Phase II **R**andomized Trial C**o**mparing Percutaneous Ablation to Hypofractionated Image-Guided Radiation Therapy in **Ve**teran and Non-Veteran, Non-surgical **H**epato**c**ellular **C**arcinoma Patients (PROVE-HCC)

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LIST OF ABBREVIATIONS

ADLs	Activities of Daily Living
AFP	Alpha-fetoprotein
BMP	Basic Metabolic Panel
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CT	Computerized Tomography
DLT	Dose Limiting Toxicity
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary (Version 4)
GTV	Gross Target Volume
HCC	Hepatocellular Carcinoma
HIGRT	Hypofractionated Image-Guided Radiation Therapy
INR	International Normalized Ratio
ITV	Internal Target Volume
LFTs	Liver Function Tests
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
OS	Overall survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PLA	Percutaneous Local Ablation
PTV	Planning Target Volume
QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
QOL	Quality of Life
RILD	Radiation Induced Liver Disease
RT	Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
VAMC	Veteran's Affairs Medical Center

1. BACKGROUND AND SIGNIFICANCE

Primary liver cancer is the world's third most common cause of cancer death. In the United States -unlike other malignancies such as breast, prostate and lung cancer- the incidence of hepatocellular carcinoma (HCC) is increasing. The present gold standard, for the less than a third of the HCC patients who are medically fit and technically resectable, is HCC resection or liver transplant. For the patients who are not operative either due to underlying liver disease with associated liver dysfunction or other comorbidity, a number of non-operative treatments are available for treatment including percutaneous tumor ablation (i.e. radiofrequency ablation [RFA], microwave ablation (MWA), percutaneous ethanol injection [PEI], cryotherapy). In addition newer external beam radiotherapy techniques, such as hypo-fractionated image guided radiation therapy (HIGRT) –also known as stereotactic body radiotherapy (SBRT)– , have been used in the treatment of these patients.

Percutaneous local ablation (PLA) selectively targets the tumor with an additional intentional margin of 0.5-1cm of non-cancerous liver tissue and induces tumor cell death, most often via coagulative necrosis. Local application of chemical agents or microwave/radiofrequency waves does not induce systemic effects and is typically performed under real-time ultrasound or CT guidance using local anesthesia and conscious sedation or general anesthesia. Worldwide, RFA is the most commonly used ablation technique. In the US, MWA is quickly becoming the preferred modality of PLA. MWA induces thermal injury through the delivery of electromagnetic energy and the application of rapidly alternating microwave frequency current leads to coagulative necrosis of tissue. Compared with RFA, MWA appears to be more effective for lesions in close proximity to the portal or hepatic veins; heat sink is less of an issue given increased speed with which therapy can be delivered. Additionally, tumor sizes >3cm sometimes can be effectively treated with MWA. A recent meta-analysis comparing RFA to MWA for primary HCC showed they had similar efficacy[1], however, MWA appeared to have improved local tumor control over RFA in the treatment larger tumors.

Advances in radiotherapy simulation, treatment planning and delivery integrated together collectively termed HIGRT or SBRT, have facilitated safe dose escalation to HCC. A number of small, single institutional prospective studies have evaluated the use of HIGRT for treatment of HCC. These experiences suggest that HIGRT is well tolerated and yields excellent local control rates, however, follow up is short and thus many institutions and consensus guidelines favor ablation for early stage HCC patients who are not surgical candidates. The benefits of HIGRT are that it is a non-invasive, outpatient procedure typically delivered in 3-10 fractions. Although no randomized studies have compared HIGRT with other local therapies, in retrospective analysis outcomes appear comparable[2], warranting further evaluation.

Health-related quality of life for patients with HCC is important. QOL targets are important post-treatment metrics; previous studies have shown that both pretreatment QOL[3] and post-treatment QOL[4] have been associated with overall survival in various cancers. While both PLA and SBRT can ablate tumors, they do have known impacts on patients' QOL. QOL has recently been reported as a clinically important target in patients treated with HIGRT for HCC. A randomized study evaluating the use of PLA in patients with metastatic colorectal cancer evaluated health related QOL as a secondary endpoint via the EORTC QLQ-30 questionnaire at baseline and every 6 weeks. Mean global QOL dropped 27 points approximately 6 weeks post PLA and recovered to near baseline shortly thereafter[5]. QOL was also assessed in a prospective evaluation of SBRT for primary intrahepatic malignancies using the EORTC QLQ-30 and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) at baseline and 1, 3, 6, and 12 months post-treatment. While appetite and fatigue domains dropped markedly at 1 month post-SBRT, global QOL remained stable at this time point. Baseline FACT-Hep and EORTC-QLQ scores were associated with improved survival in this analysis[6].

There are unique challenges within the VA patient population specifically with regards to the effective and efficient treatment of HCC. The VA has a higher portion of HCC patients than the average US population given higher base rates of HCV infection and alcoholic cirrhotic liver disease. Transplant options are limited due to extensive co-morbidities. Lack of easy access to a transplant center also creates geographic access issues. New limits on the Model for End Stage Liver Disease (MELD HCC) exception scores (now capped at 34 as of October 8, 2015) are already reducing overall transplant candidacy for many HCC patients. Alternative treatments to transplant and surgery based on strong evidence-based medicine are essential. This is particularly true in a new era of curative HCV treatment which -when combined with non-transplant based therapies for HCC- would potentially obviate the need for any additional therapies and break the cycle of cirrhosis, cancer and mortality.

2. PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

2.1 Purpose

Given that many patients with HCC are not surgical candidates (for either resection or transplant), PLA techniques have become the standard non-operative approach. Non-randomized data have shown that the local control of HIGRT is comparable to that of PLA. Direct comparison of these two modalities via a randomized controlled clinical trial is the next logical step.

This research protocol will directly compare Percutaneous Local Ablation (PLA) to Hypofractionated Image-Guided Radiation Therapy (HIGRT) for patients with Hepatocellular Carcinoma (HCC) who are not surgical candidates or decline surgery while undergoing care at the Durham VA or at Duke Cancer Center.

Primary Objective

To compare change in Quality of Life (QOL), as defined by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC C-30), from baseline to 1 month post treatment in patients receiving PLA vs HIGRT.

