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

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NCT #: NCT03960008

Protocol #: LHMC 20193013

Protocol Signature Page

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Protocol Synopsis

Title	A Randomized Multicenter Phase III Study of Individualized Stereotactic Body Radiation Therapy (SBRT) versus Trans-Arterial Chemoembolization (TACE) as a Bridge to Transplant in Hepatocellular Carcinoma.
Objective	**Primary:** • To compare the duration of disease control in treated lesions when utilizing SBRT versus TACE as a bridging strategy for patients with HCC eligible for liver transplantation. **Secondary:** • To determine health related quality of life (HRQL) for both treatment arms • To compare toxicity • To compare number of further interventions • To compare pathologic response of treated lesion(s). • To compare radiologic response of treated lesion(s). • To assess 60 day Post-transplant morbidity and mortality
Study Design	A multicenter prospective randomized phase III trial
Sample Size	196 subjects will be enrolled

Eligibility	**Inclusion Criteria**
	1. Subjects with HCC are eligible for this trial. HCC is defined as having at least one of the following:
	  • Biopsy proven HCC or:
	  • A discrete hepatic tumor(s) as defined by the Barcelona (29) criteria for cirrhotic subjects, ≥2cm with arterial hyper vascularity and venous or delayed phase washout on CT or MRI.
	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.
	3. Subjects must be within UCSF criteria (one solitary tumor smaller than 6.5 cm, or patients having 3 or fewer nodules, with the largest lesion being smaller than 4.5 cm or having a total tumor diameter less than 8.5 cm without vascular invasion) and eligible for potential liver transplant.
	4. Subjects must be eligible for TACE and SBRT procedures.
	5. Subjects must have a life expectancy of at least 12 weeks.
	6. 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.
	7. Subjects must sign an informed consent form approved for this purpose by the Institutional Review Board (IRB) of record.
	8. Subjects must have a Child-Turcotte-Pugh (CTP) score ≤8.
	9. Patients must have adequate organ function within 2 weeks of enrollment.

	• Bone marrow: Platelets ≥30,000/mm3 • Renal: BUN ≤40 mg/dl; creatinine ≤2.0 mg/dl • Hepatic: INR ≤ 1.5 or correctable by Vitamin K, unless anti-coagulated for another medical reason • Bilirubin < 3.0 mg/dl (in the absence of obstruction or pre-existing disease of the biliary tract, e.g. primary sclerosing cholangitis). 10. Patients' uninvolved liver volume will be estimated and must be > 700ml. 11. Patients must have a Zubrod performance status of ≤2. 12. Patients who are sexually active must agree to the use of contraception throughout the duration of the study. **Exclusion Criteria** 1. Subjects in a "special category" as designated by FDA and the Canadian Institutes of Health or Canadian Panel on Research Ethics , Including subjects younger than 18, pregnant women, and prisoners. 2. Refractory ascites that requires paracentesis for management. 3. Known allergy to intravenous iodinated contrast agents unresponsive to prednisone pre-treatment. 4. History of prior radiation to the liver. 5. Evidence of metastatic disease. 6. Presence of a Trans-jugular intra-hepatic porto-systemic shunt (TIPS). 7. Untreated varices at high risk of bleeding 8. Bile duct occlusion or a prior diagnosis of an incompetent papilla 9. Acute infection. 10. Uncorrectable bleeding disorder. 11. leukopenia, ANC <1000/ul 12. hepatic encephalopathy 13. portal vein thrombosis
Intervention	Stereotactic Body Radiation Therapy (SBRT) versus Trans-Arterial Chemoembolization (TACE)
Assessments	Physician Exam, Abdominal MRI or CT, Chest CT or X-ray, MELD-Na, ALBI score, CTP score, Labs, HRQL

Table of Contents

A. ABSTRACT

For patients with hepatocellular carcinoma (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 (1). Retrospective single institution data suggests a survival benefit for patients undergoing bridging therapy prior to liver transplantation and a recent meta-analysis noted a non-significant trend toward reduced waitlist dropout and improved post-transplant outcomes, while acknowledging the absence of prospective randomized data (2). Additionally, there is no standard of care regarding appropriate bridging strategies, although TACE is the most commonly performed bridging procedure in The United States (3). Recently, newer bridging modalities other than TACE have shown similar rates of local regional control for patients with unresectable HCC. One such treatment modality is SBRT. SBRT has been shown to afford good local control and acceptable safety when utilized in patients with HCC. We propose to conduct a multi-center prospective randomized Phase III trial to compare SBRT to TACE as a bridging strategy for patients with HCC undergoing liver transplantation.

B. SPECIFIC AIMS

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

1.0 Primary endpoint:

Time from randomization to date of progression or residual disease of previously treated lesions as determined by the date of the radiologic imaging.

2.0 Secondary endpoints:

- Health related quality of life (HRQL) for both treatment arms
- Toxicity
- Number of further interventions
- Pathologic response of treated lesion(s)
- Radiologic response of treated lesion(s)
- 60 day Post-transplant morbidity and mortality

C. BACKGROUND AND SIGNIFICANCE

HCC is the sixth most common cancer with an increasing incidence worldwide, and is the third leading cause of cancer-related death (4-5). Given that people who develop HCC typically have concomitant cirrhosis, the best opportunity for cure for most patients is liver transplantation. Because organ donors are scarce, patients who are eligible for liver transplantation may wait many months before receiving a liver. Recently, local regional interventions have been utilized as a temporizing strategy to "bridge" individuals with HCC who are awaiting transplantation. The aims of bridging treatments include: decreasing the waiting list dropout rate for transplantation due to HCC progression beyond acceptable criteria; reducing recurrent HCC after transplantation; and improving post-transplant overall survival (6). For patients 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. 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-year and 2-year survival of 82% and 63%, respectively. Lo et al. found significant improvement in survival for Asian HCC subjects treated by chemoembolization (8,9). Drug-Eluting Beads (DEB) such as Quadraspheres® (of which there are several on the market) are an agent for chemoembolization with the ability to load doxorubicin. In vitro data has shown a slow release of doxorubicin over time with a decreased systemic blood serum levels and increased tumor tissue levels of the chemotherapeutic agent (10-13).

Several pilot studies have evaluated the safety and efficacy of DEB-TACE. 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 DEB-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 DEB-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-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 of DEB-TACE in 62 cirrhotic subjects with documented solitary unresectable HCCs. 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 treatments). 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 compared to conventional TACE regarding side effects but may elicit 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 clinically and statistically significant reduction in liver toxicity and drug-related adverse events compared with conventional TACE with lipiodoland 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, 21). As a result of these investigations, DEB-TACE has been increasingly used as therapy for bridging treatment in subjects awaiting transplantation with HCC, although embolic beads without chemotherapy are also widely used (22).

Despite its increased utilization, DEB-TACE (or any strategy) 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 DEB-TACE as an effective strategy to reduce the risk of recurrent HCC following transplantation or to improve survival (22). Furthermore, there is conflicting data regarding whether TACE should be performed with chemotherapy or as a "bland" particle and whether one or more procedures ought to be performed. Additionally, there has been no attempt to compare TACE, radiofrequency ablation (RFA), resection, or other treatment strategies utilized to bridge subjects to liver transplantation. In the absence of a standardized approach, there is no definitive standard-of-care either *within a given treatment strategy or between different treatment approaches* and hence, different preoperative treatments using varied protocols are employed by different institutions for different individual subjects awaiting transplant.

A newer strategy for the treatment of HCC is SBRT. Historically, external beam radiation lacked adequate precision and was considered too toxic to be utilized to ablate tumors within the liver. With large volume irradiation, the risk of radiation-induced liver disease (RILD) is prohibitive (23-27). However, over the past two 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 10% in early stage patients. SBRT uses a small number of high dose fractions of highly conformal radiation therapy, delivered with high geometric precision and accuracy. SBRT offers some theoretical advantages compared to other local regional strategies for the treatment of HCC. 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 such as TACE 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 than other treatment strategies as there is no requirement for hospitalization in comparison with subjects undergoing TACE.

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 (28). Data from Bujold et.al., utilizing SBRT for locally HCC, showed good effect and acceptable toxicity when compared to historical data regarding TACE or other equivalent strategies. The one year tumor control rate was 87% (29). A retrospective comparison by Sapir et.al. compared HCC patients with similar disease burdens treated with either SBRT or TACE and found SBRT to be safe for 1 to 2 tumors while providing better local control (30). Furthermore, a recent comparison of SBRT to TACE or RFA by Sapisochin et.al. found that SBRT can be safely utilized as a bridge to transplant in HCC patients as an alternative to conventional bridging strategies (31).

