

NRG ONCOLOGY

NRG-GI001

ClinicalTrials.gov NCT02200042

RANDOMIZED PHASE III STUDY OF FOCAL RADIATION THERAPY FOR UNRESECTABLE, LOCALIZED INTRAHEPATIC CHOLANGIOCARCINOMA

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, and SWOG.

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Protocol Agent (Not Applicable) (3/20/17)

Agent	Supply	NSC #	IND #
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Participating Sites

- U.S. Only
- Canada Only
- U.S. and Canada
- Approved International Member Sites

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CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (3/20/17)		
For regulatory requirements:	For patient enrollments:	For study data submission:
<p>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.</p> <p>Regulatory Submission Portal: (Sign in at www.ctsuo.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)</p> <p>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.</p> <p>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsuo.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsuocontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsuo.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</p>		
<p><u>For clinical questions (i.e. patient eligibility or treatment-related):</u> Contact the Study PI of the Lead Protocol Organization.</p>		
<p><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsuocontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Website is located at https://www.ctsuo.org.</p>		

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Randomized Phase III Study of Focal Radiation Therapy for Unresectable, Localized Intrahepatic Cholangiocarcinoma

SCHEMA (3/20/17)

Non-progressing patients who have completed 6 months of Gemcitabine/Cisplatin per institutional standard*	S T R A T I F Y	Tumor size (≤ 6cm vs. > 6cm) Satellite lesions (Yes vs. no) Months of chemo completed (4-5 vs 6)	R A N D O M I Z E	Arm 1: Liver-directed Radiation Therapy Vs. Arm 2: Observation Randomization ratio (RT:Observation) = 2:1
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* Must have received 6 months of Gemcitabine/Cisplatin chemotherapy without progression. If toxicity precludes 6 months of chemotherapy, at least 4 months of Gemcitabine/Cisplatin must have been administered.

See [Section 5.0](#) for credentialing requirements, [Section 6.0](#) for radiation therapy details.

Patient Population: (See [Section 3.0](#) for Eligibility)

Required Sample Size: 146 patients

Questions that need to be answered at the time of study entry on the OPEN system are available at: <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1320>

1.0 INTRODUCTION

1.1 Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (IHC) is a rare gastrointestinal malignancy accounting for 5-20% of primary liver malignancies. The incidence of IHC is rising in the United States and Asia. The prognosis of this disease remains dismal with a median survival of 19 months and long term survivors continue to be rare events (Shaib 2004; Endo 2008). This is partially due to the late manifestation of clinically significant signs or symptoms given the multiple drainage options around the tumor and the ability of the liver to compensate for the atrophic obstructed liver parenchyma. Complete resection remains the main treatment modality with curative intent. For patients with unresectable disease, the median survival is between 2.3 to 9 months (Endo 2008; Ohtsuka 2002). Currently, the majority of intrahepatic cholangiocarcinoma patients are still unresectable (68%). Multiple intrahepatic tumors, locally advanced disease within the liver with vascular invasion, and nodal or distant metastatic disease are the most common reasons for unresectability (Endo 2008). Multiple intrahepatic tumors, locally advanced disease within the liver with vascular invasion, and nodal or distant metastatic disease are the most common reasons for unresectability (Endo 2008).

1.2 Local-Regional Treatments for IHC

Currently, the standard of care for unresectable IHC is a combination of chemotherapy with gemcitabine and cisplatin (gem/cis), based on the results of the ABC-02 trial demonstrating a 3 month improvement in overall survival compared to gemcitabine alone (Valle 2010). Median PFS was improved from 5 months to 8 months. Interestingly, there is no current standard for local, liver-directed therapy, in spite of the observation that the primary tumor is the first site of progression in up to 70% of patients.

Small single institution series have suggested that radiation therapy is beneficial to patients with IHC (Chen 2010; Tse 2008). However, the benefit of liver-directed radiation therapy has never been formally tested.

1.3 Gemcitabine/Cisplatin

Gem/cisplatin as a control arm- chemotherapy backbone

The ABC-02 trial was a phase III study which randomized 410 patients with advanced biliary cancer to gemcitabine vs. gem/cis. Patients treated with gem/cis had an improvement in OS (8.1 vs. 11.7 months, $p < 0.001$) and PFS (5.0 vs. 8.0 months, $p < 0.001$). Based on this pivotal trial, gem/cisplatin is now the standard of care for unresectable biliary cancers.

1.4 Radiation Therapy (3/20/17)

Radiation therapy for localized intrahepatic cholangiocarcinoma cancer

The current literature for radiation therapy for unresectable, localized cholangiocarcinoma is limited. Below is a review of the available literature identified in PubMed.