Secondary Objectives

1. To estimate the difference in change in QOL in patients receiving PLA vs HIGRT, as measured EORTC C-30, from baseline to 3 months post-treatment
2. To estimate the difference in change in QOL in patients receiving PLA vs HIGRT, as measured EORTC C-30, from baseline to 6 months post-treatment
3. To estimate the difference in change in QOL in patients receiving PLA vs HIGRT, as measured by FACT-Hep, from baseline to 1 month, baseline to 3 months and baseline to 6 months post-treatment
4. To assess for grade ≥2 acute toxicity within 90 days of treatment initiation
5. To estimate the total healthcare system cost associated with PLA vs HIGRT from time of intervention through 90 days post treatment

Exploratory Objectives

1. To assess for grade 3+ late toxicity (>90 days post ablative therapy or radiation therapy)
2. To evaluate local control at the treated site within the liver
3. To evaluate distant liver recurrence (intrahepatic lesions other than treated lesion)
4. To evaluate median progression free survival (PFS)
5. To evaluate median overall survival (OS)

Hypotheses

For the primary endpoint of change in QOL at 1 month post treatment versus baseline, HIGRT will have significantly better patient reported global QOL than PLA.

2.2 Design and Procedure

This is a phase II, randomized trial comparing PLA vs HIGRT in non-surgical HCC patients at the Durham VA and the Duke Cancer Center.

2.2.1 Selection of Subjects/Subject recruitment

Patients who are potentially eligible for study enrollment will be identified within Radiation Oncology, Radiology, GI and GI oncology clinics. Patients could potentially be identified at multi-disciplinary Liver Tumor Board. The treating gastroenterologist, radiologist, radiation oncologist, medical oncologist or surgical oncologist (or their extenders) will introduce the study to patients, and if the patient is interested he/she will meet with a clinical trials coordinator for further details and consent.

2.2.2 Duration of Study

Patients will be on study therapy for approximately 6 months. The end of study participation will be at the completion of the 6 month survey, approximately 180 days post treatment (+/- 30 days). Thereafter patients will continue to be followed by the treating physician as per standard of care for follow up care and long-term follow up information will continue to be collected through review of the electronic health record.

2.2.3 Data Analysis and Statistical Considerations

Ninety patients will be randomized with equal allocation to the two arms. Randomization will be stratified by whether the baseline global QOL score is < 60 or ≥ 60, where QOL is measured by the EORTC QLQ-C30 scale (i.e., the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30) which has a score range of 0-100. The primary outcome is the change in QOL from baseline to 1 month. We anticipate that approximately 10% of the accrued patients will be withdrawn before 1 month, leaving 80 evaluable patients to be used in the statistical analyses. The general linear model will be used to test for an arm effect (in patients receiving PLA vs HIGRT) by regressing the change in QOL on arm, controlling for the baseline value of QOL and the Child Pugh score. To calculate the power of the arm effect (in patients receiving PLA vs HIGRT) on change in QOL, we first note that the standard deviation of a normally distributed change score (SD_C) depends upon the SD of the pre-score, the SD of the post-score, and the Pearson correlation (ρ) between the two scores. If the SD's of the pre-score and the post-score are assumed equal and the correlation between them is 0.50, then $SD_C = SD$. For purposes of the power calculation, we assume that SD=10 and $\rho = 0.5$; therefore $SD_C = 10$. Assuming 40 evaluable patients per arm, the two-sample t-test (1-sided alpha = 0.10) of an arm difference in change across time in QoL has power 0.82 when the true arm difference in change score is 5 (i.e., 50% of SD_C). An arm difference of 50% of a standard deviation of an outcome variable is generally considered to be a "medium"-sized effect. In order to have 80 evaluable patients, 90 patients will be accrued (assuming ~10% drop out prior to the 1 month EOTRC QOL-C30 questionnaire).

After randomization, patients who have consented to study, but in the clinical judgement of the treating physician are no longer candidates for the randomized treatment, will continue to be evaluable for all study endpoints if treated with MWA or HIGRT (per PI approval). The primary analysis will be intent-to-treat (i.e., treatment arm as randomized). A sensitivity analysis will be conducted with patients categorized by treatment received.

At Duke and the VAMC respective liver multi-disciplinary conferences meet 2-4 times a month and there are typically 3-4 patients presented at each tumor board who may be potentially eligible for this study. We anticipate accruing 20-30 patients annually.

As a secondary objective, the arm difference in the change in QOL from baseline to month 1 as measured by the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep, version 4) will be calculated with its 95% confidence interval.

Please see section 5 below for more information regarding secondary and exploratory objectives.

3. STUDY ARMS

3.1 Radiation Therapy (experimental arm)

Hypo-fractionated image guided radiation therapy (HIGRT) refers to delivery of highly precise, conformal radiation therapy with high dose per fraction using image guidance to ensure proper tumor localization with each fraction. When it is given in 1-5 fractions, it is sometimes called stereotactic body radiation therapy (SBRT). For the purposes of this clinical trial, we will refer to the treatment as HIGRT at all times. It is believed that HIGRT results in an improved therapeutic ratio over traditional radiation therapy, and HCC tumor control rates as high as 70-90% at 1-2 years have been reported[8, 9].

3.1.1 Clinical experience

HIGRT represents the only non-invasive curative modality in the management of HCC. HCC patients typically have a host of other medical comorbidities complicated by underlying liver dysfunction that makes the implementation of liver-directed therapy challenging. Presently HIGRT is typically offered only after alternative surgical (transplantation/hepatectomy) and non-operative approaches (PLA/embolization) have been exhausted. An ongoing Phase III randomized study (RTOG 1112) is attempting to establish the role of HIGRT, in addition to sorafenib, in patients with locally advanced HCC who are not candidates for any of the aforementioned modalities. While this trial will contribute valuable data to the field of radiation oncology in the next 5-10 years, it does not help guide current clinical practice. For example, in early stage lung cancer, HIGRT has become the established alternative in patients who are deemed to be poor surgical candidates.

