International Randomized Study of Transarterial Chemoembolization (TACE) Versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma After Initial TACE

Study Protocol and Statistical Analysis Plan

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September 21, 2022

International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma after Initial TACE

Protocol Number: IRB-35937

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Protocol Signature Page

INTERNATIONAL RANDOMIZED STUDY OF TRANSARTERIAL CHEMOEMBOLIZATION (TACE) VERSUS STEREOTACTIC BODY RADIOTHERAPY (SBRT)/STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR RESIDUAL OR RECURRENT HEPATOCELLULAR CARCINOMA AFTER INITIAL TACE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to the protocol and in strict accordance with all applicable U.S. Food and Drug Administration (*"FDA"*) regulations and guidelines applicable to the Study, including without limitation the regulations set forth in Parts 50, 54, 56 and 812 of 21 C.F.R., and all other applicable federal, state, or local laws, guidelines, rules, and regulations of any type.

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Clinical Site

_____ _____
Signature, Principal Investigator Date

_____
Printed Name, Principal Investigator

Contents

PROTOCOL SYNOPSIS

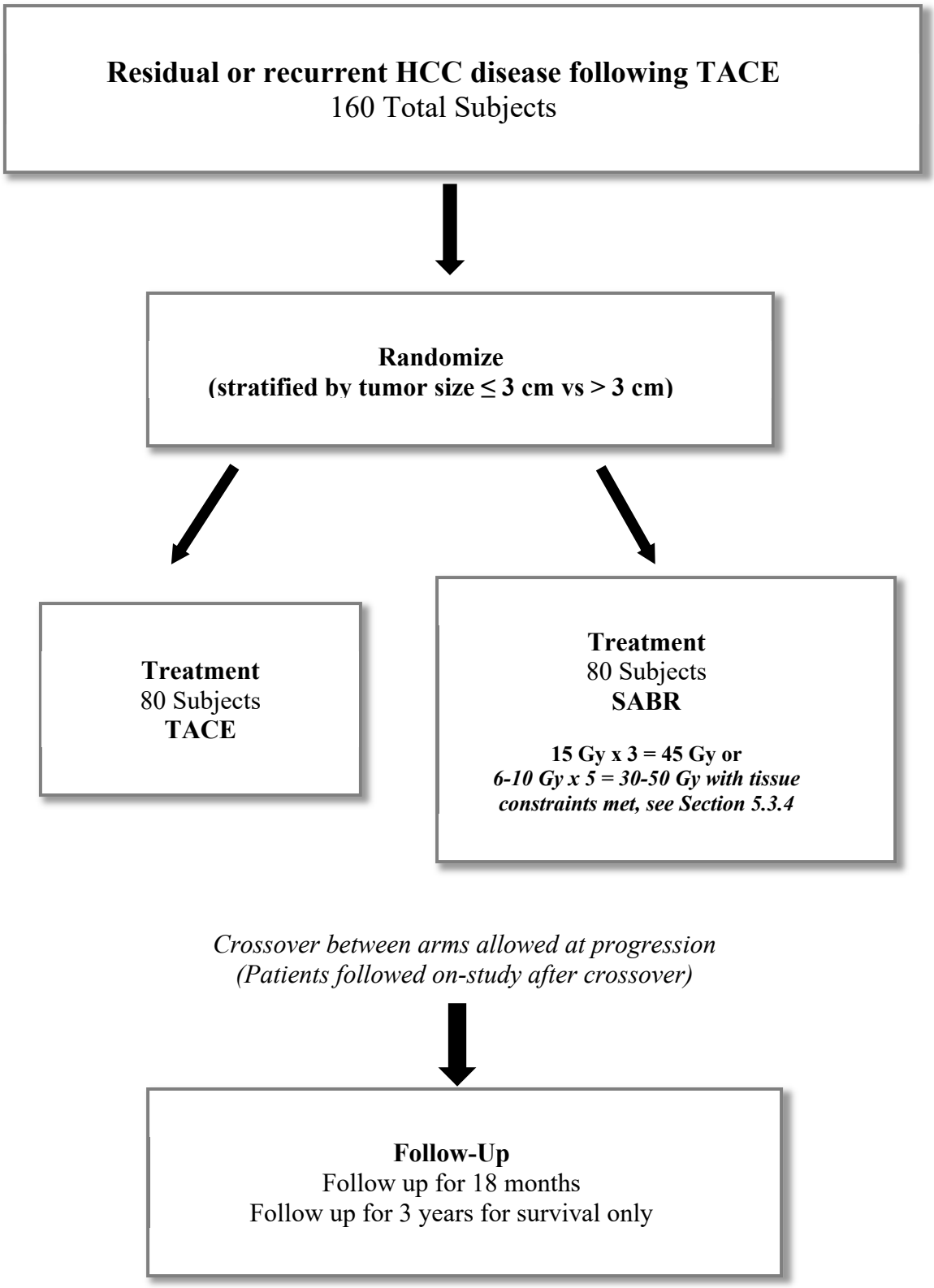
Title	**International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT)/Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma after Initial TACE**
Phase	III
Indication	Hepatocellular carcinoma (HCC) is the third most deadly cancer in the world. It is primarily seen in areas where hepatitis is endemic, such as Asia, but other risk factors include alcoholic cirrhosis. Surgical resection and/or transplantation remain the only potentially curative options. However, more than 80% of patients present with unresectable disease. For these patients with unresectable tumors, a variety of treatment options are available, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), yttrium-90 radioembolization, microwave coagulation, laser-induced thermotherapy, and percutaneous alcohol injection, each of which have limitations. Stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) for unresectable HCC is a relatively new treatment option made available because of significant improvements in diagnostic imaging and radiation delivery techniques. Although follow-up is limited, pilot study results show encouraging local control rates. Some investigators have combined TACE with fractionated conventional radiotherapy as a means of intensifying local therapy, with evidence of enhanced efficacy. TACE remains the dominant mode of local therapy for unresectable HCC. However, recurrence rates are high and residual disease is noted in approximately 1/3 of patients. Because SBRT/SABR is rapidly becoming an accepted local therapy for hepatic lesions, its role in treating HCC needs to be more precisely defined. Moreover, once patients are found to have residual disease after initial TACE, it is unclear if additional TACE will be as effective or if another mode of local therapy such as SBRT/SABR would be preferable. We propose to conduct a multicenter randomized study comparing TACE vs SABR for residual or recurrent HCC after initial therapy with TACE. Residual or recurrent HCC will include lesions that persist, progress, or recur following completion of all planned TACE

	therapy.
Primary Objective(s)	To determine the freedom from local progression (FFLP) of TACE vs SABR in patients with persistent HCC after TACE.
Secondary Objective(s)	1) To determine the overall survival of TACE vs SABR for residual or recurrent HCC. 2) To determine the progression-free survival of TACE vs SABR for residual or recurrent HCC. 3) To determine the toxicities associated with TACE or SABR in the treatment of HCC.
Hypothesis	SABR is more effective than repeat TACE in the treatment of patients with residual or recurrent HCC after initial TACE.
Study Design	Patients with residual or recurrent disease after initial TACE will be randomized to receive either repeat TACE or SABR. Residual or recurrent disease after initial TACE will be determined by CT or MRI.
TACE	• TACE study treatment must start within 3 months of eligibility confirmation/randomization date. If these dates are not the same treatment should start within 3 months of randomization. Treatment may be delivered in up to 3 staged procedures depending on the architecture of the tumor vasculature, 6-8 weeks apart.
SABR	• Patients will undergo a 4-dimensional CT scan and contrast CT scan for radiation treatment planning and target delineation. • SABR will be delivered using a respiratory compensatory method or using a margin inclusive of respiratory motion. • Image-guidance during SABR will be achieved with either implanted fiducials, surgical clips, or using the residual radio-opaque material (lipiodol) from the initial TACE. • Treatment will be delivered in 3 or 5 fractions, within 1-2 weeks (and at least 2 fractions per week), at the discretion of the investigator. • Dose will be administered according to the following recommended schedule: o Independent of tumor size, 15 Gy x 3 fractions should be utilized as long as the normal tissue constraints can be met. If the normal tissue constraints cannot be met, then it is allowable to treat tumors with 8-10 Gy x 5 fractions as long as the tissue constraints are met. o Results will be analyzed according to tumor size and radiation dose. • The following dose constraints are required to be met: o Liver (excluding tumor): 700 cc of the normal liver volume should be limited to <12 Gy (3 fractions) or <15 Gy (5 fractions)

	○ Kidney: Combined volume for both should have 75% <12 Gy ○ Adjacent bowel and stomach (within 2.5cm): Dmax < 40 Gy, V33Gy<1cc, V30Gy<10cc, V20<30cc ○ Spinal Cord max: no more than 1cc > 8 Gy ○ Esophagus max: no more than 1cc > 27 Gy
Primary and Secondary Endpoints	
Primary Endpoint	Freedom from local progression (FFLP) at 12 months as defined in Section 9. (Sample size is powered for 12-month endpoint.)
Secondary Endpoints	• Comparison of median progression free survival (PFS) and progression free survival at 12 months for individuals treated with SBRT and individuals treated with TACE • Progression free survival (PFS). • Overall survival (OS). • Serum AFP levels. • FFLP at 18 months.
Sample size by treatment group	The target accrual is 80 patients per arm for a total of 160 patients from all sites worldwide. Anticipated enrollment at Stanford is 15-30 patients over 3 years.
Summary of Eligibility Criteria	• Confirmed HCC by one of the following: ○ Histopathology ○ One radiographic technique that confirms a lesion >1cm with arterial hypervascularization with washout on delayed phase • Radiographic evidence of persistent, progressive or recurrent disease following completion of all planned TACE therapy. • Subject is within one year of initial TACE • Subject has had 3 or less TACE interventions. • Multi-specialty evaluation which should include: ○ Liver CT or MR with IV contrast within 6 weeks of date of eligibility. ○ AFP within 4 weeks of date of eligibility (recommended but not required). • Unifocal liver tumors ≤ 7.5cm in greatest axial dimension. Multifocal lesions will be restricted to lesions that can be treated within a single target volume within the same liver segment, to an aggregate of 10cm, and dose constraints to normal tissue must be met. • ECOG 0, 1 or 2 • Child Pugh class A or B, Score ≤ 9
Intervention and Mode of Delivery	• Transarterial Chemoembolization – direct intravascular---administration of chemotherapy and embolization material under general anesthesia/sedation, conscious sedation and/or local anesthesia. • SABR – Stereotactic ablative radiotherapy (outpatient procedure).

Duration of Intervention and Evaluation	The duration of intervention will be 1 to 16 weeks. The follow-up period will be 18 months following completion of treatment; and 3 years for survival only.
Statistical Considerations	56 informative subjects are required in order to have a 90% chance of detecting a 30% difference between the 2 arms. Eighty patients in each arm, for a total sample size of 160 patients, will be enrolled to account for patients who may be taken off the study (prior to the primary endpoint of FFLP) due to progression or declining performance status that would preclude necessary study follow-up. A 30% attrition rate in this patient population is a reasonable assumption.

SCHEMA


Residual or recurrent HCC disease following TACE
160 Total Subjects
Randomize
(stratified by tumor size ≤ 3 cm vs > 3 cm)
Treatment
80 Subjects
TACE
Treatment
80 Subjects
SABR
15 Gy x 3 = 45 Gy or
6-10 Gy x 5 = 30-50 Gy with tissue constraints met, see Section 5.3.4
Crossover between arms allowed at progression
(Patients followed on-study after crossover)
Follow-Up
Follow up for 18 months
Follow up for 3 years for survival only

ABBREVIATIONS

AFP	Alpha-fetoprotein
AE	Adverse events
CBC	Complete blood count
CMP	Complete metabolic panel
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DLT	Dose limiting toxicity
DVH	Dose volume histogram
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFLP	Freedom from local progression
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
GTV	Gross tumor volume
HCC	Hepatocellular Carcinoma
IMRT	Intensity-modulated radiotherapy
INR	International normalized ratio
ITV	Internal target volume
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
OS	Overall Survival
PT	Prothrombin time
PTT	Partial thromboplastin time
PTV	Planned treatment volume
RFA	Radiofrequency ablation
RILD	Radiation induced liver disease
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative radiotherapy
SAE	Serious adverse events
SUV	Standardized uptake value
TACE	Transarterial chemoembolization

1. OBJECTIVES

1.1 Primary Objectives

To determine the freedom from local progression (FFLP) of TACE vs SABR in patients with persistent HCC after initial TACE.

1.2 Secondary Objectives

1.2.1 To determine the progression-free survival (PFS) of TACE vs SABR in patients with persistent HCC after initial TACE.
1.2.2 To determine the overall survival (OS) of TACE vs SABR for persistent HCC.
1.2.3 To determine the toxicities associated with TACE or SABR for persistent HCC.