The Fudan University Experience

The role of radiation therapy for intrahepatic cholangiocarcinoma from Fudan University was first reported in 2006 (Zeng 2006) and updated in 2010 (Chen 2010). As of the most recent update, 84 patients with biopsy confirmed, unresectable intrahepatic cholangiocarcinoma were retrospectively evaluated. Patients were deemed to have intrahepatic cholangiocarcinoma by IHC (CK 7, 19 + and CK 20, AFP, Hepa -) and negative evaluation by staging for other GI primaries. Patients with Child-Pugh C cirrhosis were excluded from analysis. In this study, 35 patients received radiotherapy, and 49 patients did not. There was no difference between the two groups in regards to age, gender, stage, size, multifocality, or size of tumor. Radiation was given to the gross disease in 1.8-2.0 Gy/fraction to a dose of 30-60 Gy. Fourteen percent of patients received less than 50 Gy, 60% received 50 Gy, and 26% of patients received over 50 Gy. 8.6% of patients achieved a radiographic complete response, and 28.5% achieved a partial response for a response rate of 37.1%. SD was observed in and additional 17 patients (48.6%). Disease

control was achieved at the time of first follow up in 85.7%. One year survival for the radiation group and non-radiation groups were 38.5% versus 16.4%. Two year survival for the radiation group and non-radiation groups were 9.6% versus 4.9%, respectively. Median survival times were 9.5 ± 1.1 months versus 5.1 ± 0.3 months, respectively (log-rank $P = 0.003$). These poor survivals are a reflection of the lack of use of chemotherapy in this study. This study is severely limited by the heterogeneous population, the lack of chemotherapy, the retrospective nature, and heterogeneous radiotherapy dose. However, this study suggests that radiotherapy may have some benefit in patients with intrahepatic cholangiocarcinoma

SEER data

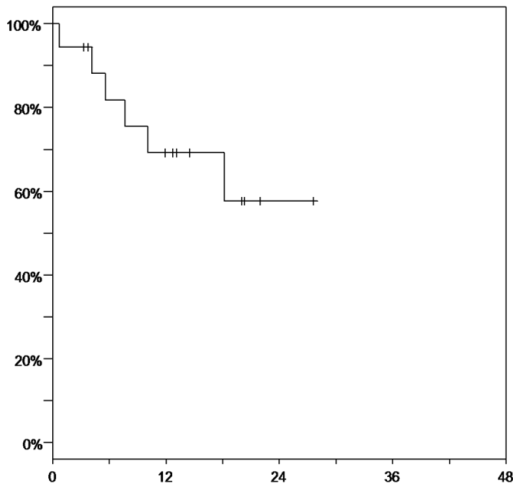
A retrospective study of 3,839 patients with intrahepatic cholangiocarcinoma was evaluated from the Surveillance, Epidemiology, and End Results (SEER) database (Shinohara 2008). Restricting analysis to patients who did not have surgery, patients receiving radiation had a median survival of 7 months, compared to 3 months with no radiation therapy. Propensity score adjusted hazard ratios (controlling for age, race/ethnicity, stage, and year of diagnosis) remained significant for radiation therapy (HR = 0.67; CI 95% 0.58-0.76). This analysis is limited by the lack of chemotherapy data and the retrospective nature of the study.

Princess Margaret SBRT Phase I study

A phase I study of 41 patients with primary liver tumors evaluated individualized stereotactic body radiotherapy (SBRT) (Tse 2008). Patients deemed not suitable for standard therapy, with Childs Pugh A cirrhosis were treated with a 6 fraction SBRT course individualized based on a 5%, 10%, and 20% risk of toxicity. Thirty one patients had hepatocellular carcinoma (HCC) and 10 patients had intrahepatic cholangiocarcinoma. The median dose delivered was 36 Gy (24-54 Gy). In the patients with intrahepatic cholangiocarcinoma, the median survival was 15.0 months, and the 1 year overall survival was 58%. Two out of ten patients with intrahepatic cholangiocarcinoma experienced unexpected transient biliary obstruction, presumably due to radiation edema.

MGH/MDACC Phase II (ongoing, unpublished)

Massachusetts General Hospital (MGH) has been treating patients with intrahepatic cholangiocarcinoma on two proton-based studies. In the first study (NCT 00465023), 15 patients with HCC, intrahepatic cholangiocarcinoma were treated on a pilot study, with doses ranging from 45-75 Gy in 15 fractions. Following this study, a phase II study, currently ongoing, was initiated at MGH and MD Anderson (NCT 00976898). On the phase II, patients with peripheral tumors received 67.5 Gy in 15 fractions. Patients with central tumors (defined as within 2 cm of the portahepatis) received 58.05 Gy in 15 fractions. No concurrent chemotherapy was given. The phase II opened in April 2010 and to this point 57 patients have been enrolled. Twenty one patients with IHC have been enrolled as of February 2013. For this analysis, 21 patients have been treated and have had one set of 3 month staging scans. With a median follow up 12 months among surviving patients, a 1 and 2-year OS is 69% and 58% respectively and PFS is 41% and 28% respectively.

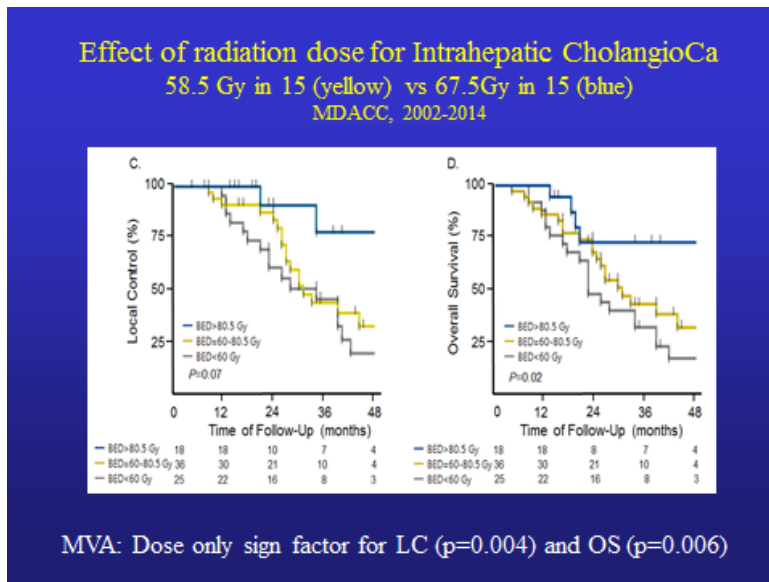


Overall Survival,
MGH/MDACC phase II interim
analysis (months)

