MELVIN AND BREN SIMON CANCER CENTER

INDIANA UNIVERSITY

Study Title

Yttrium-90 Radiation Segmentectomy versus Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Early Stage Hepatocellular Carcinoma (HCC): A Pilot Study

Protocol Number:

RADY-IUSCC-0725

Principal Investigator:

Paul Haste, MD
Indiana University
550 N University Blvd Indianapolis, IN 46202
317 944 5005
phaste@iupui.edu

Co-Investigators:

Ryan Rhome, MD PhD
Mark Tann, MD
Matthew Johnson, MD
Maximillian Pyko, DO

Study Statistician:

Yong Zang, PhD

Protocol Version:

15 DEC 2021

TABLE OF CONTENTS

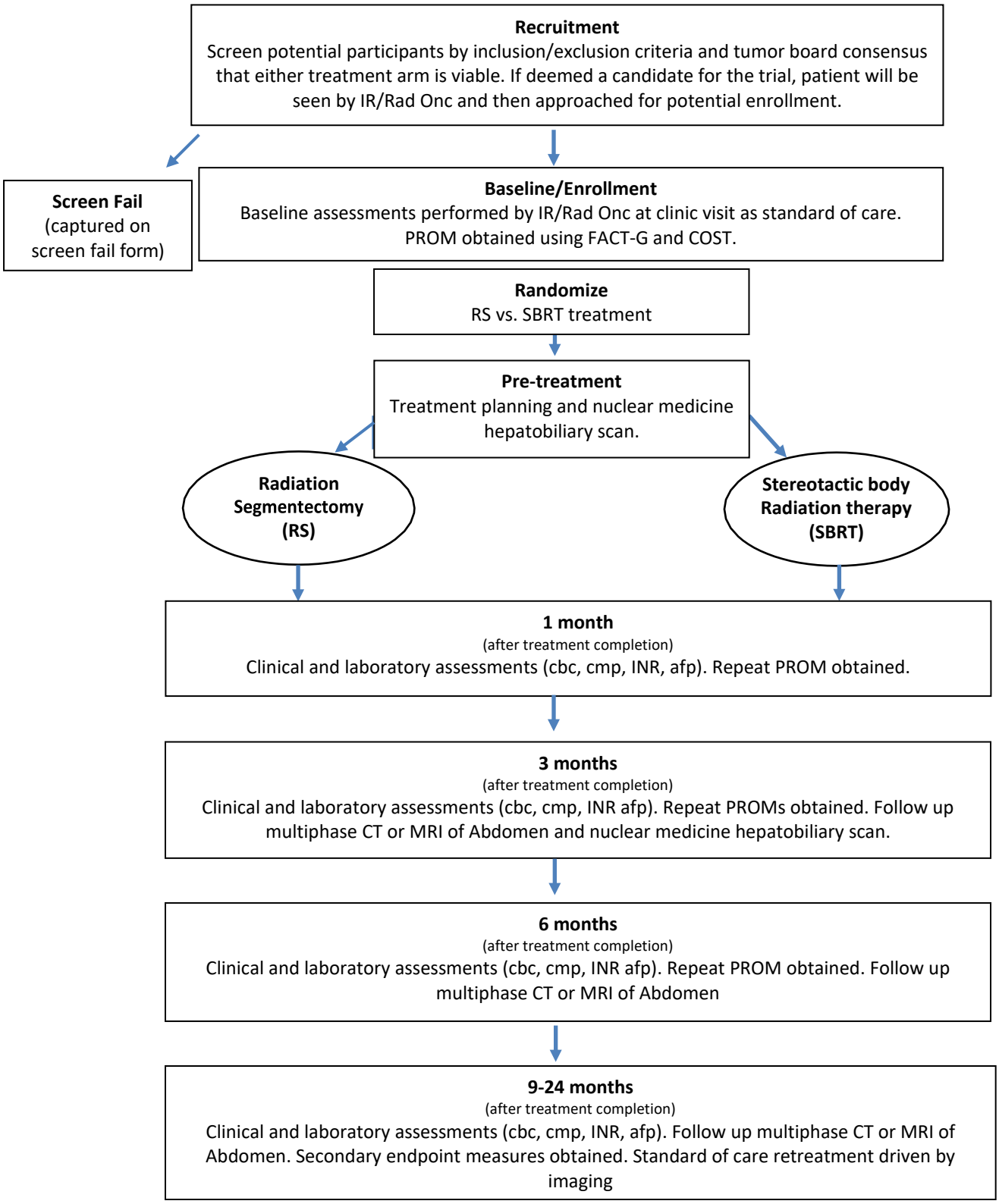
1.0 PROTOCOL SUMMARY

1.1 Synopsis

TITLE:	Yttrium-90 Radiation Segmentectomy versus Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Early Stage Hepatocellular Carcinoma (HCC): A Pilot Study
STUDY DESCRIPTION:	The proposed study is a single site, prospective, randomized pilot study to assess the feasibility of recruitment of patients into a trial evaluating the efficacy and tolerability of selective transarterial Y90 radioembolization (radiation segmentectomy) versus stereotactic body radiation therapy (SBRT) for solitary early stage (≤ 3cm) hepatocellular carcinoma (HCC).
OBJECTIVES:	**Primary Objective:** 1. To assess feasibility as measured by screen failures and rate of recruitment into a randomized trial comparing RS and SBRT **Secondary Objectives:** 1. To evaluate the proportion of patients with any toxicities (≥ grade 4) using CTCAE between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC). 2. To evaluate the mean change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC). 3. To evaluate the mean change in patient-reported outcomes from baseline, at 1, 3 and 6 months, between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using the Functional Assessment of Cancer Therapy- General (FACT-G) and COST FACIT questionnaires. 4. To evaluate the disease-free survival (DFS) rates of RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC). 5. To evaluate time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment. 6. To measure the objective response rate (ORR) of radiation segmentectomy (RS) and stereotactic body radiation therapy (SBRT) as measured at 6 months using mRECIST (appendix IV) for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) to better allow for an appropriately powered trial evaluating the efficacy of these treatments

