The Impact of 90Yttrium (Y90) Radiation Segmentectomy on Hepatocellular Carcinoma and Cirrhosis
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Study title:

The Impact of ^{90}Yttrium (Y90) Radiation Segmentectomy on Unresectable Hepatocellular Carcinoma

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The Impact of ^{90}Yttrium (Y90) Radiation Segmentectomy on Unresectable Hepatocellular Carcinoma

PROTOCOL SYNOPSIS

Protocol Title: The Impact of ^{90}Yttrium (Y90) Radiation Segmentectomy on Unresectable Hepatocellular Carcinoma

Type of Protocol: Phase I protocol to collect efficacy

Protocol Design: Prospective, open-label, single arm study.

Study Objective: The aim of this pilot study is to assess the efficacy of radiation segmentectomy with Theraspheres in patients with unresectable hepatocellular carcinoma that would qualify for thermal ablation as per the BCLC guidelines, but are unable to receive thermal ablation due to unfavorable location of target lesions.

Primary Endpoint: Efficacy of ^{90}Yttrium (Y90) Radiation Segmentectomy on Unresectable Hepatocellular Carcinoma as measured by tumor response according to mRECIST based on investigator evaluations.

Secondary Endpoints:

- Time to Progression (TTP): The length of time from radiation segmentectomy until progression of disease based on mRECIST based on investigator evaluations.
- Assess toxicity resulting from Radiation Segmentectomy with Theraspheres

Trial Population: Patients diagnosed with Hepatocellular Carcinoma as per AASLD guidelines and not eligible for surgical resection or thermal ablation.

Number of Patients: 30

Study Duration: 2 years accrual and 2 years follow-up for a total of 4 years duration.

Eligibility Criteria:

1. Age greater than 18 years, regardless of race or gender
2. Hepatocellular Carcinoma confirmed by histology for non-cirrhotic patients or non-invasive criteria according to AASLD for cirrhotic patients.
3. Child-Pugh class A or B7 without ascites
4. Single tumor nodule $\leq$ 3 cm with a maximum distance of 5 mm from either portal vein, hepatic vein, inferior vena cava, diaphragm, heart, stomach, bowel, liver capsule, gallbladder, bile duct.
5. No prior locoregional treatment or external beam therapy of current HCC (recurrent HCC after resection may be included)
6. No confirmed extrahepatic metastases
7. No evidence of macrovascular invasion
8. ECOG 0
9. Albumin $\geq$ 3.0 g/dL

10. PLT ≥ 40 x103/μL
11. WBC ≥ 1.5 x103/μL
12. AST/ALT ≤ 5 times the upper limit of normal (U/L)
13. Creatinine ≤ 2.0 mg /dL
14. No indication for any possible curative treatment after multidisciplinary assessment (surgery, ablation)
15. No contraindication to angiography or selective visceral catheterization
16. No history of severe allergy or intolerance to contrast agents, narcotics, sedatives.
17. Negative serum pregnancy test
18. Signed informed consent form

Imaging Requirements

• MRI scans abdomen/pelvis; To assess disease extension and to determine liver volume measurement and identify hepatic vascular anatomy.
• Spiral CT Chest –performed with cuts of 10 mm or less in slice thickness contiguously in the axial plane. To assess extra-hepatic lesions according to the RECIST v 1.1.
• Hepatic angiography and 99mTC-MAA – selective celiac and superior mesenteric arteriograms are needed to evaluate the hepatic arterial anatomy for the whole liver, as well as evaluation of potential sources of extra-hepatic blood supply to tumors. Repeat 99mTC-MAA may be needed to estimate cumulative lung shunt or re-asses GI flow.
• SPECT imaging may be performed according to standard of care practices for clinical management but is not a study requirement.
• PET/CT for quantification of dose to target lesion, as well as dose to non-target liver.

Sample Size Calculation and Statistical Plan

This is a pilot study seeking to determine the efficacy of radiation segmentectomy on very early to early unresectable HCC, not amenable to thermal ablation.

Current reported complete response rates of approximately 50% for BCLC A patients utilizing selective chemoembolization have been promising. (31,32,33) Radiofrequency ablation has been reported to have >80% complete response for lesions < 3 cm. (30)

Based on the assumption that a recent study reporting radiation segmentectomy rates similar to ablation, the goal is 80% complete response, compared to 50% complete response rate of TACE.

Numeric Results for testing H0: P=P0 versus H1: P<>P0

Test Statistic: Z Test using S (P0)

	Proportion	Proportion

The Impact of ^{90}Yttrium (Y90) Radiation Segmentectomy on Unresectable Hepatocellular Carcinoma

Power	N	Given H0 (P0)	Given H1 (P1)	Alpha	Reject H0 If Beta If [Z]> Then	
0.9108	30	0.5000	0.8000	0.0500	0.0892	1.9600

A sample size of 30 achieves 91% power to detect a difference (P1-P0) of 0.3000 using a two-sided Z test that uses S(P0) to estimate the standard deviation. The target significance level is 0.0500. These results assume that the population proportion under the null hypothesis is 0.5000.

Safety Analysis:

All patients will undergo safety analysis at the interval study visits outlined below in the study visits section. All adverse events will be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.03 (CTCAE). The incidence of adverse events will be summarized according to the primary system-organ class and within the category defined in the CTCAE v 4.03. The summaries will be overall (severity grades 1-4) and for grade ≥3 events and will also report the actions taken in terms of treatment discontinuation. Serious adverse events (SAE) will be tabulated by treatment. Laboratory values will be summarized by treatment group over time and overall.

