A Prospective Dose-Escalation Study to Define an Ablative Dose of Yttrium-90 Transarterial Radioembolization Using Advanced Dosimetry and Functional MRI (MARGIN Study)

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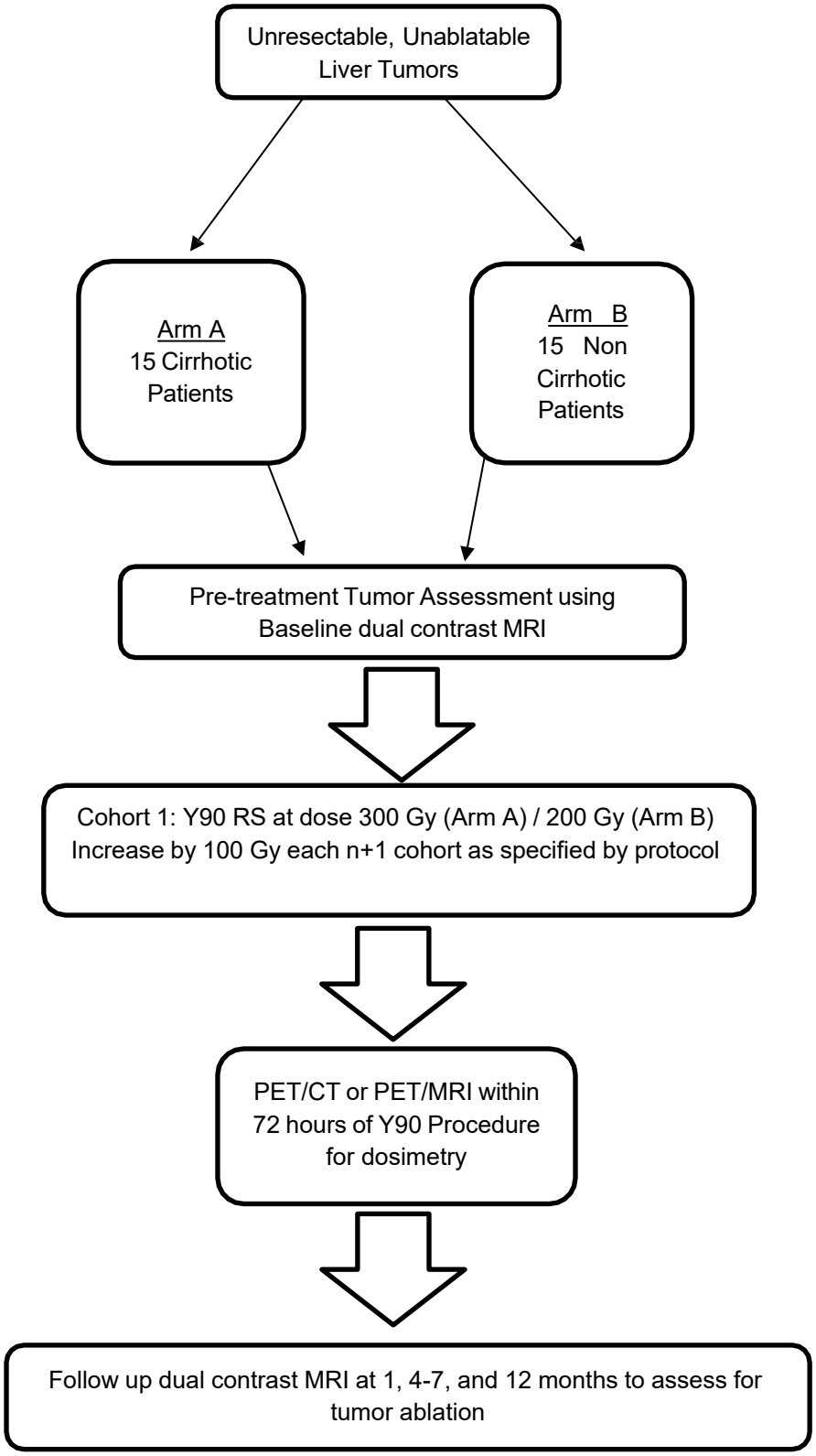
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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ADL	Activities of Daily Living
CPN	Complete Pathologic Necrosis
CT	Computed Tomography
CTA	Computed Tomographic Angiography
CTCAE v5.0	Common Terminology Criteria for Adverse Events, version 5.0
DLT	Dose-Limiting Toxicity
DARF	Drug Accountability Records Form
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ECV	Extracellular Volume
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gd	Gadolinium
Gy	Gray (unit of radiation dose)
H&E	Hematoxylin and Eosin
HCC	Hepatocellular Carcinoma
IDE	Investigational Device Exemption
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver Function Test
LTF	Lost to Follow-up
MDT	Multidisciplinary Tumor Board
MRI	Magnetic Resonance Imaging
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NHP	Normal Hepatic Parenchyma
NU	Northwestern University
PET	Positron Emission Tomography

PI	Principal Investigator
PR	Partial Response
QAM	Quality Assurance Monitor
RECIST	Response Evaluation Criteria in Solid Tumors
RNI	Reportable New Information
ROC	Receiver Operating Characteristic
RS	Radiation Segmentectomy
SAE	Serious Adverse Event
SOC	Standard of Care
SPECT	Single Photon Emission Computed Tomography
STATA	Statistical Software Package
TARE	Transarterial Radioembolization
TTP	Time to Progression
ULN	Upper Limit of Normal
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
WBC	White Blood Cell count
Y90	Yttrium-90

STUDY SCHEMA



STUDY SUMMARY

Title	A Prospective Dose-Escalation Study to Define an Ablative Dose of Yttrium-90 Transarterial Radioembolization Using Advanced Dosimetry and Functional MRI (MARGIN Study)
Version	03.13.2026
Study Design	Prospective Open label study
Study Center(s)	Northwestern: (Northwestern University, Northwestern Memorial Hospital)
Objectives	Primary Objectives • To prospectively define the "ablative dose" threshold for Y90 Radiation Segmentectomy (RS) using post-treatment PET dosimetry and hepatobiliary phase MRI. • To determine whether cirrhotic patients require a higher threshold dose for ablation compared to non-cirrhotic patients. Secondary Objectives • To evaluate the correlation between delivered Y90 dose and imaging biomarkers, including signal loss on hepatobiliary phase MRI, ablative margins, extracellular volume fraction, and perfusion changes. Assessed at 1 (±2 weeks), at 4–9, and at 12 months (±1 month) . • To assess tumor response by mRECIST and determine time to progression (TTP). • To assess the safety and tolerability of escalating segmental Y90 doses (200–500 Gy) using a dose-escalation design under DSMC oversight. Exploratory Objectives • To evaluate complete pathological necrosis in explanted tumors from patients who undergo liver resection or transplantation. • To identify novel early imaging biomarkers (Eovist hepatobiliary phase defects, extracellular volume mapping, perfusion changes) that may serve as surrogates for ablation success.
Sample Size	30 patients

Diagnosis & Key Eligibility Criteria	Disease Under Study: • Unresectable, unablatable primary or metastatic liver tumors, including hepatocellular carcinoma (HCC), cholangiocarcinoma, and liver-dominant metastatic disease. Key Inclusion Criteria: • Imaging (LIRADS) or biopsy-proven hepatocellular carcinoma (HCC). Biopsy-proven cholangiocarcinoma or liver-dominant metastatic disease (colon, neuroendocrine, breast) with discrete measurable liver tumors on imaging. • Adults ≥18 years old. • Child-Pugh Class A or B liver function. • ECOG performance status 0–2. • Ability to undergo MRI and • Ability to provide written informed consent. Key Exclusion Criteria: • Pregnant or breastfeeding individuals. • Contraindications to MRI or gadolinium contrast. • Extrahepatic metastases.
Treatment Plan	This is a prospective, single-institution, non-randomized dose-escalation study evaluating Yttrium-90 (Y90) Radiation Segmentectomy (RS) using glass microspheres administered via a transarterial route to patients with unresectable, unablatable primary or metastatic liver tumors. The intervention begins at 200 Gy for non-cirrhotic and 300 Gy for cirrhotic patients, with 100 Gy increments per cohort, using a Bayesian Optimal Interval (BOIN) dose-escalation design to determine the threshold for achieving hepatic sector ablation. Participants undergo post-treatment Y90 PET/CT or PET/MRI for dosimetry analyses. Follow-up includes dual-contrast MRI using gadoxetate disodium (Eovist) and an extracellular gadolinium agent at 1, 4–9, and 12 months post-treatment to assess hepatobiliary function, extracellular volume fraction, and perfusion. Each participant is followed for 12 months, with extended survival and outcome tracking thereafter. The overall study duration is approximately 36 months.
	The planned sample size is 30 patients (15 cirrhotic and 15 non-cirrhotic), based on a power calculation that provides 80% power to

Statistical Methodology	detect a 54% difference in threshold dose for ablation zone formation at a significance level of 0.05. Y90 dosimetry will be evaluated using logistic regression and receiver operating characteristic (ROC) analysis to identify threshold doses predictive of successful imaging-defined ablation. Kaplan-Meier survival analysis and log-rank testing will be used to compare progression-free survival (PFS) and overall survival (OS) outcomes. Safety comparisons between dose groups will use Fisher's exact test or t-tests, as appropriate.

