Assessment of Response of Unresectable Hepatocellular Carcinoma to Combination Chemoembolization and Stereotactic Body Radiation Therapy
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Study Title: Assessment of Response of Unresectable Hepatocellular Carcinoma to Combination Chemoembolization and Stereotactic Body Radiation Therapy

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1.0 INTRODUCTION

1.1 Study Design

This is a non-randomized pilot study to assess the objective response rate and durability of response of combination Trans-Arterial Chemoembolization (TACE) with immediate stereotactic body radiation therapy (SBRT) in the treatment of unresectable hepatocellular carcinoma (HCC). Eligible patients will be selected based on having a lesion greater than 3 cm which would make them ineligible for other local therapies such as TACE and thermal ablation (TA). Eligible, consented, and registered patients will be treated with two sessions of standard TACE with ethiodol separated by a 4-week interval. After ensuring adequate return to baseline liver function, the patients will then be treated with SBRT to the targeted lesion to 30-40 Gy in 5 fractions. Tumor response will be assessed using mRECIST criteria as well diffusion weight imaging (DWI) via Magnetic Resonance Imaging (MRI) surveillance. In addition, tolerability and toxicity will be recorded via CTCAE v. 5.0. The essential hypothesis of this study is that combination TACE and SBRT for > 3 cm HCC will produce higher response rates and durable control compared to historical controls of TACE alone.

1.2 Primary Objectives

1.2.1 To determine the objective response rate up to 1 year in patients with HCC treated with combination TACE and SBRT.

1.3 Secondary Objectives

1.3.1 To determine the time to progression (TTP) of the treated lesion.

1.3.2 To determine the overall survival (OS) of patients as defined from completion of treatment until death.

1.3.3 To determine the progression free survival (PFS) of patients as defined from the completion of treatment until disease progression in the treated lesion, liver, or distant metastases.

1.3.4 To determine the tolerability and toxicity of combination TACE and SBRT in this population.

2.0 BACKGROUND

Hepatocellular carcinoma (HCC) is the third ranked cause of global cancer mortality. There is an increasing incidence of HCC in the United States over the last twenty years, largely due to the Hepatitis C epidemic but increasingly related as well to nonalcoholic fatty liver disease (1,2). For patients with single HCC and compensated liver disease (normal liver function and no portal hypertension), partial liver resection (LR) is the preferred treatment, although there is significant risk of recurrence. For patients

HCC who are Barcelona-Clinic Liver Cancer (BCLC) class A (1 lesion < 5cm, or 2-3 lesions all < 3cm) and who, due to decreased liver function, are not candidates for LR, liver transplantation (LT) is the treatment of choice. The current median waiting time in New York, however, is greater than 12 months, creating the risk of dropout due to tumor progression (currently estimated to be around 20-25%). In order to mitigate this risk, patients listed for LT typically undergo locoregional therapy with transarterial chemoembolization (TACE) and/or thermal ablation (TA) as a bridge to LT (3,4). However, only 30% of patients are candidates for curative treatments (5).

Patients with BCLC A HCC who due to age, medical, or psychosocial issues are not candidates for LR or LT are typically treated with TA, which has the potential to completely destroy tumor nodules. Recent studies in selected patients demonstrated equivalent or improved rates of overall survival and recurrence-free survival between TA and surgical resection (6-8). TA is often used in combination with TACE, which both aids in accurately targeting TA and may augment the extent of resultant tissue ablation. One recent randomized study showed improvements in both overall survival and recurrence-free survival in patients receiving TA + TACE compared with TA alone (9). Application of TA is limited to tumors < 4cm, and as the performance of TA requires accurate placement of a needle probe into the tumor, nodules situated in inaccessible locations or adjacent to vital structures are not amenable to treatment. Patients with tumors beyond Milan criteria but confined to the liver and without macrovascular invasion (BCLC B) who are not candidates for resection are typically treated with TACE, which prolongs survival but does not offer hope of cure (10-11).