ENDPOINTS:	**Primary Endpoint:** Recruitment rates measured at 6 and 12 months and screen failures assessed by the detailed screen failure form at the time patients are approached for enrollment to ascertain specific reasons why patients may choose not to enroll **Secondary Endpoints:** 1. Laboratory (CBC, CMP, INR)/clinical toxicities measured using CTCAE version 5.0 2. Change in % radiotracer extraction from baseline, on functional HIDA scan, 3 months after treatment 3. Change in FACT-G and COST FACIT from baseline at 1, 3, and 6 months 4. ORR at 6 months after completion of treatment using mRECIST on multiphase CT or MR.
STUDY POPULATION:	20 (up to 10 enrolled per arm) male or female patients with small (≤3 cm) solitary hepatocellular carcinoma with relatively preserved liver function (CPS ≤ 7)
PHASE:	N/A
DESCRIPTION OF STUDY INTERVENTION:	The SBRT arm of the trial will involve standard SBRT delivered over 3-5 fractions as tolerated with dose/total therapy adjusted as needed for safety. The RS arm of the trial will involve a planning arteriogram followed by selective transarterial delivery of Yttrium-90 into the segmental (≤2) artery supplying the tumor. Administered activity will be an amount prescribed to deliver a dose ≥200 Gy to the perfused tissue.
STUDY DURATION:	Estimated 12 months for accrual with another 24 months needed to complete secondary endpoints. 6 more months for data analysis. Total: 66 months
PARTICIPANT DURATION:	24 months from therapy completion. (approximately 26 months from randomization)

1.2 **Schema**


Recruitment
Screen potential participants by inclusion/exclusion criteria and tumor board consensus that either treatment arm is viable. If deemed a candidate for the trial, patient will be seen by IR/Rad Onc and then approached for potential enrollment.
Screen Fail
(captured on screen fail form)
Baseline/Enrollment
Baseline assessments performed by IR/Rad Onc at clinic visit as standard of care. PROM obtained using FACT-G and COST.
Randomize
RS vs. SBRT treatment
Pre-treatment
Treatment planning and nuclear medicine hepatobiliary scan.
Radiation Segmentectomy (RS)
Stereotactic body Radiation therapy (SBRT)
1 month
(after treatment completion)
Clinical and laboratory assessments (cbc, cmp, INR, afp). Repeat PROM obtained.
3 months
(after treatment completion)
Clinical and laboratory assessments (cbc, cmp, INR afp). Repeat PROMs obtained. Follow up multiphase CT or MRI of Abdomen and nuclear medicine hepatobiliary scan.
6 months
(after treatment completion)
Clinical and laboratory assessments (cbc, cmp, INR afp). Repeat PROM obtained. Follow up multiphase CT or MRI of Abdomen
9-24 months
(after treatment completion)
Clinical and laboratory assessments (cbc, cmp, INR, afp). Follow up multiphase CT or MRI of Abdomen. Secondary endpoint measures obtained. Standard of care retreatment driven by imaging

1.3 **Schedule of Events**

Procedures	**Enrollment / Baseline**	**Pre-Treatment** Within 30 days from enrollment	**Intervention /Treatment** Within 45 days of pre- treatment visit procedures	**1 month visit** 30 days from end of treatment (+/- 15 days)	**3 month visit** 90 days from end of treatment (+/- 30 days)	**6 month visit** 180 days from end of treatment (+/- 30 days)	**9 month visit** 270 days from end of treatment (+/- 30 days)	**12 month visit** 360 days from end of treatment (+/- 30 days)	**15 month visit** 450 days from end of treatment (+/- 30 days)	**18 month visit** 540 days from end of treatment (+/- 30 days)	**21 month visit** 630 days from end of treatment (+/- 30 days)	**24 month visit** 720 days from end of treatment (+/- 30 days)
Informed consent	x											
Demographics	x											
Medical history	x											
Randomization	x											
Pregnancy Test (urine or serum)[G]	x											
Planning/mapping arteriogram[F]		x										
CT simulation[E]		x										
Administer Study intervention[c]			x									
Physical exam	x			x	x	x	x	x	x	x	x	x
Vital signs	x			x	x	x	x	x	x	x	x	x
Performance status	x			x	x	x	x	x	x	x	x	x
Lab tests[A]	x		x	x	x	x	x	x	x	x	x	x
Adverse event review and evaluation[H]	x	x	x	x	x	x						
Radiologic/Imaging assessment[D]	x				x	x	x	x	x	x	x	x
Complete Case Report Forms (CRFs)	x		x	x	x	x	x	x	x	x	x	x

Functional Hepatobiliary Scan		X[B]			X							
Patient Reported Outcome Measures (FACT-G, COST FACIT)	X			X	X	X						

A Complete Blood Count (CBC), Comprehensive Metabolic Profile (CMP), International normalized ratio (INR), and Alpha Fetoprotein (AFP). AFP will only continue to be drawn after baseline if initially elevated (>10 ng/mL)
B Baseline functional hepatobiliary scan should be completed after enrollment, but prior to start of treatment.
C SBRT Arm: Child Pugh A patients will receive a prescription dose of either 5000cGy in 5 fractions delivered every other day or 4800cGy in 3 fractions delivered twice weekly. Child Pugh B patients will receive a prescription dose of 4000cGy in 5 fractions delivered every other day. Patients will be seen at least once per week by a clinician to grade toxicities, with on-treatment labs (CBC, CMP, INR) each week. **RS Arm:** After planning arteriogram, subjects will return within 30 days to receive a single administration of Yttrium-90 into the segmental (≤2) artery supplying the tumor. Administered activity will be an amount prescribed to deliver a dose ≥200 Gy to the perfusedtissue.
D Multi-phase contrast enhanced CT or MR of the abdomen. Baseline imaging should be obtained within 3 months of enrollment
E To be performed in patients receiving SBRT only prior to treatment
F To be performed in patients receiving RS only prior to treatment
G Required only in women of child bearing potential
H Adverse events will be reviewed and collected from the time of informed consent until 30 days after the 6 month visit. See section 12.4 for details
I SBRT arm only: Patients will be seen at least once per week by a clinician to grade toxicities during treatment, with on-treatment labs (CBC, CMP, INR) each week.