1 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide and 3rd most common cause of cancer-related mortality (1). Each year, >0.5 million new cases of HCC are diagnosed worldwide and the incidence of HCC in the United States is projected to increase significantly (2,3). Although resection and transplantation offer the best 5-year survival rates, 70-85% of patients are not candidates for resection and few organs are available for transplantation (4).

Y90 TARE is an efficacious, well-tolerated outpatient therapy proven effective in the palliative setting and has potential to downsize tumors to curative surgery. Liver resection is the preferred therapeutic approach and a potentially curative option for patients with primary and secondary liver-dominant malignancy with preserved liver function (5). The goal of resection is to remove the diseased liver with clean margins, leaving the patient cancer-free. In patients with liver dysfunction in addition to liver cancer, there is a competing risk of death from liver failure. For these patients, locoregional therapy to maintain transplant eligibility or downstage patients is now routinely offered with Y90 TARE favored over chemoembolization as it was demonstrated to provide a longer time to progression (TTP) for HCC in a randomized controlled trial (6). Since this RCT, a paradigm shift has occurred with multiple centers now applying much higher (>120Gy) “ablative doses” to targeted hepatic segments harboring tumor, sparing the majority of the liver parenchyma and seeking complete tissue ablation. Our group pioneered this approach, termed Radiation Segmentectomy with Y90 (Y90 RS), for the selective delivery of high-dose radiation to up to 2 liver segment(s) with the intent of generating ablative effects for local tumor control and atrophy of the target liver segment. We have demonstrated the safety and efficacy of this technique in select patients both for primary liver cancers (HCC and cholangiocarcinoma) as well as in the setting of metastatic disease to the liver (7–11). Retrospective evaluation of explanted tumors demonstrates complete pathological necrosis in 86% of patients treated with >190Gy and 100% of patients treated with >400Gy (12,13). Therefore, an emerging role exists for Y90 RS to be applied with curative intent; however, this requires knowledge of delivered individual patient doses compared to a target threshold dose for achieving complete target tissue ablation, prospective evaluation of oncologic outcomes, and development of imaging biomarkers for confirmation of successful ablation.

“Ablative dosing” with Y90 RS remains undefined in non-cirrhotic versus cirrhotic and non-HCC versus HCC patients. Unlike other ablative techniques – such as microwave ablation and cryoablation – Y90 RS is not limited by tumor geometry, orientation, depth, size, or proximity to large vessels. Learning from the existing ablation literature and defining an ablative margin after Y90 RS may also provide a critical treatment endpoint, especially when there is a risk of microsatellite disease.

Conventional dosimetry approaches have allowed safe clinical usage of Y90 but paradoxically assume uniform distributions of microspheres within the targeted compartment (intratumoral, segmental, lobar or whole-liver); yet, the nonuniform preferential arterial tumor vascularity has been a central tenet for endovascular liver-directed therapy. Our group has significant experience with post-Y90 PET/CT, which outperforms Bremsstrahlung SPECT/CT with reduced scatter, and improved spatial resolution and contrast (14–17). Y90 PET/MRI enables excellent soft tissue characterization and mapping of Y90 distributions that our group has applied in a dog model of

prostate hyperplasia and also in patients with liver cancer treated with Y90 RS on a research basis (18). Multiple recent studies highlight an essential future role for Y90 PET/CT and PET/MRI as personalized tumor dosimetry significantly improves HCC patient survival (19,20).

Conventional post-therapy imaging assessments include only anatomic criteria, such as changes based on “extracellular” Gd contrast findings of tumor size and/or tumor necrosis (21–23). These changes as well as changes in irradiated hepatic parenchymal volumes evolve slowly over several months following Y90 RS with a 7-9 month expected time course. Therefore, optimizing earlier dose-response assessments should make Y90 RS more effective, bridging to surgery and other oncologic clinical endpoints such as time-to-tumor progression and overall survival, while potentially decreasing non-target toxicity. We propose developing a highly innovative multimodality imaging approach for linking Y90 PET(/CT or MRI) with a novel double-contrast advanced MRI technique to evaluate hepatic structural and functional changes, already used clinically in potential living donors (24). We theorize this double-contrast (“extracellular”/“intracellular”) technique will allow detailed MR angiography, full characterization of liver tumors (on pre, arterial, venous, and delayed phases), and critical hepatocyte-specific contrast to define post-Y90 RS ablation zones achieved. Dual contrast MRI has previously demonstrated measurable signal changes post Y90 TARE (25). Moreover, ECV mapping is used in routine clinical practice to assess cardiac fibrosis in infiltrative disease processes and increased ECV % has been associated with hepatic fibrosis in chemically induced rat models of cirrhosis (26). This work is expected to have an immediate translational impact improving imaging guidance of Y90 RS through advanced MRI for interrogation of biological processes (molecular imaging) to inform medical decision-making and provide a roadmap to potentially curative therapy.

1.2 Intervention Background & Overview

TheraSphere® (Yttrium-90 glass microspheres, Boston Scientific) is an FDA-approved Class III medical device for the treatment of hepatocellular carcinoma and is widely used in liver-directed radioembolization. In this study, it is being used in an off-label, segmental dose-escalation context to define ablative dose thresholds. Y90 emits beta radiation, which causes localized cytotoxic effects via DNA damage and cellular apoptosis. The use of voxel-based dosimetry with PET/CT or PET/MRI offers precise assessment of microsphere biodistribution, enhancing the evaluation of radiation effects at a tissue level. Y90 has demonstrated efficacy in treating HCC, cholangiocarcinoma, and liver-dominant metastases. Radiation Segmentectomy (RS), an approach pioneered by the study team, delivers high-dose Y90 to one or two Couinaud segments to achieve curative ablation. This technique involves superselective catheterization of the segmental hepatic artery supplying the tumor, enabling microspheres to deliver high-dose beta radiation confined to a precisely defined perfused volume—the segmental arterial territory targeted for treatment.

Pathologic outcomes strongly correlate with delivered dose: complete pathological necrosis (CPN) was observed in 100% of patients receiving >400 Gy, 86% receiving >190 Gy, and only 35% in those receiving <190 Gy. The LEGACY study and other prospective studies confirm the safety and oncologic efficacy of this technique. Y90 RS is generally well tolerated. Known toxicities include fatigue, abdominal pain, nausea, and transient hepatic dysfunction. Segmental dosing beyond 500 Gy has been associated with acceptable safety profiles when carefully

planned. Toxicity is monitored using CTCAE v5.0, and dose-limiting toxicities (DLTs) are overseen by a Data Safety Monitoring Board.

Despite promising retrospective data supporting high-dose Y90 Radiation Segmentectomy (RS), the optimal "ablative dose" threshold remains undefined—particularly in differentiating dosing requirements between cirrhotic and non-cirrhotic patients. This study addresses these critical knowledge gaps by integrating PET dosimetry and functional MRI to establish personalized dosing thresholds. By prospectively evaluating structural and functional hepatic changes alongside clinical outcomes, this research aims to optimize Y90 RS for curative intent and improve treatment precision in liver cancer therapy.

This is a prospective, single-institution, non-randomized, dose-escalation study using a Bayesian optimal interval (BOIN) design to evaluate escalating doses of Y90 Radiation Segmentectomy (RS). The design is appropriate for early-phase investigations where safety and dose-response thresholds are being explored. The primary endpoint is assessed using advanced PET-based voxel dosimetry and hepatobiliary phase MRI. This approach allows for precise quantification of tissue response to varying radiation doses and supports the study's goal of defining an “ablative dose” threshold.