For lesions that are not candidates for TACE and/or TA, stereotactic body radiation therapy (SBRT) has recently been shown to be an effective tool in the locoregional treatment of HCC. SBRT is a specific application of intensity modulated radiation therapy (IMRT) in which very high doses of radiation are delivered in fewer fractions to a small target. SBRT has the potential to widen the therapeutic index by delivering a much higher equivalent dose, standardized by the concept of Biological Effective Dose (BED), which measures the true biologic dose as a function of dose per fraction, total dose, and a tissue's inherent radiosensitivity (12). SBRT employs the use of image guidance, usually with iterative CT imaging moments before the radiation is delivered, with real-time fusions by the radiation oncologist of the planned treatment volume with the patient's anatomy at the time of each treatment. By utilizing SBRT, the tumor receives a very large dose of radiation while minimizing the exposure of adjacent healthy tissue, enabling clinically effective and safe radiation delivery for HCC (13-22).

There are several unique advantages of SBRT over traditional TACE with or without TA as well. To start, SBRT can be used to treat lesions adjacent to or invading vasculature which might not be a candidate for TACE or TA. While there are anatomic limitations to SBRT, these are different than other local therapies broadening the spectrum of local treatments. SBRT is also non-invasive with a relatively low toxicity profile. It can be used in combination with or adjunctive to other local therapies. This benefit might be further potentiated based on the different mechanism of action of SBRT vs. TACE and/or TA. Finally, SBRT can be used to treat larger lesions than RFA which is generally restricted to lesions less than 4 cm.

Preliminary series have demonstrated encouraging results using SBRT for the treatment of HCC. Phase I and II data from the Princess Margaret Hospital evaluated the efficacy and safety of 6-fraction SBRT to a median dose of 36 Gy in Child-Turcotte-Pugh (CTP) class A patients with HCC not suitable for surge

TACE, RFA, or ethanol ablation (23-24). Results demonstrated treatment to be well tolerated, with no classic radiation-induced liver damage (RILD) observed. 23-29% of the patients experienced a transient progression from CTP class A to B, the vast majority of which resolved by 12 months. One year local control was 87%. Other groups have demonstrated comparable safety and control, even in Child B patients, with 2 year local control rates, as defined as no progression in the treated lesion after treatment, of 90% (25). A clear dose response relationship has been established demonstrating that doses greater than 30 Gy in 6 fractions have better local control (24). Of note, delayed tumor necrosis, despite relative persistent in size, has been documented following SBRT of HCC (26).

SBRT has also been incorporated into locoregional treatment of HCC following TACE. In 50 patients who received a median of 2 TACEs prior to receiving SBRT (median dose 57 Gy in 3 fractions), a 2-year local control rate of 94.6% was achieved (27). Treatment was well tolerated with no classic RILD observed. 12.8% of patients progressed from CTP class A to B. 8.5% of patients developed ascites with normal alkaline phosphatase levels. Of note, at these high doses, 6.4% and 4.3% of patients had grade 3 or grade 4 GI toxicity, respectively. This study focuses on a heterogeneous population as well as high radiation doses resulting in higher than expected grade 3 toxicity.

The assessment of treatment response after TACE and TA is currently based on loss of internal vascularity on contrast-enhanced imaging as outlined in the mRECIST criteria. The response to radiotherapy, however, may not be as accurately assessed by mRECIST. Diffusion-weighted imaging (DWI) and uptake by hepatocytes of liver-specific contrast (Gd-EOB-DTPA) are potentially complementary methods to assess hepatocyte damage. The use of DWI has been reported in the diagnosis of liver tumors and for the evaluation of treatment response in liver metastases (treated with systemic chemotherapy) and HCC (treated with TACE) (28-34).Most studies have observed an early rise in Apparent Diffusion Coefficient (ADC)values concomitant with devascularization, with subsequent decrease in ADC values in HCC (35). A recent study successfully correlated radiographic changes on the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI with a threshold dose of radiation 3 months after SBRT (36). In their study of 50 patients undergoing SBRT for HCC, Sanuki et al proposed a threshold dose of 30 Gy for CTP class A and 25 Gy for CTP class B patients. They demonstrated that the highly irradiated area surrounded by these isodose curves on the treatment planning scan corresponded to the region of focal liver reaction identified on Gd-EOB-DTPA-enhanced MRI.

