Study Title

A Pilot Study to Assess Theragnostically Planned Liver Radiation with Functional DVH Analysis to Optimize Individualized Radiation Therapy

Protocol Number:
IUSCC-0604

IRB Number:
1701880309

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NCT03338062

Protocol Version Date:
12/28/2016- Version #1
08/01/2017 – Version #2 (Amend #1)
2/12/2018 – Version #3 (Amend #2)
3/9/2018- Version #4 (Amend #3)
8/6/2018- Version #5 (Amend #4)
2/6/2020-Version #6
7/9/20 –Version #7

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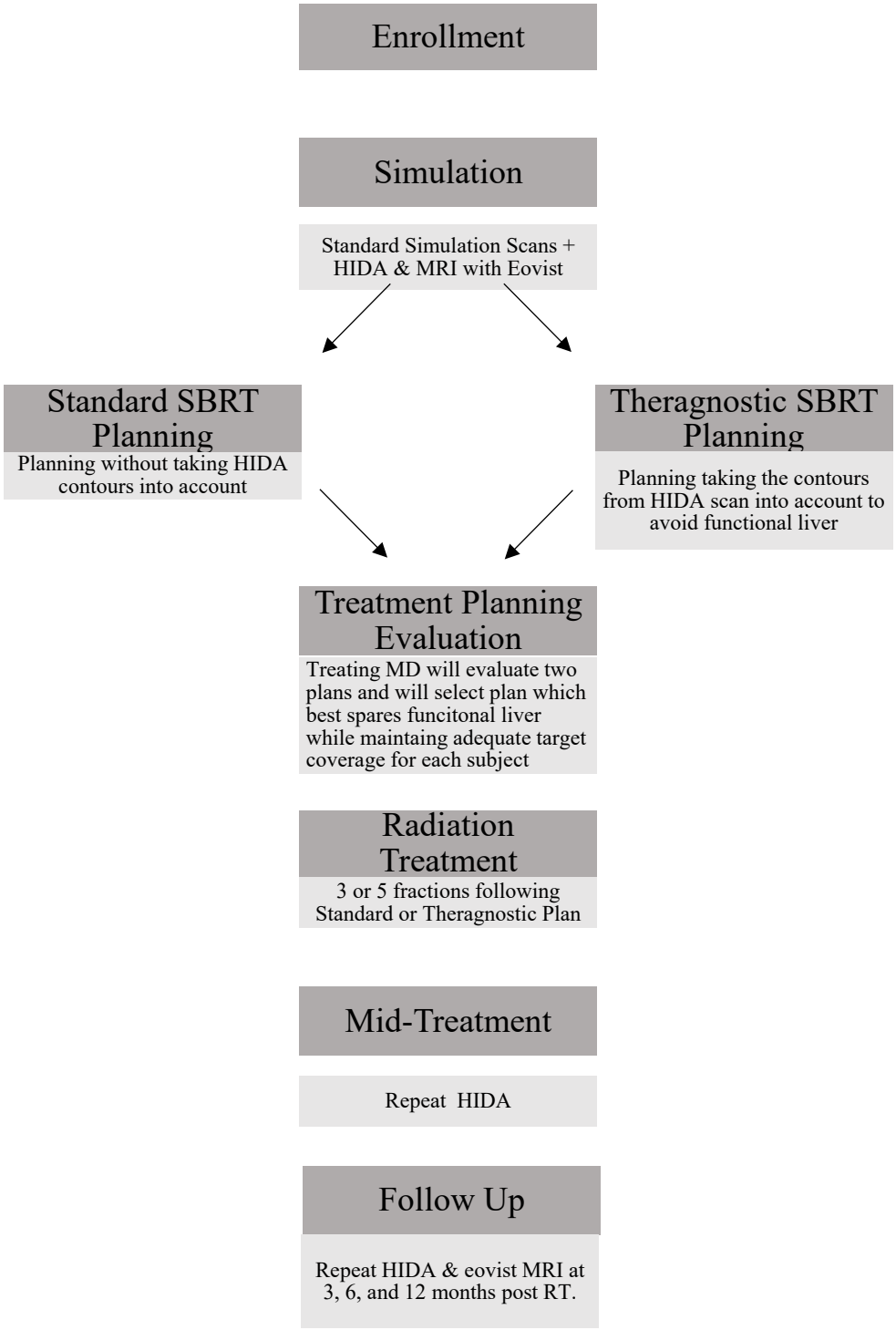
1.0 SCHEMA


Enrollment
Simulation
Standard Simulation Scans + HIDA & MRI with Eovist
Standard SBRT Planning
Planning without taking HIDA contours into account
Theragnostic SBRT Planning
Planning taking the contours from HIDA scan into account to avoid functional liver
Treatment Planning Evaluation
Treating MD will evaluate two plans and will select plan which best spares funcitonal liver while maintaing adequate target coverage for each subject
Radiation Treatment
3 or 5 fractions following Standard or Theragnostic Plan
Mid-Treatment
Repeat HIDA
Follow Up
Repeat HIDA & eovist MRI at 3, 6, and 12 months post RT.

2.0 BACKGROUND

Liver malignancies, especially hepatocellular carcinoma (HCC), often arise in patients with cirrhosis, who exhibit significant variability in their liver function. The primary methods of assessing the severity of cirrhosis are clinical scoring systems such as the Child-Turcotte-Pugh (CTP) score or the Modified End-Stage Liver Disease (MELD) score. The Barcelona Clinic Liver Cancer (BCLC) staging, Cancer of the Liver Italian Program (CLIP) score, and the newest albuin-bilirubin (ALBI) grade have been proposed as alternative ways to assess the severity of liver dysfunction. Patients with liver tumors who need radiation may not be diagnosed with cirrhosis but may have significant alteration in their liver function due to prior chemotherapy or other local therapy. The gold standard lab test for global liver function evaluation is indocyanine green retention at 15 minutes (ICG15). However, one of the most clinically important limitations of all these tests is the lack of information that they provide regarding regional variations in hepatic function within the liver of an individual patient, which are increasingly well described. Such regional variability can have important implications for radiation treatment (RT) planning, delivery, and outcome assessment in patients with liver cancer. Recently, visualizing regional differences in hepatic function has become possible with the development of imaging techniques using technetium-99m (Tc99m) hepatobiliary iminodiacetic acid (HIDA) scans, Tc99m galactosyl human serum albumin (GSA) scans, dynamic contrast enhanced (DCE) computed tomography (CT), DCE magnetic resonance imaging (MRI), and functional MRIs (fMRIs) using contrast agents such as Eovist. Theragnostic imaging is the application of quantitative information from imaging studies to guide therapeutic interventions. These technologies therefore may have important applications in RT for liver cancer as they can provide a “road map” for how to design radiation plans to avoid functioning liver.