Rationale for the 15 fraction conformal radiation alone schedule

Conventional chemoradiation (50-54 Gy in 1.8-2.0 Gy/fraction with concurrent fluoropyrimidine) is the most widely used regimen for gastrointestinal cancers, but without surgery, the schedule has limited efficacy and ablative potential. The SBRT approach used at Princess Margaret has ablative intent. However, given the biliary events seen in 20% of the intrahepatic cholangiocarcinoma patients, as well as the concern for late biliary strictures, the extreme hypofractionated regimen has some potential safety issues.

The 15 fraction schedule used in the MGH/MDACC phase II is associated with excellent efficacy. In the original pilot study, there were no local recurrences in the 15 patients treated (11 HCC, 3 intrahepatic cholangiocarcinoma, 1 hepatic metastasis) with no late liver or biliary toxicity.



58.5 Gy in 15 (yellow) vs. 67.5 in 15 (blue) - There are 50% local failures compared to 20% with 67.5 Gy at 4 years based on the MDACC study. (MDACC, 2002-2014 the results of this study have been submitted for publication.)

(3/20/17)

2.0 OBJECTIVES

2.1 Primary Objective (3/20/17)

- 2.1.1 To evaluate liver-directed radiation therapy with respect to overall survival (OS) for patients with unresectable, localized intrahepatic cholangiocarcinoma.

2.2 Secondary Objectives (3/20/17)

- 2.2.1. To evaluate liver-directed radiation therapy with respect to local control for patients with unresectable, localized intrahepatic cholangiocarcinoma.
- 2.2.2 To evaluate liver-directed radiation therapy with respect to adverse events for patients with unresectable, localized intrahepatic cholangiocarcinoma.
- 2.2.3 To evaluate liver-directed radiation therapy with respect to regional control for patients with unresectable, localized intrahepatic cholangiocarcinoma.
- 2.2.4 To evaluate liver-directed radiation therapy with respect to distant metastases for patients with unresectable, localized intrahepatic cholangiocarcinoma.
- 2.2.5 To evaluate liver-directed radiation therapy with respect to progression-free survival for patients with unresectable, localized intrahepatic cholangiocarcinoma.

3.0 PATIENT SELECTION (3/20/17)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

Questions that need to be answered at the time of study entry on the OPEN system are available at: <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1320>

3.1 Conditions for Patient Eligibility

For questions concerning eligibility, please contact the study data manager.

- 3.1.1 Pathologically (histologically or cytologically) proven diagnosis of IHC without distant extrahepatic metastasis prior to study entry. Patients with an adenocarcinoma suggestive of a pancreaticobiliary primary with radiographic findings consistent with an intrahepatic cholangiocarcinoma are eligible.
- 3.1.2 Patient must have 1 lesion with a maximum AXIAL diameter of 12cm at the time of study entry. Up to 3 satellite lesions are permitted. Satellite lesions, are defined as lesions less than 2 cm that are within 1 cm of the periphery of the dominant lesion (GTV) are permitted. The satellite lesions are NOT included in the AXIAL diameter measurement. Regional Lymph Node involvement within the porta hepatis (as medial as SMV portal vein confluence) is permitted if nodes are deemed clinically positive (i.e. FDG avid) See [Appendix V](#);
- 3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:
- Pre-study entry Scan (REQUIRED for All Patients to confirm no progression): CT scan chest/abdomen/pelvis with multiphasic liver CT scan within 30 days prior to study entry. If CT contrast is contraindicated, CT chest without contrast and MRI of abdomen and pelvis is permitted (See [Appendix IV](#) and [Section 4.1.5](#) for details);
- 3.1.4 Zubrod Performance Status 0-1 at the time of study entry;
- 3.1.5 Age \geq 18;
- 3.1.6 CBC/differential obtained within 21 days prior to study entry, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) \geq 1,000 cells/mm³;
 - Platelets \geq 75,000 cells/mm³;
 - Total bilirubin < 2.5 mg/dl;
 - AST (SGOT) and ALT (SGPT) < 5.0 X institutional upper limit of normal;
 - Albumin \geq 2.5mg/dl;
 - Creatinine within normal institutional limits or creatinine clearance \geq 60mL/min/1.73 m² for subject with creatinine levels above institutional normal;
 - Hemoglobin \geq 9.0 g/dl. (Note: The use of transfusion or other intervention to achieve Hgb \geq 9.0 g/dl is acceptable.)

- 3.1.7 Patient must provide study specific informed consent prior to study entry;
- 3.1.8 Negative bHCG prior to study entry if patient is pre or peri-menopausal.
- 3.1.9 Must have received 6 months of Gemcitabine/Cisplatin chemotherapy without progression. Disease response to chemotherapy is also permitted. If toxicity precludes 6 months of chemotherapy at least 4 months of Gemcitabine/Cisplatin must have been administered.