3.2 Percutaneous Localized Ablation (Microwave Ablation, control arm)

Microwave Ablation (MWA) is a form of percutaneous localized ablation using thermal ablation techniques to treat cancer via direct coagulative necrosis. Microwaves can generate high temperatures in a short period of time; MWA has the potential to improve treatment efficacy over radiofrequency ablation as it can be used to treat larger lesions and has less susceptibility to heat-sink due to vessel proximity. MWA uses electromagnetic waves (300 MHz to 300 GHz) to produce oscillation of polar molecules within tissue; this generates tissue necrosis through frictional heating. For HCC, one or more microwave antennae are inserted into the liver, usually under the guidance of ultrasonography or computed tomography (CT). Frequency and length of treatment is determined on a case by case basis depending on tumor size and proximity to vessels or other organs at risk. PLA is administered as a single treatment.

4. ENDPOINTS

QOL surveys such as European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) measure patient reported symptoms including fatigue, difficulties with activities of daily living (ADLs) and psychosocial needs. Specific liver QOL assessments such as the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) additionally assess liver-specific symptoms including jaundice, itching and abdominal pain.

Primary Endpoint:

The primary endpoint is change in global QOL score measured from baseline to month 1 post treatment. This change will be compared between treatment arms.

Higher average global QOL scores indicate better QOL. We hypothesize that the HIGRT arm will have significantly better QOL at month 1 than the PLA arm. A significantly greater drop in the average global QOL score at 1 month post treatment versus baseline is expected with PLA than with HIGRT, i.e., we expect the average change in the global QOL score to be less on HIGRT indicating higher QOL at 1 month post treatment with HIGRT.

Ninety patients will be randomized with equal allocation to the two arms. Randomization will be stratified by whether the baseline global QOL score is < 60 or ≥ 60, where QOL is measured by the EORTC QLQ-C30 scale. We anticipate that approximately 10% of the accrued patients will withdraw before 1 month, leaving 80 evaluable patients to be used in the statistical analyses. The general linear model will be used to test for an arm effect (in patients receiving PLA vs HIGRT) by regressing change across time in QOL on arm, controlling for the baseline value of QOL, Child Pugh score, and time between baseline and end of treatment. To calculate the power of the arm effect (in patients receiving PLA vs HIGRT) on change in QOL, we first note that the standard deviation of a normally distributed change score (SD_C) depends upon the SD of the pre-score, the SD of the post-score, and the Pearson correlation (ρ) between the two scores. If the SD's of the pre-score and the post-score are assumed equal and the correlation between them is 0.50, then SD_C = SD. For purposes of the power calculation we assume that SD=10 and ρ = 0.5; therefore SD_C= 10. Assuming 40 evaluable patients per arm, the two-sample t-test (1-sided alpha = 0.10) of an arm difference in change across time in QoL has power 0.82 when the true arm difference in change score is 5 (i.e., 50% of SD_C). An arm difference of 50% of a standard deviation of an outcome variable is generally considered to be a "medium"-sized effect. In order to have 40 evaluable patients per treatment arm, 90 patients will be accrued (assuming drop out prior to the 1 month EOTRC QOL-C30 questionnaire).

After randomization, patients may decline the randomized treatment but will continue to be evaluable for all study outcomes if treated with MWA or HIGRT. All endpoints will be analyzed per randomized arm and per treatment delivered. If the patient does not receive either SBRT or MWA, the patient will be withdrawn from the study.

Secondary Endpoints:

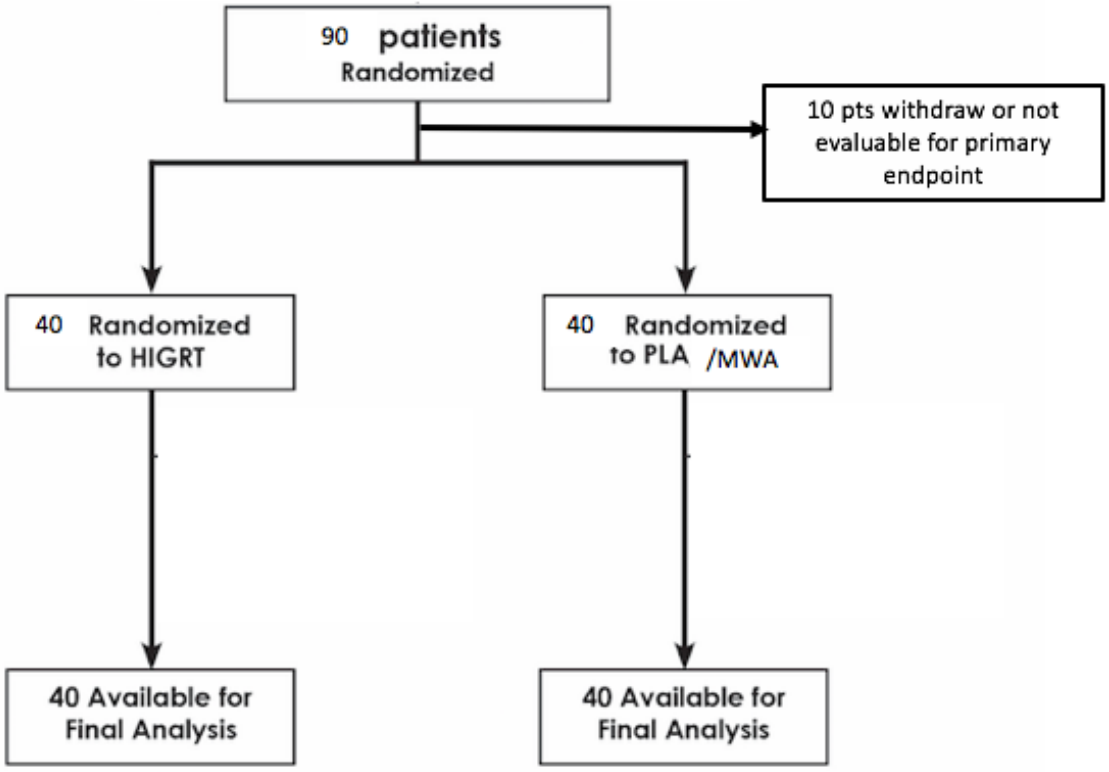
1. *To estimate the change in QOL* in patients receiving PLA vs HIGRT*, as measured by EORTC C-30, from baseline to 3 months post-treatment.* The mean difference between arms in change from baseline to 3 months in QLC-C30 will be estimated with their 95% confidence intervals [CI]. To calculate these CI's, the mean arm difference in QOL and its standard error will be estimated from a general linear model in which change in QOL is regressed on arm, controlling for the baseline value of QOL and the Child Pugh score.
2. *To estimate the change in QOL* in patients receiving PLA vs HIGRT*, as measured by EORTC C-30, from baseline to 6 months post-treatment.* The mean difference between arms in change from baseline to 6 months in QLC-C30 will be estimated with their 95% confidence intervals [CI]. To calculate these CI's, the mean arm difference in QOL and its standard error will be estimated from a general linear model in which change in QOL is regressed on arm, controlling for the baseline value of QOL and the Child Pugh score.