Screening:

• Informed Consent
• Demographics
• Physical examination
• Medical history
• Child-Pugh assessment of chronic liver disease
• ECOG Performance Status assessment
• Abdomen/pelvis MRI to assess liver tumor presentation, calculate liver volume.
• Chest CT to rule out extra-hepatic metastases
• Required laboratory blood work plus alfaphetoprotein (AFP)
The date of screening is the date all screening procedures are completed.

Treatment:

Radiation segmentectomy protocol:

a. *MAA mapping*:
- Patients will undergo pretreatment angiography under transfemoral or transradial access with conebeam CT to:

  (**1**) determine vascular anatomy of the region
  (**2**) determine vascular supply of tumor
  (**3**) prophylactically embolize vessels that may lead to aberrant deposition of radioembolic microspheres

(**4**) perform technetium-99 m macroaggregated albumin (99mTc-MAA) scans to determine lung shunt fraction (LSF) and splanchnic shunting.
(5) Patients will not be eligible for TheraSphere infusion if the potential radiation dose to the lungs exceeds 30 Gy for a single treatment or cumulative 50 Gy or embolization cannot be performed to effectively block GI blood flow from the hepatic arterial system.

- In all patients, the vessel feeding the segment(s) being targeted for treatment will be identified and catheterized using standard angiographic techniques and conebeam CT.

b. Dosimetry:

- Based on the pretreatment angiography and conebeam CT, the volume of the perfused liver will be calculated on either the pretreatment CT or MRI, which will not be > 6 weeks from time of MAA mapping.
- Assuming uniform distribution and complete 90Y decay in situ, radioactivity required for desired dose delivery to the injected tissue can be calculated using the pretreatment dose-planning formula A = (D x M)/50, where A is the administered activity (activity of the vial that is to be infused) in gigabecquerels, D is the desired treatment dose in grays, and M is the mass of the tissue perfused by the microspheres in kilograms. M is determined after converting the volume of that tissue to kilograms using the conversion factor of 1.03 $x10^{-3}kg/cm^{-3}$.
- Target dose will be >205 Gy, assuming that is the threshold for tumor destruction (29).
- After treatment, actual dose delivered to the tissue is determined after correcting for fraction of activity remaining in the vial (R) and LSF, using the formula for the posttreatment dose delivered: D = 50 (A) (1 - LSF) (1 - R)/M.

c. *Delivery of Y90*:

- Radiation segmentectomy will be performed with Yttrium-90, whereby a high radiation dose is delivered to the tumor via radioactive microspheres infused through the hepatic artery. The radioactive microsphere delivery device used will be glass-based (TheraSphere; BTG, Ottawa, Ontario, Canada), in which 90Y is an integral constituent of the biocompatible glass matrix.
- Patients will be subsequently imaged the same day with PET-CT to calculate dose to target tissue, as well as dose to the non-target liver. This will be performed on a PET-CT system (Siemens).

Patients who consent to the procedure, but cannot proceed with treatment due to dose resulting in >30 Gy to the lungs or inability to target feeding vessels ≤ 2 Couinaud segments will be regarded as treatment failures.

Study Visits and Follow-up

Screening:

Images and test results obtained for clinical patient management and before signing of informed consent do not need to be repeated and may be used for screening assessment provided images were taken within 28 days. These evaluations will be the baseline values for patients in the trial.

Follow-up:

Patients will be followed within 6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years. Follow-up will be within 7 days of scheduled times post-treatment.

Visits include assessment of:
o ECOG[1] Performance Status assessment
o Standard laboratory blood draw for CBC, differential, electrolytes, BUN, glucose, liver function test, coagulation panel, and α-fetoprotein biomarker
o Adverse event reporting
o Abdomen/pelvis MRI (6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years. Imaging will be performed within 7 days of scheduled visits.)
o Chest CT scan (6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years. Imaging will be performed within 7 days of scheduled visits)

Progression:

Definition of tumor progression is defined as:
• Radiological progression as defined by mRECIST
• Development of extra-hepatic disease beyond the limits defined in the eligibility criteria
• ECOG Performance Status ≥2

[1]ECOG Performance Status
Score Characteristics
0 Asymptomatic and fully active
1 Symptomatic; fully ambulatory; restricted in physically strenuous activity
2 Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.
3 Symptomatic; limited self-care; more than 50% of waking hours are spent in bed
4 Completely disabled; no self-care; bedridden.

STUDY RATIONALE

The aim of this pilot study is to assess the efficacy of radiation segmentectomy with Theraspheres in patients with unresectable hepatocellular carcinoma that would qualify

for thermal ablation as per the BCLC guidelines, but are unable to receive thermal ablation due to unfavorable location of target lesions.

BACKGROUND

There is an increasing incidence of HCC in the United States over the last twenty years, largely due to the hepatitis C epidemic but increasingly related as well to nonalcoholic fatty liver disease(1,2).

For patients with single HCC and compensated liver disease (normal liver function and without portal hypertension), partial liver resection (LR) is the preferred treatment. Unfortunately, only 5-10% of these patients are resectable due to a variety of factors, which may include portal hypertension, total bilirubin > 1.0 mg/dL and platelets less than 100,000/mm^3. For patients with HCC who are Barcelona Clinic Liver Cancer (BCLC) Guidelines Class A (1 lesion < 5cm, or 2-3 lesions all < 3cm) who are not candidates for LR, liver transplantation (LT) is the treatment of choice. The current median waiting time in New York, however, is greater than 12 months, creating the risk of dropout due to tumor progression (currently estimated to be around 20-25%). In order to mitigate this risk, patients listed for LT typically undergo locoregional therapy with TACE and/or thermal ablation (TA) as a bridge or downstage to LT (3,4).