3.2 Conditions for Patient Ineligibility (3/20/17)

- 3.2.1 Multiple lesions that don't meet the criteria as satellite lesions as defined in [Section 3.1.2](#);
- 3.2.2 Extrahepatic metastases or malignant nodes beyond the periportal region. Celiac, pancreaticoduodenal and para-aortic nodes > 2 cm are ineligible. Note that benign non-enhancing periportal lymphadenopathy is not unusual in the presence of hepatitis and is permitted, even if the sum of enlarged nodes is > 2.0 cm;
- 3.2.3 Hepatic insufficiency resulting in clinical jaundice, encephalopathy and/or variceal bleed at the time of study entry;
- 3.2.4 Prior radiotherapy to the region of the liver that would result in overlap of radiation therapy fields;
- 3.2.5 Prior selective internal radiotherapy/hepatic arterial Yttrium therapy, at any time;
- 3.2.6 Direct tumor extension into the stomach, duodenum, small bowel or large bowel;
- 3.2.7 Prior invasive malignancy, excluding the current diagnosis, (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years. (Note: carcinoma in situ of the breast, oral cavity, or cervix is all permissible);
- 3.2.8 Prior systemic chemotherapy for the study cancer other than gemcitabine/cisplatin; note that prior chemotherapy for a different cancer is allowable;
- 3.2.9 Currently receiving other anti-cancer agents;
- 3.2.10 Participants who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin;
- 3.2.11 Prior surgery for the IHC. (Liver resection is not allowed);
- 3.2.12 Severe, active co-morbidity, defined as follows:
 - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months of study entry;
 - Transmural myocardial infarction within the last 6 months of study entry;
 - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of study entry;
 - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to study entry;
 - HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter at the time of study entry. Note also that HIV testing is not required for eligibility for this protocol;
 - End-stage renal disease (ie, on dialysis or dialysis has been recommended).
- 3.2.13 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic;
- 3.2.14 Grade 3 or higher peripheral neuropathy at the time of study entry.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (3/20/17)

See [Section 11.1](#); note that failure to perform one or more of these tests may result in assessment of a protocol violation.

- 4.1.1 Documentation of liver disease, including cirrhosis, Hepatitis history [Hepatitis B and Hepatitis C status, hemochromatosis, alcohol, autoimmune disease, non-alcoholic steatohepatitis (NASH)];

- 4.1.2 CA19-9 and CEA within 21 days prior to study entry.
- 4.1.3 Alkaline phosphatase (ALP), phosphate, sodium, potassium, chloride, magnesium, calcium within 21 days prior to study entry.
- 4.1.4 Documentation of any extrahepatic disease status, number of sites and sum of maximum diameter of extrahepatic disease.
- 4.1.5 Submission of IV contrast diagnostic or planning CT or MRI scan no later than 1 day after study entry (See [Section 3.1.3](#) and [Section 6.7](#) for details).
 - For all patients, this scan must include:
 - Contours of GTV (gross tumor volume = volume of all parenchymal and intrahepatic cholangiocarcinoma)
 - Contours of the liver (whole liver including GTV)
 - GTV Liver volume

4.2 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

- 4.2.1 If randomized to RT, consultation with interventional radiology or surgery for possible fiducial marker insertion and/or tissue expander placement to move tumor away from luminal GI structures if this is estimated to benefit the patient and center has expertise in these procedures.
- 4.2.2 For all patients, the following criteria calculated from baseline CT or MR scans (see [Section 4.1.5](#)) should be met:
 - Liver volume minus intrahepatic GTV > 700 cc.
 - Intrahepatic tumor GTV/liver volume ratio <80%.
 - Minimal distance from GTV to stomach, duodenum, small or large bowel > 1 cm.

5.0 REGISTRATION PROCEDURES

Access requirements for OPEN, Medidata Rave, and TRIAD:

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' website. To obtain an active CTEP-IAM account, go to <https://eapps-ctep.nci.nih.gov/iam>

5.1 Digital RT Data Submission to NRG Oncology Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to [Section 5.0](#) of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. Users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG website Core lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org

5.2 Pre-Registration Requirements for all Radiation Techniques (3/20/17)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study.

Proton therapy may be used on this protocol if the proton therapy treatment modality to be used has been approved by the Imaging and Radiation Oncology Core (IROC) Houston QA Center [formerly Radiological Physics Center (RPC)] and other credentialing procedures described above have been met. Investigators using proton therapy must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the website of IROC Houston (<http://irochouston.mdanderson.org>).

RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org				Key Information
	Treatment Modality				
	SBRT	3DCRT	IMRT	Proton	
Facility Questionnaire	X	X	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	X	X	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Knowledge Assessment	N/A	N/A	N/A	N/A	
Benchmark Cases	N/A	N/A	N/A	N/A	

Phantom Irradiation	X	X	X	X	A liver phantom study provided by the IROC QA Center Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used. Tomotherapy, Cyberknife and proton treatment delivery modalities must be credentialed individually.
IGRT Verification Study	X	X	X	X	The institution must submit a sample of verification images showing their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e., the GTV falls within the CT simulation defined PTV). The patient (“as if patient”) used for this study must have a target (or mock target) in the liver. The information submitted must include 2 IGRT datasets (from 2 treatment fractions) for a single patient and must employ the method(s) that will be used for respiratory control for patients entered from a particular institution (e.g. abdominal compression, breath hold, etc). This information with a spreadsheet (the spreadsheet is available on the IROC Houston web site: http://irochouston.mdanderson.org)
Credentialing Notification Issued to:					
Institution					IROC Houston QA Center will notify the institution and NRG Oncology that all desired credentialing requirements have been met.