2.0 BACKGROUND AND RATIONALE

2.1 Study Rationale

Primary liver cancer is one of the five the most frequently diagnosed cancers in the world and is the second leading cause of cancer death worldwide. Early stage HCC (≤3 cm) is often treated by surgical resection with curative intent. Patients are often not candidates for surgery and there are multiple locoregional therapy options that exist as second line therapy options. Two of these options focus on directed radiation delivery to the tumors, either externally via SBRT or internally via transarterial radioembolization. There are currently limited data on differences in efficacy and safety between these modalities. At our institution, both of these treatments are offered as comparable first line options for unresectable HCC. A direct comparison of these two-radiation based locoregional therapies is therefore felt to be valuable. Unfortunately, the majority of published data with these treatments are retrospective, single institution studies. A direct comparison of the published results is made more difficult by the fact that most literature for radioembolization reports response rates using specific imaging response criteria (i.e. RECIST, mRECISCT, EASL) while most studies on SBRT report efficacy in terms of disease control rate. Given these limited data, with response rates reported using different criteria, a pilot study measuring ORR using the modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma criteria is proposed to better estimate the true ORR to help aid in the power calculation for a full trial.

2.2 Background

Primary surgical resection remains the first-line treatment for small HCC (<3 cm) in patients with preserved liver function. Child-Pugh class A patients with small HCC have shown a 5-year overall survival rate around 70% following surgical resection. Unfortunately, many patients are not eligible for surgical resection either secondary to tumor location, underlying portal hypertension or co-morbidities. The NCCN guidelines recommend surgical resection when possible, with locoregional therapy being recommended for patients who are not candidates for resection (recommending ablation, arterial directed therapies, and external beam radiation therapy as category 2B recommendations).

There are no data directly comparing stereotactic body radiotherapy (SBRT) to high-dose segmental radioembolization (radiation segmentectomy). Both of these treatment approaches have relatively small published data sets demonstrating efficacy and relative safety, but a head-to-head comparison has yet to be performed. In addition to efficacy and toxicity, patient-reported outcomes (PROs) such as quality of life (QoL) and patient out-of-pocket cost of care should play a role in the choice of treatment of these patients. The majority of patients with HCC have chronic liver disease which may already affect their QoL. Many patients, particularly at our institution, also travel multiple hours for their treatments and the difference between the number of visits required for radioembolization and SBRT may affect their treatment choice and PROs.

2.3 Risk/Benefit Assessment

There is very minimal risk outside the standard of care as both treatment options are currently utilized and have category 2B recommendations from the NCCN. Expected toxicities of both treatment arms include fatigue and potential worsening of liver function.

The only added non-standard of care risk would be for RS patents surrounding their functional HIDA scan. The risks involved in a HIDA scan are minimal. They include the following:

1. Radiation exposure; a very small amount of radioactive material is used and the radiation exposure is well below the level that causes adverse effects.
2. Allergic reactions to the radioactive material; however, this is extremely rare, without documented cases.
3. Discomfort, bruising or rash at the injection site or discomfort while lying on the table for the required amount of time for the scan.

3.0 STUDY DESIGN

The proposed study is a single site, prospective, randomized pilot study to assess the feasibility of recruitment of patients into a trial evaluating the efficacy and tolerability of selective transarterial Y90 radioembolization (radiation segmentectomy) versus stereotactic body radiation therapy (SBRT) for solitary early stage (≤ 3cm) hepatocellular carcinoma (HCC).

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

To assess feasibility as measured by screen failures and rate of recruitment into a randomized trial comparing RS and SBRT

Primary Endpoint: Recruitment rates measured at 6 and 12 months and screen failures assessed by the screen failure form at the time patients are approached for enrollment to ascertain specific reasons why patients may choose not to enroll

4.2 Secondary Objectives (SO)/ Secondary Endpoints (SE)

1. **SO:** To compare the proportion of patients with toxicities (≥ grade 4) using CTCAE version 5.0 between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC). Only those toxicities at least possibly related to treatment will be considered.
   SE: Laboratory (CBC, CMP, INR)/clinical toxicities measured using CTCAE version 5.0 up to 6 months post treatment.

2. **SO**: To compare the mean change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC). SE: Change in % radiotracer extraction from baseline, on functional HIDA scan, 3 months after treatment

3. **SO:** To compare the mean change in patient-reported outcomes (PROs) from baseline, at 1, 3 and 6 months, between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using FACT -G and COST FACIT questionnaires. **SE:** Change in FACT-G and COST FACIT from baseline at 1, 3 and 6 months

4. **SO:** To compare the disease-free survival (DFS) rates of RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).**SE:** DFS at 2 years after treatment completion as measured with mRECIST on CT or MR

5. **SO:** To compare time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment. SE: TTST for target tumor up to 2 years following treatment.

6. **SO:** To measure the objective response rate (ORR) of radiation segmentectomy (RS) and stereotactic body radiation therapy (SBRT) as measured at 6 months using mRECIST (appendix IV) for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) to better allow for an appropriately powered trial evaluating the efficacy of these treatments. **SE:** ORR at 6 months after completion of treatment using mRECIST on multiphase CT or MR.