3.0 PARTICIPANT SELECTION

All patients will be evaluated in the multidisciplinary Liver Tumor Board where eligibility criteria, entry, and disease parameters will be evaluated and documented. In addition, all patients are required to consult with a radiation oncologist, interventional radiologist, and medical oncologist before starting the study. Subjects who enroll in this study must have a single HCC > 3 cm and not be candidate for upfront surgical resection. Patients must not have had any prior radiation to the thorax or abdomen. Potential patients will be screened based on their past medical history, radiological scans, blood work, competing clinical trials, transplant eligibility, and overall ability to comply with the protocol.

3.1 Inclusion Criteria

Participants must meet the following criteria to be eligible to participate in the study:

3.1.1 Participants must be diagnosed with HCC either pathologically or by the American Association for the Study of Liver Diseases (AASLD) radiographic criteria (Bruix Hepatology 2011). The criteria specifies CT or MRI intense arterial uptake followed by "washout" of contrast in the venous-delayed phases. Any atypical lesions must be confirmed by biopsy.

3.1.2 A single liver lesion with tumor size $\geq$ 3 cm as defined as maximal diameter in the axial dimension on MRI. Included in the measurement are both enhancing and non-enhancing components of the lesion.

3.1.3 Maximum tumor size of 7 cm as defined as maximal diameter in the axial dimension on MRI.

3.1.4 Age $\geq$ 18 years

3.1.5 Child-Pugh class A or B7 without ascites

3.1.6 ECOG score 0

3.1.7 No prior treatment of current HCC. However, recurrent HCC after resection may be included.**3.1.8** Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria:

Participants will be excluded from participation in the study if they have any of the following exclusionary criteria:

3.2.1 Pregnancy which will be assessed via pregnancy test prior to TACE and repeated prior to SBRT.

3.2.2 Metastatic disease outside of the liver

3.2.3 Vascular invasion as evidenced by vessel occlusion or radiographic evidence of tumor thrombus.

3.2.4 Contraindications to MRI, including claustrophobia, metallic implants, and pacemakers

3.2.5 Tumor for which adequate radiation dosage cannot be safely delivered (see dose constraints below)

3.2.6 Prior therapeutic radiation therapy to the abdomen and/or lower thorax as defined as below the carina to the pelvic inlet.

3.2.7 Inability to provide informed consent based on persistent lack of understanding, inability to find adequate translation, impaired mental status such as mental retardation, drug induced, or traumatic brain injury.

3.2.8 Multiple liver tumors making the patient a BCLC Stage B

3.2.9 Prior treatment, except for surgical resection, to the lesion being targeted in the protocol.

4.0 DELIVERY OF TACE

4.1 Initial TACE will be delivered per standard protocol

4.2 After 3 to 8 weeks following the intial TACE, patients will return for labwork and consideration for a second TACE to the same site. TACE will not be repeated if the bilirubin is > 3 ng/mL.

4.3 Prior to preceding to radiation therapy, the patient will have labwork done including CBC and LFTs to assess return to within grade 2 elevations of baseline labwork prior to proceeding onto radiation.

5.0 DELIVERY OF STEREOTACTIC BODY RADIATION THERAPY

5.1 Dose Specifications

5.1.1 The primary tumor(s) and any tumor vascular thrombus must be treated. Treatment volume will include both the residual TACE site, ethiodol marker, and any residual enhancing disease. Volume design is at the discretion of the radiation oncologist.

5.1.2 Treatment Schedule: All patients will receive radiation treatment with SBRT. Treatment will optimally be delivered every other day with no more than 3 fractions per week. The ideal treatment team will be less than 15 total days.