The study targets a clinically important subset of patients with unresectable, unablatable liver tumors, stratified into cirrhotic and non-cirrhotic cohorts. This distinction is critical, as cirrhotic liver tissue may respond differently to radiation due to altered vasculature and impaired regenerative capacity. By studying both populations separately, the study addresses an unmet need in personalizing Y90 dosing based on underlying hepatic condition.

The objective of this study is to define an optimal “ablative dose” range for Y90 Radiation Segmentectomy that achieves complete sectoral ablation detectable on dual contrast MRI and to determine whether this dose-response relationship differs between cirrhotic and non-cirrhotic patients.

We hypothesize that an optimal ablative dose exists between 200–500 Gy, with increasing ablation rates as dose increases, and that the threshold dose to achieve ablation differs between cirrhotic and non-cirrhotic livers. This hypothesis will be tested using voxel-based Y90 PET dosimetry and hepatobiliary MRI to assess dose-response relationships in both structural and functional imaging endpoints.

1.3 Exploratory Studies

The study PI has completed an MD and PhD work on optimizing Y90 TARE with PET and is a practicing Interventional Oncologist at Northwestern Memorial Hospital. Selected relevant preliminary data are provided:

Y90 Radiation Segmentectomy is Safe and Potentially Curative with Dose-dependent CPN Rates
Study 1: Y90 RS in 102 patients with solitary HCC (≤ 5cm) not amenable to ablation with radiologic-pathologic correlation following transplantation (32% of patients). Doses >190Gy provided complete pathologic necrosis in 67% (14/21) vs 25% (3/12) in patients with ≤190 Gy dosing (P=.03) (8).

Study 2: Y90 RS in 34 transplanted patients with treatment-naïve solitary HCC (≤ 8cm). Doses >190Gy provided complete pathologic necrosis in 86% (24/28) vs 35% (6/17) in patients with ≤190 Gy dosing (P=.001). 100% of patients dosed >400Gy had CPN (12).

Study 3: Y90 TARE results in longer TTP than chemoembolization (>26 months vs 6.8 months, P=.0012) with fewer adverse events in a phase II trial of 45 patients (13).

Implications to the current proposal: Y90 RS is a safe and efficacious outpatient intra-arterial therapy for patients with unresectable, unablatable HCC. Retrospective data indicates a range of 67-86% of patients with dose >190Gy achieve CPN, but prospective data for threshold dosing is unavailable. Validation with Y90 PET/CT is required to prospectively evaluate radiation dosimetry and optimize this treatment.

Y90 PET/CT and PET/MRI Allow Accurate Post-treatment Assessments of Y90 Distributions

Study 1: Y90 PET/CT allows localization of Y90 glass microspheres with simple, rapid, and universally applicable method of confirming microsphere deposition (17).

Study 2: Y90 PET/CT measurements are strongly correlated with tumor tissue microsphere concentrations in a VX2 rabbit model of liver cancer (27).

Study 3: Y90 PET/MRI enables assessment of in vivo Y90 biodistributions and allows evaluation of physiologic tissue responses following Y90 arterial radioembolization of the prostate in dogs (18). PI has also performed Y90 PET/MRI in post-Y90 RS patients on a limited pilot research basis allowing superior resolution to SPECT/CT and co- registration with multiple MR pulse sequences.

Implications to the current proposal: Y90 PET/CT and PET/MRI allow dosimetry assessments with superior spatial resolution compared to SPECT/CT. Further, these techniques demonstrated correlation between microsphere distribution and imaging responses at 1-month and strong correlation with tissue microsphere concentrations. These dosimetry techniques now require validation for predicted ablation success confirmed on advanced MRI.

1.4 Illustrative Clinical Examples of Ablation Zone Post-Y90 RS

Representative cases are included below to demonstrate typical imaging findings following Y90 Radiation Segmentectomy (RS), with a focus on hepatobiliary phase MRI appearance, PET dosimetry correlation, and treatment response.

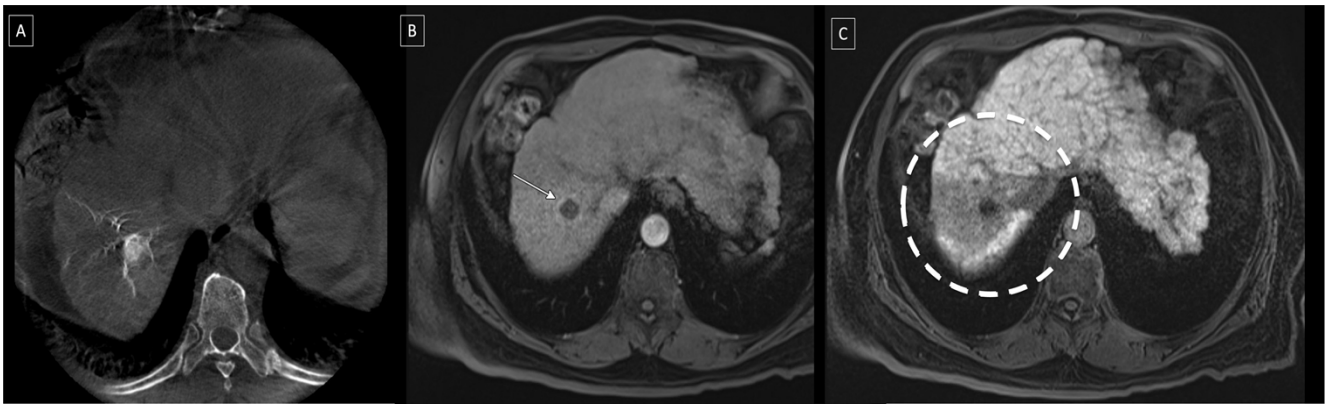


Figure 1. HCC with Complete Response on MRI
A) Intra-procedural cone beam CT demonstrates an enhancing hypervascular tumor (Hepatocellular carcinoma, HCC) with surrounding angiosome at the time of Y90 TARE. B) Post-Y90 arterial phase MRI demonstrates no tumor enhancement (arrow, complete response). C) Surrounding hypointense hepatic parenchyma within the treatment field around the tumor (circle) on hepatobiliary phase images defines an ablation zone surrounding the tumor in the center.

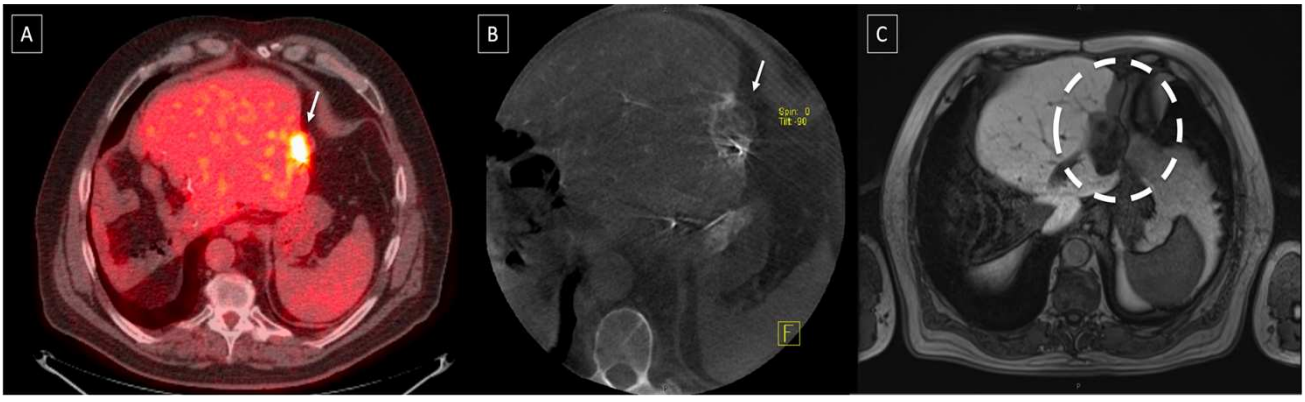


Figure 2. Cholangiocarcinoma with ablation zone surrounding the tumor on MRI
A) FDG PET/CT showing a hypermetabolic tumor (arrow) in the left lobe of a patient with cholangiocarcinoma. B) Intra-procedural cone beam CT of the TARE treatment field (angiosome) and enhancing tumor. C) Surrounding hypointense hepatic parenchyma within the treatment field around the tumor (circle) on hepatobiliary phase images defines the ablation zone surrounding the tumor.