2. BACKGROUND AND RATIONALE

2.1 Study Disease

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and represents more than 5% of all cancers, while accounting for 80-90% of all liver cancers. Approximately 500,000 cases of HCC are diagnosed each year, and it is the third leading cause of cancer-related deaths worldwide (1). There are wide geographical variations in the incidence of the disease, with the highest rates in the developing countries of Asia and Africa. However, the incidence of HCC is increasing in North America and Europe (2, 3). HCC occurs more often in males than females and is more common in people aged 50 to 60 years.

HCC most commonly appears in patients with chronic viral hepatitis, alcoholism, and cirrhosis. In particular, cirrhosis is the strongest predisposing risk factor for HCC; exposure to aflatoxin, hemochromatosis, certain autoimmune diseases of the liver, and other diseases that instigate chronic inflammation of the liver are also risk factors.

The reported prognosis of HCC used to be poor, and most patients died within 1 year regardless of the treatment they received (4). However, with the introduction of screening programs for high risk patients, 30-40% of patients are diagnosed at the early stages when curative treatments are possible (5). Very early HCC patients have the best survival rates, reporting a 5-year survival rate of 89-93% following resection, and 71% following percutaneous treatment (5).

Early stage patients are also less prone to recurrence after curative treatments. In contrast, prognosis for patients with endstage HCC remains poor. Life expectancy is less than 6 months with no survival benefit from any treatment (6, 7). In general, early detection offers the only possibility for cure. Unlike other cancers, prognosis of HCC does not solely depend on tumor stage, but is also determined by cancer related symptoms (i.e. performance status), and degree of liver function compromise. The usual TNM cancer staging system is not a useful indicator for prognosis. The Barcelona group has worked out a staging system, called the Barcelona Clinic Liver Cancer (BCLC) Classification, incorporating the three main prognostic factors and linking the classification with a treatment approach and prognosis (8).

The American Association for the Study of the Liver Diseases has published a guideline on the treatment of hepatocellular carcinomas (9). Surgical resection, liver transplantation and percutaneous treatments are considered to be highly effective, even curative if the patients have only mild cirrhosis (Child-Pugh A), only 1 nodule that is smaller than 5 cm or less than 4 nodules smaller than 3 cm. In fact, hepatic resection is the treatment of choice, certainly in non-cirrhotic patients where it can be performed with low rates of life-threatening complications (10). Surveillance programs for HCC have increased the proportion of patients diagnosed at an early stage. Nevertheless, half of all patients are still diagnosed at an intermediate-advanced tumor stage. This stratum is composed of patients who do not qualify for curative options, but who have not reached a terminal stage as reflected by heavily impaired liver function with intense physical deterioration (11).

2.2 Transarterial Chemoembolization

Patients who are classified as intermediate stage according to the BCLC Classification and present with a larger nodule or multiple nodules, have well-preserved liver function (Child-Pugh A), but no extrahepatic invasion or symptoms benefit most from embolization of the arterial network supplying the tumor. A comparative survey of 310 patients found that patients with larger tumors treated by TACE had a significant better survival than when treated with percutaneous acetic acid injection (12). Both transarterial embolization (TAE) and TACE induce tumor necrosis in more than 50% of the patients. Meta-analysis showed survival benefits for TACE, but not for TAE (13). This outcome was confirmed in two randomized controlled trials (14, 15) and is now recommended as standard practice in the specified subset of patients by the American Association for the Study of the Liver Diseases.

As for the chemotherapy used in TACE procedures, cisplatin, doxorubicin, and mitomycin are the most frequently used in the United States, usually given as a single agent or combination of agents emulsified with lipiodol (ethiodized fatty acids of poppyseed oil). Solid embolic material may be mixed with the chemotherapy and lipiodol, or may be administered separately after completion of chemotherapy administration. These materials may include gelatin sponge, polyvinyl alcohol particles, or embolic beads. Methods using lipiodol are referred to as conventional TACE, or cTACE. No direct comparative data are available to conclude which chemotherapeutic agents, dosage, or treatment schedule is most effective. From the few randomized controlled trials and published protocols, the standard of practice is to perform multiple treatment sessions initially every 6-12 weeks until technical success is achieved (all visible tumor tissue treated, requiring 1-4 treatments), with follow-up diagnostic imaging approximately quarterly with retreatment dictated by imaging findings for the duration of the patient's life (13).

With the drug shortages prevalent in the past decade, protocols for TACE have evolved to exploit available materials. For cTACE, single agent treatment using doxorubicin has become most common, although alternatives including epirubicin, oxaliplatin, and gemcitabine may be substituted or added. In the Western world, using ion-exchange resin microspheres rather than lipiodol as the carrier has become the dominant method. These microspheres are calibrated to match arteriolar lumen diameters, and can be loaded with chemotherapeutics with cationic moieties such as doxorubicin or irinotecan. After intra-arterial delivery, these microspheres lodge downstream in the arterioral bed, causing ischemia, and elute the chemotherapeutic agent over a period of weeks. This method, sometimes referred to as drug-eluting bead TACE or

DEB-TACE, has been shown to have lower hepatic and systemic toxicity, and efficacy at least equivalent to that of cTACE (16)

TACE procedures can derive efficacy by two related mechanisms. One is that the infusion of chemotherapeutic with a viscous material that impedes flow in the tumor microvasculature (e.g. lipiodol) along with macroscopic embolization of the blood vessel with particles or spherical embolic agents will interrupt the arterial blood supply to the tumor, causing infarction and necrosis of the tumor. Secondly, focused administration of the chemotherapeutic agents allows a higher drug concentration to be delivered to the tumor with reduced systemic exposure, which is the dose-limiting factor in most systemic chemotherapy. This effect is further enhanced by arterial embolization which prevents the chemotherapeutic agents from being washed out of the tumor bed. TACE has a tumor necrosis rate on histopathology of 56%–100% depending on tumor size, location, and morphology (17-19). Jang and colleagues found that subsequent TACE did not reduce tumor recurrence or improve survival when complete necrosis had been achieved in the first TACE procedure (20).

Liver transplantation provides the highest possibility of cure for HCC. Survival at 4 years has been reported to be 75% in patients with single tumors < 5cm or up to 3 tumors < 3 cm (21). However, this treatment option is limited by the strict eligibility criteria and the availability of donor livers. Even after satisfying the criteria and being listed for transplantation, many patients drop out of eligibility before receiving a transplant, with a rate of >40% at 2 years. Drop out can be due to comorbidities or change of social support status, but is commonly due to progression of intrahepatic malignancy or development of extrahepatic metastases.

TACE is the established standard initial therapy for a subgroup of HCC patients with adequate hepatic function, no extrahepatic disease, and who are not eligible for other potentially curative treatment options. Unfortunately, the 3-year overall survival is only 20%-40% (22). Recurrence of HCC following initial remission occurs after 27 months on average (23). A meta-analysis has shown that adjuvant therapy with TACE may increase survival (24). However, TACE alone may not be sufficient, especially for larger tumors. Numerous pilot studies suggest that combination therapy of TACE plus radiofrequency ablation (RFA) or other locoregional therapies may reduce the incidence of recurrence, and may extend patient survival.

2.3 Stereotactic Ablative Radiotherapy for Liver Tumors

For selected patients, aggressive focal radiation can deliver tumoricidal doses using 3-dimensional treatment planning techniques, including intensity modulated radiotherapy (IMRT). Experience with 3-dimensional treatment planning has allowed the safe irradiation of two thirds of the normal liver to 48-52.8 Gy and one third of the liver to 66-72.6 Gy (fraction size 1.5-1.65 Gy administered twice per day) (25-28). Further dose escalation with conventional radiation therapy techniques risks injury to adjacent abdominal organs.

Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Radiotherapy (SABR) has emerged as a novel approach for the local ablation of liver tumors. SABR provides a conformal isodose distribution with a steep radiation dose gradient allowing much higher doses of radiation than conventional radiation therapy and conformal radiotherapy techniques to be

delivered safely with high precision to focal liver tumors while minimizing the radiation dose to normal liver and adjacent organs (*44,45*).

The first published SBRT/SABR results were a phase I/II study by Herfarth and colleagues. This study delivered single-dose stereotactic radiation therapy to 60 liver tumors (29). The dose was escalated from 14 to 26 Gy (reference point), with the 80% isodose surrounding the planning target volume. Median tumor size was $10cm^3$ (range, 1 to $132cm^3$). All patients tolerated the treatment well without any major side effects. Eleven patients experienced intermittent loss of appetite or mild nausea for 1-3 weeks after treatment. None of the treated patients developed clinically detectable radiation-induced liver disease (weight gain, ascites, newly developed increase of alkaline phosphatase concentration). The overall actuarial local tumor control rates were 75%, 71%, and 67% at 6 months, 12 months, and 18 months of follow-up, respectively. There was a statistically significant difference in Kaplan-Meier estimates of local tumor control between tumors treated with 14-20 Gy vs. 22-26 Gy but the local control may have also influenced a "learning" phase. The investigators noted that the local control was improved in patients treated later in the study after establishing the proper margin expansion. In the patients treated after this phase, the actuarial local tumor control rate was 81% at 18 months. Stratification by size did not reveal a statistically significant difference in the local control rate for larger lesions ($\geq 15cm^3$) compared with smaller one ($<15cm^3$) in the 22-26 Gy range.

Wada et al delivered 45 Gy in 3 fractions to 11 primary and secondary liver tumors (treatment of lung lesions was also reported in this study) (30). Local control of liver lesions was approximately 85% at 6 months and 71% at 18 months. Local control was enhanced for smaller lesions (95% at 18 months for lesions less than 3cm diameter [liver and lung lesions combined] versus 58% for lesions over 3cm). No serious adverse events were reported. Mendez-Romero et al utilized 12.5 Gy in 3 fractions or 5 Gy in 5 fractions for patients with primary and secondary liver lesions (31). One-year and two-year local control rates were 94% and 82% for all patients and 100% and 86% for patients with metastases. Survival ranged from 92% overall at 6 months to 70% overall at 18 months. They noted 3 instances of acute grade 3 or higher toxicity, including a Childs B patient that died secondary to liver decompensation, esophageal bleeding, and infection 2 weeks post-radiosurgery. More recently Tse et al delivered 24-54 Gy in 6 fractions to 41 patients with primary liver tumors in a dose escalation study (32). Local control was 65% at 1 year, with 50% of patients surviving at 1 year. Grade 3 changes in liver function indexes and platelet count were noted in 12 patients within 3 months of radiosurgery. Two late GI toxicities, one leading to death, were also reported.

More recently, Hoyer et al reported a phase II study in which patients with colorectal hepatic metastases were treated with 15 Gy in 3 fractions. They demonstrated a 2-year local control rate of 86% and a 38% overall 2-year survival rate (33). This treatment was well tolerated. In another phase I study for liver metastases, Schefter *et al* dose escalated to 20 Gy in 3 fractions without reaching maximum tolerated dose (MTD). These investigators limited 700cc of normal liver to less than 15 Gy and included tumors up to 6cm in maximum dimension (34).

Lee et al reported a phase I study using SBRT/SABR for liver metastases in 68 patients (35). They used a 6-fraction schedule based on the risk of liver toxicity. With a median dose of 41.4 Gy (range: 27.7-60 Gy), they reported a 1-year local control rate of 71% and 10% rate of grade ≥3 toxicity. No cases of radiation induced liver disease were noted.

Rusthoven et a. reported results from a multi-institutional phase I/II study using SBRT/SABR for liver metastases using a 3-fraction regimen escalated to a total dose of 60 Gy (36). Forty-seven patients were enrolled, and the 1-year and 2-year local control rates were 95% and 92%, respectively. One case of grade 3 toxicity was noted.

Examination of these and other studies (34, 37-41) suggests that hypofractionated treatment of liver with doses in the range of 20-60 Gy delivered in 1-5 fractions can control tumor growth in about 90-100% of tumors in the first 6 months post-treatment, and about 70-90% of tumors at 18 months post-treatment. Survival in this relatively heterogeneous group of patients ranges from about 80-95% at 6 months to 40-70% at 18 months. Very few serious acute or late toxicities have been reported; many of the toxicities noted are related to the dose received by adjacent organs (31, 32, 40). Some studies limited the size of lesions treated to 5 or 6cm or less (29, 30, 40). Outcomes are likely improved when smaller lesions are treated (30) but studies addressing this issue specifically have not been conducted. Although patients in these studies often receive chemotherapy before or after radiosurgery, this variable is usually not uniformly controlled and its contribution to local control, survival, and toxicity is difficult to gauge.

Very little data exists for radiation to primary liver tumors. Tse et al conducted a phase I study demonstrating the feasibility and safety of SBRT/SABR for HCC and intrahepatic cholangiocarcinoma using a 6-fraction regimen (32). In addition, Takeda et al reported on 14 patients treated with TACE and SBRT/SABR with a 5-7 fraction regimen, reporting 1 local recurrence and no serious adverse toxicity (42).

Stanford University has recently completed a Phase I dose escalation trial using SBRT/SABR for unresectable liver tumors (43). In this single institution study, patients were treated with a single fraction of 18 Gy, 22 Gy, 26 Gy, and 30 Gy. In these patients, 3 to 5 gold fiducial seeds were implanted percutaneously for tumor tracking, and 4D CT and FDG-PET CT scans were utilized for treatment planning. These investigators demonstrated that treating patients in this manner was feasible and that SBRT/SABR could be applied with minimal toxicity even at the highest dose.