Hepatobiliary tumors globally are the fifth-most common cause of cancer and the second leading cause of cancer death.[1] In the United States in 2015, there are expected to be 46,570 hepatobiliary malignancies with 28,250 deaths. Hepatocellular carcinoma (HCC) is the most common type of hepatobiliary tumor. The primary risk factors for HCC are chronic hepatitis B and C infections, although cirrhosis of any cause increases the risk. The rising incidence of hepatitis C has caused HCC to become one of the fastest-growing cancers in terms of incidence and death in North America.[1] Surgical resection and liver transplantation offer the best outcomes, with 5-year overall survival (OS) rates of 50-85%.[2-5] Unfortunately, many HCC patients are not candidates for surgical resection due to the presence of locally advanced disease or medical comorbidities. In addition, only select patients with early stage HCC (tumors <5 cm) are candidates for liver transplantation.[6] For patients who are not surgical candidates or who refuse surgery, a variety of nonsurgical treatment modalities are available, including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), radioembolization (Y-90), chemotherapy (primarily sorafenib-based), and radiation therapy (RT). TACE, RFA, and RT can be used as “bridging” therapies to prevent disease progression in patients awaiting transplantation. However, to date, there have been no randomized trials comparing these modalities. A discussion at a multidisciplinary tumor board where physicians from each respective specialty of surgery, interventional radiology, radiation oncology, hepatology, and radiology often determines which modality is pursued. Similarly, the other hepatobiliary tumors, namely cholangiocarcinoma and gallbladder cancer, are primarily treated with surgery if possible. An additional indication for focal liver radiation therapy exists in patients with oligometastases from certain primary malignancies, such as colon, lung, or breast cancer.

Historically, the use of radiation in cancers of the liver was limited due to the risk of radiation-induced liver disease (RILD), which is characterized by anicteric ascites and elevated transaminase levels. No standard method of reversing RILD is known, and it can lead to fatal liver failure. The risk

of RILD is best correlated with mean liver dose, reflecting the presence of a strong dose-volume correlation with the risk of RILD. Additionally, the liver is considered a "parallel" organ that can be treated with ablative radiation doses as long as adequate reserve tissue is maintained.[7, 8] Therefore, radiation therapy (RT) has gained an increasing role in the treatment of liver tumors given the development of highly conformal methods of delivery, including intensity modulated radiation therapy (IMRT), proton therapy, and stereotactic body radiation therapy (SBRT). Unlike conventionally fractionated radiotherapy, where a treatment course is administered daily over the course of a few weeks, SBRT delivers highly focused radiation with sharp dose gradients over a shorter treatment course, usually 1 to 6 fractions. Liver SBRT has been established as a safe and effective option in both liver metastases and HCC.[9-12] Rusthoven et al treated patients with SBRT (54 Gy in 3 fractions) for liver metastases and found a 2-year local control (LC) rate of 93% and no grade 3 hematologic or hepatic toxicity.[9] A phase I/II trial in HCC patients from Indiana University reported 2-year LC rates of 90%.[10] The largest prospective phase I/II trial in HCC patients from Princess Margaret reported a 2-year LC rate of 74%, but 55% of these patients had vascular invasion, which is a poor prognostic factor.[12]

Significant variability in liver function is present in the population of patients with liver tumors and cirrhosis. Different models for grading the severity of cirrhosis are available, including the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) score. To date, CTP score has been the preferred scoring system in evaluating patients for consideration of SBRT. There are other staging and prognostic scores for patients with HCC including the AJCC stage, BCLC stage, CLIP score, and ALIBI score. The CTP score is based on the levels of bilirubin, albumin, and PT/INR; it also incorporates a subjective grading system for ascites and encephalopathy. The range of scores is 5 to 15, with scores 5-6 classified as CTP A, 7-9 CTP B, and 10-15 CTP C.[13] The risk of side effects has been suggested to increase with higher CTP scores. In the study by Choi et al, 75% of their patients had CTP A disease, and there were no grade 3 toxicities reported in their trial.[11] One-third of patients in the phase I/II trial at Indiana University experienced grade 3 hematologic or hepatic toxicity, although 17 out of 21 of those patients had pre-treatment grade 2 dysfunction in that category. In addition, there were 4 patients who had progressive liver dysfunction, 2 of whom went on to liver transplantation and the other 2 who died as a result of liver failure. All 4 of these patients had CTP ≥B8, and 2 of those patients were treated with 42 Gy in 3 fractions, which was concluded to be unsafe in CTP B patients.[10]

In addition to baseline liver dysfunction, many of the patients who are referred for liver SBRT have had prior therapies such as surgical resection, chemotherapy, RFA, TACE, or conventional radiotherapy, which can adversely affect liver function. A recent retrospective study from Michigan comparing their institutional experience of SBRT with RFA found that patients who were treated with SBRT were more likely to have received prior liver-directed therapies with a median of 2 treatments in SBRT patients compared to 0 in RFA patients.[14]

We propose that, by assessing global and regional liver function before and after liver radiation, we will be able to identify correlations between radiation dose to the normal liver and the risk of RILD. An improved understanding of the relationship between radiation dose and the risk of liver toxicity will permit assessment of the risk of RILD before RT, thereby improving the safety profile of liver RT, allowing appropriate patient selection and dose determination, and establishing a standard approach for theragnostically planned radiation therapy.

Theragnostic imaging is a term coined by Soren Bentzen to describe the application of quantitative information from biomedical imaging to guide therapy.[15] He proposes a technique which he calls "dose-painting by numbers," suggesting that imaging techniques that can visualize areas that may

potentially be radioresistant such as hypoxic areas can serve as a map on which dose can be escalated to in a voxel to voxel manner.[16] This protocol would apply the technique of theragnostic imaging in a new way. We propose the idea of "dose-erasing by numbers" to optimize our radiation dose away from areas of functional liver. In taking the regional variation of liver function into account, we propose that radiation plans designed in such a way that maximizes safety by minimizing risk of toxicity. This protocol will aim to determine the clinical feasibility of applying such a technique in the clinic.