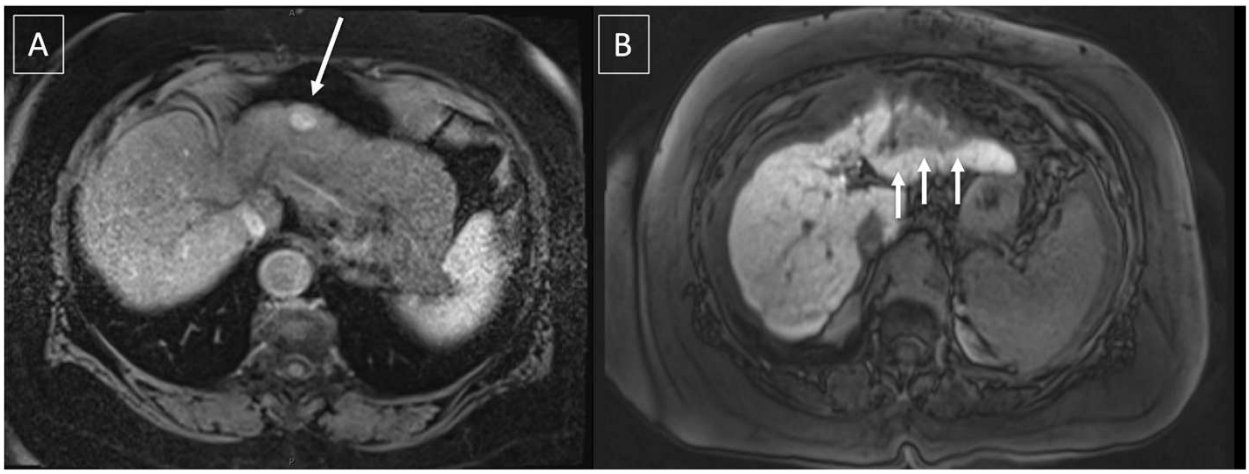


Figure 3. HCC with an ablation zone surrounding the tumor on MRI
A) Arterial phase MRI demonstrates a hypervascular HCC tumor (arrow) in a patient with HCV cirrhosis prior to treatment. B) Hepatobiliary phase (20min) image after Y90 RS with a single-compartment dose of 549Gy demonstrated sectoral atrophy and a hypointense ablation zone (arrows), corresponding to an isodose contour of 80Gy (not shown). The minimum margin was 11mm.

2 OBJECTIVES

2.1 Primary Objective

2.1.1 To prospectively define the "ablative dose" threshold for Y90 Radiation Segmentectomy (RS) using post-treatment PET dosimetry and hepatobiliary phase MRI.

2.1.2 To determine whether cirrhotic patients require a higher threshold dose for ablation compared to non- cirrhotic patients.

2.2 Secondary Objective

2.2.1 To evaluate the correlation between delivered Y90 dose and imaging biomarkers, including signal loss on hepatobiliary phase MRI, ablative margins, extracellular volume fraction, and perfusion changes. Assessed at 1, 4–9, and 12 months.

2.2.2 To assess tumor response by mRECIST and determine time to progression (TTP).

2.2.3 To assess the safety and tolerability of escalating segmental Y90 doses (200–500 Gy) using a Bayesian optimal interval (BOIN) dose-escalation design under DSMC oversight.

2.3 Exploratory Objective

2.3.1 To evaluate complete pathological necrosis in explanted tumors from patients who undergo liver resection or transplantation.

2.3.2 To identify novel early imaging biomarkers (Eovist hepatobiliary phase defects, extracellular volume mapping, perfusion changes) that may serve as surrogates for ablation success.

2.4 Table Summarizing Primary and Secondary Objectives

Primary and secondary objectives are summarized in the table 1 below.

Objective	Type	Description	Assessment Method
Primary Objective	Ablative Dose Threshold	Prospectively define the "ablative dose" threshold for Y90 RS using post-treatment PET dosimetry and hepatobiliary phase MRI.	PET dosimetry; Double Contrast MRI
	Cirrhotic vs. Non-Cirrhotic Ablation Threshold	To determine whether cirrhotic patients require a higher threshold dose for ablation compared to non-cirrhotic patients.	PET dosimetry; Double Contrast MRI
Secondary Objectives	Dose to Imaging Correlation	To evaluate the correlation between delivered Y90 dose and imaging biomarkers, including signal loss on hepatobiliary phase MRI, ablative margins, extracellular volume fraction, and perfusion changes. Assessed at 1, 4–9, and 12 months.	PET dosimetry; Double Contrast MRI
	Tumor Response	To assess tumor response by mRECIST and determine time to progression (TTP).	mRECIST criteria applied to follow-up imaging
	Dose Escalation Safety	To assess the safety and tolerability of escalating segmental Y90 doses (200–500 Gy) using a Bayesian optimal interval (BOIN) dose- escalation protocol.	Adverse event monitoring; DSMC review
Exploratory Objectives	Pathologic Validation	To evaluate the presence of complete pathological necrosis in explanted tumors from patients undergoing resection or transplantation.	Histopathologic evaluation of explanted liver tissue
	Novel early imaging biomarkers	To identify novel early imaging biomarkers (Eovist hepatobiliary phase defects, extracellular volume mapping, perfusion changes) that may serve as surrogates for ablation success.	PET dosimetry; Double Contrast MRI

Table 1. Primary and secondary objectives.

3 PATIENT ELIGIBILITY

The target population for this study is patients with primary and secondary liver malignancies, including those with and without underlying cirrhosis. This will be a single-center trial conducted at Northwestern Memorial Hospital of Northwestern University. Northwestern University will serve as the lead site and coordinating center for this study.

Potential patients may be referred to the Principal Investigator (PI) at Northwestern University.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Patients must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Any questions or concerns regarding eligibility should be directed to the lead PI and assigned QAM. Study treatment may not begin until a patient is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a diagnosis of hepatocellular carcinoma (HCC), cholangiocarcinoma, or liver-dominant metastatic disease not amenable to surgical resection or ablation.

3.1.2 Patients must be aged ≥18 years.

3.1.3 Child-Pugh class A or B liver function.

3.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

3.1.5 Patients must have adequate organ and bone marrow function as defined below:

Laboratory Test	Value
Leukocytes (WBC)	≥ 3,000/mcL
Absolute neutrophil count (ANC)	≥ 1,500/mcL
Hemoglobin (Hgb)	≥ 9 g/dL
Platelets (PLT)	≥ 50,000/mcL
Total bilirubin	≤ 3.0 mg/dL
AST (SGOT)/ALT (SGPT)	≤ 100 / ≤ 120 U/L
Creatinine, OR	≤ 2.0
Glomerular filtration rate (GFR) eGFR is estimated GFR calculated by the abbreviated MDRD equation : 186 x (Creatinine/88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black)	≥ 40 mL/min/1.73 m2
Leukocytes (WBC)	≥ 3,000/mcL

3.1.6 Ability to undergo imaging and lab evaluations required.

3.1.7 Ability to understand and willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Extrahepatic metastases.

3.2.2 Pregnant or breastfeeding individuals.

3.2.3 Tumors requiring more than two Couinaud segments for treatment.

3.2.4 Known hypersensitivity to gadolinium-based contrast agents.

3.2.5 Contraindications to MRI (e.g., incompatible pacemakers, claustrophobia unresponsive to sedation).

3.2.6 Coagulopathy or clinical instability precluding angiographic intervention.

3.2.7 Prisoners or individuals under legal custody.

3.2.8 Adults unable to consent.

3.2.9 Individuals under 18 years of age.

4 TREATMENT PLAN

4.1 Overview

This is a prospective, non-randomized, single-center, dose-escalation study to evaluate the use of Y90 PET dosimetry and dual contrast MRI to define an “ablative dose” in cirrhotic and non-cirrhotic patients with unresectable, unablatable liver tumors.