Table 1: Justification for Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFCATION FOR ENDPOINTS
Primary		
1. To assess feasibility as measured by screen failures and rate of recruitment into a randomized trial comparing RS and SBRT	a. Recruitment rates measured at 6 and 12 months b. Screen failure form	a. Given the technical differences between the two modalities, recruitment may prove difficult so analyzing recruitment rates at 6 and 12 months may reveal futility. b. Screen failure form will help PI assess feasibility for a larger scale study.
Secondary		
1. To compare the proportion of toxicities (≥ grade 4) using CTCAE between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).	Laboratory (CBC, CMP, INR)/clinical toxicities measured using CTCAE	Provide a measure of each treatment's potentially deleterious effect on the surrounding liver parenchyma.
2. To compare the change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).	Change in % radiotracer extraction from baseline, on functional HIDA scan, 3 months after treatment	Provide a measure of each treatment's potentially deleterious effect on the surrounding liver parenchyma.
3. To compare the change in patients reported outcomes from baseline, at 1, 3 and 6 months, between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using FACT-G and COST FACIT.	Change in FACT-G and COST FACIT from baseline at 1, 3 and 6 months	Provide insight into whether or not one treatment is more deleterious to a patient's quality of life overall, as measured by the patient themselves.

4. To compare the disease-free survival (DFS) rates of RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm)	DFS at 2 years after treatment completion as measured with mRECIST on CT or MR	DFS at 2 years will allow for assessment of both target and non-target recurrence in this population who are often prone to have new tumors secondary to cirrhosis.
5. To compare time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment.	TTST for target tumor up to 2 years following treatment.	TTST will allow for some measure of the long term efficacy of the treatment as these tumors are often treated multiple times.
6. To measure the objective response rate (ORR) of radiation segmentectomy (RS) and stereotactic body radiation therapy (SBRT) as measured at 6 months using mRECIST for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).	ORR at 6 months after completion of treatment using mRECIST on multiphase CT or MR.	ORR is a common endpoint for the measure of efficacy of liver directed therapy. This may also help provide an estimate which will be used for the sample size calculation for the following large scale study

5.0 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to provide written informed consent and HIPAA authorization
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged ≥ 18 years at time of informed consent
4. Solitary HCC (≤3 cm) diagnosed by imaging (LI-RADS 4-5) or histology
5. Childs-Pugh score ≤ 7
6. ECOG performance status 0-1
7. Tumor location/characteristics eligible for either SBRT or Y90 therapy as deemed by local tumor board
8. Adequate organ function defined as:
    a. serum bilirubin < 4.0 mg/dL
    b. albumin > 2 g/dL

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Any prior locoregional therapy to the target tumor
2. Any prior radiation therapy to the liver
3. Pregnancy or lactation: Women of childbearing potential must have a negative pregnancy test within 14 days of protocol registration. Women are considered to have childbearing potential (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) unless they meet one of the following criteria:
    i. Has undergone a hysterectomy or bilateral oophorectomy; or
    ii. Has been naturally amenorrheic for at least 24 consecutive months
4. Known severe allergic reaction (anaphylaxis) to iodinated contrast
5. Coagulopathy (platelets < 50 K/mm^3 and/or INR > 2) not correctable by transfusion
6. Macrovascular invasion or extrahepatic HCC

5.3 Strategies for Recruitment

The majority of patients will be initially evaluated through the local liver tumor board. Currently, 1-2 patients who fit criteria are presented most weeks. It is estimated that around 50-60 patients in a year's time would be eligible. These patients will be set up to come to a multi-disciplinary clinic where they will have back-to-back clinic visits with both Interventional Radiology and Radiation Oncology on the same day. After both clinic visits are performed, a research coordinator (or if not available, an investigator) will approach eligible subjects and explain the trial and attempt enrollment. Direct referrals to either clinic who are eligible will also be seen by both specialties, and approached for the study, although this group will likely be much smaller than those discussed in tumor board.

6.0 PATIENT REGISTRATION

Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the eligibility criteria. Eligible patients who complete the Informed Consent Process will be registered in the OnCore® database and assigned a patient ID number. Regulatory files will be maintained by the Department of Radiology. Applicable regulatory documents must be completed and on file prior to registration of any patients.

7.0 STUDY INTERVENTION

7.1 Study Interventions

There are two comparative intervention arms, both of which are currently standard-of-care.

7.1.1 Selective transarterial radioembolization (Radiation Segmentectomy (RS)):

This therapy arm involves two separate steps, a planning/mapping arteriogram and a therapy delivery. The planning arteriogram will be performed to confirm arterial anatomy is acceptable for RS (≤2 segment delivery) and that lung shunting is not too high to preclude treatment with RS. Once confirmed, patients will return for RS (within 45 days of mapping). Dose will be calculated based off the desired treatment volume using pre-treatment cross-sectional imaging. The desired segmental dose will be calculated to be ≥ 200Gy. RS will be performed by one of three separate interventional radiologists with experience in radioembolization. Actual administered activity and location of dose administration will be recorded.

7.1.2 Stereotactic Body Radiation Therapy (SBRT):

SBRT will be delivered with linear accelerator-based photon beams with either fixed angle non-coplanar fields or dynamic arcs. For treatment planning, CT simulation with triple phase IV contrast would be performed in the treatment position (supine, arms up). Tumor motion management would be assessed with 4D CT through the breathing cycle. Abdominal compression or breath-hold may be used at physician discretion for diaphragmatic excursion of 1cm or more. Available pre-treatment diagnostic imaging will be fused with the planning CT by deformable registration to assist in target and normal tissue delineation. An internal target volume (ITV) will be generated to account for tumor movement during breathing cycle. Finally, a planning target volume (PTV) will be an expansion of 3- 5mm from the ITV. For Child Pugh A patients, prescription dose will either be 5000cGy in 5 fractions delivered every other day or 4800cGy in 3 fractions delivered twice weekly. For Child Pugh B patients, prescription dose of 4000cGy in 5 fractions delivered every other day. Inverse planning will be used. 95% of the PTV or more will receive at least 100% of the prescription dose. Normal tissue dose constraints for each dose level will be respected with acceptable deviations permitted as outlined in appendix VII. Patients will be seen at least once per week by a clinician to grade toxicities, with on- treatment labs (CBC, CMP, INR) each week.