Patients with BCLC A HCC who due to age, medical, or psychosocial issues are not candidates for LR are typically treated with TA. Thermal ablation is effective in lesions that can have precise placement of ablation probes and are accessible from a percutaneous approach. Local Time to Progression in patients, who have received TA has been demonstrated to be 10% at 3 years by studies from Lee at el. (36)
However, some of these lesions have demonstrated incomplete ablation cavities on follow-up due to adjacent heat sinks. Serious adverse events from thermal ablation, although small, have been well documented and associated with unfavorable locations, such as adjacent to heart, bowel, gallbladder and diaphragm. As a result, some thermal ablations have resulted in abscesses, bowel perforation, hemothorax, cardiac tamponade, hematoma from superficial lesions near the liver capsule, gallbladder perforation, as well as seeding from the ablation tract. (37-41)

Transarterial chemoembolization (TACE) has demonstrated a survival benefit in BCLC B, or intermediate stage, patients. Recent studies have also demonstrated an approximately 50% complete response rate for single lesions, when sub-selective catheterization is utilized. (31, 32, 33) However, tumors treated with TACE have demonstrated viable components on explanted livers by pathology.

Studies with transarterial radioembolization with Yttrium 90 (Y90) have offered a potential benefit compared to TACE in BCLC B patients with a longer time to progression (TTP). This may provide a benefit for patients awaiting transplantation.

TheraSphere consists of insoluble glass microspheres in which yttrium-90 is an integral component of the glass. The sphere diameter ranges from 20 to 30 μm with 22,000 to

73,000 microspheres per milligram. TheraSphere is available in dose sizes ranging from 3 GBq to 20 GBq, each supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vial secured within a clear acrylic vial shield. A pre-assembled single-use TheraSphere Administration Set is provided for each dose. Each user site is provided with a reuseable TheraSphere Administration Accessory Kit that provides both radiation protection for the user and physical support of the dose vial and Administration Set during administration of the product. Yttrium-90 is a pure beta emitter which decays to stable zirconium-90 with a physical half-life of 64.1 hours. The average energy of the beta emissions from yttrium-90 is 0.9367 MeV with mean tissue penetration of approximately 2.5 mm.

TheraSphere is administered through the hepatic artery which supplies blood to tumor tissue (the portal vein supplies blood to the normal hepatic tissue). The microspheres are trapped in the vasculature of the tumor due to arteriolar capillary blockage where they exert a local radiotherapeutic effect. In clinical use, the glass microspheres remain permanently trapped in the vasculature where the isotope decays to infinity leaving background radiation with no therapeutic value.

Salem et al demonstrated the tolerability of TheraSphere in treatment of patients with HCC and branch PVT and patients with unresectable HCC. Salem et al recently published their long-term experience of TheraSphere in the treatment of patients with HCC. In this report, patients with HCC (n=291) were treated with TheraSphere as part of a single-center, prospective, longitudinal cohort study. Toxicities were recorded using the Common Terminology Criteria version 3.0. Response rate and time to progression (TTP) were determined using World Health Organization (WHO) and European Association for the Study of the Liver (EASL) guidelines. Survival by stage was assessed.

Univariate/multivariate analyses were performed. A total of 526 treatments were administered (mean, 1.8; range, 1-5). Toxicities included fatigue (57%), pain (23%), and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%. Response rates were 42% and 57% based on WHO and EASL criteria, respectively. The overall TTP was 7.9 months (95% confidence interval, 6-10.3). Survival times differed between patients with Child-Pugh A and B disease (A, 17.2 months; B, 7.7 months; P = .002). Patients with Child-Pugh B disease who had portal vein thrombosis (PVT) survived 5.6 months (95% confidence interval, 4.5-6.7). Baseline age; gender; performance status; presence of portal hypertension; tumor distribution; levels of bilirubin, albumin, and alpha-fetoprotein; and WHO/EASL response rate predicted survival. These investigators concluded that patients with Child-Pugh A disease, with or without PVT, benefited most from treatment. Patients with Child-Pugh B disease who had PVT had poor outcomes. TTP and overall survival varied by patient stage at baseline.

The clinical experience of Salem et al and a recent meta-analysis of yttrium-90 microsphere radioembolization13 indicates that TheraSphere is very well tolerated when appropriate patient selection criteria are used. Early reports of serious adverse events

possibly associated with the use of TheraSphere, as described in the package labeling documents in Appendix 1, included death, hepatorenal failure, liver abscess, hepatic encephalopathy, hepatic decompensation, radiation hepatitis, radiation pneumonitis, duodenal ulcer, gastrointestinal bleeding and cholecystitis. These more severe events are now uncommon as patients with the high risk factors associated with the occurrence of these events are typically excluded from treatment with TheraSphere. Patients in whom TheraSphere should be used with caution include those with infiltrative tumor type, bulk disease (tumor volume >70% or nodules too numerous to count), AST or ALT > five times the upper limit of normal, bilirubin > 2 mg/dL, tumor volume >50% in the presence of an albumin < 3 g/dL, and those in whom extra-hepatic shunting to the lungs or gastrointestinal tract cannot be managed through standard angiographic techniques.

More recently, the technique of radiation segmentectomy utilizing TheraSphere has been described by Riaz et al. with treatment along an arterial anatomic plane confined to ≤ 2 Couinaud segments (>190Gy), resulting in complete pathological necrosis of targeted segments while limiting radiation exposure of non-targeted tissue.

In a prospective study, eighty-four patients with hepatocellular carcinoma confirmed by biopsy or radiographic evidence as defined by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) criteria were treated with TheraSphere utilizing a segmental approach (Riaz A, et al). The objective of the study was to define radiation segmentectomy by calculating the dose delivered to the segment in addition to assessing safety and efficacy.