Participants will undergo radiation segmentectomy (RS) using FDA-approved Yttrium-90 (Y90) glass microspheres (TheraSphere®, Boston Scientific). The dose will begin at 200 Gy for non-cirrhotic and 300 Gy for cirrhotic patients, increasing in 100 Gy increments up to 500 Gy, using a Bayesian Optimal Interval (BOIN) design. Patients will undergo dual-contrast baseline MRI, immediate post-treatment PET/CT or PET/MRI, and follow-up MRIs at 1, 4–9, and 12 months. All interventions will follow institutional radiation safety guidelines. Participants will be enrolled for 12 months; the total study duration is 36 months. Patients will first be evaluated for eligibility as part of the institutional multidisciplinary tumor board (MDT), which represents standard of care for patients being considered for Y90 transarterial radioembolization. If deemed potentially eligible for the study based on tumor characteristics, liver function, and clinical context, patients will be contacted in clinic to undergo the informed consent process.

Following enrollment and consent, participants will undergo a baseline dual contrast MRI within 1 month prior to Y90 treatment. Y90 administration will be performed via radiation segmentectomy, a selective, high-dose form of transarterial radioembolization targeting ≤2 hepatic segments. Treatment planning will include diagnostic angiography and technetium-99m MAA simulation prior to Y90 delivery. Glass-based Y90 microspheres will be administered per institutional standard operating procedures. To be deemed evaluable for endpoints, patients must receive adequate Y90 treatment to the measurable index tumor, defined as delivery within 20% of the intended Y90 dose target for their respective cohort.

Post-treatment dosimetry will be assessed with Y90 PET/CT or PET/MRI performed within 72 hours of treatment. Imaging follow-up will include dual contrast MRI at 1 month (±2 weeks), at 4–9 months, and at 12 months (±1 month) to evaluate tumor response and regional liver function over time.

4.2 Dose Escalation Scheme

This trial will employ the Bayesian Optimal Interval (BOIN) design to determine the maximum tolerated dose (MTD) of Yttrium-90 (Y90) delivered via radiation segmentectomy, with stratification by liver status (cirrhotic vs. non-cirrhotic). The target toxicity rate for the MTD is ϕ = 0.25 and the maximum sample size is 15 for each cohort. We will enroll and treat patients in cohorts of size 3. DLTs are defined below. As shown in Figure 4, the BOIN design uses the following rule, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is > 0.298, de-escalate the dose to the next lower dose level;

- otherwise, stay at the current dose.

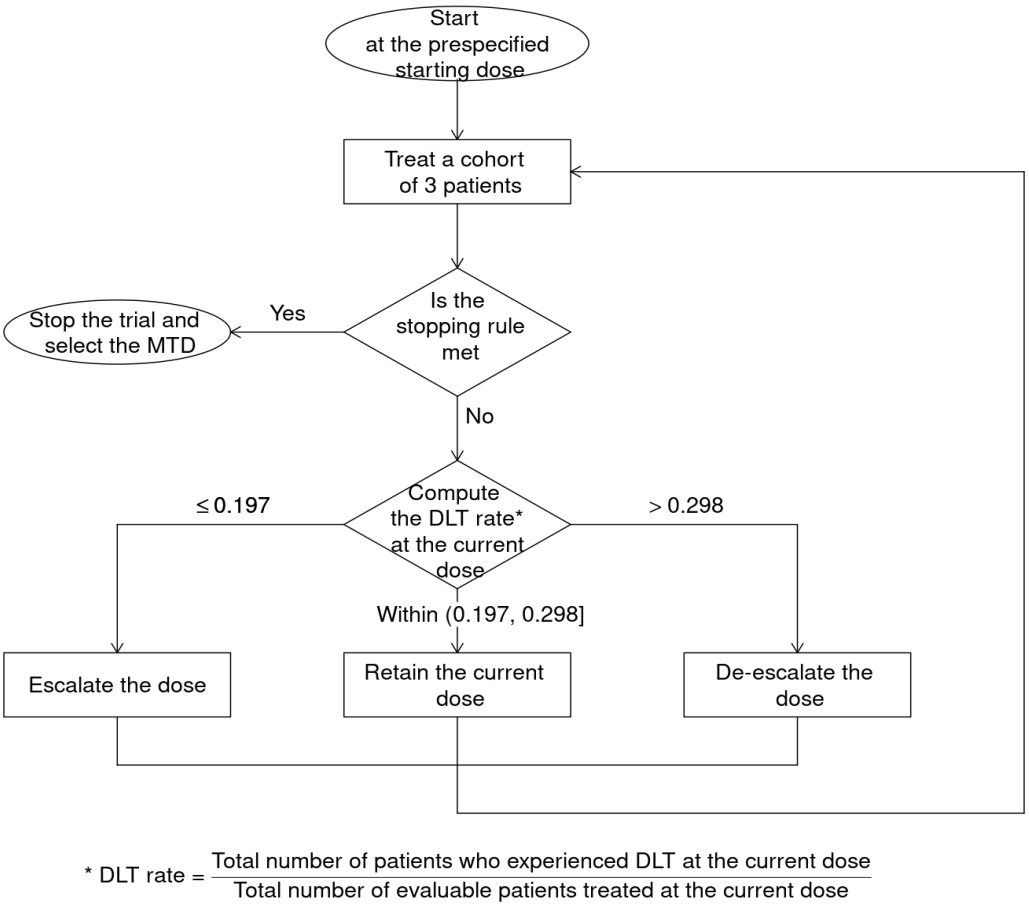


Figure 4. Flowchart for trial conduct using the BOIN design

The rule is optimized to minimize the probability of incorrect dose assignment under alternative hypotheses ϕ! = 0.15 (underdosing) and ϕ" = 0.35 (overdosing). For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if Pr(p# > 0.25 | data) > 0.95 and at least 3 evaluable patients have been treated at dose level j, where p# is the true DLT rate of dose level j, j = 1,⋯, 4. This posterior probability is evaluated based on the beta- binomial model y# | p# ~ binomial-p#. with p# ~ uniform(0,1), where y# is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate <=1/6, a dose with 2/3 patients experienced DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 2, which will be used to conduct the trial.

The steps to implement the BOIN design are described as follows:

1. In the first cohort, non-cirrhotic patients will be treated at dose level 1, and cirrhotic patients at dose level 2.

2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 2. When using Table 2, please note the following:

    a. “Eliminate” means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.

    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.

    c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.

    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.

    e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

3. Repeat step 2 until the maximum sample size of 15 is reached, or stop the trial if the number of evaluable patients treated at the current dose reaches 12 and the decision according to step 2 is to stay at the current dose.

	The number of evaluable patients treated at current dose											
Decision	**3**	4	5	**6**	7	8	**9**	10	11	**12**	13	14
Escalate if # of DLT <=	**0**	0	0	**1**	1	1	**1**	1	2	**2**	2	2
Stay if # of DLT =	**NA**	1	1	**NA**	2	2	**2**	2	3	**3**	3	3-4
De-escalate if # of DLT >=	**1**	2	2	**2**	3	3	**3**	3	4	**4**	4	5
Eliminate if # of DLT >=	**3**	3	3	**4**	4	4	**5**	5	6	**6**	6	7