5.1.3 Prescription Dose: Radiation is to be delivered to 30-45 Gy in 5 fractions. 40 Gy in 5 fractions will be utilized, unless dose constraints preclude it.

5.1.4 Dose Specifications: The prescription isodose is planned to encompass 95% of PTV. The highest allowable doses to the target volumes that maintain normal tissue constraints should be used. A goal is that 100% of CTV is encompassed by the prescription dose.

5.1.5 Dose Prescription: Will be based on the volume of normal tissues irradiated based on mean liver dose and proximity to adjacent critical structures. In the absence of adjacent GI luminal structures that may limit dose (mean liver dose (MLD), as defined as liver minus GTV), prescription dose should be 40 Gy in 5 fractions. Vascular tumor thrombosis dose should be the same as the as the HCC prescription dose. However, lower doses are acceptable if require to meet normal tissue constraints. Non-tumor bland thrombosis is not recommended to be irradiated but can be included in the CTV if felt to be at risk for microscopic disease. Maximum dose w[illegible] the PTV is 115% but below 110% is preferred. Maximum dose for any given axial slice shou[illegible]

be within the PTV. Efforts should be made to keep the prescription dose as conformal as possible.

5.2 Technical Factors

5.2.1 Megavoltage equipment with photons of at least 6 MV, capable of daily cone beam CT imaging, with a multileaf collimator for intensity modulation is required. All plans should use IMRT.

5.2.2 CT based planning is required. A minimum of 5 beam angles is strongly recommended. Arc therapy is permitted.

5.2.3 Image guided radiation therapy (IGRT) is mandatory

5.2.4 Breathing motion is strongly management is strongly recommended if breathing motion is greater than 5 mm. Breathing motion assessed on 4D CT and adequately treated with PTV margins < 1 cm is encouraged.

5.3 Localization, Simulation, and Immobilization

5.3.1 Custom immobilization with an alphacradle or Vac-lock is required

5.3.2 Treatment planning CT scans will be required to define GTV. IV contrast is recommended for the planning CT. Oral contrast with simulation is encouraged.

5.3.3 Breathing motion is to be assessed using a 4D CT whenever possible. Use of an abdominal compression belt is encouraged as well, even when using a 4D CT. If 4D CT is not available, a breath hold technique is required.

5.3.4 Fusion or reference to a MRI with contrast is strongly encouraged to facilitate in defining treatment volumes.

5.4 Treatment Planning Volumes/ Target Volumes

5.4.1 The Gross Tumor Volume (GTV) is defined as all parenchymal and vascular HCC visualized on contrast enhanced CT and/or MRI, most often best seen on arterial phase or as wash out in venous or delayed phase. Non-tumor thrombi should not be considered part of the GTV. Liver-to-liver fusion with diagnostic MRI is recommended to facilitate treatment planning.

5.4.2 An Internal Target Volume (ITV) will be created when 4D CT simulation is used. This will be accomplished by contouring GTV through the binned respiratory cycle through each axial slice. If tumor is not visible, it is permitted to use 'surrogates' such as liver shape, defects, clips, etc. to estimate GTV location.

5.4.3 A Clinical Target Volume (ITV) is created by expanding the ITV to include additional areas of possible microscopic spread. Typical expansions are 5 to 10 mm beyond the ITV. CTV can be shaved off of natural barriers to spread (ie. chest wall, heart, etc.).

5.4.4 A Planning Target Volume (PTV) will be added to the CTV to compensate for set-up error and unaccounted organ motion (different breathing patterns on different days). The PTV expansion should be at that discretion of treating physician but will range from 5 to 10 mm.

5.4.5 All dose distributions shall include corrections for tissue heterogeneities. Arterial vascular contrast is recommended to be converted to water equivalent density if used for planning.

5.4.6 Goals of planning are to maximize dose to the target volumes, while maintaining all normal tissue constraints. Reducing the maximal dose to all luminal GI normal tissues should be a priority to reduce the risk of GI toxicity. Beam angles may be individualized to minimize the path length through the liver and through adjacent organs at risk. Conformality of the prescription dose is a secondary goal.