Given these potential advantages, in September 2014 Lahey Hospital and Medical Center initiated a randomized feasibility trial prospectively comparing SBRT to DEB-TACE in the treatment of HCC as a bridge to liver transplantation. With an expected enrollment of 60 patients, we have presently enrolled 45 patients with 31 eligible for evaluation. These data were presented as an Oral Abstract at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium in January 2017. While preliminary, our data indicate that SBRT appears at least as effective as DEB-TACE at controlling tumors prior to transplant, may engender less toxicity, may better preserve quality of life, and may cost less (32-33).

In the current study, we propose to compare individualized SBRT to TACE as a bridge to liver transplantation in patients with HCC.

D. RESEARCH DESIGN AND METHODS

1.0 Eligibility

1.1 Inclusion Criteria

- Subjects with HCC are eligible for this trial. HCC is defined as having at least one of the following:
  - Biopsy proven 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.
- 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.
- Subjects must be within UCSF criteria (one solitary tumor smaller than 6.5 cm, or patients having 3 or fewer nodules, with the largest lesion being smaller than 4.5 cm or having a total tumor diameter less than 8.5 cm without vascular invasion) and eligible for potential liver transplant.
- Subjects must be eligible for standard TACE and SBRT procedures.
- Subjects must have a life expectancy of at least 12 weeks.
- 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.
- Subjects must sign an informed consent form approved for this purpose by the Institutional Review Board (IRB) of record.
- Subjects must have a Child-Turcotte-Pugh (CTP) score ≤8.
- Patients must have adequate organ function within 2 weeks of enrollment.
  - Bone marrow: Platelets ≥30,000/mm3
  - Renal: BUN ≤40 mg/dl; creatinine ≤2.0 mg/dl
  - Hepatic: INR ≤ 1.5 or correctable by Vitamin K, unless anti-coagulated for another medical reason
  - Bilirubin < 3.0 mg/dl (in the absence of obstruction or pre-existing disease of the biliary tract, e.g. primary sclerosing cholangitis).
- Patients' uninvolved liver volume will be estimated and must be > 700ml.
- Patients must have a Zubrod performance status of ≤2.
- Patients who are sexually active must agree to the use of contraception throughout the duration of the study.

1.2 Exclusion Criteria

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

- Refractory ascites that requires paracentesis for management.
- Known allergy to intravenous iodinated contrast agents unresponsive to prednisone pre-treatment.
- History of prior radiation to the liver.
- Evidence of metastatic disease.
- Presence of a Trans-jugular intra-hepatic porto-systemic shunt (TIPS).
- Untreated varices at high risk of bleeding
- Bile duct occlusion or a prior diagnosis of an incompetent papilla
- Acute infection.
- Uncorrectable bleeding disorder.
- leukopenia, ANC <1000/ul
- hepatic encephalopathy
- portal vein thrombosis

2.0 Pretreatment Evaluation

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

2.1 Subjects will undergo a comprehensive liver evaluation per the treating physician's discretion, including a complete history of viral status (Hep. C, Hep. B or No) and physical examination, baseline assessments of organ function and documentation of measurable disease (contrast-enhanced CT or MRI) parameters chest CT or Chest X-ray), weight, and health related Quality of Life measures.

2.2 Laboratory evaluation.

2.3 Assessment of clinical measures of severity of liver disease: The Model for End-Stage Liver Disease (30) (MELD-Na) 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 radiation therapy (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-Na and CTP, and Albumin-Bilirubin (ALBI)) score, and assess their potential contribution to individualize our assessment of liver injury that could be used to adjust liver dose.

2.4 Assessment can be performed by any medical provider in the liver transplant team including hepatology/gastroenterology, medical oncology, radiation oncology, interventional radiology and transplant surgery or as medically necessary per standard treatment

3.0 Randomization Plan

All consented subjects will receive a Study Identification Number (SID) in the EDC system. The SID number will be a 4 digit number. The first two digits are site number. Site number will be assigned by the Coordinating Center at Lahey and it will start with 01 with 1 increment for each site (that is 01, 02, 03, etc.). The last two digits are the patient screening order starting from 01. Eligible subjects will be randomized after eligibility is confirmed by the provider, as soon as practical to the baseline tumor scan. Randomization will be performed using randomly selected block sizes of 2, 4 and 6 and stratified by the

following factors identified at screening: CTP score (either A or B) and disease etiology (with or without Hepatitis C). The randomization ID will be a 5 digit number in the form of ABCDE where, AB denote the site number, C indexes the four strata used for the randomization and DE index the order of screening at that site. C will be one of the numbers from 1 to 4. DE is the patient screening order starting from 01.Each study site will receive randomization list from the Coordinating Center at Lahey and randomize the eligible subjects individually. Site staff involved in randomizing subjects will not be aware of the randomization sequence before randomization. Randomization will be documented on both source document and EDC indicating assignment. If a patient is lost from the study because they are unable to receive their randomized treatment then an additional patient will be enrolled.(i.e., unable to meet SBRT dose constraints or achieve an acceptable respiratory motion strategy for SBRT). Individual randomization codes will be not be reused.

4.0 Treatment Plan for SBRT

4.1 Once randomized, subjects will be consented per the site's standard for SBRT or TACE prior to starting treatment.

4.2 Placement of Fiducial Markers

Fiducial markers are highly encouraged but not mandatory. This will be decided by the treating radiation oncologist based on clinical information and treatment delivery capabilities. If used, fiducials will be placed percutaneously within the liver in close proximity of the target tumor. At least 3 fiducial markers are recommended when used.

4.3 Stereotactic Body Radiotherapy

4.3.1 Conformal treatment planning will be used for all subjects, based on a simulation CT scan. Either 3D Conformal Radiation Therapy, Intensity Modulated Radiation Therapy, or Arc Rotational Therapy may be used as appropriate.

4.3.2 Energy: Treatment will be delivered with 6 - 18 MV photons

4.3.3 Localization, simulation, and immobilization: All subjects must undergo CT simulation prior to treatment. A patient will be simulated using an immobilization device that allows for reproducible treatment setup using an Alpha Cradle, Vac-Lok, or other commercially available SBRT immobilization system. Patients will be simulated supine with both arms up if tolerated. IV and oral contrast will be used at the discretion of the treating radiation oncologist. CT images should be obtained from at least 2cm above the dome of the diaphragm to the bottom of the kidneys. 1-2mm cuts should be performed for high resolution delineation of the tumor and surrounding structures.

A motion management strategy is strongly encouraged to minimize liver motion. Acceptable motion management strategies include active breathing control (ABC) or similar breath hold device, respiratory gating, tumor tracking using Cyberknife synchrony system, or abdominal compression using an abdominal belt or paddle. Patients who cannot be treated using one of these techniques may be treated free breathing with a tumor-specific internal target volume (ITV) if tumor motion is ≤10 mm in maximal extent in any one direction and treatment planning dose constraints can be met. 4DCT scan is required when a tumor-specific internal target volume (ITV) is being used.

Prior to each SBRT treatment, the liver will be imaged. For patients with fiducial markers within the liver, the tumor may be localized using fluoroscopy, orthogonal kV images, or cone-beam CT scans using the fiducials as surrogate markers for the liver tumor. For patients without fiducial markers, cone-beam CT or other types of volumetric image guided radiation therapy (IGRT) available (e.g.

MR guidance) will be used to image the tumor and/or portion of the liver where the tumor lies as and soft tissue surrogates for the tumor for positioning prior to treatment.

Documentation of CT-based simulation including setup, use of IV contrast, type of motion management, and image-guidance used for treatment delivered is required.

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 (contrast-enhanced CT or MRI). GTV is defined as all parenchymal HCC. No clinical target volume (CTV) will be used in this study. The PTV expansion will be determined based upon the immobilization device(s) used. Minimum PTV margin will be 0.5 cm circumferentially.

4.4 SBRT Planning Guidelines - Radiation Doses:

4.4.1 PTV Target Doses

4.4.1.1 The highest allowable doses to the target volumes that maintain normal tissue constraints should be used. The prescription isodose surface covers at least 95% of PTV. A goal is that 100% of the GTV is encompassed by the prescription dose. Prescription dose should not extend beyond the PTV.

4.4.1.2 Variations

- Minor variation is defined as minimum PTV dose falling between 85% and 94.9% of the prescription isodose line
- Major variation (unacceptable) is defined as minimum PTV dose < 85% of the prescription isodose line.