2.4 Rationale for Study

TACE remains the dominant mode of local therapy for unresectable HCC. Recurrence rates after TACE are high (60-70% at one year). Because SABR is a rapidly emerging local therapy for hepatic lesions with encouraging results (local control 70-100% of liver tumors in the first 12 months post-treatment), its role in treating HCC patients should be further defined.

Because of the association of hepatitis liver disease and alcoholic cirrhosis, many patients with HCC have compromised liver function. Precise ablation of the tumor with SABR and continuous tumor and respiratory tracking have the potential to reduce the radiation to normal liver and adjacent organs with minimal toxicity even for patients with large tumors or compromised liver function (*47*).

While safety data is known in patients receiving TACE, fractionated radiation and combination TACE and fractionated radiotherapy, no efficacy and toxicity data exists on SABR after TACE.

The present study will investigate the efficacy, survival and toxicity of TACE vs. SABR for persistent or recurrent HCC in a multi-institutional setting. SABR has the potential of significantly improving tumor control of HCC, even for large tumors or tumors close to critical organs, which could translate into more effective palliation, less toxicity, better quality of life, and longer patient survival.

3. PRE-TREATMENT AND PATIENT SELECTION

3.1 Patient Eligibility

3.1.1 Inclusion Criteria (to be verified with source documents, See Appendix III).

- Confirmed hepatocellular carcinoma (HCC) by one of the following:
  - Histopathology
  - One radiographic technique that confirms a lesion $\geq$ 1cm with arterial hypervascularization with washout on delayed phase

- Radiographic evidence of persistent, progressive, or recurrent disease following completion of all planned TACE therapy.
- The subject is within one year of initial TACE.
- The subject has had 3 or less TACE interventions.

- Unifocal liver tumors not to exceed 7.5 cm in greatest axial dimension. Multifocal lesions will be restricted to lesions that can be treated within a single target volume within the same liver segment and to an aggregate of 10 cm as long as the dose constraints to normal tissue can be met

- ECOG PS (Eastern Clinical Oncology Group) performance status 0, 1 or 2 (Appendix I)

- Patients with liver disease classified as Child Pugh class A or B, with score $\leq$ 9 (within 4 weeks of treatment)

- Life expectancy $\geq$ 6 months

- Age $\geq$ 18 years old

- Ability of the research subject or authorized legal representative to understand and have the willingness to sign a written informed consent document

3.1.2 Exclusion Criteria (to be verified with source documents, See Appendix III).

- Prior radiotherapy to the upper abdomen

- Prior radioembolization to the liver

- Prior RFA to index lesion
- Liver transplant
- Active gastrointestinal bleed within 2 weeks of study enrollment
- Ascites refractory to medical therapy (mild to moderate ascites is allowed)
- Women who are pregnant or breastfeeding
- Administration of chemotherapy within the last 1 month
- Extrahepatic metastases
- Participation in another concurrent treatment protocol
- Prior history of malignancy other than HCC, dermatologic basal cell or squamous cell carcinoma.

3.2 Pretreatment Studies

Pretreatment tests required for eligibility should be performed within specified timeframes as follows:

- CT of the liver with IV contrast within 6 weeks of enrollment showing residual or recurrent disease after initial TACE. If the patient is unable to have CT contrast, a liver MRI may be done.
- Labs including CBC with differential, coagulation labs (PT or INR, PTT), and CMP (comprehensive metabolic panel or chemistry panel with liver function tests [LFTs]). Other labs as needed may be ordered by treating physician. Labs should be done within 4 weeks of treatment to determine the Child Pugh Score.
- Serum AFP levels is not required within 4 weeks of enrollment, but recommended.

3.2.1 Additional Pre-treatment Instructions:

- Subjects should have a multi-specialty evaluation whereby the residual or recurrent liver lesion is deemed amenable to treatment by either modality, by both the attending radiation oncologist and interventional radiologist. This should be documented in a note signed by the physician, or included in the consultation note of each physician.

3.3 Informed Consent Process

- The Principal Investigator (PI) is responsible for ensuring that proper informed consent has been obtained from the subject before any study/research activity is conducted. The PI can designate authorized members of the research team to obtain the informed consent.
- The protocol and Informed Consent Form must have Stanford and local institution's IRB approval prior to research activity. The PI at each participating center is responsible for

ensuring that proper consent process is performed and the most current study-specific IRB-approved consent form is signed properly by participant and research staff.

- The PI at each participating center is ultimately responsible for determining whether a subject has the capacity to consent. If the subject is lacking such capacity, whether due to cognitive impairment or other causes, the PI/designee may obtain consent from a legally authorized representative.
- As part of the consent process, the subject's or his/her representative's questions must be answered prior to consent being given and throughout the study. The subject or his/her representative should be asked if there are any questions prior to consent being obtained.
- When giving consent, the subject or an authorized legal representative needs to verbalize understanding and sign and date the appropriate page(s) of the Consent Form along with the investigator or designated research staff member.
- Consent forms will be maintained according to the standards of Stanford University as well as each collaborating center's regulations. This includes, but is not limited to, providing the subject or his/her authorized representative a copy of the consent form; keeping a copy in the patient's study chart and medical record; and keeping the original consent form in a secured appropriate place for the required period set forth by Stanford's IRB.
- The written consent document should embody, in a language understandable to the participant, all the elements necessary for legally informed consent. For research conducted in a language other than English, consent forms must be translated accurately.
- The sponsor may audit any or all consent forms at participating sites during monitoring site visits to determine whether the informed consent process has been appropriately completed and documented.

Remote consenting may be conducted during the COVID outbreak to limit exposure risk.

3.4 Planning quality assurance

3.4.1 Benchmark (Dry run) case review

All sub-sites shall receive, prior to patient enrollment, an anonymous electronic patient data set including diagnostic images. The sub-site will develop a treatment plan for review by a Stanford PI or designated Stanford Co-Investigator. Completion of a satisfactory dry run case review for each site and verification by a Stanford Co-Investigator is required prior to opening the site for patient enrollment.

3.4.2 Treatment Plan Review (pre-treatment)

The treatment plan for each patient enrolled at each site must be reviewed and approved by a Stanford PI or designated Co-Investigator prior to beginning SBRT. The Principal Investigators (or qualified co-investigator designated by the PIs) shall be notified at the time of enrollment for each patient, and of the proposed treatment date, to assure a PI's availability for review. After planning is complete, the treating site will submit the following information to the Stanford research team for a PI review:

1) De-identified copy of the treatment planning data sets (including fused primary and secondary imaging studies, contour sets, and isodose distributions/DVHs), and
2) Treatment Plan QA form.

The review will be completed within 3 working days of receipt; treatment will only begin after all necessary corrections are implemented and the final plan is approved from Stanford. Evaluation of the plans will be based on the dose constraints described in Section 5.3.4. Criteria for allowed major and minor protocol modifications are also described in Section 5.3.4.

3.4.3 Patient post-treatment review

In addition, a post-SBRT treatment plan (treatment summary) and treatment delivery records of the first protocol patient from each participating site, as developed by the site's radiation oncologists and physicists, shall be reviewed by a Stanford PI or designated Co-Investigator. Additionally, treatment plans and treatment delivery records of three additional randomly chosen cases from each site per year, may be reviewed. If warranted by the outcomes of the above QA reviews, a PI may request additional cases to be submitted for review prior to further patient treatments.

4. STUDY ENROLLMENT AND REGISTRATION

4.1 Registration and Enrollment

Prior to enrollment of study participants, each sub-site must have completed all requirements for site activation and a site initiation visit, as detailed in Section 12 of the protocol. All research staff involved in this study at the sub-sites will have completed Good Clinical Practice and Human Subjects Protection training, and have been documented on the site specific delegations log, signed off by the site-PI.

The PI at each sub-site will ensure that all requisite procedures and tests have been performed and complete an Eligibility Checklist (See Appendix III) to submit to Stanford research staff for review with applicable source documents and/or records. Records to be used for source documentation will be translated into English by the sub-site's university translation center and sent with the records in the original language. When patient's eligibility is confirmed by the Stanford research staff, the patient will be assigned a unique study identifier and the sub-site will be notified of approval of patient's study participation. Participating sites must obtain Stanford approval prior to study activities taking place.

Documents to be provided in this order, from sub-sites, required for eligibility confirmation:

- Most recent version of signed ICF approved by EC (in local language)
- Completed Eligibility Checklist (Appendix III) (completed in English)
    - Source documentation (translated into English):
        - History and Physical note by treating physician
        - Pathology Report confirming diagnosis or one radiographic technique that confirms a lesion >1cm with arterial hypervascularization with washout on delayed phase.

The sub-site will then register subjects according to their institutional guidelines, as well as enter patient data into OnCore, Stanford's clinical trials management system. Required data in OnCore includes but is not limited to: demographics, on-study information, consent date, eligibility verification, deviations (if any), and Serious Adverse Events (SAEs). Remaining

information, including data for outcomes and final analysis, will be entered into Stanford's secure study patient database.

Each center must also begin a patient paper study chart to collect and maintain subjects' records and study-related documents. Patient study charts will be reviewed by Stanford research team and the Stanford DSMC to ensure data validity, integrity, and safety of subjects throughout the trial (Section 11).

Shared data will be de-identified and unique identifiers will be assigned to ensure patient confidentiality. Unique identification numbers for each subject will be assigned by Stanford at randomization.

Participating sites must also have a designated research staff person to serve as main contact for questions, issues, and communications.

4.2 Online Registration

Patient registration will be done via OnCore, Stanford's clinical trials management system. Data may also be entered and maintained in Stanford's secure study patient database. Access to these systems will be created once the collaborating institution has obtained all regulatory approvals and becomes a participating center in the study.

Patients may be registered only after all eligibility criteria are met and verified, (see Inclusion and Exclusion Criteria in Section 3.1); and after the patient signs and dates the IRB-authorized consent form which includes an authorization for the release of protected personal health information ("Authorization To Use Your Health Information For Research Purposes"). The authorization that each institution obtains to use and disclose protected health information must include the Stanford research team or entities with which they may share data. Participating sites should register the patient in OnCore within 5 days of enrollment.

Subjects' unique ID numbers assigned by Stanford should be used in patient registration, as well as to identify patients in Case Report Forms; Notes to File; patient-related notes or records; and reports of patients' events or deviations.

4.3 Randomization procedures

Registered patients will be stratified according to tumor size; ≤ 3 cm and > 3 cm, and randomized to receive TACE or SABR. Freedom from local progression, progression free survival, overall survival and toxicities will be analyzed and compared between the two modalities. Subset analysis for efficacy endpoints will be done based on tumor size (≤ or > 3 cm).

Randomization will be provided by Stanford. Participating centers will have a certified local agency translate the source documentation in both the local language as well as the translation to accompany the eligibility checklist and the informed consent form of the patient in a secure electronic mail message to the PI (Dr. Daniel Chang) and Study Coordinator (Rachel Freiberg or Samantha Wong) with subject line: "SECURE: HCC STUDY PATIENT FOR RANDOMIZATION". Once verification is completed, the research staff will ask the study coordinator to randomize the subject by participating site and within the next business day,

research staff will send an electronic message to the PI and Research Coordinator from the participating center with the outcome and instructed treatment plan.

Randomization will be done with a randomized block design software. It will be performed by the Stanford study coordinator who will maintain a password-protected list and assign patients to the treatment arms as each patient is enrolled at each institution.

5. TREATMENT PLANNING AND DELIVERY

5.1 Study Design and Schedule

Assessment of response after TACE will occur at least 12 weeks after the initial procedure and patients will be eligible for enrollment if there is radiographic evidence of residual or recurrent disease within one year. If initial TACE is delivered in stages, the 12 week assessment of response should be determined from the date of the last TACE treatment.

If patients are randomized to the SABR arm, radiotherapy will be delivered using image-guidance and respiratory compensation techniques. Tumor location may be determined by imaging either the residual radio-opaque material (lipiodol) from the initial TACE or implanted fiducial seeds or clips. Treatment will be delivered in 3 fractions within a 7-day window, or 5 fractions within a 2-week window (minimum 2 fractions per week).

Subjects will be followed with consultations with physical exams, routine blood tests, serum AFP, and CT/MRI scans according to the calendar in Section 8.

If a patient develops unmanageable toxicity deemed related to treatment before the completion of TACE or SABR, no further protocol therapy will be administered and the patient will be removed from the protocol and monitored only for survival. Further treatment may be continued off study and will be at the treating physician's discretion.

If a subject shows evidence of disease progression, s/he will be removed from the protocol and followed for survival only; continued treatment will be as per local standard of care and may include TACE or further radiation therapy.

Patients will be followed for 18 months after the completion of protocol therapy and thereafter up to 3 years for survival.

5.1.1 Study Treatment Start Date Parameters

Study treatment must start within 3 months of eligibility confirmation/randomization date. If these dates are not the same, treatment should start within 3 months of randomization.