5.5 Critical Structures Maximal Doses

5.5.1 All dose values are provided as maximum total dose to be delivered in 5 equal fractions as follows:

Liver minus GTV	700cc receiving < 15 Gy
Esophagus max (to. 0.5 cc)	32 Gy
Stomach max (to 0.5 cc)	30 Gy
Duodenum max (to 0.5cc)	30 Gy
Small bowel max (to 0.5 cc)	30 Gy
Large bowel max (to 0.5 cc)	32 Gy
Cord + 5mm max (0.5cc)	25 Gy
Kidneys: bilateral mean dose	<10 Gy

OR – if one kidney mean dose > 10 Gy, remaining kidney V10 Gy < 10%

5.5.2 The following organ dose constraints are guidelines, not mandatory:

Stomach (to 5 cc): < 25 Gy
Duodenum (to 5 cc): < 25 Gy
Small bowel (to 5 cc): < 25 Gy
Heart max (30cc): < 30 Gy
Great vessel max (0.5 cc): < 60 Gy
Skin (external) max (0.5 cc): < 32 Gy
Chest wall max (0.5 cc): < 50 Gy
Gallbladder max (0.5 cc): < 55 Gy
Common bile duct max (0.5 cc) < 50 Gy (even though the bile duct is not often well visualized, it is always within the portal region and may be within high dose volumes for central targets, so efforts to reduce hot spots in this region are warranted)

5.6 Timing of Radiation

5.6.1 The first radiation treatment should begin within 7 days of the second TACE. Acceptable variation would be within 21 days of completion of TACE.

5.6.2 Per protocol, all external beam radiation treatments should be delivered within 15 calendar days. An acceptable variation is 16-21 calendar days. Treatment requiring greater than 22 calendar days constitutes a major protocol variation.

5.7 PTV coverage: The intent is for the prescription dose to cover 95% of the PTV. The PTV should be treated to as high a dose as possible, respecting normal tissue constraints, as a dose response has been observed. Modifying a PTV due to close proximity of adjacent OARs is not permitted. An acceptable variation per protocol would be 90-95% PTV coverage.

5.8 Radiation Therapy Adverse Events

The criteria used for the grading of toxicities encountered in this study are Common Toxicity Criteria (CTC) version 4.0.

Very likely (80-90%)

- Fatigue (which generally goes away after the radiation therapy is completed)
- Skin irritation, redness, itchiness, discomfort
- Temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (30%)

- Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated
- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes)
- Chest wall pain, rib fracture (< 10%)

Less likely, but serious (<20%)

- Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver.
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

5.9 Radiation Therapy Toxicity Assessment During Therapy

Patients will be assessed at least once during radiation therapy for toxicity. Radiation therapy will be continued as long as there is no grade 3 or 4 toxicity. Treatment delays or discontinuation of radiation will be at the discretion of the treating physician.

5.9.1 Radiation Modification Table

TOXICITY	MODIFICATION
Hematologic	
Grade 1 or 2	Continue radiation
Grade 3	Hold radiation until ≤ Grade 2, then continue
Grade 4	Hold radiation 1 week until ≤ Grade 2, then continue
Gastrointestinal	
Grade 1 or 2	Continue radiation
Grade ≥ 3 diarrhea	Hold radiation until ≤ Grade 2, then continue
Grade 1 or 2 nausea or vomiting	Initiate anti-emetics prior to radiation and as needed and continue radiation
Grade 3 nausea or vomiting	Hold radiation until ≤ Grade 2, then continue with anti-emetics prior to radiation and as needed
Hepatic	
Grade 1 or 2 AST or ALT	Continue radiation
Grade 3 but less than 10x upper limit of normal AST or ALT	Continue radiation
Grade 3 and > 10x ULN AST or ALT	Hold radiation until improves to ≤ grade 2, then resume
Grade 4 AST and ALT	Hold radiation for one week and until improves to ≤ grade 2, then resume
Child-Pugh score > 7	Hold radiation until improves to Child-Pugh score ≤ 7
Other Non-hematologic	
Grade 1 or 2	Continue radiation
Grade 3	Hold radiation until ≤ Grade 2, then continue
Grade 4	Discontinue radiation

6.0 DATA COLLECTION

6.1 Before enrollment, patients will be interviewed and assessed for meeting inclusion and exclusion criteria. Patients will also be assessed for ability to complete the protocol and follow up. Follow up and data collection will proceed as outlined below and summarized in Appendix D.