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

4.4.2 Critical Normal Tissue Constraints

<u>Mandatory dose constraints:</u>
Liver minus GTV's: volume >700cc
Liver minus GTV's: Mean <18 Gy
Spinal Cord: 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)
Heart max 0.5cc <105% PTV prescription dose

<u>Optional Dose Constraint</u>:
Liver minus GTV's: V10Gy <70%
Common bile duct: max dose to 0.5cc <50Gy
Skin external: max 0.5cc<32 Gy

4.4.3 Radiation Schedule

4.4.3.1 SBRT will be delivered in five total fractions. 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: The goal is to use the highest allowable prescription dose to the primary target while respecting normal tissue constraints. 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 based on mean liver dose (MLD is the mean dose to the liver minus GTV's). See table below.

The dose to multiple PTVs within the same subject may vary. Conformality of the prescription dose and the 30Gy isodose lines are planning goals.
For CTP A: 27.5 Gy - 50 Gy in 5 fractions
For CTP B: 27.5 Gy - 40 Gy in 5 fractions.

Table 1: Priority Constraint - Mean Liver Dose (Gy) [liver-GTV's]

GTV	Prescription Dose If max MLD exceeded
<15.0	50 Gy
15.0	40 Gy
15.5	35 Gy
16.0	30 Gy
17.0	27.5 Gy

5.0 Treatment Plan for TACE

Subjects will be consented to TACE with Quadrasphere® Microspheres either with or without doxorubicin as per standard of care at the treating institution.

5.1 Unilateral femoral approach

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 the 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, and a cone-beam CT is available, a cone-beam CT will be performed to assess appropriate segmental contrast distribution covering the target.
5.2.2 TACE will be performed with (see Appendix C). Two vials of beads will be prepared with, per the discretion of the treating physician, 50mg of Doxorubicin. Iodine contrast will be mixed

according to manufacturer guidelines and used to guide the delivery. Bead size will be at the discretion of the treating physician.
5.2.3 TACE without doxorubicin will be performed in an identical manner. Bead size will be at the discretion of the treating physician.
5.2.3 Target area will be embolized until segmental arterial stasis is achieved. In the presence of multifocal disease selective catheter positioning will be repeated for each lesion.
5.2.4 If available, 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 extended recovery.

5.4 If stasis of arterial flow to the tumor(s) was not achieved, additional TACE treatments will be administered, each approximately 4-6 weeks after the prior TACE procedure was performed until stasis is achieved with a maximum of three TACEs administered as initial therapy. After the first TACE, any additional treatments will be performed per the discretion of the treating Interventional Radiology Team.

Completed treatment will be defined by the date of the final TACE procedure considered as part of initial therapy (up to 3 TACE treatments).

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.

If there is a radiological discrepancy regarding findings of residual, recurrent or progressive disease, the site must submit the subject's de-identified images to the centralized radiology panel overseen at LHMC. The panel will make the final determination and notify the site investigator. Any additional ablative treatment, be it to repeat TACE or SBRT or other therapy will be determined at that time. All treatment will be individualized by subject at the discretion of the transplant team.

5.6 Additional local treatment to the target lesion(s) in the assigned treatment arm:
Group 1: SBRT (Arm A), subjects with residual disease or local recurrence ***in the previously treated lesion(s)*** on radiologic imaging at any point in follow up will be considered as having met the primary endpoint of the trial and they are off the study. Patients may be considered candidates for additional local regional therapy to the treated lesion of any kind per the discretion of the treating.

Group 2: TACE (Arm B), subjects with residual disease or local recurrence ***in the previously treated lesion(s)*** on radiologic imaging at any point in follow up will be considered as having met the primary endpoint of the trial and they are off the study. Patients may be considered candidates for additional local regional therapy to the treated lesion(s) of any kind per the discretion of the treating providers.

5.7 Patients in either group who develop new ***intrahepatic lesion(s)*** at any point in follow up will ***not have met the primary endpoint as they have not progressed at the site of previous treatment.*** They may be considered candidates for additional local regional therapy to the new site of disease ***of any kind*** per the discretion of the treating providers and will be followed per Table 4 thereafter.

5.8 If patients have no evidence of progression or residual disease in the treated lesion(s) ***but develop new tumors outside the previously treated field*** and, per the discretion of the treating providers, require treatment with systemic therapy, the patient will be censored from the data analysis for the primary endpoint and will be discontinued from the study.

6.0 Health Related Quality of Life (HRQL)

To assess HRQL, subjects with be assessed using the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) Questionnaire (Appendix D). This 45-item self-report instrument is designed to measure HRQL in patients with hepatobiliary cancers and is one of the most widely-used instruments in this clinical area. The FACT-Hep consists of the 27-item FACT-G, which assesses generic HRQL, and the 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues such as pain, appetite, and cramping.[3,4] The FACT-G is divided into four HRQL domains: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items). All items have a 7-day reference period and are scored from 0-4 ("not at all" to "very much"), with higher scores indicating better HRQL. Score ranges are 0-28 for physical well-being, 0-28 for social/family well-being, 0-24 for emotional well-being, 0-28 for functional well-being, and 0-72 for HS. All subscale scores from the FACT-G and HS can be summed together to create a total FACT-Hep score, with a possible range of 0-180. The FACT-Hep takes approximately 10 minutes to complete.[5]

Subjects assigned to the SBRT arm will complete the FACT-Hep at baseline/screening, at the time of the second fraction of the SBRT treatment (post treatment prior to discharge), on the last day of treatment (post treatment prior to discharge), 2 weeks after treatment, and at the time of follow-up scans at 3, 6, 9, 12, 15, 18, 21 and 24 months from randomization or until liver transplantation.

Subjects assigned to the TACE arm will complete the FACT-Hep at baseline/screening, TACE treatment #1(post treatment prior to discharge), 2 weeks after treatment #1, at TACE treatment #2 (post treatment prior to discharge), 2 weeks after treatment #2, at TACE treatment #3(post treatment prior to discharge), and 2 weeks after treatment #3. The number of TACE treatments will vary from 1 to 3, so not all HRQL assessments will be collected for all subjects. The HRQL assessment at the time of the last TACE will serve as the HRQL assessment on the last day of treatment, while the HRQL assessment done 2 weeks after the last TACE assessment will serve as the 2 weeks after treatment assessment. HRQL will then continue to be collected at the time of follow up scans at 3, 6, 9, 12, 15, 18, 21 and 24 months from randomization or until transplantation.

7.0 Study Calendars

Table 2: Study Calendar for SBRT (Arm A)

Active Treatment-SBRT	Pre-Rx Eval[1] (screening)	SBRT fractions (5 in 2 week period)[7]	Last fraction of treatment (prior to discharge)	2 Week Follow up post treatment (+/- 3 days)
History and Physical Exam	X			X
Weight	X			X
CBC with differential	X[2]			X
AST, ALT, Alk Phos, Total Bilirubin, Albumin	X[2]			X
Na, BUN/Creatinine	X[2]			X
INR	X[2]			X

AFP (for HCC)	X[2]			
Toxicity Notation	X		X	X
Multiphasic 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, ALBI, and CTP assessment	X[3]			X
HRQL[4]	X	X [7]	X	X
Randomization[5]	X			
Simulation	X			
Treatment: SBRT[6]		X (over a two week period)		

[1] Within 2 weeks prior to randomization unless otherwise specified
[2] If multiple lab results are available within the screening period, use the most recent results before randomization.
[3] If calculations are performed multiple times, use the most recent value before randomization
[4] HRQL questionnaire: FACT-Hep
[5] Randomization may occur after all screening procedures are complete and eligibility has been met. See section 3.0 for more details.
[6]Initial treatment should be scheduled within 3 weeks of randomization.
[7]See section 6.0 for details on HRQL administration timelines.

