre-treatment liver function, but also each patient's tolerance to radiation. In this new protocol, we intend to test our ability to further individualize and adapt treatment based on the geometric distribution of functional liver parenchyma for patients with larger tumors and poor liver function.

1.1.3 **Avoidance of Radiation Induced Liver Decompensation (Change in CP and ALBI score)**

Classically, radiation liver damage was measured with the endpoint of radiation induced liver disease (RILD) based on prior work on whole liver radiation[20,21]. However, in the modern era with daily imaging and highly conformal radiotherapy, RILD is very rare[22]. Currently, radiation liver toxicity is more aptly defined by functional liver decompensation in terms of the development of portal hypertension, new onset ascites, and encephalopathy as well as objective lab values. Many groups have published on a change in Child-Pugh score of greater than or equal to 2 and change in the albumin and bilirubin (ALBI score) as more meaningful endpoints[23-26]. One of the key hypotheses of this trial is that by avoiding functional liver and adapting dose based on liver function, we will minimize these toxic effects. The patients who are at highest risk of decompensation are patients who have poor liver function at baseline. Most patients with HCC present with concurrent cirrhosis which puts them at higher risk of decompensation post radiation. Using spatial functional information as well as direct global measures of liver function e.g. ICG, baseline CP score and ALBI, we hope to deliver a tumoricidal dose without causing toxicity.

1.1.4 **Adjusting global RT dose based on liver function as assessed through clearance of Indocyanine Green.** Although we developed the most accurate population-based model for predicting RILD for patients receiving fractionated radiation therapy, we are aware that there are limitations when applying this to individual patients, with variable sensitivity to radiation. Relying solely on the model unnecessarily exposes patients with high sensitivity to radiation to a high risk of toxicity, while at the same time, it also denies patients with average and low sensitivity to higher doses of radiotherapy, which could increase tumor control. In the preceding clinical trial, we individualized therapy based on the sensitivity of individual patient. Initial liver function was characterized by measuring the clearance of indocyanine green, a dye taken up by the plasma almost exclusively by the hepatic parenchymal cells and secreted entirely into the bile without undergoing any significant extrahepatic or enterohepatic circulation. It has been used extensively to predict mortality after liver resection and severe trauma[27 28].We delivered 3 treatments of SBRT, waited 4 weeks to detect subclinical decline in liver function, and adjusted radiation dose for 2 remaining treatments, based on the stability or decline in

function[19]. Insertion of a treatment break did not compromise tumor control. Indeed, 1 year local control for the first 76 patients was 97%, comparable to any other prospective or retrospective report. Patients with very poor liver function (Child Pugh B and even C) were treated safely on trial, suggesting that modifying radiation dose part-way through treatment successfully avoided what would have been severe toxicity. Our initial analysis of the first 20 patients evaluable on the study showed that we need to begin adapting treatment prior to the first 3/5 of radiation delivery. We plan to accrue an additional 40 patients to examine the feasibility of up front individualization in addition to mid treatment adaptation to minimize toxicity and maintain excellent local control. We have demonstrated that patients with good liver function and small tumors (<3.5 cm) have excellent local control and very low rates of toxicity. The current protocol looks at adapting therapy for patients with good liver function (CPA to B7) but larger tumors where more liver parenchyma would receive radiation thereby increasing the risk of toxicity and those with poor liver function (CPB8 and above) who at baseline are at increased risk of liver decompensation post treatment. Our interim analysis has revealed that a combination of albumin and bilirubin, called ALBI, which is an accurate predictor of survival for patients with HCC with liver dysfunction[36], is as or more useful than ICG in estimating liver function and predicting future toxicity. Thus, either ICG or ALBI can be used in this trial.



1.1.4.1 **Adjusting spatial RT distribution based on regional liver function as assessed by perfusion MRI.** This protocol builds on over 25 years of experience with high dose liver RT, and in particular adaptive RT aimed at adjusting the global radiation dose based on a patient's measured sensitivity to treatment. The next leap forward is to use functional imaging to spare highly functional portions of the liver. We have previously demonstrated that dynamic contrast-enhanced (DCE or perfusion) MRI correlates with global liver function as measured by ICG, and that regionally, function declines as a function of delivered radiation dose.[29] This and, potentially, other advanced MRI techniques, provides the opportunity to sculpt dose away from high-functioning parts of the liver to improve the safety of treatment.

1.2 Study Agent(s) Background and Associated Known Toxicities

We have over 25 years of experience with liver radiotherapy. As discussed above, change in Child Pugh status and ALBI are the primary toxicity endpoints. Additionally, depending on the tumor location and proximity to normal structures including stomach, small bowel, colon, and right kidney, there is a small risk of GI bleed or renal damage. These are quite rare in our experience, minimize with careful treatment planning and delivery. Indocyanine green is FDA approved and has been in use for 50 years to estimate liver function. In patients without an iodine allergy, it is quite safe. Patients with iodine allergies will be excluded from participation in this study.

1.3 Rationale

This is a pilot single arm study with a goal of obtaining preliminary estimates of safety and efficacy. This protocol builds on over 25 years of experience with high dose liver RT, and in particular adaptive RT aimed at adjusting the global radiation dose based on a patient's measured sensitivity to treatment. Using functional imaging to spare highly functional portions of the liver is a novel concept, and as far as we know, we are the only ones currently in a position to put this into practice. We feel this will further improve the safety and efficacy of RT for all patients by customizing treatments to each. If this approach is promising, we will proceed to a phase II randomized study of standard versus spatially and dosimetrically adapted RT.