5.2 Transarterial Chemoembolization (TACE)

5.2.1 Pre-TACE Evaluation

Patients must be evaluated prior to TACE to determine if they are suitable to undergo the procedure. One or more of the following factors may prompt the investigator to cancel the TACE procedure:

- Bilirubin > 3mg/dL
- Encephalopathy
- Gross ascites not controllable with medication
- Serum creatinine > 2.0 mg/dL

5.2.2 Pre-TACE Procedure(s)

Patients may be admitted to hospital 1 day prior to the TACE procedure or as according to hospital standards. Patients will be adequately hydrated, pre-medicated with prophylactic broad-spectrum antibiotics, and medicated as needed with anti-emetics and/or analgesics. No oral intake will be allowed from 6 hours prior to the procedure or as per hospital protocol.

Within 4 weeks prior to the TACE, the below laboratory studies below must be done; baseline labs obtained for eligibility may be used if they are within 4 weeks of the TACE procedure.

- Complete Blood Count with differential (CBCD)
- Coagulation studies (PT or INR, PTT)
- Comprehensive Metabolic Panel (must include Liver Function Tests and Renal Test [Cr or eGFR])
- AFP (tumor marker).

On the day of the TACE procedure, the following should be performed and/or noted:

- Vital signs
- Pertinant physical examination (PE) as determined by physician.
- Pre-treatment medications

This information is to be noted in the Case Report Form (CRF) in Appendix IV and sent to the Stanford Research Team.

5.2.3 TACE Procedure

TACE will be performed by transfemoral artery approach with selective cannulation of the hepatic artery. Diagnostic visceral arteriography will be carried out to delineate anatomic anomalies (found in ~50% of patients), to determine hepatic arterial supply to the tumors, to identify extrahepatic parasitized arteries supplying tumors, and to assess patency of the portal vein. Subselective catheterization or superselective microcatheterization of branch arteries directly supplying tumor(s) should be performed. Once the patient's arterial anatomy is determined, single or combination of accepted chemotherapeutic agents for cTACE (Appendix II) with or without accepted contrast agents (Appendix II) will be infused intra-arterially into the branches of the hepatic artery feeding the tumor(s). After injection of the mixture, accepted embolization agents (Appendix II) may be injected to complete the embolization, as deemed appropriate by the interventional radiologist. For DEB-TACE, doxorubicin loaded onto LC Beads or Quadraspheres may be substituted. DEB-TACE allowed as per institutional protocol.

Catheter selection will be by the radiologist's preference. Vasodilators may be used if a spasm is detected during the procedure and estimated required in the judgment of the investigator/interventional radiologist.

The entire TACE procedure is performed under fluoroscopic guidance to avoid inadvertent reflux into non-target vessels. The dose and composition of the chemotherapeutic mixture is injected based on tumor and vessel size and rate of flow. The endpoint for the procedure is administration of the entire chemoembolic mixture or stagnation of flow in the branches of vasculature-feeding tumor(s). In patients with more extensive disease, the procedure may be performed in a segmental or lobar territory of treatment. In these cases, the endpoint of TACE will be administration of 100% of the chemotherapeutic cocktail or "pruning" of the arterial vascular tree without complete occlusion of the main or lobar hepatic artery.

The exact position of the embolization will be determined by the interventional radiologist. At the end of the procedure, hemostasis can be achieved by manual compression or with a percutaneous closure device. The patient may be discharged after recovery, or can be admitted for overnight observation, according to the hospital standard medical monitoring system for post-TACE HCC patients.

TACE procedure information must be documented in the Case Report Form (CRF) found in Appendix IV. The CRF information will include:

- vessels embolized,
- amount of embolization agents used,
- pre-medications and medications used during the procedure (including analgesics, sedatives, antiemetics, chemotherapeutic agents and contrast medium).
- time of commencement and termination of the TACE procedure,
- hospital discharge date, and
- medications prescribed at discharge (proton pump inhibitor, antiemetics, and analgesics)

The TACE procedure note by the treating Interventional Radiologist should be submitted to Stanford with the CRF.

Patients may be admitted for overnight observation with analgesics for pain and antiemetics for nausea/vomiting. Patients should be discharged within 6–24 hours after the procedure with a prescription for a suitable oral narcotic medication for pain and oral antiemetic for nausea.

Any serious adverse event described in Section 5.2.1 (Pre-TACE Evaluation) must result in premature cessation of TACE procedures. Pre- and post-TACE arteriography images will be reviewed centrally. Participating sites will be expected to provide these images to Stanford in a secure and HIPAA-compliant manner.

5.3 Radiation Treatment Planning Technique

5.3.1 Tumor Tracking

Whenever possible, the residual radio-opaque material (lipiodol) from the initial TACE should be used for image-guidance during SABR. Occasionally, the diaphragm may also be used for image guidance, particularly for tumors in the dome of the liver. Clips or

gold markers (seeds) may be implanted for image guidance during SABR. Traditional fiducial markers used in target tracking are 2.5mm gold (99.9% pure) seeds that are placed through a needle into and/or around the area of the primary tumor. This provides better localization of the target, allowing for reduced margin expansion to account for uncertainty due to set-up variation and respiratory motion. The markers may be placed percutaneously, into or around the tumor under CT or ultrasound guidance. In order to minimize streak artifact from the gold, recommended seeds should be 1mm in diameter and 2.5mm in length. Seeds should be placed in multiple planes within 3cm of the tumor edge. In conjunction with the imaging system, fiducials will serve to identify the precise location of the liver tumor relative to these markers during SABR. It is expected that fiducial seed placement will be done on an outpatient basis.

Fiducials will not be implanted unless patients are enrolled onto this study **and** randomized to the SABR arm of this study.

5.3.2 Set-up Technique

Biphasic CT scans are required for set up. MRI may be substituted for biphasic CT scan in situations where a biphasic CT scan is contraindicated or cannot be obtained. Patients will be simulated in the supine position using an Alpha Cradle™ or equivalent immobilization device which will be custom made for each patient. The biphasic CT scan will be obtained to visualize the entire abdominal cavity, using 0.75-1.5mm thick slices, with the tumor centered within the scanning range. A minimum scanned region of 3cm must be obtained inferior and superior to the liver. The contrast phase should be obtained during expiration breath-hold. In addition, a 4D CT scan is strongly recommended for optimal target volume definition. FDG PET-CT scan is optional.

5.3.3 Target Definitions

The biphasic CT scan will be used to define the GTV. A 4D CT scan is strongly recommended to define the internal target volume (ITV) to account for tumor deformation and respiratory motion. Representative CT slices during inspiration, mid-inspiration, and expiration should be used. FDG PET-CT is optional.

If a 4D CT scan is used, PTV margin expansion around the ITV should be 3mm. Non-uniform margin expansion is allowable if this expansion results in excessive radiation dose to an adjacent organ at risk (OAR).

If 4D CT scan is not utilized, then the ITV will be defined as GTV+5 mm. The PTV expansion will remain 3 mm. Non-uniform margin expansion is allowable if this expansion results in excessive radiation dose to an adjacent organ at risk (OAR). An individualized treatment plan will be developed based on tumor geometry and location.

5.3.4 Dose Prescription and Constraints

The prescription dose will be dependent on the tumor size and Child Pugh score according to the following guidelines:

5.3.4.1.1.1 Child Pugh A	
Dose	# of Fractions
45 Gy at 15 Gy/fraction	3
50 Gy at 10 Gy/fraction	5
45 Gy at 9 Gy/fraction	5
40 Gy at 8 Gy/fraction	5
35 Gy at 7 Gy/fraction	5
30 Gy at 6 Gy/fraction	5

Child Pugh B	
Dose	# of Fractions
40 Gy at 8 Gy/fraction	5
35 Gy at 7 Gy/fraction	5
30 Gy at 6 Gy/fraction	5

The dose will be prescribed to the maximum isodose volume (typically >80% isodose line) which covers 95% of the PTV. All tumors should receive the higher dose unless the normal tissue constraints cannot be met.

The requirements for dose constraints are as follows:

- **Liver** (excluding tumor): 700 cc of the normal liver volume should be limited to <12 Gy (3 fractions) or <15 Gy (5 fractions), or mean liver dose < 15 Gy for Child Pugh A and 12 Gy for Child Pugh B
- **Kidney**: Combined volume for both should have 75% < 12 Gy
- **Bowel and stomach**: Dmax < 40 Gy, V33Gy<1cc, V30Gy<10cc, V20<30cc
- **Spinal Cord max**: no more than 1cc > 8 Gy
- **Esophagus max**: no more than 1cc > 27Gy

These requirements are recommended but not required;

- **Central hepatobiliary tree (portal vein from porto-splenic confluence to the** bifurcation **of the right and left main portal vein + 1.5 cm):** 5-fraction: V40<21 cc, 3-fraction: V33.8<24 cc
- **Chest Wall**: V30Gy <30cc

If the normal tissue constraints as defined above cannot be met even with the lowest prescription dose, the participating site may re-evaluate the patient's participation on-

study. Deviations for normal tissue or tumor prescription dose (periphery of tumor) which are less than or equal to 5% are deemed a minor protocol deviation, and a request for deviation may be submitted to Stanford PI or Co-PI for review and approval. If the treatment plan is not accepted by Stanford or if the deviations for normal tissue are greater than 5%, then the patient should be withdrawn from the study and treated according to the local standard of care.

Study PIs will evaluate treatment plans as described in Section 3.4.

5.3.5 SABR Treatment Procedure

- Patients should be treated within 2 weeks of the radiation set-up scan and within 4 weeks of fiducial seed implantation (if applicable).
- Treatment planning scans must be acquired at least 5 days after fiducial seed implantation (if applicable).
- Patients will be treated in the supine position.
- Respiratory compensation system should be used, and typically will be respiratory gating. If not, an ITV must include all motion due to respiration as visualized on a 4D CT.
- 3 fractions should be delivered within a 1-week time period; 5 fractions should be delivered within 2 weeks with at least 2 fractions per week.

5.3.6 Supportive Care

- Antiemetics should be administered prior to each radiation treatment and for up to 5 days as needed following SABR or as deemed needed by the treating physician.
- Proton pump inhibitors (PPIs) must be started by the first day of SABR and should be continued for 6 months, particularly if significant radiation to adjacent duodenum or stomach is anticipated. This will be at the discretion of the treating radiation oncologist.
- Treatment-related diarrhea should be managed with loperamide. The recommended dose of loperamide is 2-4 mg initially (two tablets) then 2 mg after each loose stool, not to exceed 16 mg (eight tablets) daily, but prescription is at the discretion of the treating physician.
- Platelet transfusions should be considered for thrombocytopenia.

5.4 Follow Up

Subsequent to study treatment, patients will be monitored clinically and radiographically according to the schedule below. Patients may have visits, labs, or scans sooner if deemed necessary by treating physician for clinical evaluation and surveillance. Additionally, study visits may be conducted via video (i.e., MyHealth video, telehealth, telemedicine) or phone to minimize exposure risk.

- At 1 month* which is optional, a phone call post-treatment or consultation with physical examination, labs (CBC, CMP, and tumor marker or AFP), and toxicity evaluation will be done. Toxicity will be scored according to the Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v 4.0, available at http://ctep.cancer.gov/reporting/ctc.html).

- At 3 months*, 6 months*, 12 months*, and 18 months* a consultation with physical examination, labs, Child-Pugh score, optional QOL (3,6,12 months only) and scans will be done as specified in Section 7 - Study Calendar. Scans should include triphasic CT or MRI; FDG PET-CT scans may be obtained in addition to either CT or MRI scans at intervals noted in the Study Calendar (Section 7). Toxicity at each visit will be scored according to the Common Terminology Criteria for Adverse Events version 4.0, available at http://ctep.cancer.gov/reporting/ctc.html.
- The 18 month visit will conclude the toxicity and local control efficacy endpoints of the study, though patients will be followed thereafter up to 3 years for survival only.

*2 weeks before or after each follow-up period will be permitted, e.g., for optional 1 month follow up - visit, labs, and scans can be done at 2-6 weeks; 3 months follow-up can be done at 10-14 weeks, etc.

5.5 Duration of Follow-Up

Subjects will be followed clinically and radiographically for 18 months as per Study Calendar in Section 7, and up to 3 years for survival.

5.6 Criteria for Removal from Study

Patients may be removed at any time from the study at their request. Additionally, patients will be withdrawn if they do not complete protocol therapy, develop disease progression, receive systemic chemotherapy or any treatment not as per protocol, or undergo a liver transplant. If patients are removed from the study prior to receiving protocol therapy, they will be replaced to achieve target accrual. For patients who are taken off study for disease progression, they will continued to be followed for survival.

5.7 Alternatives

Standard therapies for liver tumors include TACE alone, TACE with RFA, RFA alone, radioembolization, surgery, palliative radiotherapy with conventional fractionation, systemic chemotherapy, other ablative procedures, and supportive care only. Patients enrolled in this study will not be candidates for surgical resection. Therefore, the alternative therapy would include TACE alone, RFA, systemic chemotherapy, or supportive care.