6.1.1 Pretreatment data will include the following parameters:

1. Demographics: age, sex, etiology of liver disease
2. Past Medical History: comorbidities
3. Related symptomatology
4. Performance status according to ECOG
5. Liver and renal function tests: bilirubin, AST, ALT, albumin, alkaline phosphatase, GGTP, BUN, creatinine, Na, INR, and platelet count
6. Serum alpha fetoprotein (AFP)
7. Tumor MRI with Gd-EOB metrics: size, number of tumors, tumor location, tumor necrosis, mean ADC of whole tumor and viable component
8. Liver MRI metrics: degree of hepatobiliary phase enhancement, mean ADC
9. Chest CT

6.2 A regular on treatment visit (OTV) will be used to assess acute treatment related toxicity according to CTCAE v. 4. In the event that there is a treatment break, patients will be seen at least once a week.

6.3 Three to 6 weeks following completion of SBRT, the patient will be seen in routine follow up to assess and manage any post-treatment complications. At that time of the first visit, blood work will be obtained as follows:

Liver and renal function tests: bilirubin, AST, ALT, albumin, alkaline phosphatase, GGTP, BUN, creatinine, Na, INR, and platelet count
Serum alpha fetoprotein (AFP)

6.4 Routine follow up will be scheduled every 3to 4 months from the completion of radiation (2 to 3 months after the initial one month visit). For medical necessity, patients can be sooner. In addition to assessment of toxicity according to CTCAE, blood work will be obtained as follows:

Liver and renal function tests: bilirubin, AST, ALT, albumin, alkaline phosphatase, GGTP, BUN, creatinine, Na, INR, and platelet count
Serum alpha fetoprotein (AFP)

6.5 Every 3 to 4 months post-radiation, the patient will be have an MRI with Gd-EOB-DTPA to assess tumor response (as outlined below) up to one year.

6.6 Every 6 to 8 months, the patient will have a CT of the chest, abdomen, and pelvis to assess for systemic disease. If clinically warranted, imaging can be obtained sooner. PET/CT might be used if clinically warranted.

6.7 If a patient received his/her TACE treatments and did not receive SBRT, he/she will nevertheless be followed by the same follow up schedule as above except for the OTVs and one month post-radiation visit.

6.8 Patients will be followed after one year per standard medical care.

7.0 ASSESSMENT OF RESPONSE

7.1 MRI protocol: Precontrast sequences (T1 in- and out-of-phase, T2 fat saturated, T2 HASTE, diffusion using 3 b-values: 50-400-800, T2*) and dynamic pre- and post-contrast 3D T1-weighted imaging using Gadoxetic acid contrast (Eovist, Bayer) at the arterial, portal venous, late venous, and hepatobiliary phases will be obtained for all patients. GFR will be measured prior to examination.

7.2 MRI will be obtained every 3 months following completion of SBRT to assess for tumor response as well as to identify and monitor any additional sites of disease. MRIs will be obtained at 3, 6, 9, and 12 months.

7.3 Modified RECIST (mRECIST) will be used to assess response (Appendix B). Additional components such as extent of tumor necrosis will be used at the discretion of the radiologist.