Currently, standard constraints for liver SBRT planning stipulate that 700 cc of "uninvolved liver", i.e., the volume of liver minus the gross tumor volume (GTV), should receive <15 Gy. This constraint is derived from a phase I study conducted at the University of Colorado (which itself was based on surgical data showing that 75-80% of the liver can be safely resected).[9, 17] Since 25% of the assumed average liver volume of 2000 cc is 500 cc, 700 cc was used as a conservative limit. The basis for 15 Gy was that its BED is 40 Gy_3 which is less than the whole liver tolerance of 49.5 Gy_3 as determined from an early RTOG dose escalation study of whole liver RT.[18] The current constraint does not take into account the functional residual capacity of the untreated liver. However, information about regional variations in liver function could help to evaluate the safety of RT in patients who are borderline candidates for liver RT based on their liver function. In this protocol, we will meet the standard physical constraints but plan to increase safety further by attempting to decrease dose to functional areas.

The indocyanine green (ICG) retention study is presently the gold standard for assessing liver function, but this study only provides information about global liver function.[19] An ICG retention at 15 minutes (ICG15) of less than 14% has historically been used as a cutoff to select patients for major hepatectomy, but subsequent trials have shown that well-selected patients with ICG15 values above this cutoff had similar outcomes as those with lower ICG15 values[20, 21] According to the 2016 NCCN hepatobiliary guidelines, ICG15 is widely used in Asia but not in Western countries. Two studies from the University of Michigan reported baseline ICG values in patients' pre-treatment. They reported ICG clearance as ICG half-life, whereas the surgical data looks at ICG retention at 15 minutes (ICG15). In a total of 29 patients, the values ranged from 3.75 minutes to 14.5 minutes, which would correlate with an expected ICG15 of 6.25% to 48.8%. In this study, 14 of 29 (48.3%) of patients would have had a ICG value >14%. Clearly, the patients undergoing radiation therapy for liver tumors can have a large variation in their liver function. Having more data as to what functional residual capacity correlates with the ability to safely deliver radiation therapy would be beneficial.

Alternative radiographic assessments of regional liver function, including the hepatobiliary Tc99m-iminodiacetic acid (HIDA) scan, dynamic contrast enhanced (DCE) CT, DCE MRI, and fMRI with contrast agents such as Eovist are being explored. These have been validated by comparison to ICG to demonstrate their correlation with liver function.[22-26] Unfortunately, direct comparisons of these modalities are complicated by a lack of uniformity in reporting of imaging data. In addition, it is unknown how to best incorporate information derived from these studies in radiation treatment planning.

HIDA scans have been evaluated in both the surgery and radiation therapy settings. In the surgical setting, HIDA scans have been used in an effort to identify patients who are at higher risk for postoperative complications including liver failure and death. Much of the pioneering work for the use of HIDA scans in pre-operative evaluation has been done in the Netherlands. A Dutch study reported that HIDA scans were effective in predicting postoperative morbidity and mortality; this report showed that a 2.5%/min/m^2 of body surface area (BSA) in the residual (non-resected) liver was the threshold value that predicted for postoperative liver failure. Patients with a FRL uptake above

2.5%/min/m^2 of BSA had a 3% chance of developing postoperative liver failure and liver-failure related mortality, whereas patients with FRL uptake below 2.5%/min/m^2 had a 56% chance of postoperative liver failure. A recent update to these data gives 2.7%/min/m^2 as the safe cutoff. This study also demonstrated a weak but positive correlation (r=0.61) between HIDA scan values for predicting volume regeneration at 3 months post-resection.[27] The University of Michigan has also evaluated the potential use of HIDA in radiation treatment planning. They used a different parameter, the hepatic ejection fraction (HEF), and validated it with ICG. They obtained HIDA scans pre-treatment, during treatment (after 50-60% of the planned dose had been delivered), and 1 month post treatment. They derived models which predicted HEF-dose response and found that the model which incorporated the HIDA scan during treatment improved their predictive power given variation in individual radiation sensitivity, suggesting that adaptive radiation planning in order to direct dose through worse functioning portions of the liver may improve the safety of radiation delivery.[24] The study from Michigan provides further validation of the HIDA scan as a reasonable surrogate for liver function.

HIDA scans are a relatively inexpensive and simple imaging technique. In patients undergoing liver resection, preoperative HIDA threshold values of >2.7% uptake/min/m^2 have been shown to correlate with a decreased risk of postoperative liver failure. However, it is unknown whether similar HIDA threshold values can be used to determine the safety of radiation therapy in patients who are candidates for treatment with this modality, although some preliminary investigations of HIDA scans to measure post-RT liver function have been reported. Further work is needed to identify thresholds below which a given patient may be at high risk for developing radiation-induced liver disease (RILD).

CT perfusion and MR perfusion have also been studied at the University of Michigan in a similar fashion to the HIDA analysis, with scans obtained pre-, during, and 1-month post-treatment in patients undergoing 3D conformal liver RT. Both modalities were validated by comparison to ICG. The study evaluating CT perfusion defined a lower limit for portal vein perfusion (Fp) by determining the line of best fit with correlation to ICG. This value was Fp <20 mL/(100 g 100). The dose that decreased portal vein perfusion to 20 mL/(100 g min) for each patient ranged from 42.4 to 67.8 Gy, indicating significant individual variations in radio sensitivity. In 8 of 11 patients (73%), perfusion in the low dose regions increased post-treatment, suggesting that such regions may be able to make up for perfusion that is lost in the higher-dose region.[22] A companion MR perfusion study included patients treated with SBRT (n=5) and 3D conformal RT (n=12) and showed that on average, regional decreases in perfusion occurred at doses greater than 17 Gy.[23] This correlated with the threshold for hepatic regeneration that was described previously, where it was also suggested that doses >23.9 Gy limited regenerative capacity.[28] This study also demonstrated that pre-treatment and mid-treatment perfusion scans predicted 1 month post-treatment perfusion measurements. Interestingly, 5 of 6 patients with HCC and cirrhosis in the study had global hyperperfusion. Of these 5, 2 had improvement in perfusion post-treatment: one had a 40% improvement in ICG half-life from 10.25 minutes to 6 minutes (estimated ICG15 36.3% to 17.7%) and the other had a stable ICG half-life of 14 minutes (estimated ICG15 47.5%). In 5 of 17 patients who had scans 2 months after treatment, it appeared there was a recovery of perfusion to near the previous baseline in the lower doses but not in the higher doses.[23] No threshold was given, but the dose appears to be in the range of 35-40 Gy. This is consistent with studies done at the University of Colorado where the defined threshold for a significant change in Hounsfield units was -7 units; this change was correlated with a physical dose of 30-35 Gy, suggesting such areas are associated with scarred liver tissue.[29]