5.8 Compensation

Patients will not be paid. Patients and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol. Some data management, salary support and supplies will be provided to the sites by Varian Inc., Palo Alto, CA (project sponsor).

6. ADVERSE EVENTS AND REPORTING REQUIREMENTS

6.1 Serious Adverse Events (SAEs), Unanticipated Problems (UPs), and Adverse Events (AEs)

As Coordinating Center, we will follow guidelines from Stanford's Research Compliance Office for defining, identifying, and reporting events, as defined below.

6.1.1 Serious Adverse Events (SAEs)

A Serious Adverse Event is defined as: Any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).(28)

6.1.1.1 Reporting SAEs

SAEs that require reporting to Stanford within 24 hours include:

- Grade 5 (fatal) events
- Any unexpected and/or treatment-related gastrointestinal Grade 4 event
- Grade 4 hematological event *if within Complete Blood Count (CBC) or Liver Function Test (LFT) results*

The Stanford issued CCTO SAE case report form (CRF), completed with narrative is required to be reported to Stanford within 24 hours upon learning of the SAE. Translated or English source documents for the SAE are not required within the 24 hour reporting timeframe to give sub-sites time to obtain translation, however must be sent as soon as possible. All further enrollment for the sub-site will be held until English source documents have been received by the Stanford main site.

All other SAEs not required to be reported within 24 hours must be reported within 3 calendar days to Stanford.

SAEs should be graded according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0, available at http://ctep.cancer.gov/reporting/ctc.html.

CTCAE toxicity grades will also be used for toxicity monitoring and study analyses.

The SAE should be documented on the Case Report Form in Appendix IV and sent to Dr. Erqi Pollom and the Study Coordinator (Samantha Wong) via email ***within 24 hours of learning of the event*** with the subject line: "SECURE: INTERNATIONAL HCC STUDY CRF" and the CRF attached. If email is not available, the form can be faxed as long as the participating center contacts a member of Stanford's research team to notify it is being sent by fax and to which secured Stanford fax number. Participating sites are encouraged to confirm receipt of the CRF by Stanford.

Case Report Forms must be provided in English; accompanying source documents must also be provided in English. Additional time needed for translations may be requested from the Stanford PI or Study Coordinator. Any source document requiring English translation is the responsibility of the reporting site.

Case Report Forms of SAEs received by Stanford's study staff member will be submitted to Stanford Cancer Center Trials Office (CCTO) within 5 days of receipt, and CCTO or study research staff will submit the information to Stanford regulatory boards and committees as required.

Participating sites should also:

- Keep 2 copies of the CRF: 1 for the patient's study chart and 1 in the regulatory binder (electronic regulatory binder is allowed).
- Follow patient and provide update to Stanford until any of the below:
    - Resolution of event
    - Resolution of event with sequelae
    - Death of patient

The site Principal Investigator will also report AEs and SAEs to their individual Institutional Review Board (IRB) and/or Institutional Ethics Committee (IEC) as per local IRB and facility standards.

6.1.2 Identifying Protocol Deviations

Stanford Protocol Director (PD) will monitor research activities on an ongoing basis for adherence to the research protocol. If a protocol deviation has been identified in a Stanford subject or in a subject at a participating facility, the PD will ascertain whether the event has resulted in harm to participants or affects the study's progress and will ensure that all proper documentation and reporting of the deviation has been completed.

The following constitute protocol deviations:

- Non-adherence to exclusion and inclusion criteria
- Failure to comply with SABR dosing as described in protocol
- Test requirements not followed per protocol -- either tests not done, incorrect tests done, or not done on schedule
- Study visits not completed, or not completed at intervals specified in the protocol.

6.1.3 Unanticipated Problems (UPs) and Major Deviations

Per Stanford IRB, UPs are events involving risks to participants or others and must meet the following 3 criteria:

1. **Unexpected** - in terms of nature, severity, or frequency
   AND
2. **Related** or possibly related to participation in the research
   AND
3. **Harmful -** or that the research places subjects or others at a greater risk of harm than was previously known or recognized.

UPs generally will warrant consideration of substantive changes in the research *protocol or informed consent process/document, or other corrective actions, in order to protect the safety, welfare, or rights of subjects or others.(27) Due to this, UPs will be reported promptly to Stanford IRB following the below guidelines.*

6.1.3.1 Reporting Unanticipated Problems (UPs) and Major Deviations

UPs which are also SAEs should be reported as an SAE following the guidelines in 6.1.1.1, Reporting SAEs.

UPs that are deviations qualify as a major deviation and should be reported to Stanford PI and Study Coordinators **within 24 hours of learning of the** event, via an email sent to Dr. Erqi Pollom and the Study Coordinator (Samantha Wong) with the subject line: "**SECURE: INTERNATIONAL HCC STUDY MAJOR DEVIATION**", and the email should contain basic information about the event. If the deviation has been entered into OnCore, a pdf or saved c opy of the report is acceptable. Stanford research staff will notify Stanford IRB or other regulatory bodies of the UP/deviation as is required.

Participating sites should:

- Enter the Deviation into OnCore within 5 days of learning of the event.
- Record the deviation in the patient's study chart and in the regulatory binder (a report from OnCore is acceptable).
- Follow patient and provide update to Stanford until 1 of the below:
  - Resolution of event
  - Resolution of event with sequelae
  - Death of patient

Case Report Forms must be provided in English; accompanying source documents must also be provided in English. Additional time needed for translations may be requested from the Stanford PI or Study Coordinator. Any source document requiring English translation is the responsibility of the reporting site.

Protocol Directors or their designee must document in Oncore any deviation that could affect the safety of participants (e.g. eligibility criteria, toxicity monitoring, errors in the administration of investigational agents), or impact study endpoints (e.g. tests needed for response assessment). The DSMC will review all protocol deviations documented in Oncore at their monthly meeting. Deviations will also be reviewed at the study's monitoring sessions. Failure to properly document deviations may result in DSMC and IRB corrective action such as temporary hold on enrollment, or study closure.

6.1.4 Adverse Events (AEs) and AE Monitoring

An AE is defined as any untoward medical occurrence in a clinical investigation subject, regardless of causal attribution.

PIs at each participating institution will assess adverse events in consultations, and more frequently as needed, and grade each event according to the NCI Common Terminology Criteria for Adverse Events, Version 4.0, available at:

http://ctep.cancer.gov/reporting/ctc.html.

Grade 3 unexpected and/or treatment-related gastrointestinal AEs should be reported to Stanford *within 72 hours of learning of the event*, using the Case Report Form (CRF) in Appendix IV. Remaining AEs could be recorded and reported quarterly and/or as per request by Stanford.

Overall, **all** AEs should be:

- Recorded in the Adverse Event log (Appendix IV) and reported to Stanford as per guideline within this protocol, or upon request
- Noted in the patient study chart
- Entered into the study's secure patient database
- Reported to the participating center's IRB as per their institutional guidelines.

The site Principal Investigator ensures appropriate recording and reporting of all AEs and SAEs. Source documentation should be supplied when appropriate. Also, any source documents requiring English translation is the responsibility of the reporting site. All AEs should be followed until resolution.

The site Principal Investigator is responsible for ensuring proper reporting of AEs and SAEs to their individual Institutional Review Board (IRB) and/or Institutional Ethics Committee (IEC) as per local IRB and facility standards.

The Adverse Event Log should be kept current and be available upon request from Stanford for study renewal applications, monitoring committee audits, reports, analyses or other submissions requested by Stanford IRB, Scientific Review Committee (SRC), or Data Safety Monitoring Committee (DSMC).

Discussion of AEs will take place in conference calls performed quarterly by a study monitoring group consisting of representative PIs and/or Research Coordinators from each participating site. AEs may be reviewed by members of the study monitoring group in meetings, audits, and/or site visits.

Updates and outcomes of AEs, SAEs, UPs, and deviations will take place during regular conference call discussions or more frequently as needed.

6.2 Review and Reporting of Minor Deviations

All deviations will be recorded and reported to Stanford by the participating center's Principal Investigator or research staff member using the Case Report Form (CRF) in Appendix IV. Protocol deviations regarding the consent process and those that could affect safety or

measurement of study endpoints will be reported to Stanford PI or research staff member within *48 hours*, and will then be reported to the Stanford Cancer Center CCTO and IRB as per Stanford regulatory guidelines.

Discussions of updates and outcomes of all deviations will take place during regular conference call discussions or more frequently as needed.

6.3 Correcting Protocol Deviations

DSMC and IRB representatives will notify the PD of any necessary corrective action. Research staff should place all DSMC and IRB communication in the regulatory binder. Investigators must review and implement all corrective action, and the DSMC may conduct additional monitoring to verify that the deviation has been resolved.

6.4 Potential Adverse Events

6.4.1 Anticipated Mild and Moderate Adverse Events

TACE

- Post embolization syndrome - triad of local RUQ pain, nausea and low-grade fever lasting no more than 7 days
- Fatigue lasting < 2 weeks
- Elevated liver enzymes (AST, ALT) lasting < 4 weeks
- Hair loss

SBRT

- Fatigue
- Nausea
- Diarrhea
- Mild abdominal discomfort lasting < 30 days
- Elevated liver enzymes (ALT, AST)
- Any grade thrombocytopenia
- Any grade anemia
- Any grade neutropenia
- Grade 1 - 2 GI bleeding
- Skin erythema
- Fever
- Grade 1 - 2 bowel or gastric ulcer
- Grade 1 - 2 bowel obstruction

6.4.2 Anticipated Serious Adverse Events

TACE

- New ascites
- Encephalopathy (new onset)
- Abscess formation or infection
- Death due to toxicity
- Contrast-induced renal failure
- Hepatic artery thrombosis
- Vascular complications related to procedure

SBRT

- Grade 4 GI toxicity
- New ascites
- Encephalopathy (new onset)
- Grade 3 - 4 bleeding
- Grade 3 - 4 fistula
- Grade 3 - 4 bowel obstruction
- Grade 3 - 4 bowel or gastric ulcer/perforation
- Renal failure requiring dialysis

- Any Grade 4 toxicity possibly or likely due to treatment
- Death due to toxicity
- Rib fracture

6.5 Site Compliance

It is the Site Principal Investigator's responsibility to comply with the Monitoring Plan and site specific Monitoring Reports. Any discrepancies or complaints regarding the clinical monitoring or the Monitoring Report should be communicated directly to the Stanford PI in writing.

7. STUDY CALENDAR

Activity	Screening / Pre-Study	Study Enrollment & Registration	Treatment - Randomized SBRT or TACE		Follow-Up (in Time From Completion of Study Treatment)						
					1- 2 Wks [l]	1 Mos [l]	3 Mos ^	6 Mos* ^	12 Mos* ^	18 Mos* ^	Q 6 mos up to 3 yrs
			SBRT - 3 -14 days	TACE- to 16 wks[e]							
Eligibility Confirmation		X									
Informed consent		X									
Randomization		X									
Consult/Physical Exam	X					X	X	X	X	X	
ECOG PS	X	X+	X[f]	X[f]		X	X	X	X	X	
Child-Pugh Score	X[j]						X[j]	X[j]	X[j]	X[j]	X[j]
QOL[k]	X					X	X	X	X		
Labs											
- Liver Function[a]	X	X+	X[f]	X[i]		X	X	X	X	X	
- Renal Function[b]	X	X+	X[f]	X[i]		X	X	X	X	X	
- Chemistry Panel[c]	X	X+	X[f]	X[i]		X	X	X	X	X	
- CBC w/ diff	X	X+	X[f]	X[i]		X	X	X	X	X	
- Coags (PT or INR, PTT)	X	X+	X[f]	X[i]		X	X	X	X	X	
- AFP[m]	X[m]	X[m]	X[m]	X[m]		X[m]	X[m]	X[m]	X[m]	X[m]	
- Pregnancy Test[d]	X										
CT (or MRI)	X	X[g]					X	X	X	X	
FDG PET/CT- *Optional*[h]	X						X	X	X	X	
Phone call post-treatment-*Optional*					X	X					
AE evaluation					X---------- X						

*Freedom from local progression to be determined.

^2 weeks before or after each follow-up period will be permitted, e.g., for optional 1 month follow up - visit, labs, and scans can be done at 2-6 weeks; 3 months follow-up can be done at 10-14 weeks, etc.

+Baseline values may be used if they are within 4 weeks of treatment.