If the center is already credentialed for RTOG 1112 IGRT, no further credentialing is required, as long as the same techniques that were credentialed previously are to be used for this study. The center must still complete and update a Facility Questionnaire.

5.3 Regulatory Pre-Registration Requirements (3/20/17)

5.3.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians

involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' web site. Additional information can be found on the CTEP web site at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the CTEP Associate Registration Help Desk by email at <ctepreghelp@ctep.nci.nih.gov>.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the NRG-GI001 protocol page located on the CTSU members' web site. Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NRG Oncology link to expand, then select trial protocol NRG-GI001
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for NRG-GI001 site registration:

- IRB approval letter (For sites not participating via the NCI CIRB); local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted.
- CTSU RT Facilities Inventory Form (if applicable)
NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.
- IRB/REB approved consent (International and Canadian sites only: English and native language versions*)
***Note:** Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below).

- IRB/REB assurance number renewal information as appropriate.

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsuo.org (members' area) → Regulatory Tab → Regulatory Submission Portal

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to <https://www.ctsuo.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Non-English Speaking Canadian and Non-North American Institutions:

*Translation of regulatory documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must also complete and submit the following documents via the Regulatory Submission Portal to the CTSU Regulatory Office:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.3.3 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

For institutions that **do not have an approved LOI for this protocol:**

International sites must submit an LOI to NRG Oncology to receive approval to participate in this trial. For more details see link below:

<http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx> .

For institutions that **have an approved LOI for this protocol:**

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study

5.4 Registration (5/7/15)

5.4.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eappsctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster. See Section 5.0 for obtaining a CTEP-IAM account.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' web site <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctscontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY/FUNCTIONAL IMAGING (3/20/17)

Note: See [Section 5.1](#) and [12.2](#) for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

Note: IGRT is required (see [Section 6.3.3](#))

Note: 3DCRT, IMRT, SBRT, Cobalt based IMRT/IGRT under MRI guidance, and Protons are allowed (see [Section 6.2](#)).

Note: Pre-randomization imaging submission is required (see [Section 6.7.1](#))

Note: This protocol requires pre-approval of the contours and plan PRIOR TO DELIVERY of radiation treatment for the first 2 patients for both photons and/or protons (see [Section 6.7.2](#)). Subsequent patient case submission is allowed only after approval of the first patient.

Radiation therapy must begin within 6 weeks of study entry

6.1 Dose Specifications (3/20/17)

The primary tumor(s) and any satellite lesions must be treated. **Prophylactic nodal radiation is not permitted.** A maximum of 3 satellite lesions are permitted. Please refer to [Section 3.1.2](#) for eligibility requirements of primary tumor and satellite lesions.

6.1.2 Treatment Schedule: Treatment will be delivered in 15 daily fractions. Patients will be treated weekdays. RT is to be delivered over 15 fractions delivered over 19-26 elapsed days. Variation Acceptable is 27-34 days. The allowable break between consecutive fractions is up to 3-4 days.

6.1.3 Prescription Dose (3/20/17)

Photons:

The unit absorbed dose specifications is the Gray (Gy). The prescription dose may be 67.5 Gy, 58.05 Gy, 52.5 Gy, 45 Gy, or 37.5 Gy in 15 fractions, based on normal tissue constraints (see [Section 6.1.5](#)). The lowest allowed prescription dose to the PTVs is 37.5 Gy.

PTV Prescription Dose (Gy)	Fraction size (Gy)
37.5	2.5
45	3.0
52.5	3.5
58.05	3.87
67.5	4.5

Protons

The unit for dose specification dose is Gy(RBE). Doses are expressed in units of RBE-weighted absorbed dose, D_{RBE} . For protons the RBE is taken to be 1.1. $D_{RBE} = 1.1 \times D$, where D represents the absorbed dose in Gy. The prescription dose may be 67.5 Gy (RBE), 58.05 Gy (RBE), 52.5 Gy (RBE), 45 Gy (RBE), or 37.5 Gy (RBE) in 15 fractions, based upon normal tissue constraints (see [section 6.1.5](#)). The minimal planned prescription dose to PTVs is 37.5 Gy (RBE).

PTV Prescription Dose (Gy RBE)	Fraction size (Gy RBE)
37.5	2.5
45	3.0
52.5	3.5
58.05	3.87
67.5	4.5

6.1.4 Dose Specifications

Photons

The prescription isodose must encompass 95% of PTV ($PTV V_{Rx} = 95\%$). The dose to multiple PTVs within the same patient may vary. If there are multiple PTVs, each should be planned for one of the prescription doses listed above, with each specific covering isodose planned to encompass 95% of each PTV ($PTV V_{Rx} \geq 95\%$). If a relative dose distribution is used the normalization (100% dose) is to the PTV receiving the highest prescription dose. **The highest allowable doses to the target volumes that maintain normal tissue constraints should be used (see [Section 6.1.5](#)).** A goal is that 100% of the CTV is encompassed by the prescription dose ($CTV V_{Rx} = 100\%$).