1.4 Quality of life

The quality of life of patients with liver tumors is not well-studied. For these patients, many of whom already suffer from chronic medical problems including cirrhosis, it is particularly important to understand how tumor-directed treatments impact quality of life. The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) version 4

questionnaire will be used in this study to measure QOL. This is a 45-item validated instrument used in other clinical trials of treatment for liver cancer, including the RTOG 1112 international randomized trial of sorafenib +/- SBRT.

1.5 Correlative Studies

1.5.1 Assessment of plasma and serum biomarkers: Classic RILD is caused by veno-occlusive disease, which is likely related to endothelial cell apoptosis as an initiating lesion. Radiation also induces various proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha) and transforming growth factor-beta 1,[30] and hepatic microvascular pathogenesis that lead to apoptosis in the liver.[31] Elevation of TGF-beta has been associated with RILD in women undergoing bone marrow transplantation for breast cancer[32]. In addition, an increased TNF-alpha production has been associated with the progression of hepatic veno-occlusive diseases in stem cell transplant patients[33], suggesting the potential role of cytokines in radiation-induced liver apoptosis. Our preclinical studies demonstrate the TNF alpha may play a key role in radiation injury of the liver.[33] We have experience measuring cytokines in patient plasma.[34] We propose to measure these cytokines and other potential circulating biomarkers in plasma and serum, and retrospectively assess their potential contribution to individualize our assessment of liver injury that could be used to adjust liver dose.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1) Establish the feasibility of the proposed adaptive treatment strategy
2) Obtain preliminary estimates of the safety and efficacy of individualized adaptive RT.

2.2 Secondary Objectives

1) To collect data on biomarkers of treatment efficacy, toxicity, and liver function to plan further enhancements to individualized RT.
2) To determine the change in quality of life during and after RT.

2.3 Endpoints

2.3.1 Primary endpoints:

2.3.1.1 Feasibility: Successful completion of treatment including use of perfusion MR in plan optimization.

2.3.1.2 Safety: Rate of liver decompensation (change in Child-Pugh score >2 and ALBI score > 0.5) and grade 3 GI bleeding. The former are lab values that are already collected as standard of care. The latter will be assessed via the NCI CTCAE version 4.0.

2.3.1.3 Efficacy: Lesion-specific local control

2.3.2 Secondary endpoints: Time to any progression and overall survival

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Patients with hepatocellular carcinoma are eligible for this trial. Hepatocellular carcinoma is defined as having at least one of the following:

a. Biopsy proven hepatocellular carcinoma (HCC); or

b. A discrete hepatic tumor(s) as defined by the Barcelona[35] criteria – for cirrhotic patients, >1cm with arterial hypervascularity and venous or delayed phase washout on CT or MRI [RECIST or mRECIST measurements will be captured for the study database and response assessment, however documentation of RECIST or mRECIST is not required at the time of enrollment.]

3.1.2 Patients must not have extrahepatic cancer.

3.1.3 Patients must not be eligible for curative liver resection or has refused resection.

3.1.4 Patients must have recovered from the acute effects of prior liver-directed therapy (e.g. RT, RFA, or TACE), and a minimum of 4 weeks must have passed since the last procedure and protocol therapy.

3.1.5 Patients must have a Zubrod performance status of ≤2.

3.1.6 Patients must have a life expectancy of at least 12 weeks.

3.1.7 Patients must be 18 years of age or older.

3.1.8 Patients must have adequate organ function as defined below.

- Bone marrow: Platelets ≥30,000/mm^3
- Renal: BUN ≤40 mg/dl; creatinine ≤2.0 mg/dl
- CPB score 8 and above for any size tumor
- CPA-B7 score with tumors >3.5 cm

3.1.9 Patients must understand and be willing to sign an informed consent form approved for this purpose by the Institutional Review Board (IRB) of the University of Michigan Medical Center indicating that they are aware of the investigational aspects of the treatment and the potential risks.

3.2 Exclusion Criteria

3.2.1 Patients with known allergy to intravenous iodinated contrast agents

3.2.2 Patients with a contraindication to contrast-enhanced MRI

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria will have eligibility confirmed by the Clinical Trials Office. The patient will not be considered registered and enrolled in the study until all information is confirmed by the Clinical Trials Office Data Manager.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 30 business days of enrollment to the study.

5.1.1 Global and regional assessment of liver function

5.1.1.1 Global functional assessment with indocyanine green (ICG) clearance Preparation and administration of indocyanine green will be as per package insert by trained personnel in the Michigan Clinical Research Unit (MCRU). In some patients, indocyanine green will not be used, in favor of ALBI score.

5.1.1.1.1 Evaluations with ICG or ALBI will occur within 4 weeks prior to the start of RT, at approximately 4-6 weeks after the completion of the first 3/5 of planned treatments, and approximately 1-3 months after RT is completed.

5.1.1.1.2 For patients scheduled to have ICG testing for other reasons (including prior or subsequent enrollment in this or other protocols), every effort will be made to use results for both purposes, to avoid duplication, including extending windows by an extra 4 weeks in each direction.

5.1.1.2 Baseline bloodwork and physical exam to obtain ALBI and Child Pugh score

5.1.1.3 Regional functional assessment with perfusion MRI

MRIs will be obtained by trained personnel in the Department of Radiation Oncology at the University of Michigan.