[a]Liver Function Panel: as per institution; Required: Albumin, ALK P'TASE, ALT (SGPT), AST (SGOT),Total Bilirubin

[b]Renal function panel: as per institution; Required: Urea nitrogen, Creatinine

[c]Chemistry Panel: as per institution; Required: Glucose, Sodium, Potassium, Chloride
[d]Women of childbearing potential, urine or serum allowed.
[e]Up to 3 procedures if needed, 6-8 weeks apart, total possible time of procedures up to 16 weeks.
[f]Repeat if most recent was more than 4 weeks from first treatment, or as per MD.
[g]CT for Study Enrollment/Registration should be w/in 6 weeks of date of eligibility; may be repeated if it will be >6 weeks from date of first treatment of TACE or SBRT, or if needed per MD.
[h]PET/CTs are optional and deemed as needed per treating MD.
[i]Repeat if most recent are more than 4 weeks from TACE, or if needed per MD.
[j]Child Pugh score at study entry and every 3 months from study treatment.
[k]QOL is optional. Collected as indicated by agreement on IC document.
[l]Optional
[m]Recommended but not required

8. CORRELATIVE STUDIES

8.1 Tumor Marker Evaluation

Tumor marker evaluation is a secondary endpoint for this study. Serum AFP levels will be drawn at every consultation. For patients with elevated AFP at study enrollment, both the initial AFP and the response in AFP levels following therapy will be correlated with tumor response and disease progression. Two definitions of AFP response will be used for the analysis: 1) AFP nadir and 2) percent decrease in AFP from the initial.

Increasing AFP levels following previously decreasing AFP levels or stable AFP levels over 2 separate measurements will be defined as AFP progression. However, in the absence of clinical or radiographic evidence of disease recurrence, this will not be considered disease progression. However, AFP progression will be correlated with disease progression and survival.

For patients whose AFP was not elevated at the time of study enrollment, AFP will not be used as a correlative marker. Additional plasma for subjects may be obtained and analyzed for additional biomarkers as part of an ongoing biomarker identification effort at Stanford University.

9. MEASUREMENT OF EFFECT

9.1 Evaluation Criteria

9.1.1 Definition of Local Progression

Local control will be defined as lack of progressive disease at the site of the treated lesion. Radiographic response of the treated lesion will be defined by either contrast enhanced arterial phase CT or MRI according to EASL criteria (*9,11,49*):

- Complete response (CR) = complete disappearance of any arterial intratumoral enhancement of target lesion(s)
- Partial response (PR) = at least 30% decrease in the sum of diameters of viable (arterial enhancing) target lesion(s)

- Progressive disease (PD) = more than 20% increase in sum of the viable (arterial enhancing) target lesion(s), taking as reference the smallest sum of the diameters of viable (arterial enhancing) target lesion(s) recorded since the treatment started
- Stable disease (SD) = does not meet criteria for PR or PD

Additionally, any new enhancing lesion seen within 2 mm of the prescription isodose curve will be defined as local progression.

9.1.2 Definition of Freedom from Local Progression

Freedom from local progression at time T is defined as lack of local progression in the treated liver lesion in the set of patients alive and on study at time T and without distant progression up to time T. The rate will be determined at 6, 12, and 18 months.

Patients will be removed from the study and considered inevaluable for further assessment of local progression of the treated lesion if, within time T, they receive systemic chemotherapy (without documented progression), receive a liver transplant, or have extrahepatic progression, at which point they will be censored.

9.1.3 Definition of Progression-Free Survival

Progression-free survival is defined as the time from randomization until death or any progression including local, regional or distant progression. For progression free survival a patient will also be considered as having progression if the patient receives systemic chemotherapy or a liver transplant. The rate will be determined at 6, 12 and 18 months.

9.1.4 Definition of Overall Survival

Overall survival will be determined as a measure of time from randomization until death from any cause. The rate will be determined up to three years following therapy.

9.1.5 Serum AFP levels

Serum AFP levels will be measured at specific points during the study. The 2 endpoints to be analyzed are:

- Initial AFP levels
- AFP response - the percent decrease in serum AFP levels from the initial result to the eventual nadir after therapy

These endpoints will be correlated to the clinical endpoints (freedom from local progression, progression free-survival, and overall survival).

9.2 Evaluation of Response

Response to treatment will be monitored with CT or MRI scanning as well as physical exam and serum AFP levels. Physical exams and serum AFP levels will be done at 3 months, 6 months, 12 months and 18 months. Imaging scans will be done at 3 months, 6 months, 12 months and 18 months.

10. Response Review

All imaging scans will be determined by a central review at Stanford Cancer Center to assess response. Participating institutions will be responsible for uploading DICOM imaging datasets to the electronic database using their unique usernames and passwords. Scans will be de-identified and labeled with the

corresponding study identification number and date of scan. Diagnostic images including CT, MRI and PET/CT (optional) must be uploaded and stored in the electronic database within 1 week post treatment. Follow up images are due at 3, 6, 12 and 18 months post treatment according to the study calendar, Section 7. Imaging scans will be assessed at least quarterly for response and the reviewing radiologists will be blinded to the treatment arm

The treating radiation oncologist will perform routine physical exams to assess for clinical signs of progression.

10.1 Progression Free Survival

Progression free survival at 12 months and median progression free survival are secondary endpoints to this study. Evaluation of progression will be done at the previously established schedule.

10.2 Overall Survival

Overall survival at 6, 12, 18 months and up to 3 years is a secondary endpoint to this study.

11. DATA REPORTING AND REGULATORY CONSIDERATIONS

11.1 Monitoring Plan

With Stanford University as the Coordinating Center, the Stanford PI is responsible for ensuring all participating site investigators and their study personnel are trained on the conduct of the protocol including HIPAA and confidentiality standards; study procedures, activities, and schedules; AE/SAE, deviation and CRF documentation and reporting; and proper data collection.

The Stanford coordinator will send a delegation log to each site, to be filled out with the names, signatures, and roles of all personnel working on the study. Once complete, the delegation logs will be emailed back to the Stanford coordinator.

The site PI is responsible for providing written summaries of the status of the study to the local IRB / EC annually or more frequently in accordance with the policies and procedures established by the institution's IRB / EC. The site PI is also responsible for ensuring requests for study data, forms, document or records will be submitted appropriately and in a timely manner and in the timelines set forth in this protocol. Each participating center will create and maintain a study regulatory binder, electronic or paper, and will also maintain a patient study chart for each subject, as detailed in Section 12.

Any time an amendment is made to the protocol, the Stanford coordinator will communicate the change to all sites via email or video/phone conference session if needed. The sites will then have the amended protocol approved by the local IRB.

Overall study audits of all sites will be performed by Stanford DSMC, three patients at Stanford and one patient per sub-site will be chosen at random for audit review at a minimum of once per year; more frequent monitoring will occur as needed. All of the source documentation required for consent, eligibility, treatment and follow-up will be translated into English by a local certified translation center associated with University and sent for audit

review to Stanford University upon request. Preliminary reviews may take place by Stanford research staff participating centers, prior to Stanford DSMC audits.

Additionally, an independent monitoring committee (MC) consisting of a radiation oncologist and a research coordinator not on the study protocol will be set-up to review cumulative AEs, SAEs, and accrual. The MC will meet twice a year annually, and more often as needed.

Research staff at each center will enter subject information into OnCore after access has been coordinated by Stanford research and OnCore personnel. Clinical and other data may be entered into another designated secure study database such as Redcap. The Stanford coordinator will either hold a training session in person during site initiation visits or will create a video/phone conference training session on how to register patients in OnCore and fill out case report forms (eCRFs). The training session will be held before each site starts enrolling patients on the study. All sites will fill out the forms in English. **Important:** When the local coordinator is working in OnCore or Redcap, he or she will only be able to see local data, not Stanford data or data from the other international sites.

Participating centers will supply radiation treatment plan data upon request by uploading scan images and information. If uploading is not possible, images and reports may be supplied electronically or on encrypted and/or password-protected discs or drives. Further data may be requested from each institution for study analyses.

All tools, computers, and systems used for monitoring and analyses will be secure, password-protected, and HIPAA compliant. Shared data will be de-identified and unique identifiers will be assigned to ensure patient confidentiality.

11.2 Electronic Monitoring

Electronic monitoring will be performed when possible. Participating institutions will be advised what records will be needed for electronic review and information will be transmitted via a secure electronic mail or study database. At a minimum, eligibility checklists (with necessary source documents) will be verified via electronic exchange and after Stanford review and approval a participating center's patient may be enrolled to the study. The exchange of subject information will be done in a secure manner and transferred through Stanford's secure electronic or study data management systems. Unique identifiers assigned by Stanford at the time of patient registration will be used on subject records and any documents containing subjects' personal health information (PHI). Additional monitoring of participating center's study data will be accomplished through formal PI reviews as scheduled and needed.

Unanticipated Problems (UPs) and Significant Adverse Events (SAEs) will be and reported according to the guidelines described in Section 6.

Questions related to eligibility, response and toxicity may be communicated to the PIs on an ongoing process through secure email communications.

All tools, computers, and systems used for monitoring and analyses will be secure, password-protected, and HIPAA compliant. Shared data will be de-identified and unique identifiers will be assigned to ensure patient confidentiality.

All records must be provided or translated into English. Individual participating sites are responsible for all necessary translations.

11.2.1 Sub-Site Clinical Monitoring

Due to the distance of the sub-site locations and budgeting and language constraints, monitoring of the sites will be conducted as follows:

- **After confirmation of Site Activation,** *every subject* enrolled by the sub-sites must submitted to Stanford for central review of eligibility
  - *Site Activation includes submittal of all regulatory documents required for enrollment detailed in Section 11.2.2*.
- **Initial Review**: Each of the sub-sites must submit source documents (English translated) for review at each of the following time points for at least the first subject enrolled, with the ability to review subsequent subjects if errors are identified:
  - *Baseline* (eligibility source documents, baseline imaging and labs, treatment plans)
  - *End* of Treatment (treatment summary)
  - *After* the 1st Follow Up Visit
- **Annual Review**: Each sub-site will be required to submit one complete study binder (English translated) of one patient chosen at random for review by the Stanford *DSMB*, per institutional requirements. This will accompany the 3 random subjects reviewed at Stanford annually.
- **An Independent Monitoring Committee** (MC) consisting at least of a radiology oncologist and research coordinator not on study protocol will monitor the cumulative AEs (reported in RedCap), SAEs, and accrual for the overall study and each individual site, on a bi-annual basis, or more often as needed
  - The MC monitor will complete a Monitoring Report which describes the findings and conclusions, noted in the visit. Additional information may be documented in the monitoring report such as number of subjects screened, enrolled, withdrawn, and treatments completed. The regulatory binder, new adverse events or serious adverse events, staff changes and protocol violations and deviations will also be properly documented.

  - A copy of the report will be sent to the participating sub-site's investigators and staff after the visit. Sites will have 60 days to make corrections and respond to this report. If serious deficiencies are found during the visit, the Stanford PI may require the institution to submit copies of documentation to satisfy information gaps or queries, or require other appropriate remedies. The Stanford PI may also suspend the sub-site's patient enrollment privileges if warranted until the site's issues are addressed and resolved.

- These clinical study reports will also serve as feedback for adequate adjustments of the monitoring plan to ensure quality control and patient safety throughout the study. Appropriate documentation of regular communication and meetings with all participating sites will be collected by Stanford and filed in the study binder.

- **A Conference Call** with all sub-sites will be conducted upon eligibility of the first patient to be enrolled to discuss questions regarding eligibility, treatment, or adverse events once the first patient is enrolled. Thereafter we will have a mandatory quarterly call if the first 3 patients pass *Initial Review* and there are no outstanding safety concerns. Other issues from sub-sites will be addressed directly with the Stanford investigators.

11.2.2 Regulatory Binder

The Stanford research team may visit the institution and review the study regulatory binders and examine the institutional records for study participants. Source documents will be reviewed to verify eligibility, treatment compliance, treatment toxicity, response assessment and overall record-keeping. Source documentation should be independently verifiable. The sub-site will be given a minimum of 60 days notice for this possible visit.

Records and source documents in binders should include but are not limited to:

- Documentation of IRB approval and renewal letters and relevant correspondence with local site's IRB
- Protocol signed by the investigator (with amendments and subsequent versions including the final version approved by local IRB)
- IRB-approved Consent Form and all amendments
- Study personnel CVs and Medical Licenses
- Laboratory Licenses and information; and copies of normal range values for each lab
- Study Subject Log including patient name or identifier, Consent Date, Treatment Dates, and Off-Study date with reason
- Site Signature/Delegation log
- SRC approval and correspondence
- DSMC Correspondence
- Any other pertinent reports or records

Records and study-related documents in patient study charts include but are not limited to:

- Completed Eligibility Checklists accompanied by all related source materials
- Pre-study reports, scans, labs and notes
- Signed Informed Consent Forms
- Radiation treatment records
- Treating physician's notes
- Consultation or visit notes, medical oncology records (as applicable), interventional radiology notes and procedure reports
- Laboratory results
- Scan or radiology reports
- Follow-up records
- Notes to file
- Deviation records or notes with source documents
- SAE, AE, and toxicity reports with source documents

Prior to leaving the facility, the monitor(s) may discuss with the investigator(s) and staff any discrepancies or problems identified during the visit. If significant noncompliance or suspected data fabrication/falsification are identified during the audit, the monitors will immediately notify the Stanford PIs and the Stanford Clinical Trials Office for further actions.

Records requested for review must be translated into English. Individual sites are responsible for any necessary translations.