3. *To estimate the change in QOL as measured by FACT-Hep* in patients receiving PLA vs HIGRT. Change in FACT-Hep score from baseline to 1 month, baseline to 3 months and baseline to 6 months will be calculated for each patient, and the mean arm difference in change will be estimated with its 95% CI. The CI will be estimated as described for Secondary Objective 1.
4. *To estimate grade ≥2 acute toxicity within 90 days of treatment initiation*. CTCAE version 4 will be used for all toxicity assessments. The acute toxicity rate will be defined as any grade 2+ toxicity occurring during treatment through 90 days post-PLA or post-HIGRT. The acute toxicity rate with its exact 95% confidence interval will be estimated within each arm. The arm difference in acute toxicity rate will be estimated with its 95% CI. We will also estimate the rate of hospitalization due to treatment complications with its 95% CI and the proportion of patients requiring treatment breaks longer than 7 days from HIGRT, with its 95% CI.
5. *To estimate the total healthcare system cost associated with PLA vs HIGRT from time of intervention through 90 days post treatment.* Costs will be estimated based on national averages for billable charges for all codes associated with PLA vs HIRGT throughout the course of treatment and the post-treatment follow up. This includes costs associated with any hospitalizations related to either procedure. Total costs per arm will be described with boxplots. Arm differences in the health care cost will be estimated using the statistical method best suited to the observed distribution of cost in these data (for example, a single distribution generalized linear model specifying, perhaps, a Gamma distribution).

Exploratory Endpoints:

1. *To assess for late toxicity (>90 days post PLA or HIGRT).* Late toxicity will be defined as any Grade 3+ toxicity occurring after the completion of the treatment regimen up to 6 months post-PLA or HIGRT. The proportion of patients experiencing any type of late toxicity will be estimated with an exact 95% confidence interval, by arm.
2. *To evaluate local control at the treated site within the liver.* Time to local failure will be defined as the length of time from enrollment to local failure at the site of treated disease within the liver (within the PTV). Intrahepatic sites distinct from treated lesions and distant failures will be ignored and deaths will be censored. The distribution of time to local failure will be estimated with the Kaplan-Meier method, by arm.
3. *To estimate distant liver recurrence (intrahepatic lesions other than treated lesion).* Time to distant liver recurrence will be defined as the length of time from date of enrollment to intrahepatic failure not within the site of treated disease; distant failures will be ignored and deaths will be censored.
The distribution of time to distant failure will be estimated with the Kaplan-Meier method, by arm.
4. *To estimate median progression-free survival (PFS).* PFS will be defined as the length of time from enrollment to local or distant failure or death, whichever comes first. The distribution of PFS will be estimated with the Kaplan-Meier method, by arm.
5. *To estimate median overall survival (OS).* Overall survival (OS) will be defined as the length of time from enrollment to death due to any cause. The distribution of OS will be estimated with the Kaplan-Meier method, by arm.

5. STUDY SCHEMA (Pooled patients from Durham VAMC and Duke)



6. SUBJECT ELIGIBILITY (Eligibility checklist will be used to confirm [VA patients only]: see Appendix)

6.1 Inclusion Criteria

1. Patient has signed informed consent
2. HCC diagnosed either by histology/pathology or Liver Imaging Reporting and Data System (LIRADs 5 per the ACR's LIRADs criteria[10]) by CT or MRI
3. Patient is 18 years or older
4. ECOG Performance status of 0-2
5. Child Pugh score A5, A6, B7 or B8 (see Appendix)
6. Lesion $\leq$ 5cm in size
7. $\leq$ 3 lesions in the liver to be treated on protocol
8. Lesion amenable to treatment with both PLA and HIGRT; for PLA treatment this requires the lesion be visible via ultrasound and/or non-contrast CT or feasible per treating physician

6.2 Exclusion Criteria

1. Child Pugh score B9 or C10
2. Fluctuating ascites
3. Inability to complete baseline QOL forms
4. Concurrent administration of systemic therapy for HCC

5. Prior liver RT is an exclusion unless subject participation is approved by the PI
6. Positive serum pregnancy test

7. INVESTIGATIONAL PLAN

7.1 Study Design

- 90 patients will be accrued to this prospective, randomized multi-institutional study.
- Please refer to study schema in section 5.
- Eligible subject population is outlined in section 6.

7.1.1 Stratification

Patients will be stratified by whether their baseline value on the EORTC QLQ-C30 is <60 or ≥ 60.
Two randomization strata will be formed according to the patient's baseline value on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) [i.e., <60 and ≥ 60].

7.1.2 Randomization

Patients will be sequentially randomized with equal allocation to the two arms in Research Electronic Data Capture (REDCap**).**

7.1.3 Safety Considerations

An interim analysis will be performed after the first 40 patients have been followed for 90 days after completion of study therapy. Accrual will not be halted during this analysis. All treatment-related grade 4-5 AEs occurring within 90 days of treatment will be tabulated and reviewed. If > 20% of patients experience grade 4-5 AEs attributable to treatment, a decision will be made to either: 1) halt the trial and all further accrual, 2) amend the protocol for more aggressive dose modification and/or 3) institute additional clinical monitoring.