Protons

The prescription isodose (PTV $V_{Rx} = 95\%$) for the target with the highest prescribed dose must encompass 95% of PTV (PTV $V_{Rx} \geq 95\%$). The dose to multiple PTVs within the same patient may vary. If there are multiple PTVs, each must be planned for one of the prescription doses listed above, with each specific covering isodose planned to encompass at least 95% of each PTV (PTV $V_{Rx} \geq 95\%$). If a relative dose distribution is used for normalization (100% dose) is to the PTV receiving the highest prescription dose. **The highest allowable doses to the target volumes that maintain normal tissue constraints should be used (see [Section 6.1.5](#)).** A goal is that 100% of the CTV is encompassed by the prescription dose (CTV $V_{Rx} = 100\%$).

6.1.5 Dose Prescription Allocation Table (3/20/17)

The Liver PTV dose prescription is based on the volume of normal tissues irradiated (correlated with mean liver dose), as well as the proximity of stomach, duodenum, small and large bowel (GI luminal structures) to the target volumes, as normal tissue constraints must be maintained in this study (see OAR does constraints in [Section 6.5.1](#)).

In the absence of adjacent GI luminal structures that may limit dose, the PTV dose prescription should be as high as possible based on mean liver dose (MLD, defined as the mean dose to the liver minus all GTVs), with 5 potential dose levels.

Priority dose constraint Mean Liver Dose, MLD (Gy or Gy (RBE))	PTV Prescription Dose (Gy or Gy (RBE))
22 Gy	67.5Gy
24 Gy	58.05 Gy
24 Gy	52.5 Gy
24 Gy	45 Gy
27 Gy	37.5 Gy

6.1.6 If multiple PTVs are treated, the MLD should be evaluated with the prescription dose corresponding to the highest dose level of any PTV treated. Queries should be directed to the study PI.

6.2 Technical Factors (3/20/17)

6.2.1 Equipment

Photons – 3DCRT, IMRT

Megavoltage equipment with photons of at least 6 MV, capable of daily image guidance (IGRT), and intensity modulation IMRT with multileaf collimator is required. (Cobalt based IMRT/IGRT is permitted only if using the View Ray system under MRI guidance.) In the case of robotic based delivery, treatment with cones, iris, or MLC are allowed, however, the institution must be credentialed for the specific mode of delivery used. Inverse-planned IMRT, inverse-planned arc therapy, forward planned IMRT and conventional 3D-CRT are permitted.

Protons

The proton delivery system must deliver protons of sufficient energy to cover the target.

6.2.2 Image guided radiation therapy (IGRT): Daily pre-treatment IGRT is mandatory (See [Section 6.3.3](#)).

6.3 Localization, Simulation, and Immobilization (3/20/17)

6.3.1 Immobilization

Custom immobilization is recommended (e.g. With vacuum immobilization, patient positioning boards, knee cushions, and/or breath hold immobilization with active breathing control).

6.3.2 Simulation Image Acquisition

A liver protocol CT (See [Appendix IV](#)) must be obtained for treatment planning. Treatment planning CT scans are required to define GTV. Multi-phasic IV contrast is recommended for the planning CT (arterial phase and/or delayed phase imaging recommended for GTV delineation, and venous phase for portal vein thrombosis delineation). If oral contrast is used at simulation, similar timing and volume of oral contrast is suggested to be used at the time of treatment.

Exhale breath hold CT or average phase CT (from 4D CT) may be used as the baseline CT for radiation therapy planning. CT scans obtained during free breathing are strongly discouraged, but may be used if breath hold scanning is not possible for individual patients or if breathing motion is < 5 mm. CT scans used for target delineation are recommended to be multi-phase IV contrast scans obtained in exhale breath hold. Exhale breath hold is preferred as it most often is closer to the average position than inhale breath hold, and exhale is more reproducible than inhale. If IV contrast scans cannot be obtained at the time of radiation planning, IV contrast CT scans from diagnostic radiology may be fused to the primary planning dataset to aid in target definition.

If contraindications to IV CT contrast exist, contrast multiphase MR can be used to define GTV and may be fused to the primary planning dataset to aid in target definition.

Any other relevant diagnostic imaging can be imported to the planning system to aid in target delineation.

All scans used for target delineation should be fused to each other so that the livers are registered to each other for target delineation. **Registration will be performed with the best fit liver-to-liver image registration**, focusing on the region of the GTVs if deformation or rotation occurs between scans. Imaging details are in [Appendix IV](#).

It is recommended that arterial vascular contrast from the CT dataset be converted to water equivalent density if used for planning.

A maximum slice thickness of 3 mm is allowed.

6.3.3 Localization / IGRT (3/20/17)

IGRT images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. These IGRT images may include 1) three-dimensional (3D) or 4-dimensional (4D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (kV) x-ray) or 2) paired kV 2D images with fiducial markers. Planar 2D MV images are not permitted to be used as the only tool for IGRT. Daily IGRT using MRI is permitted when using Cobalt based IMRT/IGRT under MRI guidance. In all cases, the NRG Oncology/RTOG Image Guidance Guidelines must be followed.

6.3.4 Breathing Motion Assessment

Measurement of target/liver breathing motion is required, unless breath hold is to be used for liver immobilization during treatment. Motion may be assessed using 4D CT, fluoroscopy and/or cine MR.

Breathing motion management is recommended if breathing motion is > 5 mm.