5.1.1.3.1 Evaluations will occur within 4 weeks prior to the start of RT, at approximately 4-6 weeks after the completion of the first 3/5 of planned treatments, and approximately 1-3 months after RT is completed.

5.1.1.3.2 For patients scheduled to have perfusion MRI for other reasons (including prior or subsequent enrollment in this or other protocols), every effort will be made to use results for both purposes, to avoid duplication, including extending windows by an extra 4 weeks in each direction.

5.1.1.4 Functional assessment with MRI

MRIs will be obtained by trained personnel in the Department of Radiation Oncology at the University of Michigan.

5.1.1.4.1 Evaluations will occur within 4 weeks prior to the start of RT, at approximately 3-6 weeks after the completion of the first 3/5 of planned treatments, and approximately 1-3 months after RT is completed.

5.1.1.4.2 For patients scheduled to have MRI for other reasons (including prior or subsequent enrollment in this or other protocols), every effort will be made to use results for both purposes, to avoid duplication, including extending windows by an extra 4 weeks in each direction.

5.1.2 Initial radiotherapy plan

5.1.2.1 CT with or without MRI simulation will be performed in treatment planning position, with appropriate immobilization, as is standard of care.

5.1.2.2 Radiation target volumes. The gross tumor volume (GTV) will be defined on CT or MRI. Appropriate patient-specific margins for motion will be added for patients unable to tolerate breath hold for treatment. No margin will be added for microscopic extent, as per routine clinical practice. A PTV margin will be added as per standard practice, typically 5mm radially and 8mm superiorly and inferiorly.

5.1.2.3 PTV Target Doses. Doses will be prescribed to a peripheral covering isodose covering the PTV, except in cases where this would exceed recommended doses to organs at risk (OARs). In these cases, heterogeneous dose distributions sparing these OARs are expected. The dose per fraction will be determined by the risk of liver damage, which will be fixed at ≤10% for the initial 3/5 of treatment. The full treatment plan will be devised at this time in order to account for total normal tissue dose if patients are able to proceed with the entire treatment. The remaining 2/5 of treatment will be determined as per section 11 and potentially reduced based on liver function. Maximum prescribed tumor dose will be 55 Gy in 5 fractions, which we have shown that this dose is adequate for 95% local control at 2 years even for large tumors.

5.1.2.4 OAR Limits. Standard OAR limits in routine clinical practice will be applied and will take priority over target coverage.

5.1.3 Radiation Schedule. The first 3/5 of the treatment plan will be delivered in the initial phase. The dose of radiation will be based on baseline ICG or ALBI, CP score, and functional liver imaging for an NTCP < 10% for a predicted CP score change of greater than or equal to 2. After an approximately 4 week break and re-assessment of liver function with ICG testing or ALBI, the final 2/5 of treatment may be delivered, as per section 11. Patients who have, or would be predicted to have, unacceptable Toxicity (as defined in section 8.6) at the reassessment point will receive no additional therapy at that time.

5.1.4 Adaptive radiotherapy plan for the final 2/5 of treatment. Each patient will be treated in two parts. In the first part, the dose will be determined using the current normal tissue complication probability (NTCP) model and spatial liver function considered in treatment planning. The patient's baseline and 2nd global and spatial liver function assessments will be used to individualize the second part of treatment. Based on the MRI, adjustments in the dose distribution will be made to maximize remaining liver function and target active tumor subvolumes. Accumulated data from the trial will be used to update the individualization model.

5.2 Toxicities and Dosing Delays/Dose Modifications

Patients who receive radiation treatment on this protocol will be evaluable for toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. If these toxicities occur **during treatment**, then RT will be held until resolution: Grade ≥3 ascites, change in ALBI score by 0.5, Child Pugh score greater than or equal to 2.

5.3 Duration of Therapy

Therapy would typically continue until delivery of the intended number of fractions. If liver function declines after the first 3/5 of treatments and does not recover sufficiently for additional therapy, then treatment will also be considered complete after 3 fractions (see above for definition).
Treatment will also be complete if a patient voluntarily withdraws from treatment or changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.3 apply, with documentation provided. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 6.3. The only exception to this requirement is when a subject withdraws consent for all study procedures, loses the ability to consent freely, or is removed from follow up per the investigator's discretion, as in Section 5.6.

5.5 Duration of Follow-Up

Patients will be followed for 2 years after completion of treatment or until death, whichever occurs first. If patients progress outside of the treated tumor, they will only be followed for survival, without mandated visits with study personnel, as long as they are being seen routinely every 3-6 months by an oncologist or hepatologist. These clinic notes can be requested for study purposes, and tumor measurements tracked from clinical scans.

5.6 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. Patients will be considered off study after completion of protocol treatment and follow-up criteria.
The reason(s) for discontinuation from study will be documented and may include:
5.6.1 For patients planning to receive ICG testing in lieu of ALBI, patients will be removed if

they are unable to complete the pre-treatment and post- 3 fraction IC Green tests, as these are necessary for dose adjustment.

5.6.2 Patients will be removed if they are unable to receive RT treatments.

5.6.3 Patients may be removed from study at any time by patient request.

5.6.4 Patients who enroll in subsequent liver radiation therapeutic trials are considered off study for initial enrollment. Local control for all treated lesions will be tracked on the follow up schedule for the subsequent enrollment to avoid duplicate procedures.

5.6.5 Patients who have progression of the treated lesion will be followed for survival and toxicity only.

5.6.6 Patients who go on to receive additional liver-directed to the treated lesion or systemic therapy (non-radiation therapy, on or off protocol) will be followed for survival only.