Anticipated risks associated with PLA include:

- pain (muscle aches or spasm may occur for 3-5 days)
- nausea/vomiting
- infection
- fever
- liver damage
- blood vessel/nerve damage; this could require admission to hospital

Rare but very serious PLA risks include:

- liver damage which could cause liver failure
- bleeding from the liver which could be life threatening
- liver abscess (serious infection)

Anticipated risks associated with HIGRT include:

- fatigue
- pain
- nausea/vomiting

- **Rare but very serious HIGRT risks include:**
- liver damage which could cause liver failure
- rib fracture
- chest wall pain

7.1.4 Treatment Interruptions during RT

Although we do not anticipate side effects resulting in a break during treatment, there is the low possibility of Radiation Induced Liver Disease (RILD) or bleeding secondary to radiation treatment. Prior retrospective studies have been used to define our current dose limitation guidelines to reduce risk of RILD to a negligible level. HIGRT will be discontinued at the discretion of the treating physician according to best clinical practice.

7.1.5 Concomitant Medications/Therapies

Patients will receive no additional HCC directed therapy (i.e. sorafenib) during active protocol participation. There are no limitations regarding what treatment they can receive after treatment completion including HCC directed therapies and/or repeat ablation or HIGRT treatments if needed.

7.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

HIGRT dose will be defined depending on primary tumor size and risk to neighboring organs at risk (OAR); see Section 9.3 for specifics. HIGRT dose and constraints are based on prior research into treated organ tolerance[11] and optimal treatment strategies[12, 13].

7.3 Data collection for Quality of Life Surveys (Appendix)

Two surveys will be used to collect baseline, 1 month, 3 month and 6 month QOL information. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) will be used to assess general symptom burden, social, financial and psychological burden. The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) survey will be used to assess liver specific symptom burden. Both surveys will be collected at baseline (prior to initiation of any therapy) and at 1, 3 and 6 month time marks. Good faith effort will be made to collect survey data in person and on paper if at all possible. If in person or on paper survey collection is not possible, oral survey data collect is allowed by authorized study staff either in person or on the phone. Good faith effort to collect data will allow that surveys may be mailed to subjects. Alternatively surveys may be completed via a secure link electronically. Surveys will be collected within a 2 week period of the planned time mark.

7.4 Definition of Evaluable Subjects, On Study, and End of Study

Patient are “on study” during the intervention time period (either ablation or HIGRT) and the 6-month follow up while additional survey data is being collected. End of study is defined as 180 days post-therapy (+/- 30 days) at the time of the last follow up survey. We will continue to collect patient data from the EHR for 5 years after study enrollment or until death. For the purposes of the primary endpoint of QOL, a patient who has received either ablation or HIRGT and completed at least the baseline and month 1 follow up QOL surveys will be analyzed.

7.5 Early Study Termination

This study can be terminated at any time for any reason by the PI. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 11.7, which describes procedures and process for prematurely withdrawn patients.

RADIATION THERAPY

8.1 Type, Classification, Location, and Short Description

Therapy is high dose image guided radiotherapy (HIGRT) delivered in 5-10 fractions.

8.2 Equipment

A linear accelerator with on board imaging is used for treatment delivery.

8.3 Dose Specifications

The treatment dose is 50 Gy in 5 or 10 fractions. Please see section 9.6 for more details.

8.4 Localization, Simulation

All patients will undergo standard of care CT-based treatment planning in custom made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used) and be adequate to ensure contouring of all targeted lesions, as well as necessary organs at risk (OAR). High-resolution CT scans should be obtained with uniform slice thickness of ≤ 3mm throughout.

The use of IV contrast if preferred. If there is a contraindication for IV contrast an abdominal MRI must be available for treatment planning. The use of other contrast agents is left to the discretion of the treating oncologist. If possible, the use of triphasic (arterial, portal venous, and delayed imaging) is recommended using a flow rate of 4-5ml/sec and 175ml of contrast.

Regions of high vascular contrast in the planning dataset are recommended to be converted to water equivalent density if used for planning (at the discretion of the treating physician). Planning datasets without intravenous contrast may be used for dose calculation.

Ideally a liver-specific MRI will be available and possibly fused with the treatment planning CT scan for target delineation.

8.5 Respiratory Motion Assessment and Management

All respiratory motion should be evaluated by appropriate means including 4D CT scan, imaging of implanted fiducial marker, or fluoroscopy at the time of simulation.

Respiratory motion management (RMM) including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking, is recommended for any lesion to be treated with motion > 5mm. A recommended approach would be to use an ITV technique for motion <1cm, but for motion >1cm (typically too large for a free breathing ITV) motion management including but not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used.

8.6 Treatment Planning/Target Volumes

CT images (ideally triphasic images) will registered to MRI images (by soft tissue alignment) to assist in contouring the GTV. Registration will be performed with the best fit liver-to-liver image registration focusing on the region of the PTV if deformation or rotation occurs between scans.

The GTV represents the target lesion and should be identified on the arterial, portal venous, and delayed CT image sets (if multiple phase CT images are available) as well as on MRI images.

An ITV expansion of the GTV will be created to fully account for the magnitude of the motion observed in the 4D simulation evaluation. If multiple contrast phases are available from CT simulation these will be registered to bony anatomy to verify that the GTV remains encompassed by the ITV.

The ITV will be expanded by 5-10mm radially and 7-10mm superior/inferiorly to arrive at the PTV.

The treatment dose is 50 Gy in 5 or 10 fractions over 2 or 3 weeks, respectively. Lesions in close proximity to a GI structure (colon, small bowel, duodenum, stomach), in a patient with Child-Turcotte-Pugh (CTP) classification B, or a patient with prior radiotherapy to the abdomen will be treated with 50Gy in 10 fractions. Fractionation determination is at the discretion of the treating physician.

Conformal 3D or arc radiotherapy, IMRT or VMAT are acceptable methods of treatment delivery.

All patients must be imaged prior to treatment with volumetric imaging.

8.6.1 General Considerations

A variety of planning techniques can be used to deliver HIGRT for each lesion. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- A minimum field dimension of 3 cm should be observed treating small lesions.
- Dynamic conformal arcs are acceptable.
- The prescription isodose line covering 95% the PTV will generally be 80-90% but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 45Gy/0.6 = 75Gy when 45Gy is prescribed to the 60% isodose).
- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.