Table 3: Study Calendar for TACE (Arm B)

		Active Treatment – TACE			
	Pre-Rx Eval[1] (screening)	Initial TACE	2 week Follow up post initial TACE (+/- 3 days)	Second and Following TACE treatments	2 week Follow up post TACE (+/-3 days)
History and Physical Exam	X	X	X (per MD SOC only)	X	X (per MD SOC only)
Weight	X	X	X	X	X
CBC with differential	X[2]	X[7]	X	X[7]	X
AST, ALT, Alk Phos, Bilirubin, Albumin	X[2]	X[7]	X	X[7]	X
Na, BUN/Creatinine	X[2]	X[7]	X	X[7]	X
INR	X[2]	X[7]	X	X[7]	X
AFP (for HCC)	X[2]	X[7]		X[7]	
Toxicity Notation	X	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 ALBI, and CTP assessment	X[3]		X		X
HRQL[4, 5]	X	X[5]	X	X[5]	X
Randomization[6]	X				
Treatment:TACE[6]		X		X	

[1] Within 2 weeks prior to randomization unless otherwise specified.
[2] If multiple lab results are available within the screening period, use the most recent results before randomization.
[3] If calculations are performed multiple times, use the most recent value before randomization.
[4] HRQL questionnaire: FACT-Hep
[5] See section 6.0 for details on HRQL administration timelines.
[6] Randomization may occur after all screening procedures are complete and eligibility has been met. Initial treatment should begin within 3 weeks of randomization. See section 3.0 for details on randomization.
[7] If required labs were performed within 3 days of a TACE procedure, they do not have to be repeated unless requested by treating physician.

Table 4: Study Calendar for FOLLOW-UP (Both Arm A and Arm B)

Follow-up After Initial Treatment Phase				
	3 months (+/- 4 weeks) post randomization	6 months (+/- 4 weeks) post Randomization	Q 3 months to 24 months post-randomization (+/- 4 weeks)	60 days post-transplantation (+/- 2 weeks)
History and Physical Exam	X	X	X	
Weight	X	X	X	
CBC with differential	X	X	X	
AST, ALT, Alk Phos, Bilirubin	X	X	X	
Na, BUN/Creatinine	X	X	X	
INR	X	X	X	
AFP (for HCC)	X	X	X	
Toxicity Notation	X	X	X	
Survival Status	X	X	X	X
MRI or CT of the abdomen[1] (mRECIST for HCC)	X	X	X	
Chest CT or X-ray[1]	X	X	X	
MELD-Na CP ALBI assessment	X	X	X	
Assessment of disease progression, recurrence and transplantation status	X	X	X	
HRQL[2]	X	X	X	
Mortality and Morbidity				X

[1] Scans will be obtained in accordance to liver transplantation protocols and timeframes and may not occur within the allotted time frame noted above. This will not be considered a protocol deviation as long as they are performed per United Network for Organ Sharing (UNOS) guidelines.
[2] HRQL questionnaire: FACT-Hep

8.0 Treatment Modifications

8.1 Hepatic Toxicity: Subjects will be evaluated for symptoms and signs of RILD or other toxicity. 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 per the schedule described in the protocol or more frequently depending on the clinical judgment of the treating team. If recovery of hepatic function requires an interruption of treatment of more than 30 days, patients will be withdrawn from the study.

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 per each institution′s standard of care. 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 require discontinuation of therapy

- Grade 3 or 4 asymptomatic hypo-albuminemia or decreased lymphocytes.
- Transient (< 48 hours) asymptomatic grade 3 fasting hyperglycemia in type II diabetics.

9.0 SBRT Dost Adjustment

There will be no dose adjustments for SBRT treatment.

10.0 Toxicity Considerations

The criterion used for the grading of toxicities is the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

10.1 Expected Toxicities after TACE:

- Abdominal pain
- Nausea
- Vomiting
- Fatigue

10.2 Expected Acute Toxicities after SBRT:

- Fatigue
- Weight loss
- Nausea, vomiting, or anorexia.
- Abdominal discomfort.
- Skin irritation
- Increased frequency of bowel movements or change in stool consistency

10.3 Possible long term toxicities after SBRT:

- Gastric or Bowel injury (ulceration, bleeding, perforation, fistula formation, or obstruction)
- Biliary obstruction due to inflammation or sclerosis
- Liver abscess
- Hepatic subcapsular injury
- Decreased renal function.
- Rib fracture
- Myositis
- Radiation-induced liver disease (RILD) including potentially fatal liver injury.
- In subjects who have Grade 4 elevation of liver enzymes 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.

Only grade ≥2 toxicities will be considered in the statistical analysis. The following toxicities will require subjects to be removed from protocol treatment if the protocol treatment has not yet been completed. Patients will be followed per physician standard of care.

- 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.
- Grade ≥4 Upper GI bleeding (**attributed to treatment**, and not attributable to disease progression).
- Death due to any cause.

11.0 Assessment of Radiologic Response

11.1 Imaging Acquisition

Participating centers will need to comply with minimum technical requirements for CT and MR as shown in Tables 5 and 6.

11.1.1 Importance of High-Quality, Carefully Timed Multiphasic Contrast-Enhanced Imaging

It is well known in the imaging community that optimal detection of liver nodules with predominant arterial vascular supply (such as HCC) on cross-sectional imaging (CT or MRI) requires careful timing of image acquisition to take place during late arterial phase of contrast enhancement. At that point in time there is maximal signal-to background contrast between capillary enhancement in the lesion and surrounding hepatic parenchyma. In most patients, early arterial phase imaging does not improve tumor conspicuity by either quantitative or subjective analysis.

There is a relatively small time window for acquisition of the late arterial phase, which persists for approximately 10 seconds in most patients and explains the need for careful timing.

While also important for diagnostic purposes, the time window of opportunity to acquire images of the hepatic parenchyma during portal vein and equilibrium (delayed) phase is much wider. Therefore it is permissible to use fixed-time delays (approximately 60 to 75 seconds post injection preferred) of the liver which must be obtained in a single breath hold helical acquisition. HCC has a range of presentations on CT. The most diagnostic images are the properly timed multi-phase contrast-enhanced images. The following section covers the key elements necessary to achieve optimal diagnostic sensitivity and specificity, as well as an optional pre-contrast imaging sequence recommended especially after ablative therapy.

11.1.2 Guidelines for Multiphasic Contrast-Enhanced CT Imaging

11.1.2.1 Pre-contrast: Recommended but not required

Non-contrast imaging through the liver prior to contrast-enhanced imaging is optional and not required for the purpose of this protocol.

11.1.2.2 Late arterial phase

Imaging characteristics include the following:

- Fully enhanced hepatic artery and branches;
- Early contrast enhancement of portal vein;
- Lack of enhancement of the hepatic venous system.

Time to peak enhancement in abdominal aorta at celiac axis level can be determined either by timing bolus injection or through the use of triggering facility provided on newer scanners. Some scanners have an auto triggering feature that commences the scan when a pre-defined threshold (typically 100 HU) is reached in the target area; some scanners will display a time-density curve at the pre-defined anatomic location to the technologist and require a manual start of the exam. Either mechanism optimizes timing of the scan to the cardiac output and circulatory time of the individual participant and is strongly preferred over a fixed-time delay exam. Late arterial phase scanning should typically commence 5 to 10 seconds after peak enhancement in the upper abdominal aorta at the level of the celiac axis. In the unlikely event that fixed time delay needs to be used, an empirical delay of 25 to 30 seconds may work for most participants.

11.1.2.3 Portal vein phase

Imaging characteristics include the following:

- Fully enhanced portal vein;
- Peak liver parenchymal enhancement;
- Early contrast enhancement of hepatic veins.

The time window of opportunity to acquire images of the hepatic parenchyma during portal vein and equilibrium (delayed) phase is relatively wide. Portal vein phase images should typically be acquired 35 to 55 seconds after initiation of late arterial phase.

11.1.2.4 Equilibrium/Delayed phase

Imaging characteristics include the following:

- Variable appearance;
- >120 to <180 seconds after initial injection of contrast.

The time window of opportunity to acquire images of the hepatic parenchyma during portal vein and equilibrium (delayed) phase is relatively wide. Equilibrium phase images should typically be acquired 120 to 180 seconds post initial contrast injection.

Table 5: Minimum technical specifications for multiphasic contrast-enhanced CT of the liver

Feature	Specification	Comment
Scanner type	*Multidetector row scanner*	
Detector type	*Minimum of 8 detector rows*	*Need to be able to image entire liver*

		during brief late arterial phase time window
Reconstructed slice thickness	*Maximum of 5 mm reconstructed slice thickness*	*Thinner slices are preferable, especially if multiplanar reconstructions are performed*
Injector	*Power injector, preferably dual chamber injector with saline flush*	*Bolus tracking desirable*
Dynamic phases on contrast enhanced MDCT (comments describe typical hallmark image features)	*0)* ***OPTIONAL:*** *Pre-contrast* *1)* ***MANDATORY:*** *Late arterial phase* *2)* ***MANDATORY:*** *Portal venous phase* *3)* ***MANDATORY:*** *Equilibrium/Delayed phase*	*1) Artery fully enhanced, beginning contrast enhancement of portal vein* *2) Portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins* *3) Variable appearance, >120 sec after initial injection of contrast*
Dynamic phases (timing)	*Bolus tracking preferred over timing bolus for accurate timing*	

11.1.3 MR Imaging

11.1.3.1 General MRI parameters are outlined in the table and text below.

- Field strength of 1.5 Tesla or greater.
- Imaging must be performed with a specialized torso array coil or other local coil combinations appropriate for body imaging. Body coil for signal reception is not acceptable.
- Image slice thickness should be ≤ 10 mm.
- Field of view (FOV) as appropriate for given patient body habitus.
- Matrix for T1 and T2 weighted images should be no less than 256 (frequency) x 128 (phase).
- Diffusion-weighted imaging may be used by sites per institutional protocol but is not required by this trial protocol. If sites perform this type of imaging, the use of lower resolution matrices is acceptable.
- For axial imaging, phase encoding should be anterior–posterior.
- For contrast-enhanced scanning, standard extracellular gadolinium chelates that do not have dominant hepatobiliary excretion should be used at a dose of 0.1 mmol/kg to a maximum of 20 mL.
- Injection rate should be 2 cc/sec, and all injections must be followed by a saline flush of 30 cc. Peripheral IV access is preferred.

11.1.3.2 Abdominal MRI

Contrast-enhanced imaging with a standard extracellular gadolinium chelate that does not have dominant hepatobiliary excretion is required for MRI. Scanning protocol should be per institutional standards, but should include at a minimum: pre-contrast (mandatory) and dynamic post-extracellular-gadolinium T1-weighted (T1W) gradient echo sequence (3D preferable), T2W (with and without FAT

SAT), T1W in and out of phase imaging. The inclusion of other imaging techniques/planes is acceptable per institutional/imaging center‘s standard.

11.1.3.3 Guidelines for Multiphasic Contrast-Enhanced MR Imaging

HCC has a range of presentations on MRI. The most common is a circumscribed mass that may be inconspicuous on pre-contrast T2W and T1W imaging. The strongest diagnostic images are the multiple contrast-enhanced timed T1W images. The key elements necessary to achieve optimal diagnostic sensitivity and specificity are the following:

- 3D Gradient Echo (GRE) fat-suppressed acquisitions acquired with identical parameters throughout the pre- and post-contrast series. 3D volumetric imaging is preferred, but multiplanar 2D imaging is acceptable.
- Pre-contrast T1W images:
  - 2D or 3D in- and opposed-GRE;
  - 3D GRE (depending on scanner platform used: Vibe; Lava-xv; Thrive) with fat suppression.
  - Parameters identical to the post-contrast 3D GRE sequence:
  - Avoid misinterpreting a nodule intrinsically with high T1W signal as an enhancing mass, as can be seen in regenerating nodules or dysplasia. Comparison must always be made between the pre-contrast and arterial phase images. Use of subtraction images is strongly recommended.
  - Examine the in/out-of-phase images for fat. Occasionally the T1 signal may be lower than adjacent liver on fat-suppressed 3D GRE due to lipid, < 10% incidence.

11.1.3.3.1 Pre-contrast: Mandatory

Non-contrast imaging through the liver prior to contrast-enhanced imaging is mandatory.

11.1.3.3.2 Arterial phase

- Imaging characteristics include the following:
  - Fully enhanced hepatic artery and branches;
  - Early contrast enhancement of portal vein;
  - Lack of enhancement of the hepatic venous system.
- Acquisition of a properly timed late arterial phase is the most technically challenging and diagnostically critical element of the dynamic liver examination.
- Using set (empirical) timing delays from the start of the injection will be associated with a large range of contrast arrival times (from < 12 to > 30 seconds range timed from the start of the contrast injection to the arrival in the hepatic artery) and will not provide the most optimized method.
- HCC will transiently enhance over a period of 5 to 10 seconds above the adjacent liver parenchyma signal, therefore the timing is critical and is optimized if:
  - The gadolinium bolus is injected in as short a time as possible;
  - Peak HCC enhancement must be aligned in time with the time during the 3D GRE acquisition that accumulates low k-space frequencies (e.g., linear order = align at middle of breath hold; low to high ordering = align at beginning of breath hold, which means adding a longer delay time to account for this).
- The following is required for optimized timing in order to achieve an arterial-phase breath hold liver examination (ABLE):
  - Dual chamber power injector;

- Injection of contrast at 2 cc/sec (measured to the recommended dose by weight; standard extracellular gadolinium chelates that do not have dominant hepatobiliary excretion should be used at a dose of 0.1 mmol/kg to a maximum of 20 mL);
- Chase with saline at 2 to 3 cc/sec x 30 cc;
- Start a real-time reconstruction high–speed, low-quality coronal (suggested) GRE (e.g., care-bolus) at the start of the infusion for bolus monitoring;
- Field of view on coronal set to allow visualization of the heart, mediastinum, and centered on the diaphragm to visualize the celiac axis;
- Technologist trained to recognize filling of the right side of heart, pulmonary artery, left heart, aorta, in preparation for recognizing bolus arrival;
- Stop the bolus imaging and start timing when the contrast arrives at the celiac axis (diaphragm);
- Count 8 sec if using a linear ordered 16 to 18 sec breath hold acquisition time 3D GRE (based on data looking at perfusion kinetics of arterial enhancing tumors);
- During this time give the breathing commands and train the technologists to provide adequate time for the participant to complete the breath hold maneuver 2 to 3 sec prior to initiation of the sequence to allow the participant to complete following the command and stop all voluntary movements;
- Start the arterial phase acquisition.

- An approximate guide to show that an ideal acquisition was obtained usually shows the hepatic artery fully enhanced and the portal veins centrally just enhancing to well enhanced; hepatic veins show no enhancement.

11.1.3.3.3 Portal venous phase (AKA venous and blood pool phase)

- Imaging characteristics include the following:
  - Fully enhanced portal vein;
  - Peak liver parenchymal enhancement;
  - Early contrast enhancement of hepatic veins.
- Images captured just after the hepatic veins have filled with contrast. Timing is less critical and can be acquired (35 to 55 sec after initiation of late arterial phase scan). Typically the portal venous phase is started one or two breathing cycles after completion of late arterial phase.
- This provides adequate time for the participant to regain their breath before being asked to perform the next breath hold and reduce motion effects from poor breath holding due to rushing this second enhanced acquisition.
- This acquisition provides optimal visualization for portal or superior mesenteric vein (SMV) thrombosis and varices.

11.1.3.3.4 Equilibrium phase (AKA extracellular, interstitial, or delayed phase)

- Imaging characteristics include the following:
  - Variable appearance;
  - >120 to <180 seconds after initial injection of contrast.
- Timing less critical and can be acquired at 120 to 180 sec post injection as a third breath hold. This provides adequate time to visualize HCC ―wash-out.
- The signal in the HCC is lower in this phase due to a combination of lower vascular volume and interstitial uptake than in the adjacent liver.
- The margins of the HCC enhance, forming an apparent thin pseudocapsule.

Table 6: Technical specifications for multiphase contrast-enhanced MRI of the liver

Feature	Specification	Comment
Scanner type	*1.5 T or greater magnetic field strength*	*Low-field magnets not suitable*
Coil type	*Phased-array multichannel torso coil*	*Unless patient-related factors preclude use (e.g., body habitus)*
Gradient type	*Current generation high speed gradients (providing sufficient coverage)*	
Slice thickness	*5 mm or less for dynamic series; 8 mm or less for other imaging*	
Injector	*Dual chamber power injector recommended*	*Bolus tracking desirable*
Contrast injection rate	*2–3 mL/sec of extracellular gadolinium chelate that does not have dominant hepatobiliary excretion*	*Preferably resulting in vendor recommended total dose*
Required non-dynamic sequences	*T1W in and out of phase imaging T2W (per institutional standard, not STIR)*	*Optional diffusion imaging*
Dynamic phases on contrast-enhanced MRI (comments describe typical hallmark imaging features	*0) **MANDATORY:** Pre-contrast T1W*	*0) Do not change scan parameters for post contrast imaging*
	*1) **MANDATORY:** Late arterial phase*	*1) Artery fully enhanced, beginning contrast enhancement of portal vein*
	*2) **MANDATORY:** Portal venous phase*	*2) Portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins*
	*3) **MANDATORY:** Equilibrium/delayed phase*	*3) Variable appearance, > 120 sec after initial injection of contrast*
Dynamic phases (timing)	*The use of a bolus tracking method for timing contrast arrival for late arterial phase imaging is preferable. Portal venous phase (35–55 sec after initiation of late arterial phase scan), equilibrium/delayed phase (120–180 sec after initial contrast injection)*	
Breath holding	*Max length of series requiring breath hold should be about 20 sec with a minimum matrix of 128 x 256*	*Compliance with breath hold instructions very important, technologists need to understand the importance of participant instruction before and during scan*

11.1.3.4 Serial imaging

Participants who are listed for liver transplant will undergo serial imaging scheduled in accordance with the 90-day intervals required for cyclical update of the HCC-exception points with UNOS. These images will be used to measure outcomes. For patients not on the transplant list, radiologic imaging will occur

four months (± 4 weeks) after randomization and then every three months thereafter until the primary endpoint is met.

11.1.4 Ablative Therapy and Post-ablation imaging
If multiple TACEs are planned, participants need to first complete the entire treatment scheme per institutional SOC before undergoing response assessment. In some participants, the post-ablation imaging time point may occur closer than 90 days to the next serial imaging time point required for liver transplant waitlist updates. Sets of post-ablation imaging studies that are less than 90 days old at the time of the next scheduled UNOS HCC-exception point update (serial) images do not have to (but may) be repeated at the time of exception point update and may count towards the serial imaging time point for the purpose of the trial. For the remainder of the trial, these participants continue to be imaged according to the OPTN/UNOS schedule for updating HCC-exception points. Should another round of ablative treatment become necessary, the above rules apply for all post-ablation imaging sets and subsequent serial time points.

Serial MR or CT imaging will be performed at distinct time points as dictated by OPTN/UNOS until transplantation. Timing of serial SOC imaging in waitlisted patients is dictated by OPTN/UNOS HCC-exception point update requirements (90 day intervals). Waitlisted patients are defined as those eligible for/scheduled to undergo LDALT as well as those waiting for livers from deceased donors to become available. Postablation imaging studies that are less than 90 days old at the time of the next scheduled UNOS HCC exception point update (serial) images do not have to (but may) be repeated at the time of exception point update and may count towards the serial imaging time point for the purpose of the trial.

11.2 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). All imaging will be assessed at the treating institution. If concern for residual or progressive disease is raised, imaging will be reviewed a second time at the individual institutions' multi-disciplinary conference review.

If there is a discrepancy between the two interpretations, imaging will be de-identified (responsibility of the site sending) and transferred to Ambra, to be shared in a group. The panel of radiologists who will be providing the consensus opinion will access the images through Ambra. To accomplish this, the treating institution will pull the data out of PACS, de-identify the data using LB Compass (or similar software, depending on the institution preference) and then will visually inspect the data to confirm de-identification. Further tracking of the data will be done by the individual patients' assigned tracking number, by the treating institution. The treating institution will upload the data to Ambra for the radiology panel (only users internal /external that are pre-configured will have access). The treating site will add the assigned tracking number to a Google sheet that will track the pre and post PHI. The treating institution will email Dr. Zarwan (or designated individual) notifying that the data/images are available in Ambra for review. An email will then be sent to the panel of three independent radiologists so that a final radiologic consensus assessment can be made. The committee's judgment will be final. The treating institution will be notified of the result and the data will be uploaded to the EDS by the treating institution subsequently.

11.3 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.

12.0 Criteria for Discontinuation of Protocol Treatment

12.1 Off-Treatment Conditions

- Unacceptable toxicity as defined in section 10.
- Therapy may be discontinued prematurely at any time by subject request without prejudice to subsequent care.
- Subjects may be removed from the treatment at any time per investigator discretion.

12.2 Off Study Conditions

- Subjects will be removed if they are unable to receive either SBRT or TACE due to decompensation prior to initial therapy.
- Subjects may be removed from the study at any time by subject request.
- Subjects who go on to receive additional non-radiation therapy (i.e., treatment that is not TACE or SBRT related) will be followed for progression within the treated lesion(s). They will no longer receive protocol-directed treatment or testing.
- Subjects who develop extra-hepatic tumor will not be followed and will be censored from the data analysis.
- Subjects who undergo a liver transplant will be considered off study and will not be followed from that time point (except to determine 60-day post transplantation survival status).
- Subjects permanently removed from Liver Transplant list and will not be followed.

12.3 Adverse Event 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 an adverse event.
- All AEs ≥ grade 3 will be collected and attributed either as possibly, probably or definitely related to protocol treatment or not related to protocol treatment. Additional AE′s collected are, any grade ≥2 abdominal pain, nausea, vomiting, and fatigue. The NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) will be utilized to grade AE's for AE reporting.

12.3. 2 Adverse Event 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. Adverse

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

12.4 SAE Guidelines
12.4.1 A serious adverse event (SAE) shall be defined as an adverse event 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 site investigators and will be labeled as either related to treatment, or not related to treatment.

12.4.2 **Only adverse events deemed serious <u>AND</u> related will be reported to the IRB within 10 days of awareness of the event, or per institutional Policy. All other events will be noted in the subjects' medical record.**

12.4.3 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.

12.4.4 SAE Reporting
All serious adverse events (SAE) (including death and hospitalization), premature withdrawal, and emergency treatment disclosures must be reported to the Project Manager at the Lahey Hospital & Medical Center within one working day. Applicable SAE forms should be completed in the electronic data capture system (EDC) within 10 days of their occurrence and updated as new information becomes available.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention. All deaths occurring on study must be reported to the Lahey Hospital & Medical Center. These include deaths within 30 days of the end of study visits.

13.0 Efficacy Variables

Primary and secondary efficacy variables are described below.
13.1 Primary Variable
Time to residual/recurrent disease is defined as the time from the date of randomization until the date of residual/recurrent disease within the treated lesion(s). Any subject not known to have had residual/recurrent disease before transplant will be censored based on the last recorded date on which the

subject was still on study. The percentage of subjects who had residual/recurrent disease will also be derived.

13.2 Secondary Variable

To assess HRQL, subjects with be assessed using the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) Questionnaire (Appendix D). This 45-item self-report instrument is designed to measure HRQL in patients with hepatobiliary cancers and is one of the most widely-used instruments in this clinical area. The FACT-Hep consists of the 27-item FACT-G, which assesses generic HRQL, and the 18-item Hepatobiliary Subscale (HS), which assesses disease-specific issues such as pain, appetite, and cramping.[3,4] The FACT-G is divided into four HRQL domains: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items). All items have a 7-day reference period and are scored from 0-4 ("not at all" to "very much"), with higher scores indicating better HRQL. Score ranges are 0-28 for physical well-being, 0-28 for social/family well-being, 0-24 for emotional well-being, 0-28 for functional well-being, and 0-72 for HS. All subscale scores from the FACT-G and HS can be summed together to create a total FACT-Hep score, with a possible range of 0-180. The FACT-Hep takes approximately 10 minutes to complete.[5]

Subjects assigned to the SBRT arm will complete the FACT-Hep at baseline, at the time of the second fraction of the SBRT treatment , on the last day of treatment, 2 weeks after treatment, and at the time of follow-up scans at 3, 6, 9, 12, 15, 18, 21 and 24 months from randomization or until liver transplantation.

Subjects assigned to the TACE arm will complete the FACT-Hep at baseline, TACE treatment #1, 2 weeks after treatment #1, at TACE treatment #2, 2 weeks after treatment #2, at TACE treatment #3, and 2 weeks after treatment #3. The number of TACE treatments will vary from 1 to 3, so not all HRQL assessments will be collected for all subjects. The HRQL assessment at the time of the last TACE will serve as the HRQL assessment on the last day of treatment, while the HRQL assessment done 2 weeks after the last TACE assessment will serve as the 2 weeks after treatment assessment. HRQL will then continue to be collected at the time of follow up scans at 3, 6, 9, 12, 15, 18, 21 and 24 months from randomization or until transplantation.

14.0 Safety Variables

Adverse events will be captured throughout the study along with, physical exams and standard laboratory tests.

15.0 Statistical Considerations

This is a randomized, non-blinded, Phase III trial to characterize the safety and efficacy of individualized SBRT, compared to TACE, for subjects who have primary HCC. The trial endpoints are time to progression or residual disease in the treated lesion(s), number of retreatments, radiologic response, pathologic response, toxicity, and HRQL, overall survival, and 60 day post-transplant morbidity and mortality.

16.0 Sample Size

This study is sized for hypotheses testing of improved time to residual or recurrent disease within the previously treated lesion(s) due to SBRT versus TACE treatment arms in the overall population of patients who are eligible for liver transplant and are on the waiting list. It is believed that more than 50% of patients will receive a transplant within 2 years of listing, but that far fewer patients will receive

a transplant within 1 year of study begin. Therefore we base power calculations on one year follow up and a drop rate of 15%. Based on initial data, we estimate a median time to residual or recurrent disease of 134 days in the TACE group. Based upon these numbers and a hazard ratio of 0.6 for the SBRT relative to the TACE group, a two-sided test controlling the overall type 1 error to 5% requires a total of 161 events (i.e. residual/recurrent disease) and about 131 patients per treatment arm to achieve a power of 90%. To achieve a power of 80%, a total of 120 events and about 98 patients per treatment arm are required. These calculations are made accounting for follow-up on patients once every three months where the calculated HR of 0.6 for this discrete model corresponds roughly to a HR of 0.54 if recurrent disease could be measured on the continuous time scale (days).

Table 7 Sample Size Calculation

HR	Median time[1] TACE (days)	Median Time[1] SBRT (days)	Power (%)	Nb of Events	Nb of patients per arm
0.6	134	223	90	161	131
0.6	134	223	80	120	98

[1] Median time is the median time to residual or recurrent disease.

Recruitment period of 365 days, duration of study of 2 years, yearly dropout rate of 15% (following exponential distribution), alpha=5%, two-sided test.

17.0 Statistical Analysis

Baseline as well as post treatment measures will be summarized by descriptive statistics as appropriate such as mean, median, standard deviation, range and interquartile range. Comparison between treatment groups at baseline as well as changes from baseline will be made as appropriate using t-tests, Wilcoxon, chi-square and McNemar's tests as appropriate.

17.1 Primary endpoint

The primary analysis of the primary endpoint of time from randomization to residual or recurrent disease will be based upon the Kaplan-Meier estimates of time to event for the two groups where the two groups are compared using the log-rank test. Patients will be censored at time of transplantation or two years, whichever comes first. The primary analysis will treat patient death as residual or recurrent disease (effectively the compound endpoint of residual or recurrent disease or death). During the time frame of two years mortality should be low, but treatment of death as residual or recurrent disease is conservative. Secondary analyses using the Cox regression model will explore predictors of recurrence beyond group assignment, and also explore interactions between treatment and these other factors. We will also explore sex and treatment center differences. Secondary analyses will also censor for deaths unrelated to treatment. Statistical tests will be made at the two-sided 5% level.17.2.1 HRQL analyses

17.2 Secondary Endpoints Analysis

17.2.1 Analysis of Long term HRQL outcomes

The main HRQL outcome will be of the overall FACT sum score (FACT-G + FACT-Hep). The main analysis will be a random effects (repeated measures) analysis of the HRQL measures obtained using data taken at baseline, end of treatment, 2 weeks after treatment completion, and every 3 months thereafter (until 24 months). Depending on the amount of missing data at later time points, including for those patients who experience the primary outcome, are transplanted, or are loss to follow-up, the HRQL analysis may be truncated before 24 months (e.g., 12m months). For each patient the model will fit a random intercept and slope term. We will center time to the assessment time point nearest the center of

the time points of the data. Data will be inspected for linearity in time as well as constancy of variances. If the data show deviations from these linearity or constancy of variables we will attempt to remedy this through addition of nonlinearity terms or transformations.

The specific domains of HRQL that are impacted by the different treatments will be analyzed as secondary variables using the same analysis plan as the overall FACT score.

Additionally we will analyze both the primary (overall FACT score) and secondary (domain scores) long term HRQL measures in a descriptive manner both numerically (e.g. means, medians, standard deviations, ranges and interquartile ranges) comparing the groups, testing using analysis of covariance (ANCOVA accounting for baseline values) and graphically by plotting measures using jit plots, spaghetti plots (plots through time where individual patients data from multiple time points are connected with lines) and plots of the means or difference from baseline as estimated from the ANCOVA, or similar plots as suggested by the data. We will examine missing data for systematic bias.

17.2.2 Analysis of Short Term HRQL Outcomes
We will use descriptive statistics (e.g., mean, standard deviation, median, ranges and interquartile ranges) to describe the overall FACT sum score and each domain score by treatment arm at each assessment period from baseline through the end of treatment. We will graph the data over the appropriate time frame similar to the analysis of the long term HRQL measures. This will inform us about the HRQL trajectories during treatment by treatment arm. If the data suggest it is reasonable we will calculate HRQL life years from areas under the curves and compare the treatment arms using ANCOVA or Wilcoxon test, as indicated by the data. We will examine missing data for systematic bias.

17.2.3 Other Secondary Endpoints
Quantitative outcomes like number of retreatments and number of toxicities will be described by mean, standard deviations, median, minimum and maximum by treatment group and treatment group will be compared using a t-test. Categorical outcomes like any retreatment, any toxicity, radiologic response, pathologic response will be described by counts, percent and groups compared using the chi-square test. Overall survival, and 60 day post-transplant morbidity and mortality will be described by Kaplan-Meier estimates, and groups compared using the log-rank test and Cox model as for the primary outcome. Note, with 98 patients per arm, each arm will have 99% and 95% probabilities of observing at least one event of toxicity when the true probabilities per patient are 0.05 and 0.03. Further, when estimating proportion of patients to have a particular toxicity, the 95% confidence intervals will have precision of 10% or tighter, for each treatment group.

We will analyze secondary endpoints relating to time to event analogously to time to recurrence, and quantitative outcomes analogously to the analysis the HRQL endpoints.

Safety Measures
Lab measures will be described and groups compared as described using t-tests or Wilcoxon tests as appropriate.

Adverse events
Adverse events will be described by body system and severity, on a per patient basis as well as a number per patient basis, and groups compared using chi-square and t-tests as appropriate.

18.0 Project Management, Data Management, and Site Monitoring

Lahey Hospital & Medical Center (i.e., Sponsor) staff will accomplish all the tasks necessary for preparation and implementation of the project, including the drafting and refinement of the study protocol, development of the model consent document, assisting the PI in communications, developing project timelines, compiling required documents, preparing the detailed operations manual that outlines all the tasks required for study implementation at the sites, overseeing the distribution of documents, updating the protocol and operations manual as needed, updating regulatory files for the study overall, supervising the timely renewals of IRB approvals at the sites, and overseeing enrollment.

18.1 Records to Be Kept

Each participating site will maintain appropriate medical and research records related to this trial in compliance with regulatory and institutional guidelines for the protection of subject confidentiality.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to hospital records, clinical and office records, laboratory notes, subjects' HRQL data, radiology records, and treatment related records.

18.2 Role of Data Management

Lahey Hospital & Medical Center in conjunction with Quartesian will design and distribute source worksheets and the electronic data capturing system that will maintain all data collected as part of the protocol.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. Collected study data must be promptly entered into the EDC system used by the Sponsor. Source worksheets should be used as the primary data collection instrument for the study, when possible. The investigator should ensure the accuracy, completeness, and timeliness of the data reported in the EDC and all other required reports. Data reported in the EDC, that are derived from source documents, should be consistent with the source documents and any discrepancies should be explained. Any missing data must also be explained. An audit trail will be maintained by the EDC system.

Sites are required to provide the Sponsor with de-identified source documents supporting the data entered into the EDC system within 1 week of each completed visit. Data must be shared via a Dropbox account approved by Lahey. If a site is unable to provide data via Dropbox, then an alternate method of data sharing maybe employed. Approved methods include mailing and faxing documents or through secure email.

All serious adverse events (SAE) (including death and hospitalization), premature withdrawal, and emergency treatment disclosures must be reported to the project program manager and Dr. Zarwarn at the Lahey Hospital & Medical Center within one working day of site becoming aware of the event. Sites will notify Dr. Zarwan and the project program manager by emailing li.zhang@lahey.org. Please include Site Name, Patient study ID, SAE event term, grade and pertinent de-identified source documents. Applicable SAE forms should be completed in the electronic data capture system (EDC) within one week of their occurrence and updated as new information becomes available.

A data monitoring committee comprised of Dr. Zarwan along with two Co-Investigators from Lahey Hospital will review all Adverse Events on a quarterly basis. All Serious Adverse Events will be reviewed as they occur in real time.

18.3 Data Verification & Quality Assurance

The site monitoring, regulatory review, adverse event reporting and quality assurance issues will be overseen by Lahey Hospital & Medical Center. Each site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. The Coordinating Center at Lahey will review and track Adverse Events, Serious Adverse Events, and Unanticipated Problems.

Centralized remote monitoring will be carried out by Coordinating Center at Lahey Hospital & Medical Center. Monitoring will occur through periodic review of submitted source data and data in the EDC system. A sample of enrolled patients may be randomly selected for a focused comprehensive audit of all data. Depending on enrollment progress, the goal will be to audit a 10% sample of enrolled patients from each site involved. The audit will be performed by comparing data submitted through the EDC against source documentation submitted by the site. If a greater than 10% error rate is discovered, an additional 10% sample will be selected to audit. Additional auditing may be initiated per the Sponsor's discretion.

19.0 Human Subjects

19.1 Institutional Review Board (IRB) Review and Informed Consent

Informed consent must be obtained prior to performing any study specific procedures. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject or legal guardian, and this fact will be documented in the subject's record.

This protocol and corresponding informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form will be obtained from each subject prior to any study intervention. For subjects who cannot consent for themselves, a legal guardian, or person with power of attorney, must sign the consent form in accordance with institutional policies and state laws; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study.

19.2 Subject Confidentiality

All laboratory specimens, source documents case report forms, and other records that leave the site will be identified only by the SID to maintain subject confidentiality. All computer entry and networking programs will be done using SIDs only. Identifiable clinical information will not be released without written permission of the subject, except as necessary for monitoring by the study monitor, IRB, the sponsor, or the sponsor's designee.

19.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the sponsor or IRB as part of their duties to ensure that research subjects are protected.

E. REFERENCES

1. Clavien P, Lesurtel M, Bossuyt P, Gores G, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncology* 2012;13: 1111-22.
2. Kulik L, Heimbach J, Zaiem F, Almasri J, Prokop L, Wang Z, Murad H, Khaled M. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology*. 2018 Jan; 67(1):381-400. doi: 10.1002/hep.29485. Epub 2017 Nov 29.
3. Lesurtel M, Müllhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA. Trans-arterial Chemoembolization as a bridge to Liver Transplantation: an evidence based analysis. *Am J Transplant*. 2006 Nov; 6(11):2644-50. Epub 2006 Aug 25
4. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; 340: 745–750.
5. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; 94:153–156.
6. Okuda K. Hepatocellular carcinoma--history, current status and perspectives. *Dig Liver Dis* 2002; 34:613-616.
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. 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.
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. 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
19. 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
20. 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.
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. 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.
29. 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.

Sapir E[1], Tao Y[2], Schipper MJ, Feng M et al. Stereotactic Body Radiotherapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys*. 2018 Jan 1; 100(1):122-130. doi: 10.1016/j.ijrobp.2017.09.001. Epub 2017 Sep 14.

30. Sapisochin G, Barry A, Doherty M, Knox JJ, Dawson LA, Grant DR Stereotactic Radiotherapy versus TACE or RFA as a Bridge to Liver Transplant in patients with Hepatocellular Carcinoma: An Intent to Treat Analysis. J Hepatol. 2017 Jul; 67(1):92-99. doi: 10.1016/j.jhep.2017.02.022. Epub 2017 Feb 28
31. Nugent F, Flacke S, Qamar A, Hunter K. *et al*. Oral Presentation, *American Society of Clinical Oncology Gastrointestinal Symposium*, San Francisco, CA. "A randomized phase II study of individualized stereotactic body radiation therapy (SBRT) versus transarterial chemoembolization (TACE) with DEBDOX beads as a bridge to transplant in hepatocellular carcinoma (HCC)". Oral Abstract Presentation, American Society of Clinical Oncology Gastroiestinal Cancer Symposium. San Francisco 2017.
32. Nugent F, Packard A, Flacke S *et al*. Economic Analysis of Trans-arterial chemoembolization compared to Stereotactic body radiotherapy for the treatment of Hepatocellular carcinoma. Abstract, American Society of Clinical Oncology Gastrointestinal Cancer Symposium. San Francisco 2018.
33. 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.
34. 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. 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
35. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020-1022
36. Kamath PS, Wiesner RH, Malinchoc M*, et al.* A model to predict survival in subjects with endstage liver disease. *Hepatology* 2001; 33:464-470.
37. 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.
38. 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.
39. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med* 1995; 14:357-379.
40. 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) and Child-Turcotte-Pugh (CTP)

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 or equal to12. 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.

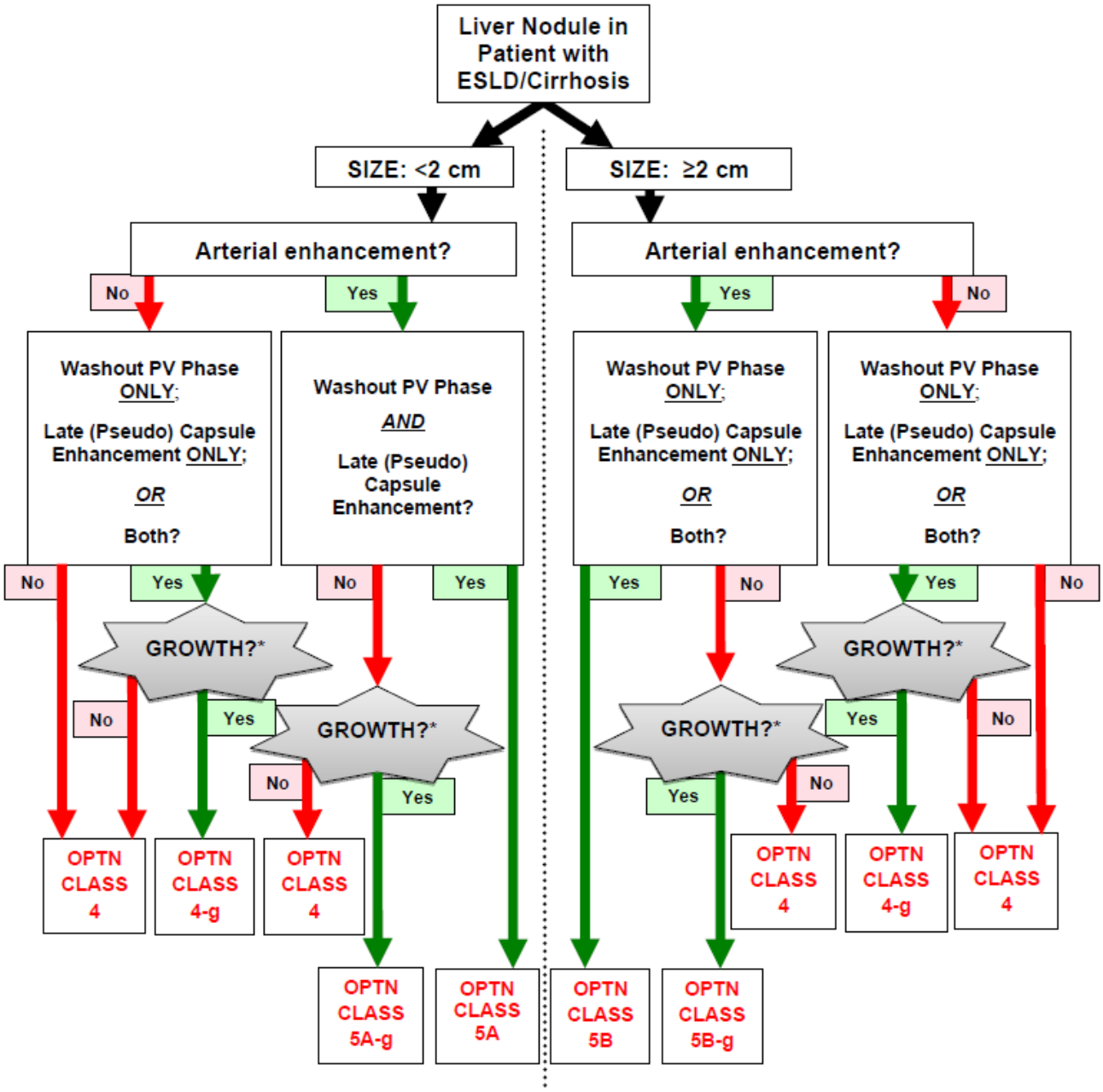
CTP class: A = 5-6 points **B = 7-9 points** **C = 10-15 points**

Appendix B: mRECIST for HCC[A]

Response	Longest viable tumor diameter[B]
Complete Response (CR)	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial Response (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
Stable Disease (SD)	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 viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

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

Appendix C: TACE Quadrasphere® Microspheres



* **Growth** is defined as: *Maximum diameter increase by 50% or more documented on serial MRI or CT obtained ≤ 6 months apart.*

Appendix D: FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4

GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4

Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4