Table 2. Dose escalation/de-escalation rule for the BOIN design

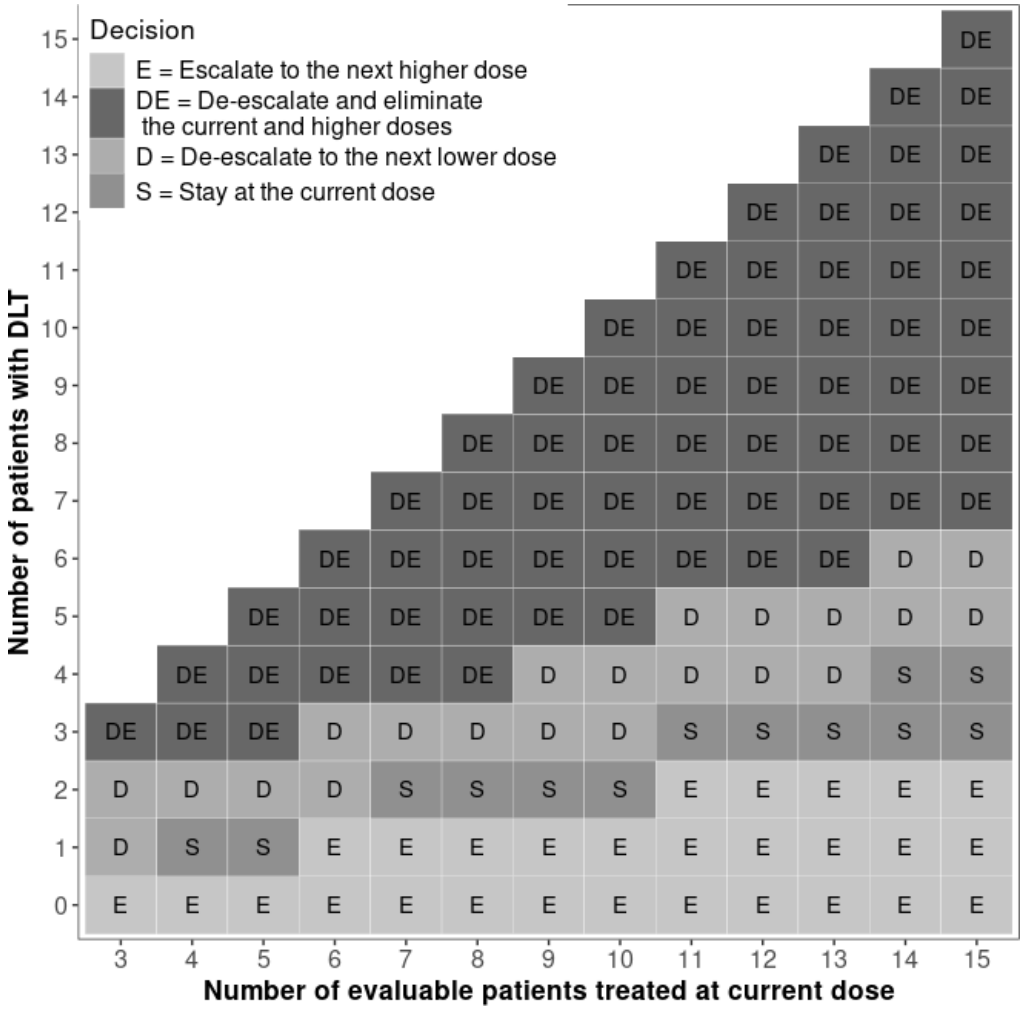
	Dose Level (Gy)				Number of Patients	% Early Stopping
	1 (200 Gy)	2 (300)	3(400)	4(500)		
Non-Cirrhotic patients						
True DLT Rate	0.25	0.35	0.45	0.55		
Selection %	51.6	34.2	7.9	1.1		5.2
% Pts Treated	43.9	42.3	11.8	2	14.8	
Cirrhotic patients						
True DLT Rate	0.05	0.1	0.15	0.2		
Selection %	1.7	16.8	27.9	53.6		0
% Pts Treated	8.4	35.9	28.1	27.6	15	

Table 3: This Table shows the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app "BOIN" (BOIN V3.0.15.0) available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates a high percentage of patients to the dose levels with the DLT rate closest to the target of 0.25. % Early Stopping"" refers to early stopping due to excessive DLT.

Dose levels will escalate in 100 Gy increments up to 500 Gy within each stratum. Each dose cohort will be evaluated for dose-limiting toxicities (DLTs). Dose escalation, de-escalation, and elimination decisions will follow BOIN-calculated thresholds:

- Escalate if observed DLT rate ≤ 0.197
- De-escalate if observed DLT rate > 0.298
- Stay at the current dose otherwise

Patients will continue to be enrolled until either: The maximum sample size (n = 15) is reached, or stopping rules for safety or futility are met. After trial completion, the MTD will be selected using isotonic regression: the dose with the estimated DLT rate closest to the target rate ($\phi = 0.25$). If ties occur, preference will be given to the higher dose when the estimate is <0.25, or the lower dose when the estimate is ≥0.25.



Only the Y90 dose will be escalated; all other interventions and supportive care measures will remain constant across cohorts. Safety data will be reviewed continuously by the Data Safety Monitoring Committee (DSMC), which will make recommendations regarding dose escalation, cohort expansion, or trial modifications as needed.

All study teams are expected to notify the Principal Investigator and assigned QAM when a DLT has occurred.

The Dose-Limiting Toxicity (DLT) observation period will extend for 30 days following the Y90 administration, which is within the clinical standard of care.
DLTs will be assessed using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Toxicities must be at least possibly related to the study device and radiation dose (Y90 RS) to be considered a DLT.

DLTs are defined as:

- Any treatment-related Grade ≥3 non-hematologic toxicity (excluding: adverse reaction to moderate sedation, nausea, or vomiting responsive to treatment, vascular injuries relating to procedure, contrast reactions)
- Any treatment-related Grade ≥3 bilirubin elevation lasting >7 days
- Any treatment-related Grade ≥3 albumin decrease lasting >7 days
- Any treatment-related Grade ≥3 gastrointestinal ulceration, gastrointestinal hemorrhage, or radioembolization-induced liver disease

4.3 Toxicity Management & Dose Delays/Modifications

This study involves a single treatment, Yttrium-90 (Y90) glass microspheres (TheraSphere®), delivered as a one-time, segmental transarterial radioembolization (Radiation Segmentectomy, RS). As such, there are no intra-patient re-dosing adjustments. However, participants will be monitored for toxicities during a 30-day post-treatment DLT window and up to 12 months for adverse events as discussed in the adverse events section below.

4.4 Duration of Therapy

No additional Y90 treatments are planned apart from standard of care. The duration of imaging procedure are as follows:

- Baseline dual contrast MRI: typical scan duration is approximately 45–60 minutes.
- Post-treatment PET/CT or PET/MRI: PET/CT t akes approximately 60–90 minutes; PET/MRI takes approximately 90–120 minutes.
- Follow-up dual contrast MRI: performed at 1 month, 4–9 months, and 12 months post Y90; each scan takes approximately 45–60 minutes.

Study participation continues through completion of the 12-month imaging follow-up, unless withdrawn earlier due to clinical progression, toxicity, or patient/investigator decision.

4.5 Duration of Follow Up

Participants will complete an end-of-treatment visit approximately 30 days after Y90 administration to assess for late adverse events. Those withdrawn from therapy due to toxicity will be followed until resolution or stabilization of the adverse event. Patients will continue to be followed through 12 months post-Y90 treatment with scheduled MRI and laboratory assessments. After this period, additional clinical follow-up may occur at the discretion of the treating physician or based on clinical need but will not be mandated by the study.

4.6 Removal of Patients from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

Criteria for Removal from Study Treatment:

- Patient meets any of the stopping points per Section 4.7.
- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates confirmed disease progression If appropriate, include a definition of disease progression (i.e. clinical vs. radiological progression as defined by RECIST v 1.0).
- Patient demonstrates clinical progression
- Intercurrent illness that prevents further administration of treatment
    - General or specific changes in the patient's condition that renders the patient unacceptable for further treatment in the judgment of the investigator
- Patient develops a second malignant neoplasm
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant

- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF) per institutional standard
- Termination of the study by Sponsor

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

Off Study Criteria:

- Death
- Lost to follow-up
- Patient enrolls on another therapeutic clinical trial
- Withdrawal of consent for any further data submissions
- Follow-up period is met as outlined in the protocol

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in NOTIS and NOTIS eCRFs.

5 STUDY PROCEDURES

This is a single-institution, prospective, non-randomized, dose-escalation clinical study designed to define an "ablative dose" threshold of Yttrium-90 (Y90) radioembolization using PET dosimetry and functional MRI in patients with unresectable, unablatable primary or secondary liver tumors. The study specifically evaluates differences in treatment response and tolerance between cirrhotic and non-cirrhotic patients undergoing Radiation Segmentectomy (RS), with patients stratified into two parallel arms (n=15 cirrhotic; n=15 non-cirrhotic).

Dose escalation will begin at 200 Gy for non-cirrhotic and 300 Gy for cirrhotic patients, with increments of 100 Gy per cohort, using a Bayesian Optimal Interval (BOIN) design. In this model, three participants are initially enrolled and treated at each dose level. If no dose-limiting toxicities (DLTs) are observed, the study proceeds to the next higher dose tier. If one DLT is observed among the initial three participants, two additional participants are enrolled at the same dose level to better assess safety. If two or more DLTs are observed at any given dose level, that level is considered to exceed the maximum tolerated dose (MTD), and the previous dose tier may be defined as the recommended Phase II dose or the dose threshold for achieving an ablative effect (28).