8.6.2 Dose calculations

All dose distributions shall include corrections for tissue heterogeneities. RPC approved algorithms must be used. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium. Successful treatment planning will require accomplishment of all of the following criteria: These criteria will be assessed on dose calculated independently for each lesion (i.e., not from composite dose calculations) if more than 1 lesion is present.

1. **Normalization:** The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.
2. **Prescription Isodose Surface Coverage**: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be ≥ 60% and ≤90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.
3. **Target Dose Heterogeneity**: Rather than prioritizing target dose homogeneity, HIGRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR.
4. **Critical Organ Doses**: Respect all critical organ dose-volume limits listed below
5. **High-Dose Spillage:**

a. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.

b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.

   i. The ratio of the prescription isodose volume to the PTV volume should ideally be < 1.2.
   ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV. Because it may become more difficult to restrict the 50% isodose volume when dose is summed from treatment of multiple lesions, this ratio should be evaluated for dose calculated for a single lesion (i.e., not for composite dose). Additionally, the 50% isodose volume may be elongated deliberately in order to avoid OAR thereby making it difficult to meet the constraint guidelines. This is acceptable as long as normal tissue constraints are met.

8.7 Dose Limitations for Normal Tissue

The following normal tissues will be contoured if they are evident within 5 cm of the liver on the planning CT scan:

- Spinal cord
- Esophagus
- Heart/Pericardium
- Stomach
- Duodenum
- Bowel, large/small
- Kidney, left/right
- Chestwall/rib
- Liver

All OAR should be contoured 1cm above and below the PTV with the exception of the liver which should be contoured in its entirety. The following constraints are recommended for a **5-fraction regimen** but can be modified at the discretion of the treating physician:

Serial Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Spinal Cord	<0.03 cc	28	Myelitis (Timmerman)
	<0.35 cc	22	Myelitis (Timmerman)
	<1.2 cc	15.6	Myelitis (Timmerman)
Esophagus (Non-adjacent wall)	<0.03cc	35	Stenosis/Fistula (Timmerman)
	<5 cc	27.5	Stenosis/Fistula (RTOG 0813)

Heart/Pericardium	<0.03 cc	38	Pericarditis (Timmerman)
	<15 cc	32	Pericarditis (RTOG 0813)
Stomach	< 0.5cc	35	Ulceration/Fistula (Timmerman)
	< 5cc	26.5	Ulceration/Fistula (Timmerman)
Duodenum	< 0.5 cc	30	Ulceration (RTOG 1112)
	< 5 cc	18.3	Ulceration (Timmerman 2006)
Bowel	< 0.03 cc	40	Ulceration (Timmerman)
	<20 cc	28.5	Colitis/Fistula (Timmerman)
Renal hilum/Vascular Trunk	<15 cc	23	Malignant Hypertension (Timmerman)
Chest wall	<0.03 cc	57	Pain or Fracture (Timmerman)
	<5 cc	45	Pain or Fracture (Timmerman)
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Ipsilateral Kidney	< 130 cc	14.5	Basic Renal Function (Timmerman)
Total Kidney	< 200cc	18	Basic Renal Function (Timmerman)
Liver	<700 cc	21	Basic Liver Function (Timmerman)

The following constraints are recommended for a **10-fraction regimen** but can be modified at the discretion of the treating physician:

Serial Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Spinal Cord	<0.03 cc	30Gy	Myelitis (Milano)
Esophagus	<0.03 cc	40Gy	Stenosis/Fistula (Milano)
Stomach	<0.03 cc	50Gy	Ulceration/Fistula (Milano)
Duodenum	<0.03 cc	40Gy	Ulceration/Fistula (Milano)
Bowel	<0.03cc	50Gy	Ulceration/Fistula (Milano)

Kidneys	<50%	16Gy	Basic renal function (Milano)
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Liver-GTV	≥1000cc		Basic Liver Function (Milano)
Liver	mean	13Gy	Basic Liver Function (RTOG 1112)

8.8 Treatment Delivery

Ideally treatment will be delivered on consecutive days, for both the 5 and 10 fraction regimens. It is recommended that all treatment be completed in 2 weeks (for 5 fraction regimen) and 3 weeks (for 10 fraction regimen).

8.9 Localization Using Daily IGRT

Patients require daily image guidance prior to treatment delivery. Orthogonal kV imaging to align bony anatomy (and fiducials if present) followed by cone-beam CT to align soft tissue anatomy is ideal.

Additional IGRT may be employed at the discretion of the treating physician (i.e., orthogonal kV imaging prior to required volumetric imaging or volumetric imaging even if only orthogonal kV imaging is required).

9. IMAGE GUIDED ABLATION TECHNIQUES

9.1 Type, Classification, Location, and Short Description

Subjects will be scheduled for PLA as an outpatient treatment. Each subject will report to the Radiology department at the hospital on the day of the treatment for patient registration and nursing intake into the pre-procedure area as per normal hospital protocol. PLA is administered as a single treatment.

The procedure may be performed under moderate sedation or general anesthesia based on operator discretion. All patients will be maintained NPO after midnight the preceding evening. Patients on extensive medications, in particular hypertension and cardiac medications may take these medications in the morning with a small quantity of water. Insulin-dependent diabetic patients should administer half of their usual morning insulin dose. Patients will be administered prophylactic anti-emetic (ondansetron 4mg IV) and antibiotics (Unasyn 3g IV).

The patient positioning for ablation will be determined by the operator based on the location of the lesion. With the patient in position on the CT table, a preliminary non-contrast CT will be performed for localization of the target tumor and to allow planning for an appropriate percutaneous approach. Administration of intravenous iodinated contrast may be deemed necessary for inconspicuous lesions on the preliminary CT scan. An ultrasound will also be performed for localization of the target lesion. Ultrasound should be the first choice primary modality for antennae guidance with CT-fluoroscopic guidance as second choice. The operative site is cleansed, prepped and draped in sterile fashion. After infiltration of the target site with 1% lidocaine, a small skin incision is made at the correct skin entry site with a #11 scalpel. For lesions well-visualized with ultrasound, real-time sonographic guidance is then utilized to guide the microwave antennae into the lesion. CT-fluoroscopy is used for confirmation of positioning and adjacency to critical structures. For lesions inconspicuous on ultrasound, CT-guidance is initiated and an image is taken with the localizer needle in place to identify proper table position and needle angle. Repositioning can be performed with the localizer needle if necessary. The microwave antenna is then guided into the lesion using real-time CT fluoroscopic guidance. If there is concern for non-target ablation of adjacent structures, adjunct techniques such as infusion of artificial ascites, hydro-dissection, or intentional pneumothorax may be utilized.