The patient cohort was vastly male (58) with a median age of 68 years (range 43-90 years) and in good performance status 0 (61) and 1 (25). Hepatitis C virus (HCV) was the etiology of their liver disease (34) and the majority of tumors were staged as T2 (32) and T3 (25) according to UNOS stage. There was similarity among Barcelona Clinic Liver Cancer stage (A = 27; B = 25 and C = 31) and all patients were Child-Pugh A (41) and B (42) with the exception of one Child-Pugh class C patient. All tumors were angiographically isolatable, specifically located in two or fewer Couinaud segments that have the capability to be perfused at the intended catheter position.

Each patient underwent pretreatment angiography and ^{99}Tc-MAA injection for shunt detection. Standard dosimetry was calculated based on catheterizing the lobar branch and exposing the lobe with a target of 120Gy. Following treatment, the actual dose delivered was calculated by assuming uniform and non-uniform microsphere distribution within the treatment volume. All 84 patients received infusion at the level of the segmental artery.

Response rate was determined utilizing the World Health Organization (WHO) and necrosis (EASL) guidelines and the time to progression (TTP) and survival analyses are captured in Table 3.

Table 3. Time to Progression and Survival Analyses

Efficacy Parameter	Time (Months)	One Year Rates (%)	Two Year Rates (%)	Three Year Rates (%)
Overall Survival (Median)	26.9 months	56	23	12
Time to Progression (Median)	13.6 months	74	55	27

It was demonstrated that a median segmental dose of 521 Gy assuming uniform microsphere distribution translated to a traditional lobar dose of 97 Gy which was further comparable to a whole liver dose of 35.5 Gy. Furthermore, given the hypervascular nature of HCC and assuming that hepatic arterial blood flow is preferentially directed to the tumor, the median dose estimated to be delivered to the tumor was even greater (1657 Gy). Thus, the high response rates presented in this study may be due to the higher radiation doses selectively delivered to the tumor.

The most common clinical toxicities reported were fatigue (44), abdominal pain (15), and nausea/vomiting (11) and grade 3/4 laboratory abnormalities reported were bilirubin (5) and albumin/alkaline phosphatase (2). Twenty-nine patients experienced no adverse reactions. Both clinical toxicities and laboratory abnormalities following a segmental approach were lower than that described following a typical lobar infusion method which further supports the decrease in radiation exposure to normal hepatic parenchyma and the utility of this methodology. Refer to Table 4 for adverse reactions experienced in this patient cohort.

Table 4. Toxicities

Toxicity	n (%)
Clinical Toxicities (All Grades)	
Fatigue	44 (52)
Abdominal pain	15 (18)
Nausea/Vomiting	11 (13)
Anorexia	7 (8)
Diarrhea	1 (1)
Fever/chills	4 (5)
Weight loss	3 (4)
None	29 (35)
Laboratory Abnormalities	
Bilirubin	5 (6)
Albumin	2 (2)
ALT	0
AST	1 (1)
Alkaline phosphatase	2 (2)

A retrospective, multi-center study was also conducted in which 102 treatment-naïve patients with unresectable HCC ≤5cm according to AASLD (American Association for the Study of Liver Diseases) guidelines and the absence of portal vein thrombosis (PVT) were treated with TheraSphere in a segmental fashion (Vouche M, et al). The objective of the study was to assess the efficacy including response rates, overall survival, and pathologic analysis.

Radiation segmentectomy is achieved by prospectively determining lobar volumes and prescribing an intended lobar dose of 120-150Gy. The activity vial(s) is then injected within the segmental feeding vessel which will minimize radiation to the normal parenchyma and increase safety to the patient. As a result, segmental doses are higher than the prescribed dose by the ratio of lobar to segmental volumes.

The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{\text{[Desired Dose (Gy)] [Liver Mass (kg)]}}{50}$$

The actual dose delivered to the perfused tissue can be assessed by utilizing cone-beam CT, the perfused volume and mass can now be measured during mapping angiography, resulting in real-time dosimetry in planning for radiation segmentectomy. This method of utilizing cone-beam CT has resulted in a radiation segmentectomy typically being performed with a 3,5,7, or 10 GBq vial, depending on the vascular capacitance of the segmental vessel (s).

Demographic and baseline characteristics revealed 59 males and 43 females with a median age of 64 years (range 58-75 years). Although lesions were classified as small, forty percent of the patients were greater than an ECOG performance status 0 (41/102) and 61 BCLC A and 41 BCLC C. Additionally, two patients had a Child-Pugh C score >9. The majority of lesions were not amendable to radiofrequency ablation due to location in the dome of the liver specific to segments 4, 7, and 8 and T2 (82 tumors) according to the UNOS stage. The median size of the tumor was 2.6cm (range 2.1-3.6cm).

Slightly greater than half of the patients experienced adverse reactions and none required admission. The most common clinical toxicities according to the Common Terminology Criteria for Adverse Events v4 were fatigue (46), abdominal pain (10), nausea (8), fever (3), appetite loss (2), dyspnea (1), vomiting (1), and weight loss (1). The first four adverse events were all mild in nature. The most common grade 3/4 laboratory toxicities were lymphopenia, platelets, bilirubin, AST and ALT, hence many of these were present at baseline and not altered over a period of 24 months as demonstrated in Table 5 below.