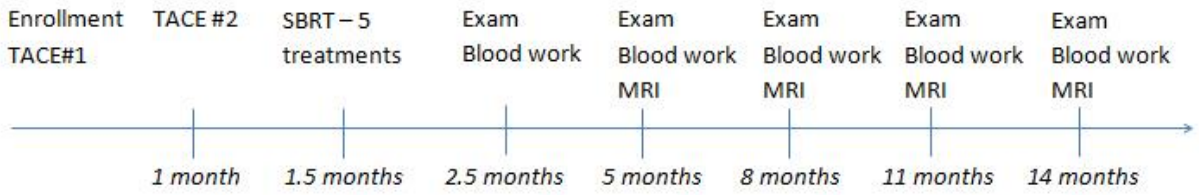
7.4 DWI will also be utilized at the discretion of the radiologist to assist tumor response and progression.

8.0 STATISTICAL ANALYSES

8.1 Sample Size

In March 2020, we increased our target enrollment goal from 30 patients to 40 patients. A more recent systematic review with data from more than 10,000 patients with HCC undergoing TACE found that the objective response rate (ORR) was 52.5%1 which is greater than the ORR of 35% assumed in our original sample size calculation. If we assume the proposed treatment regimen of TACE+SBRT to be ineffective in this patient population if the ORR is less than 52% and continue to consider the proposed treatment regimen effective if it can improve the ORR to at least 75%, then increasing the sample size to 40 patients yields 82% power with a type I error rate of 0.05 to detect an ORR >75% using a two-sided exact test for one proportion.

Study treatment will consist of three parts: a TACE, followed by another TACE after one month, followed in approximately 2 weeks by 5 radiation treatments given every other day. After the treatments, the subject will be followed with clinical exams, blood work, and MRIs approximately every three months up to one year. The full duration of a participant's time on study is 14 months. A timeline of the treatment is as follows:



The overall study timeline will be approximately 7 years to completion, resulting in publication. The study was initially IRB approved on 11/18/2014 with a target enrollment of 17 patients. The modification to increase the target enrollment to 30 patients was IRB approved on 11/8/2016 in the continuation submission. The 30th patient was enrolled on 11/19/2019. Primary analyses are being done as of this submission and we anticipate having a preliminary manuscript submitted by May 2020. With the additional enrollment goal, there will likely be subsequent analyses after the initial publication. The additional 10 patients will be enrolled in the next 12-18 months and will be used to strengthen the study results. With this additional enrollment and study timeline extension, we anticipate enrollment to close by mid-2021 and the study to close by early 2022 or become a phase II trial.

8.2 Data Analysis

Descriptive statistics (median, min-max, range, and percentages) will be provided for the pretreatment data such as demographics and comorbidities, and post-treatment complications. To assess the 1-year response rate in patients, one-sample binomial test will be conducted. For the secondary objectives,

descriptive analysis will be applied to determine the median survival times and Kaplan-Meier survival curves will be plotted for the endpoints:

-Time to progression

-Progression-free survival

-Overall survival

All analysis will be performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

9.0 REGULATORY CONSIDERATIONS

9.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The MSSM Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

9.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- MSSM research policies and procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

9.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

9.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

10.0 REFERENCES

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Karnofsky		ECOG	
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his	60		

Appendix A: Karnofsky and ECOG Performance Scales

needs			
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non-imminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