Imaging and response assessment will follow a standardized schedule. All participants will undergo baseline dual contrast MRI within 1 month prior to treatment to establish functional liver reserve and tumor characteristics. Post-treatment dosimetry will be evaluated using Y90 PET/CT or PET/MRI performed within 72 hours of Y90 administration. Follow-up dual contrast MRI will be performed at 1 month (±2 weeks), 4–9 months, and at 12 months (±1 month) to assess treatment response, durability, and regional liver function over time. If a patient decides to opt-out of the research scan, they will receive standard of care (SOC) imaging at that timepoint.

	Screening	Day of Y90 RS	Post-Treatment (within 72 hours)	1 month (±2 weeks) Follow-up	4-9 months	12 months (±1 month)
Informed Consent[1]	X					
Eligibility Review (MDT) [1,2]	X					
Medical History [1]	X			X	X	X
Laboratory tests [1,3]	X			X	X	X
Baseline Dual Contrast MRI[4]	X					
Y90 RS Procedure[1]		X				
PET/CT or PET/MRI[4]			X			
Dual Contrast MRI[4]				X	X	X
Toxicity Assessment[4]			X	X	X	X
Tumor Response Assessment (mRECIST) [4]				X	X	X
Correlatives[4,5]			X	X	X	X
Survival / TTP Assessment[4]				X	X	X
Pathologic Explant Assessment[6]				X	X	X

[1] Procedures marked with (1) are standard of care.

[2] Patients are first evaluated at the multidisciplinary tumor board (MDT), where interventional oncologists, diagnostic radiologists, and surgical oncologists determine eligibility for treatment. Eligible patients are then contacted for consent.

[3] Laboratory work will follow the standard of care for Y-90 procedures and typically includes, but is not limited to, complete blood count, comprehensive metabolic panel, liver function tests, and kidney function tests.

[4] Procedures marked with (2) are research related procedures

[5] Correlatives may include imaging biomarkers such as post-treatment PET dosimetry, hepatobiliary phase MRI signal loss, ablative margins, extracellular volume fraction, and perfusion changes, collected in alignment with study objectives.

[6] If applicable in patients who will undergo liver transplant or tumor resection or tumor resection

6 STATISTICAL CONSIDERATIONS

6.1 Study Design/Study Endpoints

This is a prospective, single-center, non-randomized, dose-escalation study designed to evaluate the effects of segmental radiation dosing with Yttrium-90 (Y90) in patients with unresectable, unablatable liver malignancies. The study uses a Bayesian optimal interval (BOIN) design dose- escalation design to evaluate the safety, tolerability, and imaging-defined efficacy of escalating segmental doses ranging from 200 to 500 Gy. The primary objective is to define the “ablative dose” thresholds using dual-contrast MRI and Y90 PET-based dosimetry, while secondary endpoints assess tumor response, time to progression (TTP), pathologic necrosis, comparative dose thresholds in cirrhotic vs. non-cirrhotic livers, and safety.

6.2 Sample Size and Power Analysis

The total sample size is 30 participants, equally divided between two strata: 15 cirrhotic and 15 non-cirrhotic patients. The primary hypothesis is that a defined Y90 dose threshold will produce complete sectoral ablation detectable on dual contrast MRI with different target ablative dosing for cirrhotic and noncirrhotic patients. Based on retrospective institutional data, we performed a power analysis assuming a baseline ablative single compartment dose of 49% dosing (~196- 200Gy) and 90% (~360Gy) of the retrospectively identified 400Gy dose threshold for noncirrhotic and cirrhotic patients, respectively. A sample size of 15 per group provides 80% power at a two- sided alpha of 0.05 to detect a 54% difference in threshold dose between cohorts.

6.3 Accrual and Feasibility

The total sample size is 30 participants, equally divided between two strata: 15 cirrhotic and 15 non-cirrhotic patients. The primary hypothesis is that a defined Y90 dose threshold will produce complete sectoral ablation detectable on dual contrast MRI with different target ablative dosing for cirrhotic and noncirrhotic patients. Based on retrospective institutional data, we performed a power analysis assuming a baseline ablative single compartment dose of 49% dosing (~196- 200Gy) and 90% (~360Gy) of the retrospectively identified 400Gy dose threshold for noncirrhotic and cirrhotic patients, respectively. A sample size of 15 per group provides 80% power at a two- sided alpha of 0.05 to detect a 54% difference in threshold dose between cohorts.

6.4 Data Analyses Plans

Each objective will be addressed by a specific data analysis strategy. For the primary endpoint (ablative dose threshold determination), voxel-level Y90 dose distributions will be correlated with hepatobiliary phase signal loss on MRI. Logistic regression and receiver-operating-characteristic curves (ROC) will be used to predict the threshold dose for ablation zone formation, objective imaging response, and complete pathologic necrosis. Secondary endpoints will be analyzed as follows: tumor response will be assessed by mRECIST criteria, which define viable tumor as arterial-phase enhancing tissue on multiphasic CT/MRI, with target-lesion response determined from the sum of the longest diameters of the enhancing portions (CR = disappearance of arterial enhancement, PR = ≥30% decrease, PD = ≥20% increase and ≥5 mm absolute or new lesions, SD = neither PR nor PD) (29). Responses will be summarized categorically and compared across dose levels using Fisher's exact test. Time-to-progression will be evaluated using Kaplan–Meier analysis and compared using the log-rank test. Pathologic necrosis rates will be descriptively reported for explanted specimens. Safety outcomes will be summarized using frequency tables for adverse events, with comparisons between dose levels made using appropriate parametric or nonparametric tests. All analyses will be conducted using STATA or R statistical software.

7 DRUG INFORMATION

7.1 Agent Yttrium-90 Glass Microspheres (TheraSphere®)

7.1.1 Other names

TheraSphere®, Y-90 glass microspheres, Y90 RS

7.1.2 Classification - type of agent

Beta-emitting radiotherapeutic microspheres for intra-arterial brachytherapy

7.1.3 Mode of action

Yttrium-90 emits high-energy beta radiation (0.9367 MeV) to local tissues near the microspheres with a short mean tissue penetration of 2.5 mm and maximum penetration of 11 mm. When microspheres are administered intra-arterially, they preferentially lodge in tumor microvasculature, delivering localized radiation that causes tumor cell apoptosis and vascular injury. The radiation decays with a half-life of 64.1 hours.

7.1.4 Storage and stability

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7.1.5 Protocol dose specifics

In this study, TheraSphere® Y90 RS will be administered as part of a dose-escalation protocol within a range of doses already incorporated within the clinical standard of care. Patients will receive segmental doses beginning at 200 Gy for non-cirrhotic and 300 Gy for cirrhotic patients, with increments of 100 Gy per cohort (200, 300, 400, and up to 500 Gy), using a Bayesian Optimal Interval (BOIN) design. Actual dose delivered will be based on target volume and treatment planning using standard dosimetric equations. TheraSphere® is administered per the FDA-cleared package insert and standard operating procedures of the Northwestern Interventional Radiology team.

7.1.6 Route of administration for this study

Intra-arterial administration into hepatic arteries using microcatheter-directed selective Catheterization

7.1.7 Side Effects

Please refer to the current [**TheraSphere® Package Insert**] for a complete listing of all toxicities. The table below summarizes adverse Events occurring in ≥5% of Patients with HCC (LEGACY Study).

Adverse Event	All Grades N=162 n (%)	Grade 3–4 N=162 n (%)
Fatigue (includes asthenia)	56 (34.6%)	1 (0.6%)
Lymphocyte count decreased	46 (28.4%)	12 (7.4%)
White blood cell count decreased	21 (13.0%)	1 (0.6%)
Platelet count decreased	19 (11.7%)	2 (1.2%)
Blood bilirubin increased (hyperbilirubinemia)	29 (17.9%)	3 (1.9%)
Blood alkaline phosphatase	14 (8.6)	0
AST increased	11 (6.8)	0
Abdominal pain	34 (21.0%)	2 (1.2%)

Nausea	28 (17.3%)	2 (1.2%)
Ascites	13 (8.0%)	3 (1.9%)
Vomiting	13 (8.0%)	3 (1.9%)
Decreased appetite	13 (8.0)	0
Constipation	9 (5.6)	0
Constipation	9 (5.6%)	0
Hypoalbuminemia	14 (8.6%)	1 (0.6%)
Hyperglycemia	11 (6.8%)	0
Musculoskeletal pain (back, neck, extremity)	9 (5.6%)	2 (1.2%)

7.1.8 Drug Device Interactions

The efficacy and safety of Yttrium-90 (Y90) transarterial radioembolization (TARE) can be significantly influenced by concurrent or recently administered systemic therapies. Specific attention must be given to drug-device interactions, particularly with agents known for hepatotoxicity or those affecting hepatic blood flow.