The Michigan studies provide important data with respect to validating the role of advanced imaging

techniques in evaluating functional residual liver volume. These studies also provide preliminary image-based information about the dose-response relationship of normal liver tissue. However, these studies were limited by the heterogeneous patient population and the short follow-up period (only one month post treatment). The HIDA parameter of HEF which was studied at Michigan has not been prospectively evaluated as a predictor of worse clinical outcomes, unlike the % uptake/min/m^2 parameter, which is how HIDA scans are reported at our institution. Finally, and perhaps most importantly, the prior HIDA studies provide no information on the correlation of imaging findings with post-treatment liver function tests, CTP score, or MELD. An exploratory analysis to determine the correlation of functional imaging to liver regeneration and the standard scoring systems such as CTP or MELD is planned.

A Japanese study evaluated different MRI parameters from DCE MRI and their correlation with Tc99m galactosyl human serum albumin (GSA) scans, with validation using ICG. Interestingly, they also correlated the different functional imaging studies with CTP score, a useful clinical parameter which none of the University of Michigan papers evaluated. GSA is a radiotracer specific for hepatocytes, binding to the asialoglycoprotein (ASGP) receptor on the sinusoidal and lateral surfaces of hepatocytes. It is similar to the HIDA scan and is widely used in Asia, but GSA is currently not FDA approved in the United States. Typical parameters evaluated through GSA are the ratio of GSA radioactivity of the liver to heart-plus-liver (LHL15) and percent of cumulative uptake from 15-16 minutes (LU15). They found that the intracellular contrast uptake ratio (UR) from DCE MRI had correlations with the GSA scan parameters LHL15, LU15, CTP score, and ICG15. The weak correlation of UR with fibrosis trended toward significance. A different MRI parameter, the extracellular volume (Ve), correlated with fibrosis, but was not found to have significant correlation to the GSA parameters, ICG15, or CTP score. The authors concluded that neither MRI nor GSA was the 'correct' method, and more work is needed to investigate what the most sensitive marker for liver function is.[30] A secondary aim of the paper would be to correlate HIDA scan parameters with CTP score as well as with different parameters from other imaging techniques such as diffusion-weighted MRI. We also plan to analyze if there is a correlation between these parameters and the regenerative capacity of the liver.

In order to quantitate the dosimetric improvements that theragnostically planned radiation will offer, we plan to analyze the plans using a functional dose-volume histogram. Conventional dose-volume histograms assume that a given organ is homogeneously functioning and thus spatial and functional information is lost. Functional dose-volume histograms were proposed as a technique to analyze radiation plans in the early 1990s by Lawrence Marks of Duke and also in the Netherlands.[31, 32] Since then, most of the work with regards to the use of functional DVH analysis has been done in lung cancer with single photon emission CT (SPECT) using ^{99}Tc-labeled macroaggregatted albumin (MAA) perfusion imaging.[33, 34] A group in France described a technique of using the SPECT scan to design an IMRT plan that was optimized to reduce the V20 to functional lung. Their definition of functional lung was defined as 60% of the maximum uptake of the SPECT scan.[35] This definition of functional lung, while utilitarian, does not account for the heterogeneity that can exist from one patient to another as there is no standard "global lung function" upon which different patients' scans can be normalized. The HIDA scan technique provides a global liver function from which we can scale the regional function to know more quantitatively rather than qualitatively how a given area of liver is functioning. The only use of functional DVH use for analysis of liver radiation plans comes from a study in Japan where they were studying the use of GSA scans in liver radiation planning. They acknowledged the difficulty of defining a universal liver function. They defined functional liver as uptake of liver greater than the HCC, while dysfunctional liver was up take similar to that of HCC. Using this definition they found that if the V20 to functional liver was <20% was associated with a <20% risk of deterioration in CTP score.[36] These studies demonstrate the

feasibility of optimizing a radiation plan based on an individual patient's functional map generated from an image. The difficulty interpreting these studies is that a global organ function has not been clearly defined in a reproducible manner. For example, the uptake of a HCC can vary from one patient to another. Our technique of HIDA scan interpretation gives a reliable global liver function from which a given percentage of counts within the scan can be scaled to a quantitative value which can be compared from patient to patient.

3.0 RATIONALE

The goal of the present study is to evaluate whether theragnostically planned liver radiation through the addition of a HIDA scan can reduce the dose of radiation to functional liver as compared to conventionally planned liver radiation without compromising target coverage or tumor control. We believe that a better understanding of the application of HIDA scans in patients undergoing radiation therapy will assist in patient selection and may permit further customization of RT plans to minimize post-treatment hepatotoxicity.

4.0 OBJECTIVES

4.1 Primary Objective

1. To assess whether theragnostically planned liver radiation through the use of a HIDA scan can reduce the dose of radiation to functional liver as compared to conventionally planned liver radiation.

4.2 Secondary Objectives

1. To assess the rate at which the theragnostically planned radiation plan is chosen as the actual treatment plan instead of the conventionally planned radiation plan.
2. To collect data regarding local control (LC), progression free survival (PFS), overall survival (OS), time to transplant (TT), distant liver failure, and salvage therapy in patients undergoing functional image-guided planning for liver SBRT. To document patterns of failure so that local failure versus distant liver failure can be accounted for.
3. To assess treatment toxicity.

4.3 Exploratory Objectives

1. To identify correlations between radiation dose to the normal liver and the risk of RILD.
2. To determine the feasibility of incorporating functional liver MRI (i.e., fMRI which will be done via MRI with Eovist contrast) into theragnostic liver radiotherapy planning.
3. To assess the rate of significant change in HIDA scans midway through treatment.