9.2 Equipment/Imaging

The PLA generators to be used include the Neuwave system, Covidien Emprint, Perseon system, Amica and Boston Scientific. The specific microwave antennae utilized and the number will be at the discretion of the operator. MVA will be performed under ultrasound or CT guidance as per above (section 10.1).

CT images of the treatment antenna(e) placement within the target lesion must be obtained to document final positioning prior to treatment. These images should also be among the images transferred to imaging archive. These images are necessary to ascertain the technical success and quality of treatment. Follow up CT scan will also be obtained to evaluate for pneumothorax, hematoma or other acute complications (treated per institutional guidelines if present).

9.3 Dose specifications

Up to 3 microwave antennae will be utilized. Once the microwave antennae are adequately positioned, the antennae are connected to the generator and microwave ablation is then performed based on the individual generator IFU with power and time settings at operator discretion. For larger lesions, multiple overlapping ablation zones may be performed based on the operator discretion to ensure adequate thermocoagulation of the target lesion. The ablation zone, as evidenced by the sonographic ‘echo cloud’ will be monitored during ablation. If it is determined that there is incomplete tumoral coverage, repositioning or addition of probes may be performed. The MVA aim is to obtain a 0.5 cm ablation margin around tumor.

9.4 Post-PLA monitoring

Immediately following the intervention, the patient will be monitored in a recovery area with a dedicated nursing staff; any early procedure-related adverse event will be documented. After appropriate post-procedure monitoring, the patient is discharged to home if all necessary criteria for discharge are met.

10. PATIENT ASSESSMENTS

As per standard of care, all patients will undergo laboratory evaluation and imaging to determine current liver status as well as extent of HCC.

10.1 Pretreatment Evaluations/Management

Baseline imaging and lab work should be complete within 8 weeks of signing study consent and include

- Multi-phase contrast enhanced CT or MRI of abdomen
- CMP or BMP and LFTs (including Total Bilirubin, Albumin)
- CBC
- INR
- Hepatitis serologies (pre-existing serologies will be accepted)
- AFP
- CT chest or PET-CT
- Serum pregnancy test (if woman of childbearing age)

10.2 Screening Examination

The screening examination will take place prior to any scheduled procedures. An informed consent must be signed by the patient before any study screening procedure takes place. If standard of care evaluation procedures have been obtained and are within the screening evaluation time points, the SOC procedures do not need to be repeated and may be included in the screening examination.

If applicable, pregnancy test will be obtained per institutional policy.

10.3 Treatment Period

Treatment period will be from start to finish of HIGRT or date of ablation based on randomization. Assessment will be performed by the study key personnel at baseline then months 1, 3 and 6 post-treatment for QOL surveys. They will also undergo weekly assessment by radiation oncologist during radiotherapy.

Restaging imaging and labs (LFTs, and AFP, INR) will be performed as per standard of care for HCC (typically 1 month post-treatment, 3 months post treatment and then every 3 months thereafter). Deviations from standard of care follow up for patients are at the discretion of the treating physicians.

10.4 End of Treatment

End of active study treatment is defined as 180 days post-therapy (+/- 30 days) at the time of the 6-month survey. Toxicity will also be assessed at this visit and appropriate follow up arranged.

10.5 Follow-up Period

Patients' electronic records at clinic visits q 6 months through year 3, then annually years 4 and 5, will be reviewed for recurrence and survival via for 5 years from randomization or until death. We expect that approximately 20% of patients may survive greater than 3 years.

10.6 End of Study

Patients lost to follow up will be documented and censored at time of last follow up for statistical consideration purposes. For protocol purposes, lost to follow up is defined as no contact with the subject for 12 months despite 3 documented attempts to follow up by the study team.

10.7 Early Withdrawal of Subject(s)

10.7.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

10.7.2 Follow-up Requirements for Early Withdrawal

Subjects who withdraw prior to study completion will be followed for primary and secondary end points via an intention to treat analysis. All attempts will be made to complete QOL surveys as appropriate. Subjects may decline to complete surveys at any time during study participation; declining to complete surveys will be recorded and will not considered a reportable protocol deviation.

10.7.3 Replacement of Early Withdrawal(s)

Subjects who withdraw prior to beginning protocol therapy may be replaced.

11 Study Assessments

11.1 Medical History

Prior to enrollment, all patients will have a complete medical History and Physical. Medical history will be documented in standard format including a history and physical exam by Gastroenterology, Medical Oncology or Radiation Oncology. Weekly treatment checks during radiation therapy will be focused histories.

11.2 Surveys

Written, verbal or electronic QOL surveys via the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep, Version 4) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30) will be performed at baseline and at 1, 3, and 6 months after the completion of PLA or HIGRT treatment.

12. SAFETY MONITORING AND REPORTING

The PI or treating MD is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing liver disease. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with receiving either PLA or HIGRT. Abnormal laboratory findings without clinical significance (based on the PI's

judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 11.4), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

12.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

12.2.1 Reporting of SAEs

SAEs will be reported to the IRB as per institutional policy.

12.3 Other Reportable Information

The study team will adhere to the institutional policy on subjects and pregnancy stringently.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Data Management and Processing

13.3.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with regulatory bodies/committees, and regulatory documents that can be found in the "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

13.3.2 Case Report Forms (CRFs)

A REDCap database will be the primary data storage method. Two parallel databases will be created to manage data for the VAMC and Duke trials. The CRFs will be updated in a timely manner following acquisition of new source data. Only the PI and select persons listed as key personnel on each trial are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system, REDCap. All users of this system will complete user training, as required or appropriate per regulations.