Table 5 Laboratory Abnormalities

Laboratory Value	Baseline	1-3 months	p value	3-6 months	p value	6-12 months	12-24 months
AST	2/102	1/94	0.99	0/53	0.77	2/31	0/19
ALT	4/102	4/94	0.72	0/53	.0.34	0/31	0/19
Bilirubin	3/102	6/94	0.17	7/53	0.27	3/31	0/19
Albumin	5/102	7/94	0.77	3/53	0.87	0/31	4/19
INR	14/102	15/94	1.0	3/53	0.06	2/31	1/19
Absolute Lymphocyte	16/102	18/94	0.86	12/53	0.67	5/31	2/19

Response rates were assessed on 99 evaluable patients according to modified RECIST (mRECIST). The time-to-progression was 33.1 months for 27/102 patients, hence 16/27 patients developed new intrahepatic lesions. The median time to development of a new lesion was 6.2 months. Refer to Table 6 for response rates.

Table 6. Efficacy Outcomes

Complete Response	47/99
Partial Response	39/99
Stable Disease	12/99

Median overall survival was 53.4 months with a median follow-up of 27.1 months . Upon exclusion of those patients transplanted, survival was 34.5 months. For the thirty-three transplanted, the mean survival was 56.5 months.

Of importance, 33/102 patients were transplanted in a mean time frame of 6.3 months and pathologic analysis revealed 17/33 patients had a complete pathologic necrosis and 16/33 patients had a partial pathologic necrosis. Complete necrosis was evident when the radiation dose exceeded 190Gy to the treatment area which was statistically significant (p=0.03). Refer to Table 7 for pathologic and dose delivered correlation.

Table 7. Pathologic Analysis and Dose Correlation

Radiation Dosage	Complete Necrosis	Partial Necrosis	Total
<190Gy	3	9	12
>190Gy	14	7	21
Total	17	16	33

A univariate analyses revealed patients with ECOG Performance Status 0 had a survival benefit and in a multivariate analyses, patients with age <65, ECOG), and Child-Pugh A were also associated with longer survival.

In comparison to a lobar infusion, radiation segmentectomy has a comparable efficacy

outcomes and a lower toxicity and adverse event rate due to the limited radiation dose administered to the normal hepatic parenchyma.

The assessment of treatment response after TACE and TA is currently based on loss of internal vascularity on contrast-enhanced imaging as outlined in the mRECIST. The response to Y90, however, may not be as accurately assessed by mRECIST. Diffusion-weighted imaging (DWI) and uptake by hepatocytes of liver-specific contrast (Gd-EOB-DTPA) are potentially complementary methods to assess hepatocyte damage. The use of DWI has been reported in the diagnosis of liver tumors and for the evaluation of treatment response in liver metastases (treated with systemic chemotherapy) and HCC (treated with TACE) (19-25). Diffusion MRI (or dMRI) is a magnetic resonance imaging (MRI) method which came into existence in the mid-1980s. It allows the mapping of the diffusion process of molecules, mainly water, in biological tissues, in vivo and non-invasively. Molecular diffusion in tissues is not free, but reflects interactions with many obstacles, such as macromolecules, fibers,membranes, etc. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture, either normal or in a diseased state. In diffusion weighted imaging (DWI), the intensity of each image element (voxel) reflects the best estimate of the rate of water diffusion at that location. Because the mobility of water is driven by thermal agitation and highly dependent on its cellular environment, the hypothesis behind DWI is that findings may indicate (early) pathologic change. The apparent diffusion coefficient (ADC) measures the magnitude of diffusion (of water molecules) within tissue. Most studies have observed an early rise in ADC values concomitant with devascularization, with subsequent decrease in ADC values in HCC (19). The extent of tissue cellularity and the presence of intact cell membrane help determine the impedance of water molecule diffusion. This impedance of water molecules diffusion can be quantitatively assessed using the apparent diffusion coefficient (ADC) value. This assessment can be done using different b values via changing gradient amplitude.

We propose to test the following **hypothesis**:

Radiation segmentectomy will provide a high response rate in patients that qualify for radiofrequency ablation as per the BCLC guidelines, but are deemed ineligible.

STUDY OBJECTIVES

The goal of this proposal is to assess the efficacy of radiation segmentectomy in patients with very early and early HCC as per BCLC, who cannot undergo thermal ablation. Towards this goal, we will also explore 1) Time to Progression 2) Quantifying dose to target lesion 3) Safety and 4) Toxicity.

Primary end point:

Tumor response: Assess tumor response according to mRECIST

Secondary end points:

1. Time to Progression: The length of time from radiation segmentectomy until progression of disease based on mRECIST.
2. Assess toxicity resulting from Radiation Segmentectomy with Theraspheres

Response assessment:

Response assessment will be performed with mRECIST 6 weeks post-radiation segmentectomy, 12 weeks post-radiation segmentectomy and every 3 months thereafter for a period of 2 years to correlate with data collection. Imaging will be performed within 7 days of scheduled visits.

DATA and METHODOLOGY

This is a prospective, single arm study. Segmentectomy within the context of this protocol will be offered to patients with a single site of HCC ≤ 3 cm diameter who are not eligible for thermal ablation. Patients may, if otherwise qualified either before or after treatment, be included on the waiting list for LT.

Diagnosis

The diagnosis of HCC will be established using updated AASLD criteria based on CT or MRI. Histological confirmation will be obtained in non-cirrhotic patients.