Appendix B: mRECIST Assessment

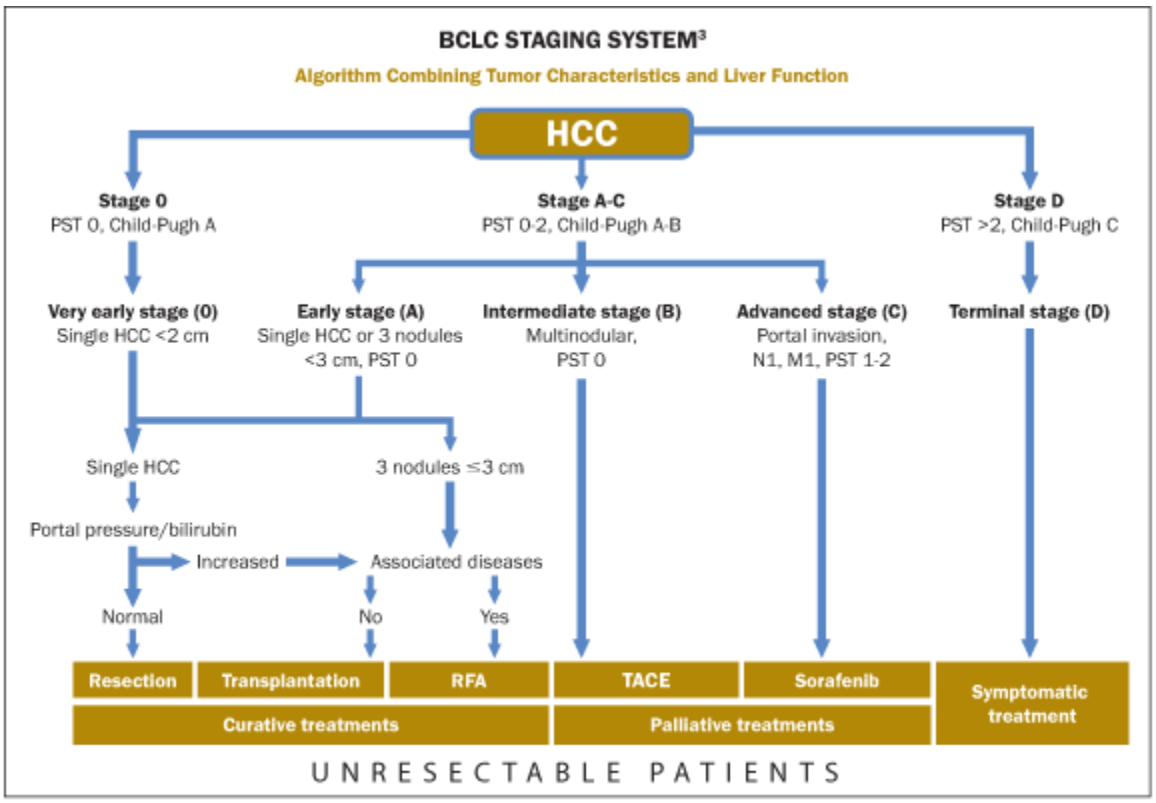
Table 2 Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline

RECIST	mRECIST for HCC
CR = Disappearance of all target lesions	CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease	SD = Any cases that do not qualify for either partial response or progressive disease
PD = An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Taken from Lencioni and Llovet. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. 2010;30:52-60.

Appendix C: Barcelona Clinic Liver Cancer Staging and Treatment Algorithm



PST=performance status test; N=lymph node; M=metastasis; RFA=radiofrequency ablation; TACE=transarterial chemoembolization.
Adapted with permission from John Wiley and Sons, Inc.[3]

Appendix D: Protocol Timeline and Required Interventions/ Studies

Time point	Activities
Enrollment	• Screening for eligibility • Consultation with Radiation Oncology • Consultation with Interventional Oncology • Consultation with Medical Oncology • History and physical including ECOG performance status • Baseline renal and liver function tests • Baseline chemistry and CBC • Baseline AFP • Baseline MRI with Eovist of the liver • Baseline CT of the chest
Study initiation – time "0"	• TACE #1
3 to 8 weeks post TACE #1	• Renal and liver function tests • TACE #2 • Simulation for SBRT
1 to 3 weeks post TACE #2	• Renal and liver function tests • SBRT
3 to 6 weeks post SBRT	• Follow up history and physical • Renal and liver function tests • AFP
3 to 4 months post SBRT	• Follow up history and physical • Renal and liver function tests • AFP • MRI with Eovist of the liver
6 to 7 months post SBRT	• Follow up history and physical • Renal and liver function tests • AFP • MRI with Eovist of the liver • CT of the chest
9 to 10 months post SBRT	• Follow up history and physical • Renal and liver function tests • AFP • MRI with Eovist of the liver
12 to 13 months post SBRT	• Follow up appointment

	• Renal and liver function tests • AFP • MRI with Eovist of the liver • CT of the chest
14 months and beyond post SBRT	• Follow up per standard of care