7.2 Measures to Minimize Bias: Randomization and Blinding

Patients enrolling in trial will undergo permuted block randomization in groups of 4 at the time of enrollment. This will happen at the time of randomization using simple randomized opaque envelopes. Overall blinding is not feasible for this trial given that each arm features a different therapy administered in different departments of the hospital. Given that the primary endpoint is ORR at 6 months, a diagnostic radiologist reviewing for response (and DFS) will be blinded to the therapy arm.

7.3 Concomitant Therapy

No active systemic therapy for the treatment of HCC will be allowed from the time of enrollment to the time of primary outcome assessment. Expected supportive medication generally given as standard of care with either therapy arm will be allowed.

8.0 STUDY EFFICACY AND SAFETY ASSESSMENTS

8.1 Efficacy Assessments

Patients will initially be flagged as potential candidates for the trial following a local tumor board discussion that the location and overall clinical picture would allow for either treatment as a viable option. Once tumor board agreement has been obtained, patients will be scheduled for a multi- disciplinary clinic visit where they will have a complete clinic visit with interventional radiology and radiation oncology back-

to-back. If after these visits patients fulfill inclusion/exclusion criteria, they will immediately thereafter be approached by a research coordinator and enrollment will be attempted.

If patients decline participation, a detailed screen fail form will be filled out to try and best ascertain reasons for declined participation. If the patient agrees to participate, they will be enrolled and randomized (as described above) at that time.

A virtual/telehealth provision will be permitted for all follow-up visits. Since the virtual visit does not allow for effective physical exam of all body systems and vitals are unable to be obtained virtually, these elements will not be required during virtual visits. Labs will be obtained, however, as well as required imaging. If questionnaires are required during a virtual/telehealth visit, they may be administered via REDCap survey.

Baseline: Labs, medical history/physical exam and PROs questionnaires will be obtained during the initial clinic visit prior to randomization. Subjects will be required to have an MRI or CT of the abdomen within 3 months of enrollment.

Pre-Treatment: Patients will return for functional hepatobiliary scan and treatment planning procedures prior to treatment (≤ 30 days from enrollment)

Treatment: Patients will undergo treatment as described above in Section 7.1.

Follow Up Visits:

One month (± 15 days) after treatment completion patients will return for a clinic visit with labs (CBC, CMP, INR, AFP (if elevated at baseline)), physical exam, and PROs using FACT-G and COST FACIT.

Three months after treatment completion (± 30 days) patients will return for a clinic visit with labs (CBC, CMP, INR, AFP (if elevated at baseline)), physical exam, and PROs using FACT-G and COST FACIT. Patients will also undergo multi-phase contrast enhanced CT or MR of the abdomen and functional hepatobiliary scan.

Six months after treatment completion (± 30 days) patients will return for a clinic visit with labs (CBC, CMP, INR, AFP (if elevated at baseline)), physical exam, and PROs using COST FACIT and FACT-G. Patients will also undergo multi-phase contrast enhanced CT or MR of the abdomen and ORR will be measured by two separate abdominal radiologists, using mRECIST, who will have been blinded to the treatment received.

9-24 months: Patients will continue to be followed every three months in clinic with labs, physical exam, and imaging per standard of care. Further intervention will be performed (if needed) as standard of care and DFS and TTST will be recorded up to 2 years from the completion of treatment.

8.2 **Safety and Other Assessments**

Both treatment arms are currently being performed as standard of care. The PI will ultimately monitor safety with direct monitoring for AEs collected by research personnel with discussion with the PI as needed. Comparison of toxicities (≥ grade 4) will be performed as a secondary endpoint. The most common expected toxicities are fatigue and liver toxicity.

9.0 PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may withdraw voluntarily from the study, the PI may discontinue a participant from the study, or patients may be lost to follow-up. The overall estimation of total unanalyzable accruals is 10%.

9.1 Study Intervention Not or Incompletely Performed

Study intervention arms both include a single treatment of the tumor, rather than an ongoing treatment. There is essentially one foreseeable area for necessary discontinuance in each arm.

Patients in the RS arm could potentially be found to have arterial anatomy precluding RS (3 or more segmental arteries supplying tumor or high lung shunt). While this is felt unlikely, it would preclude them from RS and they will be unanalyzable and removed from study to receive off-protocol treatment.

Patients in the SBRT arm will be monitored weekly for toxicities while on-treatment. While it is unexpected for patients to demonstrate toxicities that would preclude completion of the therapy cycle, if this were to occur, patients would be evaluated in the SBRT treatment arm, but designated to have had incomplete treatment.

9.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

1. Pregnancy
2. Significant study intervention non-compliance
3. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
4. The study is terminated (see section 12.1.2)

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

9.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 sequential scheduled visits and is unable to be contacted by the study site staff.

10.0 STATISTICAL CONSIDERATIONS

10.1 Executive Summary

The proposed study is a randomized pilot study evaluating feasibility as measured by screen failures and recruitment rate into a randomized trial comparing RS and SBRT. Secondary objectives will involve comparison of toxicities, effect on liver function, effect on patient reported outcomes and measurement of ORR of RS and SBRT to better allow for an appropriately powered trial evaluating the efficacy of these treatments. DFS and TTST will also be measured up to 2 years after completion of initial treatment.