Hepatotoxic Agents: Many chemotherapeutic agents, particularly anthracyclines, platinum-based compounds, and certain tyrosine kinase inhibitors, are known to cause varying degrees of hepatotoxicity. Given that Y90 relies on targeted radiation delivery to hepatic tissue, baseline liver function must be preserved to minimize the risk of radiation-induced liver disease (RILD). As a precaution, hepatotoxic therapies are typically held for 4–6 weeks prior to Y90 treatment to allow hepatic function to recover and to better assess underlying liver reserve.

Anti-VEGF Therapies: Agents that inhibit vascular endothelial growth factor (VEGF), such as bevacizumab (Avastin), can impair hepatic microvascular perfusion and potentially alter the distribution and effectiveness of Y90 microspheres. Additionally, these agents carry a risk of delayed wound healing and bowel ischemia, which can complicate the periprocedural course. Clinical protocols often recommend discontinuing anti-VEGF therapies at least 4–6 weeks prior to Y90 administration to reduce these risks and optimize microsphere deposition.

7.1.9 Availability & Supply

TheraSphere® is commercially available and FDA-approved and on-label for HCC. In this study, it will be used off-label at escalated segmental doses for non-HCC malignancies.

7.1.10 Return and Retention of Study Device

Used and residual vials are returned to the nuclear pharmacy for disposal per institutional radiation safety protocols. All radioactive waste will be managed and documented in accordance with institutional guidelines.

7.1.11 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents provided by the Study. Store and maintain separate Drug Accountability Records (DARF) for each agent.

8 ADVERSE EVENTS

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

8.2 Definitions & Descriptions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or undergoing an experimental intervention, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product or experimental intervention, whether or not related to the investigational product or intervention.

All routine AEs, regardless of attribution or clinical significance, occurring from time of registration, through 30 days after the last administration of study agent, must be recorded. See Section 10.3.1 for instructions on recording routine AEs.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms, referencing CTCAE when applicable. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). *Please note that medical history and preexisting conditions will be recorded on the medical history eCRF in order to establish if the event worsened while on*

study and thus qualifies as a reportable adverse event. Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

8.2.1.1 Adverse Event Assessment

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly as an adverse event or expedited adverse event, as applicable.

1. Identify the type of adverse event using the NCI CTCAE v 5.0.
2. Grade the adverse event using the NCI CTCAE v 5.0.
3. Determine whether the adverse event is related to the protocol therapy.
    - Attribution categories are as follows:
        - Definite: AE is *clearly related* to the study treatment.
        - Probable: AE is *likely related* to the study treatment.
        - Possible: AE *may be related* to the study treatment.
        - Unlikely: AE *not likely to be related* to the study treatment.
        - Unrelated: AE is *clearly NOT related* to the study treatment.
4. Determine the prior experience of the adverse event.

    Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
    - the current protocol
    - the drug package insert
    - the current Investigator’s Brochure
    -

8.2.1.2 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe (grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
  - **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Life-threatening (grade 4): Life-threatening consequences; urgent intervention indicated.
- Fatal (grade 5): Death related to AE.

8.2.2 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study agent, must be reported upon discovery or occurrence. See Section 10.3.2 for instructions on reporting SAE's.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- Results in *death*.
  - If death results from (progression of) the disease, should be reported as **Grade 5 "disease progression"** in the system class "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Is *life-threatening*.
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.
- Results in *persistent or significant disability or incapacity*.
- Is a *congenital anomaly/birth defect.*
- Any *important medical event* that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.2.3 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- is *unexpected* (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied
- is *related or possibly related* to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places human subjects or others at *a greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

8.3 **Adverse Event Reporting**

8.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

8.3.2 Expedited Reporting of SAEs/Other Events

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via expedited reporting via the NU CTO SAE Form. On the "Seriousness Criteria" drop down box of the SAE Form, select "Pregnancy." Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study agent must be reported and then followed for outcome.

8.3.2.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CTO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)
- Country of incidence

All SAEs will be reported to, and reviewed by, the DSMC, per the DSMP.

All expedited events require both expedited reporting and routine reporting.

8.3.2.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the study site (Northwestern University).

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Information pertaining to an NU subject that fits into any of the categories listed on the Reportable New Information page will be reported to the NU IRB within 5 business days of knowledge or notification.

9 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Amendments

Amendments to the protocol will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, device company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Radiology Society of North America. (RSNA). Amendments will be distributed by the study's institution (Northwestern) upon approval by the Northwestern University IRB.

9.3 Registration Procedures

9.3.1 Registering a Patient – Phase I, select Pilot, Safety Run-In Trials

For potential patients for phase I, select pilot, or safety run-in studies, study teams are asked to inform the assigned QAM (croqualityassurance@northwestern.edu) of the date and time that the patient will need to be registered.

BEFORE a patient can be treated on study, the following items must be completed and submitted to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review all source documentation required to confirm eligibility that is readily available in the patient's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable), and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

9.3.2 Registering a Patient – Phase II, Phase III, select Pilot Trials

For potential patients for phase II/III and select pilot studies, study teams are asked to inform the assigned QAM (croqualityassurance@northwestern.edu) of the date and time that the patient will need to be registered.

BEFORE a patient can be treated on study, the following items must be completed and submitted to confirm eligibility and receive a subject identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review the registration documents. Once review is complete, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable) and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

Participation replacement: Consented patients who do not complete any follow-up imaging may be replaced 1 to 1 if funding permits. This would involve consent and inclusion for an additional n patients where n is the number of patients consented who do not complete any additional study follow up imaging.

9.4 **Data Submission**

Data collection for this study will be done through NOTIS. Access to the trial in NOTIS is granted to appropriate roles identified at the time of participating site activation, or upon request. Site

users will not be able to access the study in NOTIS until all required and study specific trainings are completed.

Once a patient is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table. Data is due with 10 days of a visit or end of cycle. A set amount of data may also be requested for any screen failures, as is defined by the study. In most instances, this will include collection of adverse events and baseline data from the time of registration to the date of screen failure.

9.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the CTO website https://www.cancer.northwestern.edu/research/clinical-trials-office/index.html for additional information). The level of risk attributed to this study requires [insert monitoring level established during the Study Implementation Meeting (SIM), or as specified in SRC approval letter for LOI], as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

9.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial patients without prior IRB approval.

For any such emergency modification implemented, a modification must be submitted to the NU IRB within 5 business days of making the change, and the assigned QAM must be notified within 24 hours of such change. Such modifications also need to be reported to the FDA, as applicable, within the appropriate timelines.

9.6.2 Other Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants
- Has compromised the rights and welfare of the research subject
- Has damaged the scientific integrity of the data collected for the study
- Results from willful or knowing misconduct on the part of the investigator(s)
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies

All protocol deviations will be documented by the study team on a electronic deviation tracking log (see NOTIS for copy of log) as they occur. The deviation tracking log must be made available upon request for review by the assigned QAM. The deviation tracking log must be reviewed, signed, and dated by the investigator prior to each monitoring visit, or otherwise in a timely manner, whichever occurs first. The PI signed and dated deviation tracking log will be uploaded to eCRFs prior to each scheduled monitoring visit or upon request.

Deviations will be reviewed per the DSMP.

9.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

9.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made

a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

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11 APPENDICES

Appendix A – Summary of Changes

Summary of Changes Protocol Version 3/13/2026 Amendment 2 IRB: Modification 3 *Per PI request and study team request*			
Sections(s) Affected	***Prior Version***	***Changes***	***Rationale***
TITLE PAGE & Throughout	Protocol Version Date: September 15, 2025	Protocol Version Date: March 6, 2026	Administrative revision
Entire Protocol	[IRB Template]	[CTO Cancer Center Template]	Entire protocol converted to CTO Cancer Center template; administrative
Summary of Changes	Tumor size ≤5 cm not amenable to resection or ablation.	Removed	Removed in inclusion criteria
Inclusion Criteria	Tumor size ≤5 cm requiring ≤2 Couinaud segments treated.	Removed	Not required for this study; per PI request