4.4 Primary Endpoint

1. The functional reserve of liver will be calculated for both a plan that takes the HIDA scan into account and a plan that does not take this into account. The functional reserve will be calculated by (number of counts outside 15 Gy isodose line / total number of counts within the liver) * global liver function.

4.5 Secondary Endpoints

1. The rate at which the theragnostically planned radiation plan is chosen as the actual treatment plan rather than the conventionally planned radiation plan.

2. LC, PFS, OS, time to transplant, distant liver failure, and time until salvage treatment
3. Post treatment changes in liver function tests and CTP score. We plan to document the rate of decline of CTP class as well as the rate of any grade of hepatic toxicities.

4.6 Exploratory Endpoints

1. Correlations between radiation dose to the normal liver and the risk of RILD.
2. Correlation between the quantitative data from fMRI and HIDA scan values. Also, a preliminary exploration of the doses at which changes in fMRI are seen.
3. The rate at which the HIDA changed enough such that the radiation plan could have been adapted to decrease the amount of functional liver receiving >15 Gy.

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. Subjects must be ≥ 18 years of age at the time of signing informed consent
2. Diagnosis of primary liver malignancy (including hepatocellular carcinoma [HCC] or cholangiocarcinoma) or liver metastasis from any primary solid tumor site by characteristic imaging findings on CT or MRI, clinical presentation, and/or pathologic confirmation of diagnosis. Subjects with other current or prior malignancies are eligible for this study.
3. Patients with liver metastases must have at least one of the following clinical factors that may affect liver function:
    a. History of liver resection (at any time)
    b. History of cirrhosis (any cause), fatty liver disease, or hepatic insufficiency due to any cause
    c. Prior radiation to the upper abdomen including radioembolization
4. ECOG (Zubrod) Performance Status 0-2.
5. Subjects must have a Child-Turcotte-Pugh (CTP) score ≤ 7 to be eligible.
6. Patients who have been previously treated with non-SBRT liver directed therapies may be enrolled on study. At least 3 months must have elapsed between the most recent liver-directed therapy and study entry.
7. Ability to provide written informed consent and HIPAA authorization
8. Subjects with an allergy to contrast agents may be enrolled at the treating physician's discretion with appropriate pre-treatment and symptom management.

5.2 Exclusion Criteria

1. Subjects who are pregnant or planning to become pregnant during the study. Women of child bearing potential must have a negative pregnancy test
2. Subjects must not have received chemotherapy within 2 weeks of planned 1st day of RT.
3. No more than 3 lesions may be treated. The maximum sum of the diameter(s) of the lesion(s) must be ≤6 cm
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (or infections requiring systemic antibiotic treatment), active upper GI ulceration or hemorrhage, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would in the opinion of the investigator limit compliance with study requirements

6.0 STUDY DESIGN

This is a pilot non-randomized study that will enroll patients planning to undergo treatment with SBRT for liver malignancies.

7.0 PATIENT REGISTRATION AND RECRUITMENT

Potential subjects will be identified and recruited per the recommendation of surgeons, medical oncologists, tumor boards, Department of Radiation Oncology, recommendations from outside physicians, or self-referral. No advertisement will be used to recruit subjects. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the eligibility criteria. Eligible patients who complete the Informed Consent Process will be registered in the OnCore® database and assigned a subject ID number. Regulatory files will be maintained by the Radiation Oncology Research Office. Applicable regulatory documents must be completed and on file prior to registration of any subjects.

8.0 STUDY PROCEDURES

8.1 Baseline

Each subject will undergo the following baseline procedures to determine eligibility within 4 weeks of registration.

1. Informed Consent
2. History and Physical
3. Vitals
4. ECOG performance status
5. Laboratory Assessments (CBC differential, platelets, CMP, INR, AFP)
6. Urine pregnancy test (for females of childbearing potential)
7. Liver severity assessments: CTP score, AJCC stage, MELD score, BCLC stage, CLIP score, ALIBI score

8.2 Simulation Period

After subjects have been found eligible and enrolled to this study, each subject will undergo CT simulation for SBRT treatment planning. Two radiation treatment plans will be created for each subject and compared. The plan which best spares functional liver while maintaining adequate target coverage will be selected for each subject. Within 8 weeks of the simulation, the subject should have the following functional scans for enrollment:

1. HIDA scan
2. MRI with Eovist contrast (fMRI)

If a patient cannot obtain an MRI or refuses to undergo eovist MRI, the subject may be enrolled on the study at the discretion of the principal investigator.

8.3 Radiation Treatment Period

During radiation treatment, subjects will be seen at least once per week for clinical assessment that will include a limited physical exam and assessment of toxicity.

Midway through radiation treatment, subjects will have the following procedures:

1. Laboratory Assessments (CBC with differential, CMP, INR) for assessment of CTP, MELD, and ALBI scores.
2. HIDA scan

Subjects who have a total of 3 fractions will have Midway Assessments done after fraction 2.
Subjects who have a total of 5 fractions will have Midway Assessments after fraction 3.

8.4 End of Treatment Visit

Lab assessment should be performed within 30 (+/-7) days from last radiation treatment. This includes at least CBC with diff, CMP, INR

1.

8.5 Follow up

Follow up visits will occur at 3, 6 and 12 months (+/-30 days) post the end of treatment visit. Subjects will have the following procedures at this visit:

1. Physical Exam
2. Vitals
3. ECOG performance status
4. Laboratory Assessments (CBC with differential, CMP, INR +/- AFP or CEA as indicated)
5. Clinical assessment of toxicity
6. Triple-phase CT or eovist MRI
7. HIDA scan

9.0 TREATMENT PLAN

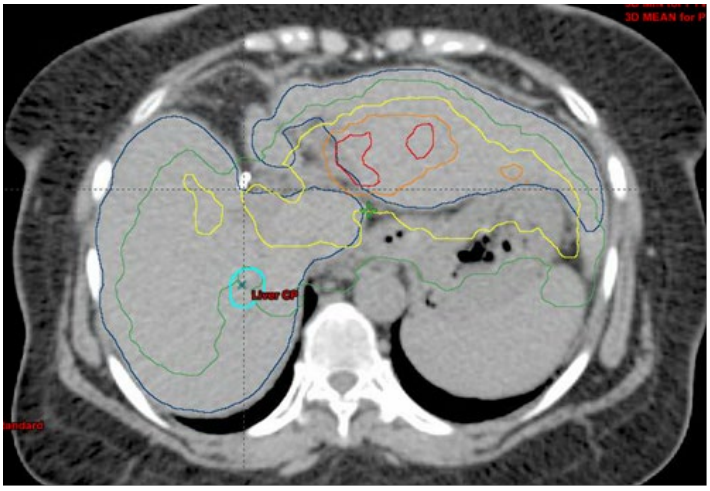
9.1 Overview

Each subject will have two radiation treatment plans created after enrollment and prior to start of radiation treatment during the simulation period. One treatment plan will follow the standard of care planning for SBRT. The second plan will incorporate functional data from the HIDA scan with the standard SBRT treatment plan. As per standard protocol, the 2 plans for a given subject will be evaluated by a dose-volume histogram to ensure SBRT constraints are met. A functional DVH will also be analyzed in order to allow a comparison of the potential relative sparing of function that the plan in which the functional data was accounted for provides.