Breathing motion assessed on 4DCT and adequately treated with PTV margins < 20mm is permitted without treatment time motion management (gating, tracking, ABC, etc.).

If breath hold is used for liver immobilization, Liver position reproducibility in breath hold should be measured using fluoroscopy, CT or MRI.

6.3.5 Proton Specific Guidelines

Localization, Simulation, and Immobilization Guidelines

Patients must be simulated on a CT scanner, which has been commissioned for protons. Proton compatible immobilization devices are required, as is a motion management system. Immobilization devices will not extend to the lower thorax so as to minimize proton entrance through them. For contrast-enhanced CT simulations (either breath-hold or free-breathing), **the initial CT sequence will be the non-contrast scan for proton planning purposes and the subsequent scan will be the contrast scan for contouring. All oral contrast Hounsfield units will be overridden during planning and replaced with a Hounsfield unit of 1 (electron density = 1). Hounsfield units for lipiodol, fiducials and clips will remain unchanged during planning.** Where possible the proton beam will not exit into GI mucosa. Breathing motion management is recommended if breathing motion is > 5 mm. Breathing motion assessed on 4DCT and adequately treated with PTV margins < 20mm is permitted. Shadowing of dose along a beam behind radio-opaque fiducials is negligible and can be discounted during multi-beam proton planning. Where fiducials are used for breath-hold set-up, reproducibility of breathing amplitude on days of treatment compared to simulation will be confirmed prior to treatment delivery.

A maximum slice thickness of 3 mm is allowed.

Radiation doses shall be prescribed using the protocol specified definitions for GTV and CTV. For set-up uncertainties and target motion, additional margin (including proximal and distal), smearing, and range of modulation will be added on a per beam basis. Proton treatment plans will be based upon a CT scanner for which the institution has defined an imaging protocol for protons which establishes the relationship between the CT number and the stopping power ratios.

Proton resources for this protocol include:

Michael T. Gillin, PhD
Professor
The University of Texas
MD Anderson Cancer Center
Department of Radiation Physics
Phone: 713-563-2507/Fax: 713-563-2545
mgillin@mdanderson.org

Theodore Hong, MD
Massachusetts General Hospital
100 Blossom Street
Boston, MA 00214
617-724-1159/Fax: 617-726-3603
TSHONG1@mgh.harvard.edu

6.4 Treatment Planning/Target Volumes (3/20/17)

6.4.1 The GTV is defined as all parenchymal (GTVp) and nodal IHC disease (GTVn) visualized on contrast enhanced CT and/or MRI, most often best seen on arterial phase (as peripheral hyperintensity) and/or venous or delayed phase (as hypointensity relative to liver) contrast enhancement imaging.

Nodal and parenchymal lesions can be combined if they are to be treated to the same dose into one GTVpn. Nodal lesions are to be treated to 40.5 Gy in 15 fx, unless the primary prescription dose is 37.5 Gy, in which case 37.5 Gy is acceptable. Nodal lesions may also be underdosed to 37.5 Gy to maintain normal tissue constraints.

The prescription dose should be annotated to each GTV after the final plan is complete (e.g. GTV_45 for a 45 Gy target).

6.4.2 The Clinical Target Volume (CTV)

It is expected that there will be no expansion from GTV to CTV for the majority of cases. However, CTV expansions to include regions at high risk for microscopic disease are permitted. Such CTVs may be treated to a minimal dose (37.5 Gy) or as high as the prescription dose for that GTV, at the investigator's discretion. The nomenclature follows that of the GTVs, (e.g. CTV_45 for the GTV_45).

6.4.3 The Planning Target Volume (PTV)

Photons

The Photon PTV will provide a margin around each CTV to compensate for set-up and internal organ motion. PTV nomenclature should follow CTV nomenclature guidelines. For example, PTV_45 for the PTV around the CTV_45.

A minimum PTV margin of 4 mm around each CTV is required in all directions (for example if active breathing control is used with excellent reproducibility).

The maximum permitted PTV margin of 20 mm is expected to be used uncommonly. PTV margins \leq 10 mm are a goal.

Asymmetric PTV margins are permitted. The actual PTV used will depend on motion management used, the patients' motion and reproducibility. PTVs should not be manually modified or cropped due to proximity of adjacent OARs. The PTVs include the ITV (internal target volume) that accounts for motion.

Protons

The Proton PTV will provide a margin around each CTV to compensate for uncertainties including set-up and internal organ motion, aperture margin definitions, compensator smearing, range of individual beams, and modulation width of the SOBP. PTV nomenclature should follow CTV nomenclature guidelines, in a similar manner to the photon PTV. For example, PTV_45 for the PTV around CTV_45. For protons, the annotated dose refers to the RBE weighted dose. Dose will be reported in Gy (RBE), where 1 Gy(RBE) = proton dose Gy x RBE (radiobiological effective dose), RBE = 1.1.

A minimum PTV margin of 4 mm around the CTV is required in all directions (for example if active breathing control is used with excellent reproducibility).

The maximum permitted PTV margin is 20 mm.

Asymmetric PTV margins are permitted, depending on institution motion management, individual patients' motion and reproducibility.

Additionally, the effect of variations in the set-up of the target with respect to tissue inhomogeneities (e.g., employing compensator smearing technique, beam-specific PTV etc.), or range uncertainties (e.g., by expanding the prescribed range and modulation, to create distal and proximal field margins) should be addressed in the design of treatment fields for each beam direction.