Inclusion Criteria:

1. Age greater than 18 years, regardless of race or gender
2. Hepatocellular Carcinoma confirmed by histology for non-cirrhotic patients or non-invasive criteria according to AASLD for cirrhotic patients.
3. Child-Pugh class A or B7 without ascites
4. Single tumor nodule ≤ 3 cm with a maximum distance of 5 mm from either portal vein, hepatic vein, inferior vena cava, diaphragm, heart, stomach, bowel, liver capsule, gallbladder, bile duct.
5. No prior locoregional treatment or external beam therapy of current HCC (recurrent HCC after resection may be included)
6. No confirmed extrahepatic metastases
7. No evidence of macrovascular invasion
8. ECOG 0
9. Albumin ≥ 3.0 g/dL
10. PLT ≥ 40 x10^3/μL
11. WBC ≥ 1.5 x10^3/μL

12. AST/ALT ≤ 5 times the upper limit of normal (U/L)
13. Creatinine ≤ 2.0 mg /dL
14. No indication for any possible curative treatment after multidisciplinary assessment (surgery, ablation). Unresectable parameters include platelets<100 x103/μL, portal hypertension, Total Bilirubin > 1.0 mg/dL, and comorbidities which exclude surgery agreed upon during the multidisciplinary meeting.
15. No contraindication to angiography or selective visceral catheterization
16. No history of severe allergy or intolerance to contrast agents, narcotics, sedatives.
17. Negative serum pregnancy test
18. Signed informed consent form

Exclusion Criteria:

1. Inability to provide informed consent
2. Pregnancy
3. Metastatic disease outside of the liver
4. Macrovascular invasion
5. Child-Pugh class > B7
6. Total Bilirubin > 2.0 mg/dL
7. Platelets < 40×10^3 per mm^3
8. Encephalopathy* (Defined below)
9. Refractory ascites
10. Greater than a single nodule > 3 cm

Study Visits and Follow-up

Screening:

Images and test results obtained for clinical patient management and before signing of informed consent do not need to be repeated and may be used for screening assessment provided images were taken within 28 days. These evaluations will be the baseline values for patients in the trial.

Follow-up:

Patients will be followed within 6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years. Visits will occur within 7 days of scheduled appointments.

Visits include assessment of:
o ECOG[1] Performance Status assessment
o Standard laboratory blood draw for CBC, differential, electrolytes, BUN, glucose, liver function test, coagulation panel, and α-fetoprotein biomarker
o Adverse event reporting
o Abdomen/pelvis MRI (6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years)

o Chest CT scan (12 months after treatment and 24 months after treatment)

Progression:

Definition of tumor progression is defined as:
• Radiological progression as defined by mRECIST
• Development of extra-hepatic disease beyond the limits defined in the eligibility criteria
• ECOG Performance Status ≥2

[1]ECOG Performance Status
Score Characteristics
0 Asymptomatic and fully active
1 Symptomatic; fully ambulatory; restricted in physically strenuous activity
2 Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.
3 Symptomatic; limited self-care; more than 50% of waking hours are spent in bed
4 Completely disabled; no self-care; bedridden

Data Collection

Patients will be interviewed and clinical information will be obtained at baseline, 6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years. Visits will occur within 7 days of scheduled appointments.

Baseline data shall include:
1. Demographics: age, sex, etiology of liver disease
2. Liver and renal function tests: bilirubin, AST, ALT, albumin, alkaline phosphatase, GGTP, BUN, creatinine, Na, INR, platelet count
3. Presence or absence of clinical ascites and encephalopathy*
4. Serum alpha fetoprotein
5. MRI abdomen/pelvis
6. Chest CT
7. Performance status according to ECOG

Follow up data shall include:

o ECOG[1] Performance Status assessment
o Standard laboratory blood draw for CBC, differential, electrolytes, BUN, liver function test, coagulation panel, and α-fetoprotein biomarker
o Adverse event reporting
o Abdomen/pelvis MRI (6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years)
o Chest CT scan (6 weeks after treatment, 12 weeks after treatment and 3 months thereafter for a period of 2 years)

Progression:

Definition of tumor progression is defined as:
• Radiological progression as defined by mRECIST
• Development of extra-hepatic disease beyond the limits defined in the eligibility criteria
• ECOG Performance Status ≥2

[1]ECOG Performance Status

Score Characteristics
0 Asymptomatic and fully active
1 Symptomatic; fully ambulatory; restricted in physically strenuous activity
2 Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed.
3 Symptomatic; limited self-care; more than 50% of waking hours are spent in bed
4 Completely disabled; no self-care; bedridden

* Grades of Encephalopathy

Grade 1	Inverted sleep pattern; forgetfulness, agitation, irritability, apraxia
Grade 2	Lethargy; Disorientation for time or place, Subtle personality change; Asterixis, ataxia
Grade 3	Somnolence but rousability; Disorientation as regards place; Asterixis, hyperactive reflexes, Babinski signs, muscle rigidity
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

MRI protocol:

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

In addition to mRECIST, radiological parameters to be measured will include:

1. Maximum tumor diameter
2. Signal intensity enhancement in tumors at the arterial and portal venous phases.
3. Degree of tumor necrosis using image subtraction (27)
4. Tumor ADC: in whole tumor and viable tumor components, we will measure mean ADC +/- SD.
5. Liver uptake: we will measure contrast uptake on the hepatobiliary phase 20 min post contrast injection in the peritumoral area to assess for hepatocyte damage.

6. Liver ADC will also be measured in the peritumoral liver area.

Brief Summary of mRECIST

mRECIST for HCC

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

Radiation segmentectomy protocol:

c. *MAA mapping*:

- Patients will undergo pretreatment angiography under transfemoral or transradial access with conebeam CT to:

  (**1**) determine vascular anatomy of the region (≤ 2 Couinaud Segments)
  (**2**) determine vascular supply of tumor
  (**3**) prophylactically embolize vessels that may lead to aberrant deposition of radioembolic microspheres
  (**4**) perform technetium-99 m macroaggregated albumin (99mTc-MAA) scans to determine lung shunt fraction (LSF) and splanchnic shunting.