10.2 Statistical Analysis

10.2.1 Primary Objectives/Endpoints

1. Primary Endpoint: Recruitment rates measured at 6 and 12 months and screen failures assessed by the detailed screen failure form at the time patients are approached for enrollment to ascertain specific reasons why patients may choose not to enroll

Primary Objective: To assess feasibility as measured by screen failures and rate of recruitment into a randomized trial comparing RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

10.2.2 Secondary Objectives/Endpoints

1. **SE:** Laboratory (CBC, CMP, INR)/clinical toxicities measured using CTCAE version 5.0

   SO: To compare the proportion of any toxicities (≥ grade 4) using CTCAE version 5.0 between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 6 months after treatment.

   NH: The proportion of any toxicities (≥ grade 4), using CTCAE version 5.0, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) are equal.

   AH: The proportion of any toxicities (≥ grade 4), using CTCAE version 5.0, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) are not equal.

2. **SE:** Change in % radiotracer extraction from baseline, on functional HIDA scan, 3 months after treatment

   SO: To compare the mean change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   NH: The mean change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, will be equal between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   AH: The mean change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, will not be equal between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

3. **SE:** Change in FACT-G and COST FACIT from baseline at 3 and 6 months

   SO: To compare the mean change in patient-reported outcomes from baseline, at 3 and 6 months, between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using FACT-G and COST FACIT.

   NH: The mean change in patient-reported outcomes from baseline, at 1, 3 and 6 months, will be equal between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using FACT-G and COST FACIT.

   AH: The mean change in patient-reported outcomes from baseline, at 1, 3 and 6 months, will not be equal between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using FACT-G and COST FACIT.

4. **SE:** DFS at 2 years after treatment completion as measured with mRECIST on CT or MR

   SO: To compare the disease-free survival (DFS) rates of RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

NH: The disease-free survival (DFS) rates will be equal between RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

AH: The disease-free survival (DFS) rates will not be equal between RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

5. **SE:** TTST for target tumor up to 2 years following treatment.

   SO: To compare time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment.

   NH: The time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment will be equal.

   AH: The time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment will not be equal.

6. **SE:** ORR at 6 months after completion of treatment using mRECIST on multiphase CT or MR.

   SO: To evaluate the objective response rate (ORR) of radiation segmentectomy (RS) and stereotactic body radiation therapy (SBRT) as measured at 6 months using mRECIST for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   NH: The objective response rates (ORR) of radiation segmentectomy (RS) and stereotactic body radiation therapy (SBRT) are equal, as measured at 6 months using mRECIST for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   AH: The objective response rates (ORR) of radiation segmentectomy (RS) and stereotactic body radiation therapy (SBRT) are not equal, as measured at 6 months using mRECIST for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

10.3 **Sample Size Projections**

The primary objective of the pilot study will be to access feasibility. 20 patients in total will be enrolled, with up to 10 patients per arm (depending on the amount of screen fails). These numbers should be sufficient for the assessment of feasibility.

10.4 **Populations for Analyses**

The study will be performed as a modified Intention-to-treat analysis. Patients who were randomized to the radiation segmentectomy arm, but were later found to be to ineligible for RS based on the planning arteriogram findings, will be considered unanalyzable as they will have not received any protocol therapy and will proceed to other standard of care therapy. If this were to occur, a replacement patient will be added into the RS arm to help ensure a total of 10 patients in each arm.

10.5 **Statistical Analyses**

10.5.1 General Approach

The general approach to the statistical analysis will involve the use of Fisher's exact test, with corresponding 95% CIs, to present comparative outcomes between the two arms. A two-sample t- test will be used to analyze outcomes comparing mean changes in liver function and Kaplan-Meier estimates with a log rank analysis used for survival comparison. The descriptive statistics such as mean, median,

standard deviation and exact confidence interval for the primary endpoint (e.g., recruitment rate and screen failures) will be provided.

A planned interim analysis looking at feasibility will be performed at 6 months after the study is open to enrollment. A similar analysis will also be performed at 12 months. The purpose of these analyses will be to evaluate the endpoint for all subjects who have reached it, and to evaluate general recruitment rates to assess feasibility/futility.

10.5.2 Analysis of the Primary Endpoint(s)

The primary research question to be addressed is to measure feasibility in terms of recruitment rate and screen failures. Recruitment rate will be measured at 6 and 12 months and screen failures assessed by the detailed screen failure form at the time patients are approached for enrollment to ascertain specific reasons why patients may choose not to enroll. Of note, analysis of the screen fail forms will serve as an instructive tool for the investigators as to feasibility for a larger scale study. The granular data collected from the screen fail forms is not intended for publication.

10.5.3 Analysis of the Secondary Endpoint(s)

The secondary research questions to be addressed are as follows:

1. To compare the proportion of any toxicities (≥ grade 4) using CTCAE between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   The proportion of patients with toxicities will be provided along with corresponding 95% confidence intervals. Toxicity rates will be compared using a Fisher's Exact Test.

2. To compare the mean change in hepatobiliary function, as measured 3 months after treatment using a functional HIDA scan, between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   A two-sample t-test will be used to analyze mean changes in liver function as measured by functional HIDA scan.

3. To compare the mean change in patient-reported outcomes from baseline, at 3 and 6 months, between RS and SBRT, for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC), using FACT-G and COST FACIT.

   A two-sample t-test will be used to analyze mean changes in patient reported outcomes as measured using FACT-G and COST FACIT.

4. To compare the disease-free survival (DFS) rates of RS and SBRT at 2 years using mRECIST on CT or MR for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC).

   DFS rates will be compared using Kaplan-Meier estimates with a log rank analysis.

5. To compare time-to-secondary treatment (TTST) between RS and SBRT for patients with small (≤3 cm) solitary hepatocellular carcinoma (HCC) up to 2 years after initial treatment.

   TTST rates will be compared using Kaplan-Meier estimates with a log rank analysis.

6. The proportion of patients with ORR at 6 months will be provided along with corresponding 95% confidence intervals. ORR rates will be compared using a Fisher's Exact Test.