13.3.3 Data Management Procedures and Data Verification

Key study personnel and clinical research nurses will have access to REDCap based on their specific roles in the protocol. The designated data manager will be managing the REDCap database.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and clinical research nurses will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

13.3.4 Coding

All medical terms will be coded with CTCAE v 4.0 where applicable.

13.3.5 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Review of site study records for completeness

14. ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 Durham VA Medical Center (DVAMC)

14.3 Institutional Review Boards (IRB)

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DVAMC IRB for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form.

The Principal Investigator must obtain protocol re-approval from the IRB as per DVAMC policy.

The protocol, informed consent form, advertising material, and additional protocol-related documents must also be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the Duke CPC and IRB.

The Principal Investigator must submit and obtain approval from the Duke IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol

amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

15 Informed Consent

The informed consent form will be submitted separately.

Before conducting any study-specific procedures, the Principal Investigator or designee must obtain informed consent from the subject. The original informed consent form will be stored with the subject's study records and a copy of the informed consent form will be provided to the subject. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

16 Study Documentation

See section 13.3.1 for details regarding documentation and case report forms.

17 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate Institutional Site Based Research group (Duke IRB and the Durham VAMC IRB).

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality at Duke, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated database (REDCap), which is housed in an encrypted and password-protected DCI file server. Access to electronic databases will be limited to specified key personnel. Key personnel who enter study data for subjects participating at Duke will not have any visibility on the data entered for subjects participating at the Durham VAMC. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be

maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

Section 17 subheadings 1 through 18 data security requirements is applicable to the study team at the Durham VAMC

1. Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information
☐ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe:	☐ Photographs, videotapes, audiotapes, or digital or other images
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: DOB, initial imaging dates, dates of treatment, dates of hospitalizations (if any) and FU visit/imaging dates and dates of questionnaire completion will be recorded	☐ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe:
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☐ Electronic mail addresses	☒ Operative reports
☒ Social Security Numbers (SSN will not be collected for subjects treated at Duke Cancer Center)	☒ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☒ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☐ Account numbers	☒ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☐ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☐ Drug abuse information
☐ Internet Protocol (IP) address numbers	☐ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: study ID number	☐ Other, describe:

2. Data and/or Specimen Acquisition:

Data for this study will be collected through (*check all that apply*):

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes: In addition to baseline characteristics, patient completed QOL surveys (see appendix) will be prospectively collected as described previously.

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): Data regarding time to event endpoints will be obtained through review of the electronic medical record by study personnel.

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .

Note: for data and/or specimens obtained from a VA approved data repository, a Data Use Agreement (DUA) must be executed prior to obtaining data and/or specimens. See VHA Handbook 1200.12 for further information.

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, but study code/ID included)
☐ De-Identified (all HIPAA 18 and study ID/code removed):
- ☐ Verified Statistically
  OR
- ☐ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set
☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. Data and/or Specimen Location: To protect confidentiality, subject files in paper format will be stored in a secure, locked office. Subjects will be identified only by a unique study number. Electronic records of subject data will be maintained using a dedicated database, which is housed in an encrypted and password-protected file server. For the patients enrolled at the VA, access to electronic databases will be limited to the research study team in the VA departments of Radiation Oncology and Medicine (Gastrointestinal). The security and viability of the IT infrastructure will be managed by the Durham VA for VA patients. Data will be stored electronically in a VA instance of REDCap and on *S:\RADIATIONONCOLOGY\Research\HCC Study*. All data will be stored electronically.

☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager. .

5. **Data Access and Data Recipients:** *Only members of our DVAMC research team will have access to identifiers and coded data. Data with direct identifiers removed (i.e., name, address, telephone numbers, SSN, DOB) and study ID/code assigned will be placed in REDCap*. The non-VA statistician and will have access to coded data for the purpose of statistical analysis.

All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins).

Access to study data will be removed for all study personnel when they are no longer part of the research team.

6. **Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:**

Data are coded and thus will be sent via a VA issued and FIPS 140-2 encrypted hard drive/flash drive using VA—approved carrier with tracking. The transmission of coded patient data will occur for statistical analysis.

I. ☐ Data and/or specimens will <u>not</u> be transported or transmitted outside of Durham VAMC environment.

II. ☐ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center.

a. ☐ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials.

b. ☐ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container):

<u>NOTICE!!!</u>

<u>Access to these records is limited to: AUTHORIZED PERSONS ONLY.</u>

Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

III. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☒ Data are coded and thus will be sent via FIPS 140-2 encrypted hard drive/flash drive using VA—approved carrier with tracking or via secure email by a member of the study team to the statistician. The transmission of coded patient data will occur for statistical analysis.

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF)

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

7. Risk Mitigation Strategies:

☐ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.

☐ Other, specify:

8. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

10. Future Use of Data:

☒ Data will be retained for future use. This is described below: Data will be retained after completion of the primary study endpoints to perform analysis regarding radiation parameters and to predict correlation with radiation toxicity.

☒ Future Use of data is optional (i.e., not required by the research subject).

☐ Future Use of data is required for participation in the study.

☐ No future use of data is currently planned.

18 Data and Safety Monitoring

See section 13.3.1 for details regarding data management procedures and data verification.

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents within the VA will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

18.1 Safety Oversight Committee (SOC) Duke Cancer Institute (sections 18.1 through 18.4 are applicable to the study team at Duke Cancer Institute)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring

Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

18.2 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

Interim analyses occur as scheduled;

Stopping rules for toxicity and/or response are met;

Risk/benefit ratio is not altered to the detriment of the subjects;

Appropriate internal monitoring of AEs and outcomes is done;

Over-accrual does not occur;

Under-accrual is addressed with appropriate amendments or actions;

Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and

additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

18.3 Audits

The Duke School of Medicine Office of Audit, Risk and Compliance (OARC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the CTQA auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARC audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

19 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

20 Records Retention

Following completion of the study and study closure, the PI will be responsible for ensuring the following activities:

Data clarification and/or resolution

Review of site study records for completeness

The Principal Investigator will maintain study-related recordsper the Duke institutional policy: at least six years after study closure in the IRB..

21 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan.

16. REFERENCES

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APPENDIX

Child-Pugh Score

Measure	1 point	2 points	3 points
Total Bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin Time, prolongation (s)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic Encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%