11.2.3 Study oversight committees

11.2.3.1 Data and Safety Monitoring Board (DSMB)
Stanford's DSMB will also conduct study audits to review each participating centers' regulatory binders and patient study charts. These audits will ensure guidelines set forth in this protocol are followed for all aspects of the study including but not limited to regulatory approvals and renewals; patient eligibility, enrollment, treatment, and follow-up; proper documentation and record-keeping; and adverse event reporting. Audits will be performed yearly by Stanford DSMC; more frequent monitoring will occur as needed.

Preliminary reviews will take place by Stanford research staff prior to audits.

12. STATISTICAL CONSIDERATIONS

12.1 Stopping rules

If, after the first 40 patients, the incidence of grade 4 or greater toxicity attributable to SABR exceeds 10% the DSMB will be informed. A decision will be made to either continue the study or to amend the protocol to reduce the radiation dose or further limit the dose to adjacent critical organs.

12.2 Data Management

The procedures for data collection, data management and data security and confidentiality used in the clinical study are described below. These procedures comply with the principles of good clinical practice, and Stanford Cancer Center Multi-Site trials SOP.

12.2.1 Data is managed via three components:

I. OnCore

Patients are registered and reported to the NCI through OnCore, a web-based database application. Patients are registered in OnCore within 5 days after signing the consent form. Patients are numbered consecutively. Each sub-site will have their study ID's assigned to their enrollees after eligibility confirmation by Stanford through the process described in Section 4.1.

II. Redcap

Case report forms (CRFs) are filled and stored electronically in Redcap, a web-based database application. Patients are numbered consecutively using the same numbers as

in OnCore. The CRFs include a Baseline Evaluation Form, Registration Form, Treatment Summary Form, and Follow-Up Form. One Follow-Up Form is filled out for each patient follow-up visit, so several Follow-Up Forms are filled out for each patient over the course of the study. The Follow-Up Form records local, regional, and distant control provided by the protocol treatment. It also records any adverse events experienced by the patient. Common adverse events are recorded using radio buttons. Other adverse events can be typed into a Comments box.

III. Document binders

Study binders/patient binders must contain records of all data pertaining to the study. This includes all primary data for the items listed in the calendar, signed/dated informed consent, documentation of consent and all data listed in section 11.2.2 above. Binders should have the following sections/tabs:

1. **Informed Consent** – Copy of the signed/dated informed consent and documentation of the consent process.
2. **Eligibility** – The eligibility checklist document from appendix III with each section filled out preferably electronically, printed out and signed. Following the checklist each supporting document should be included, in order (to the extent possible) as well as all pretreatment studies and documentation of multi-specialty evaluation.
3. **Randomization** – Documentation of Arm patient is randomized to (an email from the Stanford **site)**
4. **Treatment Plan** – De-identified copy of treatment planning data sets and treatment plan QA form.
5. **TACE** – Documentation of all data required in section 5.2.2, TACE CRF, and primary documentation of the TACE procedure from the medical record, treatment summary written by the treating physician, including adverse events.
6. **QOL** – Quality of Life EQ-5D-3L and FACT-Hep (if subject consents to questionnaires.
7. **Follow up** – Documentation of all follow up procedures/H&P/labs/and imaging as detailed in the Study Calendar (section 7).
8. **SAE/AE and Deviations** – AE logs, SAE reports with source documentation and deviation reports.

12.3 Data security and confidentiality

- Data used for the clinical study is confidential. Unique identification numbers will be assigned and used for each subject on eCRFs.
- Electronic data will be stored on devices that are back-upped in a secure and timely manner. Protocol data for this study will be stored in the secure database systems OnCore and REDCap
- The Stanford PI shall retain all records and reports for up to 10 years after the date of the last patient care activity as per Stanford Multi-Site trial SOP.

12.4 Endpoints

12.4.1 Primary Endpoints

To compare the freedom from local progression (FFLP) at 12 months.

12.4.2 Secondary Endpoints

- To compare the freedom from extra hepatic progression between individuals treated with SBRT and individuals treated with TACE
- To compare the progression free survival (PFS) between individuals treated with SBRT and individuals treated with TACE
- To compare the overall survival between individuals treated with SBRT and individuals treated with TACE
- To determine the median FFLP, progression free survival, extra hepatic progression free survival and overall survival for patients with tumors smaller than 3 cm per treatment group and for patients with tumors greater than 3 cm per treatment group
- To evaluate AFP levels as a predictor for FFLP, PFS, extra hepatic progression free survival and OS

12.5 Sample Size

12.5.1 Accrual Estimates

This is a multi-center, randomized study, designed to compare the 12-month freedom from local progression (FFLP) rate of TACE vs. SBRT in the initial management of patients with recurrent HCC after initial TACE.

After completion of an initial application, we will open this study at various institutions in the United States and in Asia and Canada with SABR capabilities. Since many of these centers will be in Asia where HCC is much more prevalent than in the U.S., we anticipate that the majority of patients enrolled onto this study will come from Asia.

Accrual will occur over 3 years with a total enrollment of 160 patients, 80 patients in each arm. Expected enrollment at Stanford is 15-30 patients over 3 years, or approximately 5-10 patients per year. As the incidence of HCC at the 3 other sub-sites are higher, we expected total accrual from each of the sites to be 40-45, with annual accrual of approximately 10-15 patients per year.

In 2007, 200 TACE procedures were performed at Stanford Hospital. From 2002 – 2006, 436 newly diagnosed patients with HCC were evaluated at Stanford Cancer Center, which is a yearly average of 87 new patients per year over that time period. Based on the number of TACE procedures performed per year, we estimate that 1 patient per 2 months can reasonably be expected to accrue onto this study.

12.5.2 Sample Size Justification

A sample size of 56 informative subjects per arm will provide at least 90% power in a two-sided log rank test of detecting a 30% difference in the 12 month of the two groups with alpha level of 0.05 given an accrual period of 36 months and a total follow up period of 36 months. The survival curves of both groups are assumed to follow an exponential

distribution and the 12 month FFLP for the TACE group is assumed to be 30% and the expected 12 month FFLP for the SBRT group is 60%.

We propose enrolling 160 patients onto this study to account for patients who may be taken off of the study prior to reaching the primary endpoint of local progression-free survival (FFLP) at 12 months because of progression elsewhere in the liver or declining performance status that may preclude follow-up scans at required intervals. We estimate that up to 30% of this patient population will not be evaluable for local progression (as defined in section 9.1.1). Starting with 80 patients per arm we expect to have approximately 56 patients evaluable for local progression at 12 months.

12.5.3 Analysis populations

In general analysis will follow the intent-to-treat principle. However, for FFLP, patients must be evaluable for FFLP as defined in section 9.1.2 (treatment will be analyzed as randomized)

Analysis for all other endpoints will be carried out for all evaluable patients with intent to treat.

Additional subset analysis for efficacy endpoints will be done based on tumor size (<= 3 cm or > 3 cm).

12.6 Plan of Analysis

12.6.1 Evaluable patients

All patients are considered evaluable except as noted in Section 9.1.2 for FFLP. Treatment is as randomized.

12.6.2 Design

This is a two-arm randomized trial. Patients will be randomly assigned to receive TACE or SABR. At progression, crossover between the 2 arms of the study will be allowed; the crossover is not mandatory and will not be analyzed statistically.

12.6.3 Freedom from local progression

Analysis will be carried out on the subset of patients evaluable for local progression (See Section 9.1.2). Freedom from local progression at time T is defined as lack of local progression in the treated liver lesion in the set of patients alive and on study at time T and without distant progression up to time T. The rate will be determined at 6, 12, and 18 months. Freedom from extra hepatic progression is defined as time from randomization until regional or distant progression. For both FFLP and freedom from extra hepatic progression, individuals who are lost to follow up will be censored at the date of the last progression evaluation. Individuals who were given systemic chemotherapy or received a liver transplant will be censored at the data of the medical intervention. The time to freedom from local progression will be estimated by competing risk models with death and regional or distant progression as competing risks. The time to freedom from extra hepatic progression will be estimated by competing risk models with death as a competing risk. For both models, risk factors such as tumor size and institution will be tested in a multivariate Cox regression model adjusting for the competing risks.

12.6.4 Progression free and overall survival

Progression-free survival is defined as the time from randomization until death or any progression including local, regional or distant progression. For progression free survival a patient will also be considered as having progression if the patient receives systemic chemotherapy or a liver transplant. Overall survival is defined as the time from randomization until death from any cause. Overall and progression free survival will be summarized using Kaplan-Meier curves and medians with 95% confidence intervals calculated using Greenwood's formula. Log rank tests will be used to compare treatment groups. Cox proportional hazard models will be used to estimate hazard ratios between treatment groups and to assess other risk factors, in particular the effect of tumor size and the impact of the different institutions.

12.6.5 Subgroup analysis

Patients will be divided into two subgroups depending on whether the size of their tumor is less than or greater than 3 cm. Within each subgroup the progression free survival and overall survival will be summarized using Kaplan-Meier curves and medians with 95% confidence intervals calculated using Greenwood's formula. Freedom from local progression and freedom from extra hepatic progression within each subgroup will be summarized by cumulative incidence function estimators adjusted for the competing risk of death or regional or distant progression.

12.6.6 AFP / Alpha fetoprotein analysis

The impact of elevated AFP level on time to event endpoints: FFLP, PFS, extra hepatic progression free survival and OS will be evaluated both in terms of the initial AFP level and on-study levels in a Cox proportional hazards model.

13. MULTI-SITE STUDY GUIDELINES

13.1 Study documents

An application and investigator packet (including the protocol, informed consent form and relevant supporting information) will be sent by Stanford to each prospective site for their Institution Review Board (IRB) or Institutional Ethics Committee (IEC) review. Each site is asked to return the completed application which includes a list of regulatory requirements according to the Stanford PI and research team.

The regulatory requirements include:

- IRB/IEC letter of approval, IRB/IEC-approved study protocol, and any other pertinent IRB/IEC documents or communications
- IRB/IEC-approved Informed Consent Form
- IRB/IEC panel members
- CVs and Medical licenses for site PI's and Co-investigators
- Financial Disclosure from participating site PI and each sub-investigator
- International participating sites must meet local country requirements.

If any additional sites were to be added in the future, a committee consisting of Stanford PIs will review each application and jointly determine site eligibility for this study. All required

regulatory documents and site communications will be filed with the Sponsor and in the central regulatory binder as well as the site investigator's regulatory binder.

13.2 Site Activation

Each sub-site will be required to complete all of the following before they can begin research related activities for this protocol:

- Provide confirmation of study documents detailed in Section 13.1
    - Stanford will then submit the local ICF and Ethics Committee approval from sub-site to Stanford IRB for approval
- Certification of GCP and HSP training for all sub-site research staff
- Delegation of Duty Log
- Site Initiation Visit (via conference or video call with Stanford University)
    - Review of Study Design and Eligibility Criteria
    - Review registration process onto secure Oncore database
    - Review SAE Reporting requirements
    - Review Data and Safety Monitoring Plan
- Submit a Benchmark (Dry Run) case review (Section 3.4) to the Stanford PIs

At the completion of the aforementioned items, Stanford will issue the sub-site an activation letter indicating that the site is ready to enroll.

13.3 Communication with the Institutional Review Board (IRB)

This protocol, the Informed Consent Form, and relevant supporting information must be submitted to the local IRB or Ethics Committee (EC) by the Site PI for review and approval, the approved ICF and approval letter must then be submitted to Stanford IRB for approval before the study is initiated. The consent will be back translated into English from the local language for confirmation. In addition, any advertising materials must be approved by the local IRB. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB requirements.

There will be one protocol document and each participating institution will utilize that document. It is the responsibility of the Stanford PI to ensure that the participating sites use the correct version of the protocol as well as subsequent amendments. The site PI is responsible for ensuring that their study team members have the current version of the protocol and informed consent documents. Site PIs are also responsible for promptly informing the local IRB or EC of any protocol changes or amendments.

The Site PI is responsible for providing written summaries of the status of the study to the local IRB at least annually and more frequently in accordance with the policies and procedures established by their local IRB. The site PI reports AEs and SAEs to their individual Institutional Review Board (IRB) and/or Institutional Ethics Committee (IEC) as required and of all unanticipated problems involving risk to human patients or others.

13.4 Site Communication

The Stanford PIs will document regular communication with all participating sites. Once a site has completed activation and enrollment has begun, a quarterly conference call will be scheduled with each sub-site to address any eligibility, treatment, adverse events, and miscellaneous issues regarding the protocol. The sub-site may contact the research team at

Stanford at any time with questions regarding the protocol or request a conference or video call to review or re-educate any members of the sub-site research team. Communication may include site visits or additional conference calls to update and inform all participating sites about the progress of the study and discuss adverse events and deviations. The minutes and reports from these site visits will be recorded by Stanford; and meetings and conference calls records will be filed in the Regulatory Binder and adequately stored and retained by the sponsor.