In the HIDA-guided plan, the target will be identical and the dose to the target will not change compared with a conventionally planned SBRT plan. Tumor coverage will be equivalent between both plans. Although HIDA-guided SBRT planning may result in changes in the geometric beam arrangement and the relative weighting of beams in order to attempt to increase sparing of functional liver, HIDA-guided planning will not result in any changes to the delineated tumor target nor in the accepted level of dosimetric coverage of the tumor target itself.

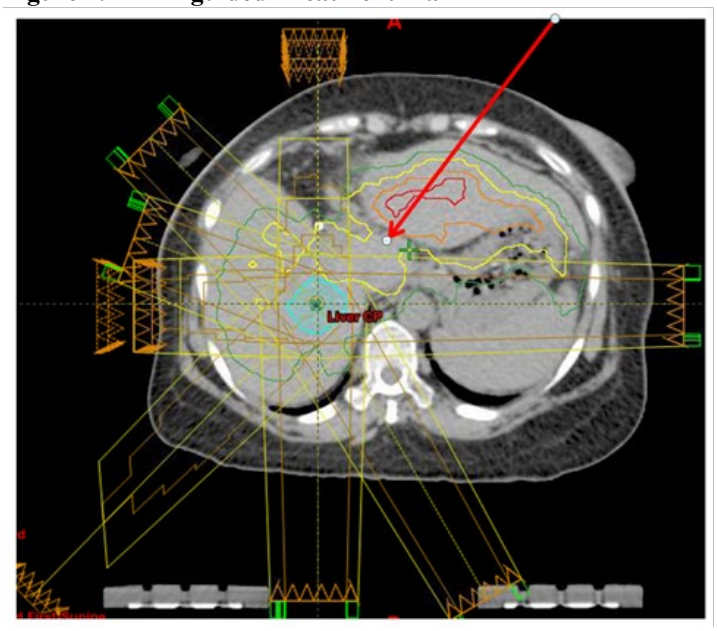
The HIDA scan will be “fused” (overlaid) over the patient’s treatment planning CT, and contours that delineate areas of differing liver function will be created. The first step in contouring is the delineation of the tumor. An example of this can be found in Figure 1 below. The tumor is shown as the turquoise-colored volume in the posterior right lobe, and the liver is indicated by the dark blue contour. The HIDA scan data will then be utilized to create contours delineating areas of higher- and lower-functioning liver. The example in Figure 1 shows contours corresponding to liver function (i.e., % maximum uptake as depicted by the HIDA scan. Here, 25%-50% max (green), 50-75% max (yellow), 75-90% max (orange), 90-100% max (red). In this case, the left lobe of the patient’s liver was providing the majority of her liver function. Therefore, the HIDA scan suggests that the left lobe of the liver should be avoided, as segments 1-4 are shown to contribute more to liver function than the right lobe of the liver.

Figure 1. HIDA-guided Contouring



Once the treatment targets and avoidance structures are contoured, the treatment planning process will begin. Generally, SBRT plans use 8-10 beams arranged at various angles around the body. The use of multiple beams allows the weight of each beam to be varied in order to deliver a highly conformal radiation plan (i.e., a plan in which the prescription isodose lines closely match the target contour). Figure 2 below demonstrates a treatment plan using the HIDA data which shows that no beam would be directed at the tumor from the left anterior oblique (LAO) angle (red arrow) in order to spare the large island of functional liver tissue in the left lobe. Without the extra information provided by the HIDA scan, a non-theragnostically planned SBRT plan likely would have used a beam arrangement that did not avoid the area of functional liver tissue in question, thereby increasing the radiation dose to functional liver tissue.

Figure 2. HIDA-guided Treatment Plan



9.2 Research Imaging Protocols

1. HIDA scan
2. MRI with Eovist contrast of abdomen and pelvis

9.3 Simulation Protocol

1. Conventional or CT flurosocopy in SBRT frame with or without abdominal compression to attempt to limit diaphragmatic motion to <1 cm.
2. CT with IV contrast (multi-phase as indicated per treating MD), supine in treatment position, 3 mm slices, per institutional protocol
3. 4D CT simulation to account for tumor motion with respiration

9.4 Radiation Planning

Standard Target Contouring guidelines

1. GTV is contoured based on CT obtained during simulation and any previous CT, MRI, or PET scans.
2. The internal target volume (ITV) will account for tumor motion as seen on 4D-CT. Viewing the lesion on individual phases may be necessary in order to adequately delineate the lesion.
3. The planning target volume (PTV) will account for set-up error and will be created by expanding the ITV 1 cm cranio-caudally and 0.5 cm radially, unless less motion can be documented on simulation scans.

Contouring from the HIDA scan

1. Based on the HIDA scan data, contours of relative functional liver will be created based on the following thresholds of maximum intensity: 0-25% maximum, 25-100% maximum, 50-100% maximum, 75-100% maximum. These structures will serve as avoidance structures in the design of radiation fields for theragnostic SBRT planning.

Standard SBRT

The standard SBRT prescription, planning, constraints, and treatment parameters are as follows:

1. Prescription**:**
   3- or 5-fraction SBRT will be utilized in this study depending on clinical scenario. It is recommended that subjects without cirrhosis or with CTP A disease are treated with 3 fractions and those with CTP B cirrhosis are treated with 5 fractions. The dose range typically will be from 4000-5400 cGy delivered over 3-5 fractions.