- In all patients, the vessel feeding the segment(s) being targeted for treatment will be identified and catheterized using standard angiographic techniques and conebeam CT.

d. Dosimetry:

- Based on the pretreatment angiography and conebeam CT, the volume of the perfused liver will be calculated on either the pretreatment CT or MRI, which will not be > 6 weeks from time of MAA mapping.
- Assuming uniform distribution and complete 90Y decay in situ, radioactivity required for desired dose delivery to the injected tissue can be calculated using the pretreatment dose-planning formula:
  A = (D x M)/50,
  where A is the administered activity (activity of the vial that is to be infused) in gigabecquerels,
  D is the desired treatment dose in grays,

and M is the mass of the tissue perfused by the microspheres in kilograms. M is determined after converting the volume of that tissue to kilograms using the conversion factor of 1.03 $x10^{-3}kg/cm^{-3}$.

- Target dose will be >205 Gy, assuming that is the threshold for tumor destruction based on the referenced paper from Garin et al, which demonstrated response to Y90 at target doses > 205 Gy (29).
- After treatment, actual dose delivered to the tissue is determined after correcting for fraction of activity remaining in the vial (R) and LSF, using the formula for the posttreatment dose delivered: D = 50 (A) (1 - LSF) (1 - R)/M.

c. *Delivery of Y90*:

- Radiation segmentectomy will be performed with Yttrium-90, whereby a high radiation dose is delivered to the tumor via radioactive microspheres infused through the hepatic artery. The radioactive microsphere delivery device used will be glass-based (TheraSphere; BTG, Ottawa, Ontario, Canada), in which 90Y is an integral constituent of the biocompatible glass matrix.
- Patients will be subsequently imaged the same day with PET-CT to quantify dose to target tissue, as well as dose to the non-target liver. This will be performed on a PET-CT system (Siemens).

Patients who consent to the procedure, but cannot proceed with treatment due to dose resulting in >30 Gy to the lungs or inability to target feeding vessels ≤ 2 Couinaud segments will be regarded as treatment failures.

Termination of Participation in Study to include those subjects who did not pass Y90 mapping test, as well as those who have clinical deterioration of concurrent medical conditions and those who decide to terminate participation.

Patients will undergo routine clinical surveillance at 6 weeks post-Y90, 12 weeks post-Y90, and at 3 month intervals post-Y90 for 2 years post Y-90 during which time they will be evaluated by the physician assistant/nurse practitioner and attending physicians, with assessment of their clinical performance, active medical issues, and any toxicities, as graded by the NCI CTCAE version 4.03. Follow-up will be within 7 days of scheduled times post-treatment.

	Screening	Mapping	Y90 Treatment	6 wks post	12 wks post	6 mo post	9 mo	12 mo	15 mo	18 mo	24 mo	End of Study
Informed Consent	X											
Demographics	X											
Medical History	X											
Physical Exam	X											
ECOG	X	X	X	X	X	X	X	X	X	X	X	X
Child Pugh	X											
AFP	X	X		X	X	X	X	X	X	X	X	
Prior Treatment Hx	X											
Hematology	X	X		X	X	X	X	X	X	X	X	

Coagulation	X	X		X	X	X	X	X	X	X	X	
Chemistry Panel, LFTs	X	X		X	X	X	X	X	X	X	X	
Serum Pregnancy	X	X	X									
Liver Volume/Tumor Mass		X										
Review Eligibility	X											
Hepatic Angio, MAA scan, Dose Calculation		X										
Quantify dose on PET/CT			X									
MRI abd/pelvis	X			X	X	X	X	X	X	X	X	
CT of chest	X							X			X	
Assess/Report Adverse Events	X			X	X	X	X	X	X	X	X	X
Review Record Study Treatment				X	X	X	X	X	X	X	X	X
Final Efficacy documentation												X

Data from this trial will be captured on case reporting forms (CRFs). An audit trail will be maintained to document all data changes in the database.
Procedures will be followed to ensure the validity and accuracy of the clinical database. The investigator will sign and date all indicated places on the CRFs. This signature will indicate that thorough inspection of the data has been made and will certify that the Site Investigator has reviewed and approved the data contained on the forms.

DATA MANAGEMENT

The investigator will ensure that trial data quality is maintained to current standards of Good Clinical Practice and that data are submitted in a timely manner as outlined in the protocol and supporting documentation. The investigator must sign an affirmation statement verifying the content of all subjects' CRFs. Errors must be corrected in accordance with EDC data entry guidelines.

ADVERSE EVENTS

Adverse experience will be considered synonymous with the term adverse event and vice versa.

DEFINITIONS OF AE/SAE FOR DRUGS

Adverse Device Effect (ADE)

An adverse device effect is an adverse event (AE – previously defined) related to a medical device and includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment, implantation, installation or malfunction of the

device; any event that is the result of user error; or any potential adverse device effect which might have occurred if suitable action had not been taken or intervention had not been made or if circumstances had been less fortunate.

Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (SAE – previously defined) or might have led to any of these consequences if suitable action had not been taken; intervention had not been made or circumstances had been less fortunate. This is classified as Grade 3-4 as per the NCI CTCAE v4.03. If 5 Serious Adverse Events are recorded, the study will be discontinued.

Unanticipated Adverse Device Event (UADE)

An unanticipated adverse device effect is any serious adverse effect which by its nature, incidence, severity and outcome has not been identified in the risk assessment, the informed consent form as well as the protocol.

RECORDING ADVERSE EVENTS

In this study, patients should be encouraged to report adverse events spontaneously or in response to general, non-directed questions. At any time during the study, the patient may volunteer information that resembles an adverse event. Once it is determined that an adverse event has occurred, the Investigator should obtain all the information required to complete the adverse event form. Any medical management of an event and the date of resolution of the event must be recorded in the source document and on the appropriate case reports form(s).