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Appendix I

ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix II

Acceptable TACE Agents

1. Acceptable embolic agents include:
   - Gelatin sponge (gelfoam)
   - Polyvinyl alcohol (PVA) particles
   - Microspheres / Embolic beads

2. Acceptable chemotherapeutic agents include (excluding drug eluting beads):
   - Doxorubicin
   - Epirubicin
   - 5-fluorouracil
   - Mitomycin C
   - Gemcitabine
   - Cisplatin
   - SMANCS (styrene maleic acid neocarzinostatin)

3. Acceptable contrast agents include:
   - Lipiodol

4. Acceptable drug-eluting bead formulations, based on provider preference and size of tumor, include :

   LC Beads, 100-300 micron and/or 300-500 microron microspheres, loaded with doxorubicin

   Quadraspheres, 30-60 micron or 50-100 micron, loaded with doxorubicin

Appendix III

Eligibility Checklist

Protocol Information

Title	International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma after Initial TACE
Protocol Number	**35937**
Principal Investigator	Daniel Chang

Subject Information

Subject Name: _____
Study ID: _____ **Gender**: ☐ Male ☐ Female

Inclusion/Exclusion Criteria

Inclusion Criteria	Yes	No	Supporting Documentation*
1. Confirmed hepatocellular carcinoma (HCC) by one of the following: • Histopathology • One radiographic technique that confirms a lesion ≥ 1cm with arterial hypervascularization with washout on delayed phase	☐	☐	
2. Radiographic evidence of persistent, progressive or recurrent disease in an area previously treated with TACE; This evaluation should be within 6 weeks of study eligibility.	☐	☐	
3. Unifocal liver tumors not to exceed 7.5cm in greatest axial dimension. Multifocal lesions will be restricted to lesions that can be treated within a single target volume within the same liver segment and to an aggregate of 10cm as long as the dose constraints to normal tissue can be met.	☐	☐	
4. ECOG (Eastern Clinical Oncology Group Performance Status) 0, 1, or 2 (Appendix I)	☐	☐	
5. Patients with liver disease classified as Child Pugh class A or B, with score ≤ 9 (within 4 weeks of treatment)	☐	☐	

a. Albumin (1, 2, 3) _____ b. Total bilirubin (1, 2, 3) _____ c. INR (1, 2, 3) _____ d. Encephalopathy (1, 2, 3) _____ e. Ascites (1, 2, 3) _____ CP score total: (5-15) _____ CP class: (A, B, or C) _____			
6. Life expectancy ≥ 6 months	☐	☐	
7. Age > 18 years old	☐	☐	
8. Ability of the research subject or authorized legal representative to understand and have the willingness to sign a written informed consent document	☐	☐	

Exclusion Criteria	Yes	No	Supporting Documentation*
1. Prior radiotherapy to the upper abdomen	☐	☐	
2. Prior radioembolization to the liver	☐	☐	
3. Prior RFA to index lesion	☐	☐	
4. Liver transplant	☐	☐	
5. Active gastrointestinal bleed within 2 weeks of study enrollment	☐	☐	
6. Ascites refractory to medical therapy (mild to moderate ascites is allowed)	☐	☐	
7. Women who are pregnant or breastfeeding	☐	☐	
8. Administration of chemotherapy within the last 1 month	☐	☐	
9. Extrahepatic metastases	☐	☐	
10. Participation in another concurrent treatment protocol	☐	☐	
10. Prior history of malignancy other than HCC, dermatologic basal cell or squamous cell carcinoma.	☐	☐	

*Supporting documentation is required to confirm subject eligibility and can include but is not limited to: clinic or consultation notes, lab results, pathology results, radiology reports, subject self-report, or MD documentation.

Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐**eligible** / ☐**ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Study Coordinator Signature:	Date:
Printed Name:	
Secondary Reviewer Signature:	Date:
Printed Name:	
Treating Physician Signature:	Date:
Printed Name:	

Appendix IV

Case Report Form and Patient Logs:

1. **Case Report Form for TACE Procedure**
2. **Subject Log**
3. **Deviation Log**
4. **Adverse Event Log**
5. **Adverse Event Tracking form**

STANFORD CANCER INSTITUTE

Protocol Title: *International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma after Initial TACE*

Stanford eprotocol #: IRB-35937 **OnCore #: HEP0052**

Case Report Form for TACE Procedure

Fill in each item below. Return the completed form, with the final report/note of the TACE procedure, to Stanford Research staff. Keep a copy of all CRFs in patient's study chart and as needed per your institution in the patient's medical record.

TACE date:_____

PRE-TREATMENT:	
Vital Signs	
Temp	ºC_____ ºF_____ ☐ Check if Oral, or if other, define: _____
Pulse	
BP	_____ / _____
RR	
PE Findings	
General	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
HEENT	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
Neuro	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
Cardio	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
Pulmonary	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
GI	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
Edema	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
GU	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done

Skin	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
Mobility (musculoskeletal)	☐ WNL ☐ Abnormal, specify: _____ ☐ Not Done
Medications	
(pre-TACE	
only)	

Continued on next page…

Complete below regarding TACE and post-TACE information:

1. **Vessels embolized:**

_____

_____

_____

_____

2. **Amount of embolization agents used:**

_____

_____

_____

3. **Medications used during the procedure (include chemotherapeutic agents, contrast medium, and agents not otherwise noted):**

_____

_____

_____

_____

_____

_____

_____

_____

_____

4. **Time of termination of the TACE procedure: _____**

5. **Hospital discharge date: _____**

6. **Medications prescribed at discharge (antiemetics and oral narcotic medication for pain, include dose, frequency, and duration):**

_____

_____

_____

_____

_____

_____

SERIOUS ADVERSE EVENT Addendum Form (Complete along with Stanford CCTO SAE Form)

1. Check if event was: ○ Serious Adverse Event (SAE) or ○ Adverse Event (AE)

   Indicate Grade*: _____
   *According to CTCAE, Version 4 or greater, available at http://ctep.cancer.gov/reporting/ctc.html.

2. Was this also an Unanticipated Problem (UP)? ○ Yes ○ No
   If Yes, check that it meets UP criteria for: ☐ Unexpected
   ☐ Related
   ☐ Harmful

3. Check the box of which therapy the event was related or possibly related to:
   ☐ TACE ☐ SBRT ☐ Other, indicate: _____

4. Indicate how much treatment the subject received up to the event:

   - For TACE, agents administered:_____

   - For SBRT, fractions_____ and cGy_____

5. Provide a brief description of the event, including (attach additional sheets as needed):
   - symptoms reported and when (dates)
   - results of scans, labs, or other procedures or tests
   - if hospital ED visit or admission, give dates and length of hospitalization
   - If Grade 5, indicate date of death, primary cause, if death certificate obtained, and if autopsy performed

   _____

   _____

   _____

   _____

6. Following the event:
   - Was therapy discontinued? ☐ No ☐ Yes ☐ N/A
   - Was dose modified? ☐ No ☐ Yes ☐ N/A
     If **Yes**, note modified dose(s): _____

     _____

7. Define the action plan and follow-up, including:

- Next visit and follow-up schedule if not per protocol
- Referrals for tests, procedures, specialty or other clinics
- Other pertinent information:

_____

_____

_____

Participating Center: _____

Subject Log

#	Subject Name	Subject Initials	Subject ID or OnCore #	Date On-Study (Date of Randomization)	Treatment Arm	Treatment Start Date (Day 1)	Date Off-Study	Reason Off-Study
1					☐ TACE ☐ SBRT			
2					☐ TACE ☐ SBRT			
3					☐ TACE ☐ SBRT			
4					☐ TACE ☐ SBRT			
5					☐ TACE ☐ SBRT			
6					☐ TACE ☐ SBRT			
7					☐ TACE ☐ SBRT			
8					☐ TACE ☐ SBRT			
9					☐ TACE ☐ SBRT			
10					☐ TACE ☐ SBRT			

11					☐ TACE ☐ SBRT			
12					☐ TACE ☐ SBRT			

Protocol: *International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma after Initial TACE*

Stanford eProtocol #: IRB-35937 **OnCore #: HEP0052**

Participating Center: _____

Protocol Deviation Log

#	Subject Initials	Subject ID or OnCore #	Date of Deviation	Category (see next page)	Code (see next page)	Brief Description	Date IRB notified, if applicable	Corrective or Action Plan
1								
2								
3								
4								
5								
6								
7								
8								
9								

10								
11								
12								

Deviation Categories

A. Safety
B. Informed Consent
C. Eligibility
D. Protocol Implementation
E. Other, specify in log

Deviation Codes (associated with Deviation categories)

Safety (Category A) 1. Not reporting SAE within 24 hours 2. Laboratory tests not done 3. AE/SAE not reported to IRB 4. Other, specify on log Informed Consent (Category B)	Eligibility (Category C) 12. Participant did not meet eligibility criteria 13. Randomization of an ineligible patient 14. Participant randomized prior to Baseline Assessment 15. Randomization or treatment of a patient prior to IRB approval of protocol 16. other, specify in log Protocol Implementation (category D)

5. Failure to obtain informed consent 6. Consent form used was not current IRB approved version 7. Consent form does not include updates or information required by IRB 8. Consent form missing 9. Consent form not signed and dated by participant 10. Consent form does not contain all required signatures 11. Other, specify in log	17. Failure to keep IRB approval up to date 18. Participant receives wrong treatment 19. Participant seen outside of window visit 20. Use of unallowable concomitant treatments 21. Prescribed dosing outside of protocol guidelines 22. Missed Assessment 23. Missed Visit 24. Other, specify in log

Protocol: *International Randomized Study of Transarterial Chemoembolization (TACE) versus Stereotactic Body Radiotherapy (SBRT) / Stereotactic Ablative Radiotherapy (SABR) for Residual or Recurrent Hepatocellular Carcinoma after Initial TACE*

Stanford eProtocol #: IRB-35937 **OnCore #: HEP0052**

Participating Center: _____

Adverse Event (AE) Log

#	Subject Initials	Subject ID or OnCore #	Date of Event	Expected (Yes or No)	Category (Per CTCAE v 4)	Grade (Per CTCAE v 4)	Description if needed	Date Reported to IRB, if applicable	Action Taken or Follow-up
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									

12									

Adverse Event Grading Sheet for International Randomized Study of TACE versus SBRT for Residual or Recurrent HCC

Site:_____ PI:_____ Date:_____ Time Point: _____
Subject Initials:_____ Subject Study ID:_____

AE	Grade					Attribution
	1	2	3	4	5	TACE or SBRT
Gastrointestinal disorders						
Abdominal Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	N/A	N/A	
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	

Note Attribution in right column. 1-Unrelated 2-Unlikely 3-Possible 4-Probable 5-Definite

Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	N/A	N/A	
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Other:						
General Disorders and Administration Site Conditions						
Low Grade Feaver (Lasting more than 7 days)	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	Yes	No	(Please circle one)		
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	N/A	N/A	
Hepatic Artery Thrombosis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL	Severe or medically significant but not immediately lifethreatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Radiation Dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death	
Rib Fracture	Yes	No	Please circle one			

Note Attribution in right column. 1-Unrelated 2-Unlikely 3-Possible 4-Probable 5-Definite

Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL	Severe or medically significant but not immediately lifethreatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Other:						
Hepatobiliary Disorders						
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Biliary fistula	N/A	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Cholecystitis	N/A	**Symptomatic; medical intervention indicated**	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Hepatic failure	N/A	N/A	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; lifethreatening consequences	Death	
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death	

Hepatic Necrosis	N/A	N/A	N/A	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death	
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	N/A	N/A	
Perforation bile duct	N/A	N/A	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Portal hypertension	N/A	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death	
Portal vein thrombosis	N/A	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Infections and Infestations						
Arterial Injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death	
Hepatic Infection	N/A	N/A	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	

Investigations						
Alanine aminotransferase increased (ALT)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	N/A	
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	N/A	
Aspartate aminotransferase increased (AST)	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	N/A	
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	N/A	
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	N/A	
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	N/A	
Platelet Count Decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0-50.0x10e9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9/L	N/A	
Weight Loss	5 to <10% from baseline; intervention not indicated	10 to <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	N/A	N/A	
Nervous system disorders						
Encephalopathy (pathologic process involving the brain)	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	

Note Attribution in right column. 1-Unrelated 2-Unlikely 3-Possible 4-Probable 5-Definite

Blood and Lumphatic System Disorders						
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death	
Other:						
Metabolism and Nutritional Disorders						
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death	
Hypocalcemia (Low Calcium)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death	
Hypokalemia (Low potassium)	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death	
Hyponatremia (Low sodium)	<LLN - 130 mmol/L	N/A	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death	
Other:						

Please indicate N/A for each event not observed.
Attribution: Circle Treatment Modality (Top of far right column).

Note Attribution in right column. 1-Unrelated 2-Unlikely 3-Possible 4-Probable 5-Definite

Physician Signature:_____ Date:_____

Note Attribution in right column. 1-Unrelated 2-Unlikely 3-Possible 4-Probable 5-Definite

Appendix V

FACT-Hep
Version 4

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 past 7 days.**

	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 past 7 days.

	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 past 7 days.

	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
Cn6	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

Appendix VI

QOL – Quality of Life
EQ-5D

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today