2. Planning**:**
   SBRT; IMRT if constraints not met or for additional functional sparing.

3. SBRT Constraints:

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

a. Variation acceptable constraints (per RTOG 1112)

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

4. Treatment Parameters:
   a. Fractionation: All subjects will have at least 48 hrs between fractions. This may be extended to weekly treatments at the treating physician's discretion.
   b. Image Guidance: Daily cone beam CT scan

10.0 STUDY CALENDAR

	Baseline	Post-Consult	Mid way through RT	End of treatment visit	Follow up
	-4 weeks of Registration	After consult and prior to treatment	Fraction 2 or 3[A]	30 ± 7 days post last treatment	3, 6, and 12-month post-RT
Informed Consent	X				
History	X				
Physical	X				X[B]
Vitals (ht, wt, bp)	X				X
Clinical Assessment			X[C]		
ECOG score	X				X
CBC w/ diff, platelets, CMP, INR	X		X[D]	X	X
AFP or CEA as indicated	X				X
Urine pregnancy test	X[E]				
CTP, MELD, and ALBI scores	X		X		
CT Simulation Scan		X			
MRI with Eovist of abdomen and/or Triple Phase ABD CTG		X[F]			X
HIDA scan		X[F]	X		X

[A] Subjects who have a total of 3 fractions will have Midway Assessments done at fraction 2. Subjects who have a total of 5 fractions will have Midway Assessments at fraction 3.
[B] Physical Exam required for Follow up visits. History not required.
[C] Subjects will be seen at least once per week during their course of RT for clinical assessment. This will include a limited physical exam and toxicity assessment.
[D] Labs may be monitored more frequently per the treating physician's discretion.
[E] Only required in female subjects of child bearing potential
[F] HIDA or Eovist MRIs obtained prior to consult can be used if performed within 8 weeks of simulation.
[G] Imaging evaluation to be determined by treating MD depending on patient's clinical situation. For Ex: some patients may have a contraindication to a certain imaging modality (e.g.CT contract allergy). As long as the patient undergoes follow-up imaging, the use of CT vs. MRI for imaging follow up will not be considered a protocol deviation

11.0 TOXICITIES TO BE MONITORED/DOSAGE MODIFICATIONS

All subjects will have laboratory evaluation prior to initiation of treatment. This includes CBC with differential, platelets, CMP, and INR.. Radiation treatment will be suspended in subjects who develop new ascites (as indicated by abdominal ultrasound, CT scan, or physical exam) or encephalopathy. If the patient's clinical status is borderline and the treating physician determines a treatment break is necessary, re-evaluation for further treatment can occur 1-2 days later.

	CTP-A	**CTP-B7**
Total Bilirubin	<3	<4
Albumin	>2.5	>2.5
INR	<1.5X upper normal	PT > 6 seconds above normal
ANC	>1000	>1000
Platelets	>50,000	>50,000
Hgb	>9	>9
Ascites	none	none
Encephalopathy	none	none

The subject will be seen at least once weekly during treatment for assessment of side effects. The most current version of Common Terminology Criteria for Adverse Events (CTCAE) will be used for grading toxicity.
For the purposes of this study, we will monitor the following:

- Labs: AST, ALT, Alkaline phosphatase, bilirubin, INR, platelets, albumin, lymphocytes, sodium
- Hepatobiliary disorders: hepatic failure, hepatic hemorrhage, hepatic necrosis, hepatic pain, perforation of bile duct, portal hypertension, portal vein thrombosis, bile duct stenosis, biliary fistula, cholecystitis, gallbladder fistula
- Gastrointestinal disorders: ascites, duodenal hemorrhage, duodenal obstruction, duodenal perforation, duodenal stenosis, duodenal ulcer, gastric necrosis, gastric perforation, gastric stenosis, gastric ulcer
- Nevous system disorders: encephalopathy
- Musculoskeletal and connective tissue disorders: chestwall pain
- Renal and urinary disorders: acute kidney injury

A copy of the most current CTCAE version is available at http://ctep.cancer.gov/reporting/

12.0 CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

Every subject should be encouraged to remain in the study. Possible reasons for early withdrawal may include, but are not limited to, the following:

1. Withdrawal of consent – Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the source documentation.

2. Principal Investigator and/or treating physician discretion – The Principal Investigator and/or treating physician may choose to withdraw a subject from the study if there are safety or other concerns.
3. Subject becomes pregnant.
4. Subject non-compliance.
5. Subject lost to follow-up.
6. Subject death.

13.0 STATISTICAL METHODS

13.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below.

13.2 Study Design

This is a pilot non-randomized study.

13.3 Analysis Population

13.3.1 Enrolled Population

The enrolled population comprises all subjects who meet the eligibility criteria and are registered onto the study.

13.3.2 Safety Population

The safety population comprises all subjects who have received at least one dose of radiation. This set will be used for safety analysis.

13.3.3 Efficacy Population

The efficacy population comprises all subjects who have received at least one dose of radiation, and have been evaluated for the primary endpoint. This population will be used for efficacy analysis.

13.4 Sample Size

20 subjects will be enrolled with the goal of 15 evaluable subjects who have one month follow-up information available. Although Child-Turcotte-Pugh A and Child-Turcotte-Pugh B7 patients are both included, they will not be analyzed separately.

The next possible step would be a Phase I trial that incorporates the data from HIDA- and functional MRI-guided radiation planning in order to permit dose escalation in liver SBRT as well as the treatment of patients with poor liver function, who are not currently SBRT candidates. As the technique of functionally guided radiation has not been previously used in the treatment of liver

tumors, a 5% relative improvement in functional reserve of the liver will be considered as beneficial. If the use of HIDA scans shows beneficial functional reserve of the liver in at least 3 of 15 of the subjects, this will help encourage further study on the use of HIDA scans for planning. If the true rate of HIDA in improving functional reserve by 5% is at least 30% or higher, we will have 87% probability detecting it with this rule:

True probability HIDA is better than conventional plan by 5%	.1	.2	.25	.3	.4	.5
Probability of seeing at least 3 where HIDA is better	0.18	0.60	0.76	0.87	0.97	≥0.99

13.5 Subject Characteristics and Significant Protocol Violations

Baseline subject characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics (Child-Turcotte-Pugh score, functional liver assessments).
Significant protocol violations such as with respect to eligibility criteria and treatment plan will be tabulated.