5.6.7 Patients can be removed from study if they are unable to comply with protocol requirements.

5.6.8 Patients can be removed from study if the treating physician judges that continuation on the study would not be in their best interest.

5.7 Patient Replacement

Patients who do not complete the pre-treatment and post 3/5 of treatment IC Green tests or bloodwork to evaluate ALBI score, along with the initial 3/5 of treatment are considered non-evaluable and will be replaced until a total of 80 evaluable patients is reached (80 patients).

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. Baseline procedures to be completed prior to radiotherapy. The screening procedures include:

6.1.1 Informed Consent

6.1.2 Medical history

6.1.3 Review subject eligibility criteria

6.1.4 Physical exam: To include ascites and encephalopathy

6.1.5 Performance status

6.1.6 Baseline adverse event assessment

6.1.7 Hematology: CBC

6.1.8 Serum chemistries: Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium), glucose, and total bilirubin.

6.1.9 Coagulation assessment: PT/INR

6.1.10 Tumor assessment: The longest dimension of each tumor to be treated will be measured and recorded either on the most recent diagnostic scan or simulation scan.

6.1.11 Indocyanine green or ALBI baseline testing: ICG retention or ALBI will be measured by blood test after study enrollment and prior to radiotherapy.

6.1.12 Blood draw for correlative studies after study enrollment and prior to radiotherapy. See Section 10.0 for details.

6.1.13 For patients who consent to this portion of the study, tumor biopsy will also be performed (see section 10.1.2) after study enrollment and prior to radiotherapy.

Generally, this would be performed at the time of clinically necessary fiducial placement for radiation targeting.

6.1.14 Quality of life assessment after study enrollment and prior to radiotherapy: FACT-HEP (Version 4).

6.2 Procedures During Treatment: See section 5

6.3 Follow-Up Procedures

Patients will be evaluated approximately 1 month after completion of therapy and then at approximately 3-6 month intervals until 2 years. Evaluation will include H&P, laboratories (CBC, comprehensive metabolic panel, INR, AFP if elevated at diagnosis), and liver imaging (beginning 3 months after treatment). QOL assessments will be obtained at the same intervals for 1 year. ICG or ALBI will be assessed approximately 1 and 3 months after completion of therapy. Blood and urine (when patient is able to provide) will be collected at approximately 1 and 3 months after completion of therapy. MRI will be assessed approximately 1 month after completion of therapy. This follow up schedule will adhere to standard of care clinical follow up. Therefore, missed visits and visits that diverge from this regimen will not be considered protocol deviations. MRI and ICG must be performed at the University of Michigan. However, if patients are not able to travel for all other follow up evaluations and procedures, they may have these performed by a local physician and records obtained by the study team. If patients are concurrently or previously enrolled in another research study which requires similar testing, all efforts will be made to avoid unnecessary repeat testing.

6.4 Time and Events Table

		Active Treatment		
	Pre-Rx Eval[1]	**Initial RT Phase**	**Evaluation Period Approximately 4-6 Weeks after Initial RT Phase**	**Final RT phase[5]**
History, Physical Exam, Performance Status, QOL[8]	X	PS	QOL	PS
Weight	X	Once	X	Once
CBC/Platelets	X		X	
AST, ALT, Alk Phos, Bilirubin	X		X	
BUN/Creatinine	X		X	
INR	X		X	
AFP (for HCC)	X		X	
Toxicity Notation	X	Once		Once
MELD/CTP assessment	X		X	
IC-Green [6]	X		X[4]	
Simulation	X		X	
Perfusion MRI[9]	X		X	
Tumor biopsy[7]	X			
Diagnostic CT or MRI of liver	X[2]			
Chest imaging with x-ray or CT	X[3]			
Plasma and serum	X		X	
Radiation Treatment (RT)		X		X

[1] From 30 days prior to signed ICF, through treatment start.

[2] From 90 days prior to signed ICF, through treatment start.

[3] Within 1 year prior to enrollment

[4] If a patient does not initially qualify for the final RT phase, he/she will undergo repeat IC-Green in approximately 4 weeks as a second attempt.

[5] Patients who do not qualify for the final RT phase will not undergo any of the treatment or testing associated with that phase. The final day of the initial RT phase will be counted as the last day of treatment, and the follow up calendar will be initiated.

[6] For patients indicated to receive IC-Green from the treating physician. If the patient was previously enrolled on any trial utilizing IC-Green (including this one), then an evaluation of IC-Green retention performed for the other trial may be used as the pre- treatment assessment for this enrollment, as long as it is within 30 days prior to initiation of this new course of RT.

[7] Biopsy only performed if patient consents

[8] QOL will consist of the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HEP) version 4. As patients can be seen in a variety of clinics, and occasionally do not follow a standard clinic schedule, missed QOLs will not be reported as a protocol deviation.

[9] Description of Perfusion MRI protocol in the appendix.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using criteria similar to the international criteria set by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. However, rather than tracking the sum of longest diameters, *each treated tumor will be assessed individually* and the longest diameter tracked in these lesion-specific tumor measurements. Additionally, at least 4mm change is required for a lesion to be deemed to have progressed or responded. mRECIST will also be tracked where possible.[30]

7.1.1 **Definitions**

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

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

7.1.2 **Disease Parameters**

All tumor measurements must be recorded in millimeters. The same method assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up if at all possible.

Target lesions. All tumors treated with radiotherapy are considered *target lesions* and measured and recorded separately at baseline and during follow up scans.

Non-target lesions. All other tumors are considered *non-target lesions* and will not be tracked except when noted as new or progressive (either within the liver or outside of the liver) on followup scans. Measurements are not required.

7.1.3 **Response Criteria**

7.1.3.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of target lesion.

Partial Response (PR): At least a 30% decrease in the longest diameter (LD) of target lesion, and at least 4mm decrease, taking as reference the baseline LD.

Progressive Disease (PD): At least a 20% increase in the LD of target lesion, and at least 4mm increase, taking as reference the smallest LD recorded since the treatment started.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest LD since the treatment started.

Note: If subjects respond to treatment and are able to have their disease resected,

the patient's response will be assessed prior to the surgery.

7.1.3.2 **Evaluation of Remote Intrahepatic Lesions:** The presence of new or growing tumors remote from previously treated tumor sites will be interpreted based on the standard criteria for the diagnosis of metastatic disease or HCC and recorded. The presence or absence of these will be tracked separately from the target lesions.

7.1.3.3 **Evaluation of Extrahepatic Lesions:** Imaging will be evaluated for the appearance of new or growing extrahepatic tumor deposits. These will be tracked separately from the target lesions and remote intrahepatic lesions.

7.1.4 **Local Control:** Local control is defined as the lack of progression of the tumors treated by RT, either by tumor size or enhancement. Progression or development of new tumors elsewhere in the liver or outside of the liver would not constitute a local control failure.

7.1.5 **Progression-Free Survival:** Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

7.1.7 **Overall Survival**: Overall survival (OS) is defined as the duration of time from start of treatment to death.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least the first part of treatment with radiation. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8.0 ADVERSE EVENTS

8.1 Adverse Event Reporting Requirements

Data on adverse events will be collected from the time of the first radiation treatment through 2 years after completion of radiation. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The definitions of AEs and SAEs are given below.

Any medical condition or laboratory abnormality with an onset date before initial study treatment is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history rather than an AE.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins treatment is also considered an adverse event if it meets the definitions below.

8.2 Definitions

8.2.1 Adverse Event

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

- All grade 3 and above AEs will be collected, in addition to any grade ≥2 gastritis, hepatic pain, vomiting, and fatigue. The NCI CTCAE v 4.0 will be

utilized to grade AEs and for AE reporting.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition or a condition entirely unrelated to the study radiotherapy (e.g. cardiac, lung, or bladder procedure).
- Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.
- When an event recurs after it is resolved, it should be handled as a new AE. However, AEs that occur intermittently can be recorded as one AE.

8.2.2 **Serious Adverse Event**

An adverse event is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease (cirrhosis or cancer), it is not considered an SAE.
- A life-threatening adverse event
  An adverse event is considered 'life-threatening' if, in the view of the investigator, its occurrence places the patient or subject at immediate risk of death.
- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours unless it was related to the disease under study, pre-existing conditions, or an accident, rather than the radiation treatments themselves.
- A congenital anomaly/birth defect

Previously planned (prior to signing the informed consent form) surgeries, hospitalizations, or procedures should not be reported as SAEs unless the underlying medical condition has substantially worsened during the course of the study, unless the investigator deems it definitely unrelated to treatment.
Hospitalization or prolongation of hospitalization without a precipitating clinical AE should not be considered SAEs.

Other adverse events that will be excluded from SAE reporting:

-Death due to cancer or cirrhosis
-Hospitalization secondary to expected cancer or cirrhosis morbidity
-Admission for palliative care or pain management
-Admission for management of biliary obstruction or cholangitis
-Admission for management of deep venous thrombosis or pulmonary embolism
-Planned hospitalizations for surgical procedures
-Accidental injury

Event reporting for oncology protocols, particularly those involving patients with liver disease, can be complicated and confusing to investigators, data managers, and regulatory oversight bodies because patients typically develop numerous complications such ascites, encephalopathy, peritonitis, GI bleed, blood clot, etc as part of the typical course of cirrhosis and not related to the study therapy.
Therefore, a well-conceived event reporting plan separates background noise as might be seen with any patient with cirrhosis and cancer from study-related events that are relevant to subject safety. In order to achieve this goal, the DSM plan for this study will focus on rapid and specific identification and reporting of the following as SAEs:

• Events which are serious and likely (probably or definitely) related to the investigational component of study therapy (high dose radiotherapy)
• Events occurring at unusual frequency or severity in study subjects compared to

non-study subjects undergoing similar treatment
• Events that are serious and unexpected

Therefore, we will not report as SAEs events that coincide with a typical cirrhosis or cancer course (ie, expected) unless they are related to the investigational therapy

8.2.3 **Expected Adverse Events**

An adverse event (AE) is considered "expected" if it is a common side effect related to abdominal radiotherapy. Examples of this include nausea, vomiting, dehydration, fatigue, musculoskeletal discomfort/pain, and dermatitis in the treatment field.

8.2.4 **Unexpected Adverse Event**

An adverse event (AE) is considered "unexpected" if it is not a common side effect related to abdominal radiotherapy.

8.3 Adverse Event Characteristics

8.3.1 **CTCAE Term**

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

8.3.2 **Attribution of the AE**

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study treatment
Probable – The AE *is likely related* to the study treatment
Possible – The AE *may be related* to the study treatment Unlikely – The AE *is doubtfully related* to the study treatment Unrelated – The AE *is clearly NOT related* to the study treatment

8.4 Serious Adverse Event Reporting Guidelines

8.4.1 The Principal Investigator must be notified within 5 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study.

8.4.2 The investigator must report all events meeting the criteria and definition of a serious adverse event that are unexpected and possibly related (definite, probable or possible) to study treatment to the local IRB within 7 days of study team's knowledge.

8.4.3 All Serious Adverse that are unexpected and possibly related (definite, probable or possible) to study treatment will be reported to the IRB using CTO Serious Adverse Event form.

8.5 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.6 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.7 Stopping Rules

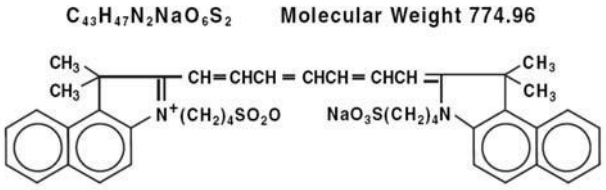
There are separate stopping rules for efficacy and toxicity. The goal is to stop the trial if there is evidence that the true rate of toxicity (defined in section 8.2) exceeds 10% OR the true rate of local progression within 6 months exceeds 30%. The efficacy rule will be evaluated 6 months after the 10th patient is enrolled. Given expected enrollment of about 1 patient per month, this evaluation will occur when approximately 16 patients have been enrolled. The trial will be stopped if 5 or more of the 10 patients with 6 month follow-up experienced disease-related progression within 6 months of treatment. When the true probability of progression within 6 months is 10, 30 or 50%, the probability of stopping is 1, 15 and 62%, respectively.

The toxicity rule will be evaluated after 15 patients are evaluable for toxicity which will occur 3 months after enrollment of the 15th patient. If 4 or more patients experience unacceptable toxicity, defined as radiation induced liver disease, the trial will be halted. When the true probability of toxicity is 5, 10 or 30%, the probability of stopping is <1, 6 and 70%, respectively.

9.0 DRUG INFORMATION

9.1 Indocyanine green: Indocyanine Green has FDA approval for determining hepatic function and liver blood flow. Please refer to the Package Insert for complete details.

9.2 Description: IC-GREEN™ is a sterile, lyophilized green powder containing 25 mg of indocyanine green with no more than 5% sodium iodide. It is packaged with Aqueous Solvent consisting of Sterile Water for Injection used to dissolve the indocyanine green. IC-GREEN™ is to be administered intravenously. Indocyanine green is a water soluble, tricarbocyanine dye with a peak spectral absorption at 800 nm. The chemical name for Indocyanine Green is 1 H-Benz[e]indolium,2-[7-[1,3-dihydro-1,1-dimethyl-3-(4-sulfobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-hydroxide, inner salt, sodium salt. IC-GREEN™ has a pH of approximately 6.5 when reconstituted. Each vial of IC-GREEN™ contains 25 mg of indocyanine green as a sterile lyophilized powder.



9.3 Side effects: Anaphylactic or urticarial reactions have been reported in patients with or without history of allergy to iodides. If such reactions occur, treatment with the appropriate agents, e.g.,

epinephrine, antihistamines, and corticosteroids should be administered. See package insert for comprehensive list of adverse events.

9.4 Drug Interactions: No interactions with patient medications. Heparin preparations containing sodium bisulfite reduce the absorption peak of IC GREEN™ in blood and, therefore, should not be used as an anticoagulant for the collection of samples for analysis.

9.5 Preparation and Dispensing: Under sterile conditions, the IC-GREEN™ powder should be dissolved with the Aqueous Solvent provided for this product, and the solution used within 6 hours after it is prepared. If a precipitate is present, discard the solution. The amount of solvent to be used can be calculated from the dosage form which follows. It is recommended that the syringe used for injection of the dye be rinsed with this diluent. Isotonic saline should be used to flush the residual dye from the cardiac catheter into the circulation so as to avoid hemolysis. With the exception of the rinsing of the dye injection syringe, saline is used in all other parts of the catheterization procedure.

9.6 Administration for patients indicated to receive IC-Green from the treating physician:

9.6.1 IC-GREEN testing will be administered according to the study calendar.

9.6.2 The patient will be studied in a fasting state. Patients should not eat 4 hours prior to the test. Coffee and/or water are allowed up to approximately two hours before the test. Patients should take all of their medications as usual. The patient will be weighed and the dosage calculated on the basis of a recommended 0.5 mg/kg of body weight. The dose given must be within 20% of the total recommended dose. There will be approximately a 6 cc blood draw followed by rapid IV push of the IC-GREEN at time 0. Following I.V. administration via catheter, serum samples will be collected at approximately 5, 10, 15 and 20 minutes after injecting the dye. Each blood draw will be approximately 6 cc. The patient will have two different catheters one will be used for the IC-GREEN infusion, and the other catheter will be used to draw the samples. The catheter will be flushed with saline following each blood draw.

9.6.3 The IC-GREEN test will be administered by trained personnel in the Michigan Clinical Research Unit “MCRU”. The dye is commercially available and will be ordered from UMHS pharmacy (formulary). Radiographic contrast agents are administered routinely in the department and it is fully equipped to treat an anaphylactic reaction, should one occur.

10.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned correlative studies is to collect data on plasma biomarkers of treatment efficacy, toxicity, and liver function to plan further enhancements to individualized RT.

10.1 Sample Collection Guidelines

10.1.1 Blood and urine sample collection and processing

10.1.1.1: Collection of approximately 30-50 mls of blood will be performed by venipuncture at the specified time points. When possible, blood collection will be coordinated with other routine blood studies. These blood samples will be drawn at the clinical blood drawing station in the Radiation Oncology department at UH or at the Michigan Clinical Research Unit (MCRU).

10.1.1.2 Blood Specimen Processing: Whole blood will be obtained by venipuncture at each time point and will be processed at Michigan Clinical Research Unit (MCRU) specimen core and processing laboratory. Blood Samples will be labeled with the subject’s coded study number and collection date.

The processing will happen as described in the current SOP of the Biorepository.
10.1.1.3 Subjects will provide approximately 20-40 ml of urine at the specified time points, if able.
10.1.1.4 Urine Processing: The urine samples will be processed at the MCRU specimen core and processing laboratory. A maximum of 20 2-ml aliquot tubes will be filled at each collection.

10.1.2 **Biopsy collection and processing:**
10.1.2.1 For patients who will undergo standard of care percutaneous fiducial placement at the University of Michigan for radiation targeting, they will optionally also consent to undergo percutaneous tumor biopsy during the same procedure. 2-3 18G cores will be obtained following routine clinical practice.
10.1.2.2 Biopsy Specimen Processing: Depending on sample abundance, the cores will be processed for RNA, DNA, and protein extraction, as well as standard histology. For RNA, the cores will be placed into an eppendorf tube and the sample covered with RNAlater completely. It will be stored in a 4 degree refrigerator for 24 hours, then transferred to a -80 degree freezer for later extraction. For frozen section, part of the sample will be placed into a plastic mold, and the sample covered with OCT compound completely, and then stored in -80 degree freezer immediately. A separate piece of tissue will be snap frozen at -80 degree freezer separately for later DNA and protein extraction. Standard methods for formalin-fixed paraffin embedding will be followed.

10.2 Specimen Banking

Blood and urine specimens not immediately utilized for plasma biomarkers will be stored for future biomarker analysis, as we anticipate advancement in experimental technology and preliminary results. Other techniques and tests also will be applied if they are found to be superior.

10.3 Virtual radiotherapy planning

CTs and MRIs obtained as part of this study will be coded and the information used for further advancements to treatment planning, including deformable registration and dose accumulation.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a pilot study of individualized adaptive RT, which consists of 3/5 of a planned total course of treatment, a one month break, assessment of global and spatial liver function change using IC-Green or ALBI, and perfusion MRI, and the remainder of treatment adjusted for global and spatial changes in liver function. The primary endpoints are to establish the feasibility of this approach and to obtain preliminary estimates of safety and efficacy both overall and as they relate to treatment and patient characteristics. At the completion of this trial we will have the necessary data to define a SBRT treatment approach that is individualized and adaptive and ready to be compared to standard SBRT in a randomized trial.

Patients will have an initial plan with total dose chosen such that the estimated probability of toxicity (increase in CP of 2 points or more within 6 months of RT) from the first three of five planned treatments is at most 10%. In order to protect the safety of individual patients, after delivering 60% of the planned total treatment, there will be a 1 month break at the end of which, ALBI or ICG will be measured again and a new treatment plan will be developed. This last course of treatment may be adapted (relative to the first course) globally in one of 2 ways. First, if there is no remaining enhancement on the MRI scan, no further radiation will be given because the tumor is likely to be cured. The second possible adaptation is intended

to prevent clinically significant decline in liver function in patients whose livers appear to be sensitive to RT. Child-Pugh (CP) score is a standard measure of liver function, and an increase of 2 points or more on this scale is considered clinically significant. Early changes in ICG retention and ALBI reveal subclinical changes in liver function that predict later liver toxicity, assessed by a change of 2 in CP score 6 months after treatment.

Maximizing tumor control and minimizing liver toxicity are competing objectives when selecting RT dose for these patients. To make this tradeoff explicit and quantitative, the dose during the second course of treatment will be selected as the minimum of

1) The dose that maximizes Prob(Local Control at 1 year) – 4*P(Toxicity)

2) The dose associated with a 25% estimated risk of toxicity.

That is, additional dose is deemed to be beneficial if the increase in local control is at least 4 times greater than the increase in toxicity. The key advantage of this approach over an isotoxic approach is that patients are exposed to risk of toxicity in direct proportion to their benefit in terms of increased local control. Thus patients are not unnecessarily exposed to higher rates of toxicity (e.g. 20%) unless the improvement in expected local control is large enough. Similarly, patients are not constrained to an arbitrary rate of toxicity (e.g. 15 or 20%) if allowing the rate of toxicity to exceed this threshold results in a large enough increase in local control. At the same time we still place a hard upper limit of 25% on the risk of toxicity to any patient. The overall rate of toxicity in this population of patients is expected to be lower than 25%.

In the above, toxicity is defined as increase in CP of 2 points or more within 6 months of RT and local control is defined as absence of tumor progression within 1 year of treatment. For purposes of this dose selection, local control will be estimated from a simple Cox model as a function of tumor dose while the toxicity model will include the change in ICGR15 at the mid-treatment timepoint.

The decision to continue treating patients with further radiation is based on analysis of the information from the ICG results or ALBI, and not RECIST measurements. These measurements are recommended and are not required to determine patients' coming off-study treatment or study protocol. In addition, baseline measurements are not needed at the time of enrollment.

11.2 Sample Size and Accrual

This is a pilot trial to gather the data necessary to plan a randomized phase II study with a control group receiving standard therapy. The planned accrual is 80 evaluable patients over two years. An evaluable patient is a patient that has received their complete prescribed treatment (including those whose ICG measurements or ALBI precluded the second phase of treatment and those for whom other toxicity prevented them from receiving a full course of treatment). The high level goal of this trial is to define an individualized and adaptive approach to use of RT in this patient population. Key components of individualizing and adapting treatment are models that relate expected toxicity and tumor control outcomes to RT dose and other patient level characteristics. Part of the reason for the sample size of 80 is to refine these models prior to initiating a randomized trial. For toxicity, our preliminary data suggests that mean liver dose (or some other measure of dose to normal liver), baseline liver function (e.g. CP score) and mid-treatment change in ICGR15 are the most important factors. If our overall event rate for toxicity is about 20%, we expect to have approximately 16 toxicity events which, in combination with some data from similarly treated previous patients, should be sufficient to estimate parameters in a toxicity model with 3 predictors. For tumor control, tumor dose is expected to be the most significant predictor. There will likely be a lower rate of local progression events so that this model may need to have fewer predictors. In addition to further defining statistical models this trial will permit us to estimate rates of toxicity and tumor control that will be key when designing a randomized trial with power to reject a specific null hypothesis.

This treatment will be considered sufficiently promising to initiate a phase II trial if itcauses toxicity (increase in CP score of 2 points or more within 6 months of treatment) in no more

than 25% of patients and results in a local control rate (at 1 year) of at least 80%.

We expect to be able to accrue 20 patients per year and thus to complete accrual in approximately 4 years.

11.3 Data Analysis Plans

Primary Aims: The first primary aim is feasibility which is defined as the ability to successfully deliver the full treatment including all adaptations and in particular the perfusion based planning and replanning. In the simplest analyses, feasibility will simply be summarized as the proportion of patients for whom the intended treatment was feasible. The reasons for lack of feasibility for any patients will be investigated individually.

The primary efficacy endpoint is local control, measured as the time to progression of the treated lesion. Patients with no evidence of local progression at the time of data analysis will be censored at the last date on which they were evaluated for local progression. Local progression will be summarized with Kaplan-Meier curves. The estimated rate of local control at 6, 12, 18 and 24 months will be estimated and reported with 95% confidence intervals. Cox regression models will be used to assess the relation between the hazard of local progression and tumor dose and other covariates.

The primary toxicity endpoint is defined as a change in Child Pugh score of greater than or equal to 2 within 6 months of SBRT. Secondary toxicity endpoints include changes in ALBI scores and grade 3 toxicities described in section 8. RILD is a rare but serious side effect that will also be summarized if it occurs. Logistic regression models will be used to estimate the association between baseline (primarily baseline liver function such as CP score and mean liver dose and other dose metrics such as D700) and mid-treatment variables (e.g. change in ICGR15) and the probability of toxicity. We will include interactions between dose and baseline liver function as there is some evidence that patients with worse liver function are more sensitive to radiation than patients with better baseline liver function.

Secondary Aims: The relation between various biomarkers and treatment efficacy will be assessed by including the biomarkers as covariates in Cox regression models for local progression. The relation between biomarkers and toxicity will be assessed in logistic regression models for the binary or ordinal toxicity outcomes and linear regression models for continuous measures of toxicity or liver function such as ICGR15 or ALBI.

Quality of life will be summarized descriptively at baseline (pre-RT) and at each post RT timepoint. Change from baseline will be calculated for each patient and summarized descriptively as well as tested for statistical significance using a paired t-test.

12.0 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan. The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, data manager or designee and other members of the study team involved with the conduct of the trial, will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness.

At the regular DSMC meetings, the protocol specific Data and Safety Monitoring Report form will be completed. The report will be signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) on a quarterly basis

for independent review.

13.0 QUALITY ASSURANCE AND AUDITS

The Data Safety Monitoring Board can request a 'for cause' audit of the trial if the board identifies a need for a more rigorous evaluation of study-related issues. A "for cause" audit would be conducted by the Quality Assurance Review Committee (QARC) of the University of Michigan Comprehensive Cancer Center.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Clinical Trials Office that such a request has been made.

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15. APPENDIX I

Liver MR Imaging Protocol (subject to minor change)

1. Breath-holding VIBE Dixon scan to obtain fat and water in-phase and out-phase, and calculated fat and water images, acquisition time ~ 20 seconds
2. Free-breathing internal-trigged T2 weighted scan, acquisition time 2-3 min
3. Free-breathing internal trigged diffusion weighted scan, acquisition time ~ 4 min
4. Free-breathing pre-contrast T1 weighted scan using a new starVIBE (or radialVIBE with radial sampling and suppressing motion artifacts) sequence, acquisition time ~ 1 min
   Or breath-holding pre-contrast T1 weighted scan using a conventional VIBE sequence, acquisition time ~20 s
5. Free-breathing T1 weighted scan with contrast injection using the starVIBE (or RadialVIBE) sequence, to reconstruct low-spatial resolution dynamic contrast enhanced images, and high-spatial resolution arterial and portal vein phase images using either vendor provided online option or an offline in-house software . Acquisition time is ~3-4 min. If **gadoxetic-acid (Eovist) is chosen as the contrast agent, acquisition will be extended up to 20 min.**
6. A late phase T1-weighted scan using the same sequence