10.5.4 Safety Analyses

Toxicity will be measured as a secondary outcome using CTCAE version 5.0. Adverse event monitoring will occur throughout the duration of the study and will be performed by research coordinators and investigators.

11.0 DATA SUBMISSION AND FORMS

REDCap (Research Electronic Data Capture) database system will be implemented to collect data for this study. The servers hosting REDCap are administered and supported by Indiana University's University Information Technology Services (UITS) and are physically located in IU's secured and environmentally structured data center on the IU Bloomington campus. To comply with HIPAA guidelines, physical, administrative, and technical safeguards and on ongoing risk management framework have been implemented and documented (NIST 800-53) to ensure the security and protection of the study data within the data center, the servers, and the database. REDCap is a software toolset developed by Vanderbilt University, with collaboration from a consortium of institutional partners, for electronic collection and management of research and clinical trial data. Indiana University has joined thisconsortium and has implemented REDCap within the Indiana University's central Information Technology Services (UITS) technical environment to enable rapid development and deployment of electronic data capture and reporting to support specific clinical and translational research projects. Access to the password-protected database will be limited to the investigators of this study, and any data that is distributed will be either de-identified or authorized by written permission from participants. All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in REDCap will be periodically monitored by the IU Simon Cancer Center Data Safety Monitoring Committee.

12.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1 Informed Consent Process

12.1.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or research personnel will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or IRB.

12.3 **Confidentiality and Privacy**

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the investigator.

Each subject in the database will be assigned a unique study identification (ID) number. Patient- derived material will be linked to patient clinical information through this study ID number. Data from the participant's medical record will be manually entered into the participant's de-identified study database and never stored in its original form, ensuring that the data cannot be traced back the actual participant in the event of a data breach. Data will be stored on the University's approved, encrypted back-up servers. The data will be maintained in the database for at least ten (10) years after collection. Records and/or data extracted from the database will be identified by the subject study ID number only and without any accompanying individually identifiable patient information. Thus, the code to the study identification numbers will be accessible only to the PI and authorized study personnel.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a secure database. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by the unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

All paper study materials will be stored in a locked cabinet that will only be accessed by IRB approved staff. Only IRB approved staff will have access to data from the participant's medical records. All research activities will be conducted in as private a setting as possible.

The study monitor, principal investigator, study team, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

13.0 ADVERSE EVENTS

13.1 **Definition of Adverse Events**

13.1.1 Adverse Event (AE)

An adverse event is defined as an untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An adverse event can be ANY unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention, whether or not considered related to the intervention (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Adverse events will be graded according to CTCAE version 5.0

13.1.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

1. Results in death or ANY death occurring within 30 days of treatment
2. Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization

   NOTE: Hospitalizations that are not considered SAEs are:
   - Hospitalization planned prior to biopsy procedure
   - Hospitalization < 24 hours in duration
   - Hospitalization for elective treatment of a pre-existing condition unrelated to biopsy procedure.
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly or birth defect
6. Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

13.1.3 Determining Attribution to the Intervention(s)

Attribution is an assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the attribution categories in Table 2 below.

Table 2: Determining Attribution

Relationship	Attribution	Description
Unrelated to investigational intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

13.2 Expectedness

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

13.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review of the medical record.

Adverse events will be recorded with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or up to 30 days (for SAEs) after the 6 month visit. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until adequate resolution or stabilization.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

13.4 REPORTING ADVERSE EVENTS

Adverse events will be recorded from the time of informed consent and for 30 days after the 6 month visit regardless of whether or not the event(s) are considered related to the study procedure. All AEs considered related to study procedures will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this is after the 6 month visit Any death occurring within 30 days after intervention must be reported as an SAE regardless of attribution.

13.4.1 Reporting to the IRB

Unanticipated problems involving risks to subjects or others will be reported promptly to the IRB if they:

1. are unexpected;
2. are related or possibly related to participation in the research; **and**
3. suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet **all three (3)** criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined **as within 5 days** from becoming aware of the event.

13.4.2 Reporting the IUSCC Data Safety Monitoring Committee

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is in addition to any other regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly and findings will be reported to the full DSMC quarterly. See section 14.5 for additional details

14.0 DATA SAFETY MONITORING PLAN

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for Moderate Risk Trials.

Investigators will conduct continuous review of data and subject safety. Monthly review meetings for moderate risk trials are required and will include the principal investigator, clinical research specialist/coordinator and/or research nurse (other members per principal investigator's discretion). Monthly meeting summaries should include review of data, the number of subjects, significant toxicities as described in the protocol, and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

14.1 Data and Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

14.2 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

14.3 Data Management/ Oncore Reporting Requirements

The DSMC will review data and study progress directly from Oncore and REDCap; therefore, timely data entry and status updates are vital. Study data must be entered promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

14.4 **Study Accrual Oversight**

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

14.5 **Oncore Safety Reporting**

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

14.6 **Protocol Deviation Reporting**

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

15.0 REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012: Global Cancer Statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87–108.

2. www.cancer.org (2017).

3 Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin. Liver Dis. 1999;19 (03): 329-38.

4. Poon RT-P, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg. 2002;235(3):373–382.

5. D.L. Andolino, C.S. Johnson, M. Maluccio, *et al.* Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys, 81 (2011), pp. e447-e453

6. N Sanuki, A Takeda, Y Oku et al. Stereotactic body radiotherapy for small hepatocellular carcinoma: A retrospective outcome analysis in 185 patients, Acta Oncologica, 53:3, 399-404.