13.6 Analysis of Primary Objective

The efficacy set will be used for all the efficacy analysis, unless otherwise noted. For the primary endpoint of difference of functional reserve of liver, the value will be calculated for each subject and described by basic summary statistics. The summary statistics will be displayed overall and by each plan chosen.

13.7 Analysis of Secondary Objectives

The rate at which the plan that utilized the HIDA scan is chosen for the actual treatment will be summarized along with the corresponding exact 95% Binomial confidence interval.

For Local Control, PFS, OS, time to transplant, time to distant liver failure, and time to salvage treatment, the median and the corresponding two-sided 95% confidence intervals will be calculated using the Kaplan-Meier method. Estimates and 95% confidence intervals will also be provided for 6 and 12 months. Local control will be evaluated using RECIST 1.1 criteria.

Changes in liver function tests using HIDA scans, standard blood tests and CTP score will be calculated and summarized. Additionally, all safety data will be listed. For the treatment-emergent AEs, namely AEs started or worsened during the on-treatment period, the incidence will be summarized by system organ class and/or preferred term, severity based on CTCAE grades, type of adverse event and the relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by and tabulated by type of adverse event. This will be done with the safety set.

Changes in liver volume in the treated and untreated segments will be summarized by basic summary statistics.

13.8 Analysis of Exploratory Objectives

To assess the correlation between the radiation dose and the risk of RILD, graphs and descriptive statistics will be used to see if any relationships may exist.

Spearman's correlations will be used to compare output from each of the HIDA and fMRI scans to see if any measures correlate to each other.

To assess significant change in HIDA and fMRI scans, the plan based off the HIDA scan done at mid-therapy would be re-optimized, retrospectively. The proportion of patients who have a change in the regional distribution of function after the initial radiation treatments will be determined. If this re-optimized plan reduces the functional liver exposed to <15 Gy by 5% or more, this would be considered significant and will provide a potential idea about the feasibility of potential adaptive radiotherapy.

13.9 Interim Analysis

No interim analysis will be performed for this study.

14.0 DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore®**.** The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCC Clinical Trials Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11.

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

All source documents are to remain in the subject's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center Data Safety Monitoring Committee.

15.0 SUBJECT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any subject being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

16.0 DATA AND SAFETY MONITORING PLAN

Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** for moderate risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Monthly** meeting summaries should include review of data, the number of patients, significant toxicities as

described in the protocol, and responses observed. Summaries will be submitted and reviewed monthly by the DSMC. Submit to DSMC@iupui.edu.

Study Auditing and Monitoring
All trials conducted at the IUSCC are subject to auditing and/or monitoring. Reports will be reviewed by the full DSMC at the time of study review (Reference Risk Table in full DSMC Charter).

Early Study Closure
At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the investigator reports.

Reporting Guidelines
The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

Reporting Death
Death will be reported per local IRB reporting guidelines (Section 5.8 of the Unanticipated Problems and Noncompliance SOP).

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

Protocol Deviations
Protocol deviations are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

17.0 REPORTING ADVERSE EVENTS

17.1 Definitions of Adverse Events

17.1.1 Adverse Event (AE)
Any untoward medical occurrence in a subject, not necessarily having a causal relationship with the study. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the study, whether or not related to the study.

17.1.2 Serious Adverse Event (SAE)
A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

1) Results in death or ANY death occurring within 28 days of date of study intervention (even if it is not felt to be study related)

2) Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3) Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization
    - **NOTE**: Hospitalizations that are not considered SAEs are:
        - Hospitalization planned prior to first study intervention
        - Hospitalization less than 24 hours
        - Hospitalization for elective treatment of a pre-existing condition unrelated to the study intervention
4) Results in persistent or significant disability/incapacity
5) Is a congenital anomaly or birth defect
6) Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

17.1.3 Unexpected Adverse Event
An adverse event not associated as a known risk or adverse event.

17.2 Determining Attribution to the Investigational Procedure

Attribution: An assessment of the relationship between the AE and the study intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

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

17.3 Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

Adverse events (AEs) will be recorded from the time of first study intervention and throughout the follow up period. All AEs considered related to the study intervention will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-study. Any death occurring within 30 days after the last study intervention must be reported as an SAE regardless of attribution.

17.3.1 Reporting to the IRB:

1. Unanticipated problems involving risks to subjects or others will be reported promptly to the IRB if they:
    - Unexpected;
    - Related or possibly related to participation in the research; and
    - Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

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

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

17.3.2 Reporting to the Data Safety Monitoring Committee (DSMC):
Regardless of study sponsorship, this study is subject to monitoring by the Indiana University Simon Cancer Center Data Safety Monitoring Committee (DSMC). The DSMC chair and/or coordinator will review all expedited SAE reports through OnCore®. Expedited reports are completed per IRB guidelines and may include the IRB prompt reporting form, non-compliance form, AdEERS reports, MedWatch, and additional SAE forms as required by the sponsor. Submission of this information to the DSMC is additional to any other protocol-specified regulatory bodies (e.g., FDA, pharmaceutical company) to be notified. When follow-up information is received, a follow-up report should also be created in OnCore®. The DSMC chair and/or coordinator will review expedited SAE reports monthly and report findings to the DSMC quarterly.

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APPENDIX 1: Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows

Measurable Lesions:

Tumor lesions – Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes:

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

Non-measurable Lesions:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Baseline documentation of "Target" and "Non-Target" lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means if a patient has only one or two organ sites involved, a maximum of two and four lesions, respectively, will be recorded.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm·x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 but < 15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Sum of Diameters
A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. As noted above, if lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Evaluation of Target Lesions

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm)
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. NOTE: the appearance of one or more new lesions is also considered progression.

Special notes on assessment of target lesions

Lymph nodes:
Target lesion lymph nodes should always have the short axis measurement recorded (measured in the same anatomical plane as the baseline exam), even if the nodes regress to below 10 mm. Thus, when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure':
All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may report them as 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is

the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (derived from 5 mm slice thickness). Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well. However, if the radiologist is able to provide an actual measurement, it should be recorded even if it is below 5 mm.

Lesions that split or coalesce on treatment:
When non-nodal lesion 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

Response	Evaluation of Non-Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Special notes on assessment of progression of non-target disease

When the patient also has measurable disease
In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease
This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in

lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial

New Lesions

There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Target Lesions	Non-Target Lesions	New Lesion?	Best Overall Response
CR	CR	No	CR
CR	Non CR/ Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD