A Randomized Phase II Study of Individualized Stereotactic Body Radiation Therapy (SBRT) versus Trans-Arterial Chemoembolization (TACE) with DEBDOX Beads as a Bridge to Transplant in Hepatocellular Carcinoma.

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A. ABSTRACT

For subjects with HCC awaiting liver transplantation, local regional treatment of their disease has become the standard of care in an effort to decrease dropout rates and as a means of reducing tumor recurrence after transplantation. However, the best modality for subjects undergoing treatment as a bridge to transplantation is unclear. The most commonly utilized treatment in this setting is TACE. Retrospective single institution data suggests a survival benefit for subjects undergoing TACE as a bridge to liver transplantation, but there remains no prospective data showing improved outcomes. Most recently, other modalities have shown similar rates of local regional control for subjects with unresectable hepatocellular carcinoma. One such treatment modality is stereotactic body irradiation (SBRT). SBRT has been shown to afford good local control and acceptable safety when utilized in subjects with locally advanced hepatocellular carcinoma. We propose to conduct a pilot study to prospectively compare SBRT to TACE as a bridging strategy for subjects with hepatocellular carcinoma undergoing orthotopic liver transplantation. The preliminary data obtained from this trial will help inform the design and sample size calculations for subsequent, multi-site trials.

B. SPECIFIC AIMS

Hypothesis: SBRT will be associated with longer time intervals between initial treatment and the need for retreatment, compared to TACE, as a "bridge" to orthotopic liver transplantation in subjects with hepatocellular carcinoma.

1.0 Primary endpoint:

Time from first treatment to date of progression of previously treated lesions as determined by the date of the radiologic imaging

2.0 Secondary endpoints:

- 2.1 Toxicity
- 2.2 Number of further interventions
- 2.3 Pathologic response of treated lesion(s).
- 2.4 Radiologic response of treated lesion(s).
- 2.5 Quality of life.

C. BACKGROUND AND SIGNIFICANCE

Hepatocellular carcinoma (HCC) is the sixth most common cancer with an increasing incidence worldwide, and is the third leading cause of cancer-related death (1-5). Given that most people who develop hepatocellular carcinoma have concomitant cirrhosis, the best opportunity for cure for many remains liver transplantation. Because cadaveric liver transplants are in short supply in the United States, subjects who are eligible for liver transplantation frequently can wait a year or longer before a transplantation. Recently, local regional interventions have been utilized as a temporizing strategy to "bridge" individuals waiting for transplantation. The aims of bridging treatments include; decreasing the waiting list drop out rate for transplantation; reducing recurrent hepatocellular carcinoma after transplantation; and improving post transplant overall

survival (6). For subjects undergoing local regional therapy as a bridge to transplantation, (TACE) is the most commonly utilized treatment (7).

TACE is a therapy that combines the local delivery of chemotherapy with the induction of tumor ischemia through obstruction of the feeding vessels. Recently two randomized controlled trials (RCTs), conducted in Europe and Asia, showed an increased survival for subjects treated by embolization with an emulsion of a chemotherapy agent and iodized oil when compared to conservative treatment. Llovet et al. reported 1 and 2 year survival probabilities of 82 and 63%, respectively. Lo et al. found significant improvement in survival for Asian HCC subjects treated by chemoembolization (8,9). The Drug-Eluting Bead (DEB) is a novel agent for chemoembolization with a unique availability to load doxorubicin. In vitro data has shown a slow release of doxorubicin over time with a decreased systemic blood serum level and an increased tumor tissue level of the chemotherapeutic agent (10-13).

Several pilot studies have evaluated the safety and efficacy of DEBTACE. Poon et al showed good tumor response and limited toxicity in subjects with incurable HCC and Child-Pugh class A cirrhosis. No dose-limiting toxicity was observed for up to 150 mg doxorubicin. The pharmacokinetic study showed a low peak plasma doxorubicin concentration and no systemic toxicity was observed. The treatment-related complication rate was 11.4%. There was no treatment-related death. Among 30 subjects who completed 2 courses of TACE, the partial response rate and the complete response rates were 50 and 0%, respectively, by response evaluation criteria in solid tumors (RECIST) criteria at computerized tomography scan 1 month after the second TACE. By modified RECIST criteria, taking into account the extent of tumor necrosis, 19 (63.3%) subjects had a partial response and 2 (6.7%) had a complete response (14). Varela et al evaluated the safety, pharmacokinetics and efficacy of TACE using drug eluting beads (DEB). DEB-TACE was well tolerated with an acceptable safety profile. Two cases developed liver abscess, one leading to death. Response rate was 75% (66.6% on intention-to-treat). Doxorubicin Cmax and AUC were significantly lower in DEB-TACE subjects than in conventional TACE. After a median follow-up of 27.6 months, 1- and 2-year survival is 92.5 and 88.9%, respectively (15).

Malagari et al conducted an open-label, single-center, single-arm study including 62 cirrhotic subjects with documented single unresectable HCC. Mean tumor diameter was 5.6 cm (range, 3-9 cm) classified as Okuda stages 1 (n=53) and 2 (n=9). Subjects received repeat embolizations with doxorubicin-loaded beads every 3 months (maximum of three). The maximum doxorubicin dose was 150 mg per embolization, loaded in DC Beads of 100-300 or 300-500 μm. Post-treatment, an objective response according to the European Association for the Study of the Liver (EASL) criteria was observed in 59.6, 81.8, and 70.8% across three treatments. At 9 months a complete response was seen in 12.2% of subjects. Severe procedure-related complications were seen in 3.2% (cholecystitis, n=1; liver abscess, n=1). Post-embolization syndrome was observed in all subjects (16). Several studies have since shown that DEB-TACE not only is favorable compare to conventional TACE with regards to side effects but also has a better overall

outcome. Song demonstrated in the Asian population a better treatment response and delayed tumor progression with DEB-TACE (17).

In a multicenter study including 201 European subjects (PRECISION V), use of DC Beads resulted in a marked and statistically significant reduction in liver toxicity and drug-related adverse events compared with conventional TACE with lipiodol and doxorubicin (18,19). Two other trials reported higher rates of tumor response and longer time to progression for the loaded DC Bead as compared to a bland embolic microsphere with similar characteristics (20). As a result of these investigations, DEBDOX has been increasingly used as the treatment of choice is local regional therapy as preoperative treatment in subjects awaiting transplantation with HCC (21).

Despite its increased utilization, TACE as a bridge to liver transplantation remains of uncertain benefit. To date, multiple retrospective analyses suggest a benefit of pre-operative treatment for subjects with HCC awaiting liver transplantation, but no data from prospective randomized trials are available establishing TACE as an effective strategy to reduce the risk of recurrent hepatocellular carcinoma following transplantation or to improve survival (22). In the absence of clear benefit, there is no definitive standard of care and different preoperative treatment strategies are employed at different institutions for different individual subjects. Additionally, there has been no attempt to compare TACE, radiofrequency ablation, resection, or other strategies when utilized to bridge subjects to liver transplantation.

A new strategy for the treatment of both cancers metastatic to the liver and primary hepatocellular carcinoma is SBRT. Historically, external beam radiation lacked adequate precision and was considered too toxic for radiation therapy to be utilized to target lesions within the liver. When attempted, external beam radiation engendered radiation-induced liver disease (RILD) at sufficient rates as to render treatment untenable (23-26). However, over the past 2 decades, advances in computer and imaging technologies have improved conformal radiation such that it has become a feasible and safe technique for focal treatment to the liver with RILD rates of less than or equal to 5% in experienced hands. SBRT uses a small number of high dose fractions of highly conformal radiation therapy with high geometric precision and accuracy. Retrospective studies and two prospective studies suggest that SBRT to the liver can be used safely for the treatment of metastatic cancer with local control rates of 75% to 100% at 1 to 2 years (27). Recently published data from Bujold et.al., utilizing SBRT for locally advanced hepatocellular carcinoma, shows good effect and acceptable toxicity when compared to historical data regarding TACE or other equivalent strategies. The one year tumor control rate was 87% (28). While not a direct comparison, SBRT may be as equally efficacious.

SBRT offers some theoretical advantages compared to other local regional strategies for the treatment of primary hepatocellular carcinoma. First, a uniform dose of radiation is delivered to the entire tumor. There is no necessity of uniform blood flow which can be an issue with treatments directed through liver vasculature. Second, no direct manipulation of the primary tumor is necessary. Hence, any concerns for HCC spread through needle tract dissemination such as can occur in radiofrequency ablation or other

percutaneous interventions are absent. Third, given that no direct manipulation of hepatic vasculature is necessary, potential damage to vascular structures is of no concern. Fourth, it may be more cost effective then other treatment strategies as there is no requirement for hospitalization in comparison with subjects undergoing TACE.

In the current study, we propose to compare individualized stereotactic body radiation therapy (SBRT) to TACE as a bridge to liver transplantation in subjects with hepatocellular carcinoma.

D. RESEARCH DESIGN AND METHODS

1.0 Eligibility

1.1 Inclusion Criteria

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

- Biopsy proven hepatocellular carcinoma (HCC); or
- A discrete hepatic tumor(s) as defined by the Barcelona (29) criteria for cirrhotic subjects, ≥2cm with arterial hypervascularity and venous or delayed phase washout on CT or MRI.

1.1.2 Subjects are liver transplant candidates (actively awaiting organ transplant per transplant services in documentation), or, potential liver transplant candidates (at the discretion of the liver team and/or Principal Investigator) advised by liver transplant services as needing local treatment prior to liver transplant evaluation.

1.1.3 Subjects should be eligible per standard of care for either TACE or SBRT procedures.

1.1.4 Subjects must have a life expectancy of at least 12 weeks.

1.1.5 Subjects must be 18 years of age or older. Adult subjects of all ages, both sexes and all races will be included in this study.

1.1.6 Subjects must sign an informed consent form approved for this purpose by the Institutional Review Board (IRB) of the Lahey Hospital & Medical Center indicating that they are aware of the investigational aspects of the treatment and the potential risks.

1.2 Exclusion Criteria

1.2.1 Subjects in a "special category" designated the Public Health Service, Including subjects younger than 18, pregnant women, and prisoners.

1.2.2 Refractory ascites or ascites that requires paracentesis for management.

1.2.3 Subjects with a solitary lesion greater than 5.0 cm in size or more than 2 discrete lesions the largest greater than 3.0 cm in size.

1.2.4 Known allergy to intravenous iodinated contrast agents unresponsive to prednisone pre-treatment.

2.0 PRETREATMENT EVALUATION

Subjects will be consented for the study prior to starting treatment.

2.1 Subjects will undergo evaluation, including a complete history and physical

examination, baseline assessments of organ function and documentation of measurable disease (CT or MRI) parameters chest CT or Chest X-ray), weight, and Quality of Life Questionnaires

2.2 Laboratory evaluation per Study Calendar

2.3 Assessment of clinical measures of severity of liver disease: The Model for End-Stage Liver Disease (30) (MELD) and the CTP classification are models used for the clinical assessment of subjects with liver dysfunction (Appendix A). Subjects with CTP classification Grade A versus Grade B appear to have increased sensitivity to radiation. Additionally, in a study of subjects treated with SBRT for HCC or intrahepatic cholangiocarcinoma, 17% experienced progression from CTP Grade A to Grade B within 3 months after RT (31, 32), suggesting that CTP may be a useful assessment of worsening liver function. MELD may perform even better than CTP at evaluating liver function (33). We propose to record these clinical measures (MELD and CTP), and assess their potential contribution to individualize our assessment of liver injury that could be used to adjust liver dose.

3.0 RANDOMIZATION PLAN

Eligible subjects will be randomized after eligibility is confirmed by provider. No stratification will be used. Randomization will be performed using randomly selected block sizes of 4 and 8, provided by Tufts CTSI prior to the start of the study. Staff members involved in randomizing subjects will not be aware of the randomization sequence. Randomization will be documented indicating assignment.

4. 0 TREATMENT PLAN for SBRT

4.1 Subjects will be consented as per standard of care for SBRT prior to starting treatment.

4.2 Placement of Fiducial Markers

4.2.1 If deemed clinically necessary, fiducial markers may be placed percutaneously within close proximity of the target tumor. Placement of markers is considered standard of care. These will be used for target localization.

4.3 Stereotactic Body Radiotherapy

4.3.1 Three dimensional treatment planning will be used for all subjects, based on a simulation CT scan.

4.3.2 Energy: Treatment will be delivered with 6 - 16 MV photons

4.3.3 Localization, simulation, and immobilization: All subjects must undergo CT simulation prior to treatment, with IV and oral contrast if clinically appropriate. Subjects will be immobilized with a body cast. Liver motion will be minimized with the use of either breath-hold technology or respiratory-gaiting technology (respiratory phase-based 4D gated technique). Subjects that are unable to tolerate either breath-hold or respiratory-gaiting will be treated free-breathing using a 4D internal target volume (ITV). Free breathing may also be used if tumor motion is <5 mm. Prior to each SBRT treatment, the liver tumor will be imaged and

localized using either an on-board imaging orthogonal pair, using implanted fiducial markers, or a cone-beam CT scan.

4.3.4 Radiation target volumes:

The gross tumor volume (GTV) will be defined using the planning CT scan with the aid of a diagnostic imaging when clinically indicated (contrast-enhanced CT or MRI must be fused with the planning CT if IV contrast is not given at the time of the planning CT scan). GTV is defined as all parenchymal and vascular HCC (excluding bland thrombus). No prophylactic nodal RT is allowed. The CTV will be defined as the GTV for the majority of cases. However, CTV expansions to include regions at high risk for microscopic disease including non-tumor vascular thrombi, prior TACE sites, or adjacent RFA sites are permitted if these are clinically felt to be at risk. These CTV's may be treated to a microscopic dose (27.5 Gy) or as high as the prescription dose as determined by the physician's discretion. The PTV around the GTV/CTV will be determined based upon the immobilization device(s) used. If breath-hold or respiratory-gaiting technology is used (with daily localization), then the total PTV margin will be approximately 0.5 cm in all directions. If the subject is treated free breathing, then an ITV will be created based on tumor motion on the 4D planning CT with the addition of 0.5 cm in all directions for PTV margin.

4.4 SBRT Planning Guidelines - Radiation Doses:

4.4.1 PTV Target Doses

4.4.1.1 Doses will be prescribed to a peripheral covering isodose covering the PTV. Prescription isodose surface covers 95% of PTV with 90% of the prescription isodose line covering 99% of the PTV. The highest allowable doses to the target volumes that maintain normal tissue constraints should be used. A goal is that 100% of the CTV is encompassed by the prescription dose. Any dose > 110% must be within the PTV (except for adjacent tumors, in which the maximum dose outside the PTV must be < 115%).

4.4.1.2 Variations

4.4.1.2.1 Minor variation is defined as minimum PTV dose falling between 85% and 90% (of the required 100% isodose prescription).

4.4.1.2.2 Major variation (unacceptable) is defined as minimum PTV dose < 85% (for the required 100% isodose prescription).

4.4.1.3 Maximum doses are defined at 1 cc of volume. Maximum dose within the PTV <150% of the prescribed dose.

4.4.1.4 Minimum dose to the PTV is defined as minimum dose to 99.0% of the PTV.

4.4.2 Critical Normal Tissue Constraints

Mandatory dose constraints:
Spinal Cord+5mm: max dose to 0.5cc is 25Gy
Stomach: max dose to 0.5cc 30Gy
Duodenum: max dose to 0.5cc is 30Gy
Small Bowel: max dose to 0.5cc is 30Gy
Large Bowel: max dose to 0.5cc is 32Gy
Esophagus: max dose to 0.5cc is 32Gy
Kidneys bilateral mean dose <10Gy, or if there is only one kidney V10Gy<10% (or constraint for contralateral kidney, if mean dose is >10Gy to combined both kidneys)

Recommended but not mandatory dose constraints:
Liver minus GTV's: >700cc and V10Gy <70%
Stomach: goal <25Gy to 5cc
Duodenum: goal <25Gy to 5cc
Small Bowel: goal <25Gy to 5cc
Lung ALARA
Heart: 30cc <30Gy
Great vessel max 0.5cc <60Gy
Skin external max 0.5cc <32Gy
Chest wall max 0.5cc <50Gy
Gallbladder max 0.5cc <55Gy
Common bile duct max 0.5cc <50Gy

4.4.3 Radiation Schedule

4.4.3.1 SBRT will be delivered in five total fractions treated 2-3 weeks, with at a minimum of one day between any two treatments. The entire treatment must be delivered within 15 total days.

4.4.3.2 Three dimensional treatment planning will be used for all subjects. Volumes of tumor and normal liver will be determined, and DVH based treatment planning will be carried out, targeted to the tumor only.

4.4.3.3 Radiation Prescription Dose: 27.5 Gy-50Gy in 5 fractions based on normal tissue constraints. The goal is to use the highest allowable prescription dose to the primary target while respecting normal tissue constraints. The minimal planned prescription dose to the PTV is 27.5Gy (total dose of 50Gy, 45Gy, 40Gy, 35Gy, 30Gy, or 27.5Gy in 5 fractions is allowed). The dose to multiple PTV's within the same subject may vary. Conformality of the prescription dose and the 30Gy isodose lines are planning goals.

Dose prescription is based on the volume of normal tissues irradiated (correlated with mean liver dose) as well as proximity of stomach, duodenum, small and large bowel (GI luminal structures) to the target volumes. In the absence of adjacent GI luminal structures that may limit dose, the PTV dose prescription should be as high as possible based on mean liver dose (MLD is the mean dose to the liver minus GTV's) and the use of effective liver volume (Veff) with 6 potential dose levels. If there are discrepancies in the Veff and MLD for the prescription dose allocation, MLD has priority.

Veff must be calculated using the methods described in the references below. The equation below may be used.

$$Veff = \sum_i \Delta v_i \left(\frac{d_i}{d_{ref}} \right)$$

where Δv_i is a volume bin of a differential DVH, d_i is the dose to that volume, and d_{ref} is the reference dose. **The prescription dose is used as the reference dose in this study.**

1. Kutcher GJ BC, Brewster L et al. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. Int J Radiat Oncol, Biol, Phys 1991;21:137-146.
2. Dawson LA, Eccles C, Craig T. Individualized Image Guided Iso-NTCP based Liver Cancer SBRT. Acta Oncol. 45: 856 – 864, 2006.

Priority Constraint-Mean Liver Dose (Gy)	Optional Constraint-Liver Veff	Prescription Dose Planned Prescription Dose/If max MLD exceeded	
13.0	<25%	50Gy	Reduce to 45Gy
15.0	25-29%	45Gy	Reduce to 40Gy
15.0	30-34%	40Gy	Reduce to 35Gy
15.5	35-44%	35Gy	Reduce to 30Gy
16.0	45-54%	30Gy	Reduce to 27.5Gy
17.0	55-64%	27.5Gy	Ineligible

5.0 TREATMENT PLAN for DEB-TACE:

Subjects will consent to DEB-TACE as per standard of care

5.1Unilateral femoral approach

5.1.1 Selective catheterization of the hepatic artery will be performed. Vascular access is obtained via the common femoral artery and a guide-wire advanced under fluoroscopy. A 5/6 F sheath is then inserted over a guide-wire. The superior mesenteric artery is selected and an angiogram performed to identify any aberrant arterial anatomy and verify antegrade portal vein flow. The celiac axis is then selected and an angiogram completed. The catheter and guide-wire are used to select proper hepatic artery and a limited angiogram performed to identify branches of the hepatic artery. The right and

left hepatic is selected distal to the cystic artery if visualized, depending of the lesion to be treated using appropriate catheter.

5.2 Super-selective chemoembolization

5.2.1 Once vascular supply of the tumor is identified super-selective chemoembolization of the tumor supplying artery is performed with catheter positioned in second or third order side branches. If the anatomy is sufficiently visualized with fluoroscopy a cone-beam CT is performed to assess appropriate segmental contrast distribution covering the target.

5.2.2 DEB-TACE will be performed with two vials of drug eluting beads of the size 75-150 μm or 100-300 μm each loaded with 50 mg Doxorubin. Iodine contrast will be mixed according to manufacturer guidelines and used to guide the delivery.

5.2.3 Target area will be embolized until segmental arterial stasis is reached. In the presence of multifocal disease selective catheter positioning will be repeated for each lesion.

5.2.4 Final cone-beam CT will be performed to document distribution of the embolic material.

5.3 Following the TACE procedure all subjects will remain in hospital per standard of care for observation.

5.4 The second TACE will be administered approximately 4 weeks after the first TACE procedure and per physician discretion.

If subject is unable to complete second TACE, they will be followed on study schedule from the time point of the first TACE.

5.5 Progression of disease will be confirmed with imaging done greater than 8 weeks from last treatment date. Images collected per transplant protocol within the 8 weeks of treatment will be repeated, as per study schematic, to confirm response to treatment or progression.

5.6 **Crossover patients and additional treatment in the assigned treatment arm**: Group 2 TACE ("Arm B"), subjects with residual disease, local recurrence or new lesions on radiologic imaging at the three month follow up, or subsequent follow ups, may be considered candidates for additional treatments with TACE or crossover to SBRT at the discretion of the provider. These subjects will be followed in accordance with the SBRT study calendar from that time point onward.

For subjects treated with TACE, additional treatments (beyond the protocol directed two treatments) may be administered. SBRT subjects may be eligible, under provider discretion, to also have additional SBRT treatment done. Refer to section 12.2 for "off study guidelines" for these subjects.

6.0 QUALITY OF LIFE

6.1 The PIQ-6 Pain Impact Questionnaire measures how a subject's pain affects every day activities. The SF-36v2 Health Survey measures functional health and well-being from the subject's point of view. Each questionnaires takes approximately 5-10 minutes to complete.

6.2 Subjects assigned to SBRT arm will complete the questionnaires at baseline, during the first week of treatment, on the last day of treatment, 2 weeks after treatment, at the 3 month follow up, and every 3 months up to 24 months

6.3 Subjects assigned to the TACE arm will complete questionnaires at baseline, TACE treatment #1 (pre and post/prior to discharge), 2 weeks after treatment # 1, at TACE treatment # 2 (pre and post/prior to discharge), 2 weeks after that treatment, at the 3 month follow up and then every 3 months up to 24 months

7.0 STUDY CALENDARS

7.1 Study Calendar for SBRT (Arm A)

Active Treatment-SBRT	Pre-Rx Eval[1] (screening)	During first week of 5 SBRT fractions	On last day of treatment (after last treatment before discharge home)
History and Physical Exam	X		
Weight	X		
CBC	X		
AST, ALT, Alk Phos, Bilirubin	X		
Na, BUN/Creatinine	X		
INR	X		
AFP (for HCC)	X		
Toxicity Notation	X		X
MRI or CT of the abdomen within 4-6 weeks prior to enrollment	X		
Chest CT or Chest x-ray within 1 year prior to enrollment	X		
MELD-Na and CTP assessment	X		
QOL[2]	X	X (first week)	X
Simulation	X		
Treatment: SBRT		Over two weeks	

[1] Within 2 weeks prior to randomization unless otherwise specified
[2]Quality of Life questionnaires include PIQ-6 and SF-36v2 Health Survey

7.2 Study Calendar for TACE (Arm B)

		Active Treatment – TACE		
	Pre-Rx Eval[1] (screening)	Initial TACE	FOLLOW-UP VISIT (2 weeks)	SECOND TACE
History and Physical Exam,	X	X	X (per MD SOC only)	X
Weight	X	X	X	X
CBC	X	X[4]	X	X[4]
AST, ALT, Alk Phos, Bilirubin	X	X[4]	X	X[4]
Na, BUN/Creatinine	X	X[4]	X	X[4]
INR	X	X[4]	X	X[4]
AFP (for HCC)	X	X[4]		X[4]
Toxicity Notation	X	X	X	X
MRI or CT of the abdomen within 4-6 weeks prior to enrollment	X			
Chest CT or chest x-ray within 1 year prior to enrollment	X			
MELD-Na and CTP assessment	X			
QOL[2,3]	X	X[2]	X	X
Treatment: TACE		X		X

[1] Within 2 weeks prior to randomization unless otherwise specified

[2] Quality of Life questionnaires include PIQ-6, and SF-36v2 Health Survey

[3]If Quality of Life questionnaires were completed within 7 days of initial TACE visit, they do not have to be completed again. Questionnaires will be done pre TACE and post TACE, preferably prior to subject discharge.

[4]If required labs were performed within 3 days of either TACE procedure, they do not have to be repeated unless requested by treating physician

7.3 Study Calendar for FOLLOW-UP (Both Arm A and Arm B)

		Follow-up After Treatment Concluded		
	Post-Treatment Evaluation Period Approximately 2 Weeks[1,4]	3 months (+/- 4 weeks)[3]	6 months (+/- 4 weeks)[3]	Q 3 months to 24 months post-treatment (+/- 4 weeks)[3]
History and Physical Exam,	X per MD SOC	X	X	X
Weight	X	X	X	X
CBC	X	X	X	X
AST, ALT, Alk Phos, Bilirubin	X	X	X	X
Na, BUN/Creatinine	X	X	X	X
INR	X	X	X	X
AFP (for HCC)	X	X	X	X
Toxicity Notation	X	X	X	X
MRI or CT of the abdomen (mRECIST for HCC)		X	X	X
Chest CT or X-ray		X	X	X
MELD-Na and CTP assessment	X	X	X	X
QOL[2]	X	X	X	X

[1]Approximately 2 weeks after second TACE or 5th SBRT fraction (or after 3rd fraction if 4th & 5th fractions will be not given).
[2]Quality of Life questionnaires include PIQ-6 and SF-36v2 Health Survey
[3] Scans will be obtained in accordance to liver transplantation protocols and timeframes and may not occur within the allotted timeframe noted above. This will not be considered a protocol deviation.

8.0 TREATMENT MODIFICATIONS

8.1 Hepatic Toxicity: Subjects will be evaluated for symptoms and signs of RILD or other toxicity.

8.1.1 It is expected that a proportion of subjects will have transient elevation of liver enzymes during treatment. Repeat of all Grade 4 LFTs is required within 5-10 days following the first abnormal lab value to determine if the Grade 4 levels are transient (defined here as <10 days) or persistent. Subjects exhibiting hepatic toxicity ≥ 5-20x baseline LFT's will be evaluated with radiological imaging procedures to assess whether change in LFTs are due to tumor progression or treatment toxicity. Subjects whose progressive liver

function abnormalities while under treatment are deemed due to tumor progression will stop all protocol treatment and will be managed and followed per physician standard of care. Subjects with treatment induced hepatic toxicity of greater than 20x baseline elevation will not receive further protocol treatment unless and until liver function tests have returned to less than 5x subjects baseline value. Subjects will be evaluated for symptoms and signs of RILD or other toxicity.

8.2 Other Toxicity: The occurrence of **treatment-related** Grade 4 adverse events in any organ system will prompt discontinuance of protocol therapy while appropriate physical examination, laboratory, and imaging assessments are undertaken. Protocol treatment will not be resumed in the absence of recovery from adverse events of this magnitude. Once recovery to ≤grade 2 has occurred, treatment may continue at the discretion of the treating physician.

8.3 Exceptions that will not be reported to IRB or require discontinuation of therapy: Grade 3 or 4 asymptomatic hypoalbuminemia or decreased lymphocytes. Transient (< 48 hours) asymptomatic grade 3 fasting hyperglycemia in type II diabetics.

9.0 SBRT DOSE ADJUSTMENT

There will be no dose adjustments for SBRT treatment.

10.0 TOXICITY CONSIDERATIONS

10.1 The criteria used for the grading of toxicities is the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.3

Toxicity of all grades ≥2 measuring only the following conditions will be collected in the database: Gastritis, hepatic pain, vomiting and fatigue.

10.2 The following toxicities will require subjects to be removed from protocol treatment and followed per physician standard of care:

10.2.1 Grade ≥4 hepatic toxicity for changes in AST, ALT, alkaline phosphatase, or platelet counts attributed to treatment and not attributable to disease progression. Transient grade 4 (less than 10 days) hepatic toxicities are acceptable.

10.2.2 Grade ≥4 Upper GI bleeding (**attributed to treatment**, and not attributable to disease progression)

10.2.3 Any complications or death due to disease progression

10.3 Items that will not be considered unacceptable toxicities:

10.3.1 Any complications (i.e. infection) resulting from a PTC tube

10.3.2 Grade 4 elevation in bilirubin during the course of therapy

10.4 **Expected Toxicities**

10.4.1 Radiation Therapy (SBRT):

- Nausea or vomiting.
- Gastric or duodenal ulceration

- Skin irritation, fatigue, and decreased blood counts

10.5 **Liver Toxicity**

10.5.1 Radiation-induced liver disease (RILD) (veno-occlusive disease), including the possibility of damage severe enough to result in liver failure which could lead to death. In some subjects it is not possible to avoid kidney irradiation which could produce a decrease in renal function RILD is a clinical syndrome of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase (ALP) relative to other transaminases that may occur 2 weeks to 4 months following radiation to the liver.

- ALP must be at least 2-fold increased above the baseline ALP.
- If ascites develops at any time within 3 months following treatment, an abdominal CT and paracentesis with pathological evaluation of the ascitic fluid is recommended. If the ascitic fluid does not reveal malignancy and there is no evidence of disease progression in the liver or abdomen, it will be assumed that RILD has occurred
- If disease progression in the liver or abdomen has occurred, no diagnosis of RILD can be made.
- In subjects who have elevation of liver enzymes near Grade 4 levels and/or in subjects with early nonspecific signs or symptoms of liver injury, close follow-up is recommended with repeat blood work. If no tumor progression is documented in these subjects, liver injury will be presumed to be treatment related.

10.6 **GI Toxicity**

10.6.1 Subjects will be followed for GI toxicity at each follow up visit.

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11.0 RESPONSE CRITERIA

11.1 Local intrahepatic tumor: The status of each treated tumor/target lesion will be assessed by MRI or CT scan and classified as progression if there is tumor growth (excluding growth due to biloma or abscess formation), residual or new enhancement **of the ablated tumor** (excluding benign peri-ablational enhancement), or contiguous viable tumor. Each treated intrahepatic lesion will be evaluated utilizing mRECIST Criteria for HCC. (Appendix B)

11.2 Disease-Specific Mortality: For this study, disease-specific mortality will be defined as death due to the subject's disease, or death due to treatment for the subject's disease. Time zero will be defined the day of the last treatment fraction.

12.0 CRITERIA FOR DISCONTINUATION OF PROTOCOL TREATMENT

12.1 Off-Treatment Conditions

12.1.1 Unacceptable toxicity as defined in section 10.

12.1.2 Therapy may be discontinued prematurely at any time by subject request without prejudice to subsequent care.

12.1.3 Subjects may be removed from the treatment at any time per investigator discretion.

12.2 Off Study Conditions

12.2.1 Subjects will be removed if they are unable to receive SBRT treatments.

12.2.2 Subjects may be removed from study at any time by subject request.

12.2.3 Subjects who enroll in subsequent radiation therapeutic trials will be followed for survival only and for progression in the treated lesion(s). To further clarify, subjects who are followed for survival only will no longer receive protocol-directed treatment or testing.

12.2.4 Subjects who go on to receive additional non-radiation therapy(i.e. treatment that is not TACE or SBRT related) will be followed for survival only. To further clarify, subjects who are followed for survival only will no longer receive protocol-directed treatment or testing. They will also be followed for progression within the treated lesion(s).

12.2.5 Subjects who undergo a liver transplant will be considered off study and will not be followed from that timepoint

12.2.6 Subjects with progression of disease as per mRECIST for HCC will be followed for survival only. To further clarify, subjects who are followed for survival only will no longer receive protocol-directed treatment or testing. They will also be followed for progression within the treated lesion(s).

12.2.7 Subjects permenantly removed from Liver Transplant list.

12.3 Adverse Event Reporting Guidelines

12.3.1 Adverse Event definitions

- An Adverse Event is any untoward medical event that occurs in a subject who has received an investigational treatment, and does not necessarily have a causal relationship with the investigational treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational treatment, whether or not related to the treatment.
- Pre-existing diseases or symptoms or abnormal laboratory values present upon recruitment are not considered an AE even when observed during the further course of the study. However, every worsening of a pre-existing condition is considered as an adverse event.

- All AEs ≥ grade 3 will be collected and attributed either as related to protocol treatment or not related to protocol treatment. Additional AE's collected are:
  Any grade ≥2 gastritis, hepatic pain, vomiting, and fatigue.
- The NCI Common Terminology Criteria for Adverse Events 4.03 (CTCAE) will be utilized to grade AE's for AE reporting.
- During the course of an adverse event, severity and/or causality and/or seriousness may change. For CRF documentation this adverse event represents one entity from onset to resolution and the worst of the observed categories shall be attributed.
- When event reoccurs after it disappeared, it should be handled as a new AE. However, AEs that occur intermittently can be recorded as one AE.
- A serious adverse event (SAE) shall be defined as an adverse advent which fulfills one or more of the following criteria:
  - Results in death.
  - Is immediately life-threatening.
  - Requires in-subject hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.
- **Any events or hospitalizations that are unequivocally due to progression of disease should not be reported as an SAE.**
- The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigators and will be labeled as either related to treatment, or not related to treatment.

12.3.2 **Only adverse events deemed serious <u>AND</u> related will be reported to the IRB and the PI within 10 days of awareness of the event. All other events will be noted in the subjects' medical record.**

12.3.3 Adverse events will no longer be reported if the subject has another liver-directed therapy or starts chemotherapy.

12.3.4 The following types of hospitalizations do not constitute SAEs:

- Hospitalization or Emergency room visits secondary to expected cancer morbidity
- Admission for palliative care or pain management
- Planned hospitalizations for surgical procedures, either

related or unrelated to the subject's cancer.

12.4 Data and Safety Monitoring

This trial will be monitored in accordance with the Lahey Hospital and Medical Center Data and Safety Monitoring Plan. The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, other health care professionals not affiliated with this study, the study data manager or designee, , will meet annualy. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), 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 DSMC. on an annual basis for independent Review.

13.0 STATISTICAL CONSIDERATIONS

This is a randomized, non-blinded, pilot Phase II trial to characterize the safety and efficacy of individualized SRBT, compared to TACE, for subjects who have primary HCC. **The trial endpoints are time to progression, number of retreatments, radiologic response, pathologic response, toxicity, and quality-of-life**.. The planned accrual is sixty (60) subjects at Lahey Hospital & Medical Center over two years, an estimate which is based on the expected number of eligible subjects seen at Lahey. While this sample size will not provide adequate statistical power to test for significant differences in treatment groups, it will provide effect estimates that will be used to inform the design of future, larger trials.

13.1 Analysis Plan

The primary analytic approach will use intent-to-treat comparisons. Reasons for any loss to follow-up will be recorded and every effort will be made to learn the outcomes for these subjects. **For the secondary objectives, subjects will be divided into those who receive transplant by one year, and those who do not (estimated at 50%),** and stratified analyses will be performed. If differential loss to follow-up occurs between groups, analyses may include per-protocol and as-treated groups. All estimates (e.g., proportions and means) will include 95% confidence intervals. Descriptive statistics of the sample will be performed to assess the balance of subject characteristics between groups, specifically age, gender, and Meld-Na score. The reasons why any enrolled subjects become ineligible for further treatment or for transplant will be evaluated.

13.1.1 Primary Objective: Subjects undergoing treatment will be imaged by MRI or triphasic CT every three months following therapy using mRECIST for HCC criteria. Any target lesions meeting radiologic criteria for residual tumor or tumor progression will undergo repeat treatment with either the modality first utilized unless such treatment is not possible, or physician discretion. The time to progression will be measured and compared between

treatment arms using cumulative incidence curves to account for the competing risks of transplant, death, and stop of treatment before re-treatment.

13.1.2 Secondary Objectives

- Toxicities will be summarized with frequency tables and will be tabulated by CTCAE grade and relatedness to treatment (as assessed by the investigator or PI). The proportion of subjects who receive any therapy that experience unacceptable toxicity will be estimated and compared.
- The rate of retreatments before transplantation will be compared between treatment groups, measured as the number of retreatments per subject-year of follow-up.
- Among subjects who undergo transplantation (estimated to be 50% of total sample, or n=30), Pathologic Response will be measured in the ex-plant liver.
- Radiologic Response to treatment of the target lesion utilizing modified RECIST (mRECIST) for HCC at three months following completion of treatment will be assessed as a dichotomous variable in subjects who complete therapy. The proportion of subjects achieving lesion control in each group at two months will be estimated.
- Quality of Life will be determined by PIQ-6, and the SF-36v2 Health Survey (35) questionnaires at baseline, during treatment and follow-up. Analysis will be completed using the QM Certified Scoring (Insight) program obtained from qualitymetric.com. Mean quality-of-life and PIQ scores will be compared between groups.

E. REFERENCES

1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153–156.
3. Okuda K. Hepatocellular carcinoma--history, current status and perspectives. Dig Liver Dis 2002; 34:613-616.
4. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430.
5. Okuda K. Natural history of hepatocellular carcinoma including fibrolamellar and hepato-cholangiocarcinoma variants. J Gastroenterol Hepatol 2002; 17:401-405.
6. Pompili M, Francica G, Ponziani F *et. Al. Bridging and downstaging treatments for hepatocellular carcinoma in subjects on the waiting list for liver transplantation*. World Journal of Gastroenterology 2013;19(43):7515-30.

7. Luna W, Sze D, Ahmed A. Transarterial Chemoinfusion for Hepatocellular Carcinoma as Downstaging Therapy and a Bridge toward Liver Transplatation. American Journal of Transplantation 2009 9:1158-68.
8. Llovet JM, Real MI, Montana X, et al. Arterial embolization or chemoembolisation versus symptomatic treatment in subjects with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359:1734-1739.
9. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35:1164-1171.
10. Johnson P, Kalayci C, Dobbs N, et al. Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocellular carcinoma: effect of coadministration of lipiodol. J hepatol 1991 13:120-7.
11. Lewis AL, Gonzalez MV, Lloyd AW, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol 2006; 17:335-342. 13. Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res 2006; 12:2563-2567.
12. Lewis AL, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006; 17:1335-1343.
13. Brown DB, Cardella JF, Sacks D, et al. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 2006; 17:225-232.
14. Poon RT et al. A phase I/II trial of chemoembolization for HCC using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol. 2007;5:1100-8
15. Varela M et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474-81.
16. Malagari K et al. Transarterial chemoembolization of unresectable HCC with drug eluting beads: results of an open-label study of 62 subjects. Cardiovasc Intervent Radiol.2008;31:269-80.
17. Song MJ, Chun HJ, Seon D et al Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. Journal of Hepatology 2012 vol. 57; 1244–1250
18. Lammer J, Malagari K, Vogl T et al (2010) Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 33:41–52
19. Vogl TJ, Lammer J, Lencioni R et al (2011) Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with Precision TACE with drug-eluting beads: results from the PRECISION V randomized trial. AJR Am J Roentgenol 197:W562–W570
20. Malagari K, Pomoni M, Kelekis A et al Prospective randomized comparison of chemoembolization with doxorubicineluting beads and bland embolization with Beadblock for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010:33:541–551

21. Nicolini A, Martinetti L, Crespi S, Maggioni M, Sangiovanni A Transarterial chemoembolization with epirubicin-eluting beads versus transarterial embolization before liver transplantation for hepatocellular carcinoma. J Vasc Interv Radiol 2010 21: 327–332.
22. Porrett P, Peterman H, Rosen M, *et. Al.* Lack of Benefit of Pretansplant Locoregional Hepatic Therapy for Hepatocellular Cancer in the Current MELD. Liver Transplantation 12:665-73.
23. Emami B, Lyman J, Brown A*, et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109-122.
24. Lawrence TS, Robertson JM, Anscher MS*, et al.* Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys* 1995;31:1237-1248.
25. Ingold JA, Reed GB, Kaplan HS*, et al.* Radiation Hepatitis. *Am J Roentgenol Radium Ther Nucl Med* 1965;93:200-208.
26. Russell AH, Clyde C, Wasserman TH*, et al.* Accelerated hyperfractionated hepatic irradiation in the management of subjects with liver metastases: results of the RTOG dose escalating protocol. *Int J Radiat Oncol Biol Phys* 1993;27:117-123.
27. Schacter L, Crum E, Spitzer T*, et al.* Fatal radiation hepatitis: a case report and review of the literature. *Gynecol Oncol* 1986;24:373-380.
28. Bujold A, Massey C, Kim J, *et. Al.* Sequential Phase I and II Trials of Stereotactic Body Radiotherapy for Locally Advanced Hepatocellular Carcinoma. Journal of Clinical Oncology 2013 31(13):1631-39.
29. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020-1022
30. Kamath PS, Wiesner RH, Malinchoc M*, et al.* A model to predict survival in subjects with endstage liver disease. *Hepatology* 2001;33:464-470.
31. Tse RV, Hawkins M, Lockwood G*, et al.* Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2008;26:657-664.
32. Mendez Romero A, Wunderink W, Hussain SM*, et al.* Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. *Acta Oncol* 2006;45:831-837.
33. Limquiaco JL, Wong GL, Wong VW*, et al.* Evaluation of model for end stage liver disease (MELD)-based systems as prognostic index for hepatocellular carcinoma. *J Gastroenterol Hepatol* 2009;24:63-69.
34. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med* 1995;14:357-379.
35. Ware JE, Kosinski M, Dewey J. *How to score version 2 of the SF36 health survey.* Lincoln, RI: QualityMetric Incorporated, 2000.

F. APPENDICES

Appendix A
Model for End-Stage Liver Disease (MELD-Na)

The MELD-Na score includes serum sodium level. Sodium has been added to the formulation *(as of January 2016)* and is calculated using a relatively simple formula that relies on four readily available objective variables:
Serum creatinine (Scr; mg/dL)
Total bilirubin (Tbil; mg/dL)
INR (international normalized ratio)
Serum sodium (mmol/L)

MELD-Na Score, UNOS modified

The MELD score will be calculated to incorporate serum sodium for candidates with a MELD score greater than 11. These candidates' MELD scores will be calculated according to the initial MELD formula, and the MELD-Na score will be derived using the initial MELD score and the serum sodium value as follows:

> **= $MELD_{(i)}$ + 1.32 x (137-Na) – [0.033 x $MELD_{(i)}$*(137-Na)]**
> **Sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137.**

This does not apply to candidates with a MELD score less than 12.

The following rules must be observed when using this formula:

- 1 is the minimum acceptable value for any of the four variables.
- The maximum acceptable value for serum creatinine is 4, to avoid higher MELD-Na scores in subjects with concomitant intrinsic renal disease
- The maximum value for the MELD-Na score is 40.

Child-Turcotte-Pugh (CTP)

	Points		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-inducted)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	> 6 >2.3

CTP score is obtained by adding the score for each of the 5 parameters.

CTP class:
A = 5-6 points
B = 7-9 points
C = 10-15 points

Appendix B

mRECIST for HCC[A]

Response	Longest overall tumor diameter[B]	Longest viable tumor diameter[C]
Complete Response (CR)	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial Response (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	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
Stable Disease (SD)	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
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	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

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A. Target tumor response measurements on arterial-phase computed tomography (CT) scans.
B. Measurement of longest overall tumor diameter according to conventional RECIST
C. Measurement of longest viable tumor diameter according to mRECIST for HCC.