7. A. Riaz, V.L. Gates, B. Atassi, *et al.* Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol Phys, 79 (2011), pp. 163-171

8. M. Vouche, A. Habib, T.J. Ward, *et al.* Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology, 60 (2014), pp. 192-201

16.0 Appendices

16.1 Appendix I Protocol Amendment History
16.2 Appendix II COST FACIT Questionnaire
16.3 Appendix III FACT-G Questionnaire
16.4 Appendix IV mRECIST Criteria
16.5 Appendix V CTCAE Version 5.0 Criteria
16.6Appendix VI Screen Fail Form
16.7 Appendix VII SBRT Constraints

16.1 **Appendix I Protocol Amendment History**

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

16.2 **Appendix II COST FACIT Version 1**

COST FACIT Version I

Study ID _____

Below is a list of statements that other people with your illness have said are important. Please mark one answer per line to indicate your response as it applies to the past 7 days.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment	○	○	○	○	○
My out-of-pocket medical expenses are more than I thought they would be	○	○	○	○	○
I worry about the financial problems I will have in the future as a result of my illness or treatment	○	○	○	○	○
I feel I have no choice about the amount of money I spend on care	○	○	○	○	○
I am frustrated that I cannot work or contribute as much as I usually do	○	○	○	○	○
I am satisfied with my current financial situation	○	○	○	○	○
I am able to meet my monthly expenses	○	○	○	○	○
I feel financially stressed	○	○	○	○	○
I am concerned about keeping my job and income, including work at home	○	○	○	○	○
My cancer or treatment has reduced my satisfaction with my present financial situation	○	○	○	○	○
I feel in control of my financial situation	○	○	○	○	○

16.3 **Appendix III FACT-G Version 4**

FACT-G (Version 4)

Study ID _____

Below is a list of statements that other people with your illness have said are important.
Please choose one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

I have a lack of energy	0 - Not at all 1 - A little bit 2 - Somewhat 3 - Quite a bit 4 - Very much
I have nausea	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
Because of my physical condition, I have trouble meeting the needs of my family	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I have pain	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am bothered by side effects of treatment	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I feel ill	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am forced to spend time in bed	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much

SOCIAL/FAMILY WELL-BEING

I feel close to my friends	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I get emotional support from my family	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I get support from my friends	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit 4 - Very much
My family has accepted my illness	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am satisfied with family communication about my illness	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I feel close to my partner (or the person who is my main support)	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
Regardless of your current level of sexual activity, please answer the following question.	◯ I prefer not to answer
I am satisfied with my sex life	0 - Not at all 1 - A little bit 2 - Somewhat 3 - Quite a bit 4 - Very much

Please choose one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

I feel sad	0 - Not at all 1 - A little bit 2 - Somewhat 3 - Quite a bit 4 - Very much

I am satisfied with how I am coping with my illness	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am losing hope in the fight against my illness	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I feel nervous	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I worry about dying	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I worry that my condition will get worse	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much

FUNCTIONAL WELL-BEING

I am able to work (include work at home)	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
My work (include work at home) is fulfilling	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am able to enjoy life	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I have accepted my illness	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much

I am sleeping well	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am enjoying the things I usually do for fun	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit ◯ 4 - Very much
I am content with the quality of my life right now	◯ 0 - Not at all ◯ 1 - A little bit ◯ 2 - Somewhat ◯ 3 - Quite a bit 4 - Very much

16.4 **Appendix IV Modified (mRECIST) Criteria Assessment for Hepatocellular Carcinoma**

An electronic copy of the mRECIST critieria can be found at the following website:
https://imaging.cancer.gov/clinical_trials/docs/mRECIST%20for%20HCC%202010.pdf

16.5 **Appendix V CTCAE Version 5.0**

An electronic copy of the CTCAE version 5.0 is available on the CTEP web site at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

16.6 **Appendix VI Screen Fail Form**

SCREEN FAIL FORM

Date: _____

Initials of person completing form: _____

If subject refuses consent, please select a reason why and provide available details:

□ **Not Interested** (prefers not to be on a research trial, prefers one treatment to another etc.)

_____
_____
_____
_____

□ **Does not have time** (i.e. lives too far away, work schedule, etc.)

_____
_____
_____
_____

□ **Prefers not to answer**

□ **Other**

_____
_____
_____
_____
_____
_____
_____
_____

16.7 **Appendix VII: SBRT Constraints**

Desired SBRT Constraints:

Structure	Volume	Dose / Constraint
PTV	>95%	Rx
GTV	>98%	>110% Rx
Liver – GTV	700cc or V10 Gy	<1500cGy or <70%
	1/3 uninvolved	<1000cGy (CTP-A), <1800cGy (CTP-B7)
	500cc uninvolved	<700cGy (CTP-A), <1200cGy (CTP-B7)
Duodenum	0.5 cc	2400 cGy (3 fraction) 3000 cGy (5 fraction)
	<5 cc	1650 cGy (3 fraction) 1800 cGy (5 fraction)
	<10 cc	1140 cGy (3 fraction) 1250 cGy (5 fraction)
Stomach	0.5 cc	2250 cGy (3 fraction) 3000 cGy (5 fraction)
Esophagus	0.5 cc	32 Gy (5 fx)
Spinal Cord	100%	<600cGy/fraction
Chest Wall	100%	<5000cGy
	<5cc	4000cGy
	<30cc	3000cGy
R Kidney	2/3	<2000cGy
L kidney	1/3	<1500cGy
Heart	0.5 cc	3000 cGy (3 fraction) 5250 cGy (5 fraction)

Variation acceptable Constraints (per RTOG 1112)

Structure	Variation acceptable	Deviation unacceptable
Esophagus max (0.5 cc)	>32 but ≤34 Gy	>34 Gy
Stomach max (0.5 cc)	>30 but ≤32 Gy	>32 Gy
Duodenum max (0.5 cc)	>30 but ≤32 Gy	>32 Gy
Small bowel max (0.5 cc)	>30 but ≤32 Gy	>32 Gy
Large bowel max (0.5 cc)	>32 but ≤34 Gy	>34 Gy
Spinal cord + 5 mm max (0.5 cc)	>25 but ≤28 Gy	>28 Gy
Kidneys: bilateral mean	>10 but ≤12 Gy	>12 Gy