For each AE, the following information will be recorded:

- Adverse event
- Serious/non-Serious
- Severity (Toxicity Grade)
- Action taken
- Relationship to study treatment
- Expected/Unexpected
- Date and time of onset
- Date and time of resolution

An expected adverse event is any AE, the nature or severity of which is identified in the relevant Package Insert. Any AE experienced by a subject will be followed until the AE has resolved to the investigator's or physician sub-investigator's satisfaction. If a problem still exists, then the investigator or physician sub-investigator at his/her discretion will ask the subject to come back to the clinic for further evaluation. Any serious adverse events should be managed as discussed.

Once the subject has been discharged from the study, the investigator has no obligation to seek further follow-up with the subject in order to identify new AEs. AEs ongoing at study exit will be followed to resolution. However, if the investigator becomes aware of an SAE that has occurred following the subject's discharge from the study and the

investigator considers the SAE possibly, probably, or definitely related to a study drug or device, then the investigator should report the SAE as described in the protocol.

CAUSALITY (RELATIONSHIP TO MEDICAL DEVICE) ASSESSMENT

The investigator or physician sub-investigator must indicate whether he/she believes the AE is not related, unlikely related, possibly related (reasonable possibility that the medical device caused the AE), probably related, or definitely related to the medical device. An adverse event becomes an adverse device effect when the adverse event is considered associated with the use of the test device if the attribution is Possibly, Probably or Definitely Related.

PERIODIC SAFETY REPORTING

Adverse events will be recorded on the AE form and coded using NCI CTCAE v 4.03. The investigator or physician sub-investigator will judge the severity of each AE and whether or not it is treatment-related. All AEs that occur after the initiation of trial treatment, including events likely to be related to the underlying disease or likely to represent concurrent illness, will be reported, including events present at Baseline which worsened during the trial.

EXPECTED ADVERSE EVENTS

THERASPHERE ADVERSE EVENT PROFILE

TheraSphere has been approved for the treatment of HCC since 1999. Adverse events known to be related to the device or the procedure listed in the current package insert (Appendix 1). Those adverse events identified in clinical trials investigating treatment with TheraSphere of liver lesions metastatic to non-HCC primary cancers are listed below in decreasing order of frequency.

Frequency	Description of Adverse Event (per NCI-CTCAE 4.03)
Common - >10%	Fatigue, pain, nausea, vomiting, anorexia and laboratory value abnormalities including increased alkaline phosphatase, AST, ALT, bilirubin and decrease albumin
Infrequent - <10%	Lymphopenia with no clinical sequellae; constipation, heartburn, weight loss, fever, ascites, muscle weakness, variations in hemoglobin, neutrophils and leukocytes, GI ulcer, dyspnea, arrhythmia, diarrhea, liver dysfunction, hypotension, insomia, rigors/chills, sweating, distension, GI obstruction, hematoma, GI hemorrhage, pleural effusion,
Rare – < 1%	Alopecia, bruising, pruritis, rash, hot flashes, dehydration, taste alteration, hemorrhage, infection, dizziness, mood alteration, sensory neuropathy, somnolence, cough, urine color change, intraoperative injury, flu-like symptoms, tumor lysis syndrome, thrombosis, metabolic/laboratory abnormalities – creatinine, hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, lipase

In addition, the following events, which may or may not be related to the use of TheraSphere or the administration procedure, have been reported in clinical trials of treatment of primary or secondary liver cancer:

Abdominal pain, dyspnoea, abdominal distention, anxiety, blurred vision, chills, hot flashes, bladder infection, lower extremity edema, gastrointestinal stoma complication including mild pain, hepatic encephalopathy, hepatorenal failure, edema, malaise, hepatic decompensation, hepatitis, duodenal ulcer, hypertension, hypertension, aspiration pneumonia, fall, gastrointestinal bleeding, elevated AFP, elevated LDH, elevated prothrombin time, elevated BUN, bacterial sepsis, hypoglycemia, abnormal platelets and electrolyte disturbances including hypercalcemia, hyperkalemia, hypomagnesemia, hyponatremia, low serum bicarbonate and low serum chloride.

STUDY MONITORING

The study will be monitored by qualified personnel, Dr. Gene Im, MD.
During the course of the trial, a study monitor or other authorized representatives of the sponsor will conduct remote monitoring and visit the investigator at suitable intervals. The purpose of these visits will be to verify adherence to the protocol, ensure correct completion of the CRFs. In order to perform his role effectively, the study monitor must be given access to source documentation (eg, clinic charts, original laboratory records), which support data on the CRF, and informed consent forms. The monitor must be able to verify data appearing in the CRFs against data in the subject's clinic chart (eg, chart notes) or in printout forms (eg, laboratory results).

STATISTICAL ANALYSIS

Sample size / Power Calculations

This is a pilot study seeking to determine the safety and efficacy of radiation segmentectomy on very early to early HCC, not amenable to thermal ablation.

Current reported complete response rates of approximately 50% for BCLC A patients utilizing selective chemoembolization have been promising. (31,32,33) Radiofrequency ablation has been reported to have >80% complete response for lesions < 3 cm. (30)

Based on the assumption that a recent study reporting radiation segmentectomy rates similar to ablation, the goal is 80% complete response, compared to 50% complete response rate of TACE.

Numeric Results for testing H0: P=P0 versus H1: P<>P0

Test Statistic: Z Test using S (P0)

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Alpha	Reject H0 If Beta If [Z]> Then

0.9108	30	0.5000	0.8000	0.0500	0.0892	1.9600

A sample size of 30 achieves 91% power to detect a difference (P1-P0) of 0.3000 using a two-sided Z test that uses S(P0) to estimate the standard deviation. The target significance level is 0.0500. These results assume that the population proportion under the null hypothesis is 0.5000.

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