The proton distal target margin range: As suggested in ICRU Report 78, paragraph 5.1.4.4, an adjustment must be made within the beam-design algorithm to take into account the margins needed to account for uncertainties along the beam direction (i.e. range uncertainties) and those included in the traditional PTV (i.e. lateral uncertainties). The proton distal target margin range will be determined as follows:

Proton Distal Target Margin Range = distal aspect of the CTV + Range Calculation Uncertainty (generally 3.5%) + Set-up Margin + Internal Margin

6.4.4 Critical Normal Structures (3/20/17)

Note: All required structures must be labeled as listed below in the table for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

The following nomenclature is required:

Description	Name
GTVn_37.5	GTVn_3750
GTVn_40.5	GTVn_4050
GTVp_37.5	GTVp_3750
GTVp_45	GTVp_4500
GTVp_52.5	GTVp_52.5
GTVp_58.05	GTVp_5805
GTVp_67.5	GTVp_6750
CTVn_37.5	CTVn_3750
CTVn_40.5	CTVn_4050
CTVp_37.5	CTVp_3750
CTVp_45	CTVp_4500
CTVp_52.5	CTVp_52.5
CTVp_58.05	CTVp_5805
CTVp_67.5	CTVp_6750
PTVn_37.5	PTVn_3750
PTVn_40.5	PTVn_4050
PTVp_37.5	PTVp_3750
PTVp_45	PTVp_4500
PTVp_52.5	PTVp_52.5
PTVp_58.05	PTVp_5805
PTVp_67.5	PTVp_6750
Liver	Liver
Liver minus GTV	Liver_nonGTV
Esophagus	Esophagus
Stomach	Stomach
Duodenum	Duodenum
Small bowel*	SmallBowel
Large bowel*	LargeBowel
Cord*	SpinalCord
Cord PRV5 (cord +5mm)*	SpinalCord_05
R kidney	Kidney_R
L kidney	Kidney_L
Kidneys	Kidneys
External Patient Contour	External
Optional contours to be contoured if > 30 Gy is planned to include these organs include:	
Outer 0.5 cm of the body surface	SkinOAR
Chest wall*	ChestWall
Gall bladder	GallBladder
Common bile duct	CommonBileDuct
Heart	Heart

Inferior vena cava	IVC
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* At minimum, these structures are required to be contoured at the level of the PTV and over any region receiving > 10 Gy.

An upper abdominal/liver atlas, posted at the NRG Oncology/RTOG website, may be used as a guide for contouring. Note, all portions of the duodenum are recommended to be contoured.

6.4.5 Heterogeneity Corrections

All dose distributions, photon and proton, shall include corrections for tissue heterogeneities. For considerations regarding planning CT and heterogeneity correction, see [Section 6.3.2](#) (for photon planning) and [Section 6.3.5](#) (for proton planning).

6.4.6 Planning Technique

Photons

A minimum of 5 beams is recommended if using fixed field photon techniques. Beam angles may be individualized to minimize the path length through the liver and through adjacent organs at risk.

Protons

A minimum of two beams should be used. Beam angles should avoid mucosal structures and minimize the amount of liver in the beam path.

6.4.7 Planning Goals

Goals of planning are to maximize dose to the target volumes (see [Section 6.5](#)), while maintaining all normal tissue constraints (as defined in [Section 6.5](#)). Reducing the maximal dose to all luminal gastrointestinal normal tissues should be a planning priority to reduce the risk of gastrointestinal toxicity.

6.5 Critical structures dose constraints (5/7/15)

Note: All required structures must be labeled as listed in [Section 6.4.4](#) for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

Dose values in this section should be read as physical dose for photons, or RBE-weighted dose for protons, in 15 fractions (assuming RBE = 1.1). Please see the table below.

6.5.1 Mandatory dose constraints

Organ at risk	Dose (Gy or Gy RBE)
Esophagus max (to 0.5cc)	$D_{0.5cc} \leq 45$
Stomach max (to 0.5cc)	$D_{0.5cc} \leq 40$
Duodenum max (to 0.5cc)	$D_{0.5cc} \leq 45$
Small bowel max (to 0.5 cc)	$D_{0.5cc} \leq 45$
Large bowel max (to 0.5 cc)	$D_{0.5cc} \leq 48$
Cord + 5 mm max (0.5cc)	$D_{0.5cc} \leq 37.5$
Kidneys: Bilateral mean dose	$D_{0.5cc} \leq 12$ Gy
<u>Note:</u> If one kidney with mean dose > 12 Gy, the remaining (or only) kidney must have $V_{12Gy} < 10\%$.	

6.5.2 Other dose constraints (not mandatory)

Organ at risk	Dose (Gy or Gy RBE)
Stomach (to 5cc)	$D_{5cc} \leq 36$
Duodenum (to 5cc)	$D_{5cc} \leq 36$
Small Bowel (to 5cc)	$D_{5cc} \leq 36$
Heart (to 30cc)	$D_{30cc} \leq 45$
Great vessel (to 0.5cc)	$D_{0.5cc} \leq 70$
Skin (to 0.5cc)	$D_{0.5cc} \leq 48$
Chest wall (0.5cc)	$D_{0.5cc} \leq 70$
Gallbladder (0.5cc)	$D_{0.5cc} \leq 70$
Common bile duct*	$D_{0.5cc} \leq 70$

*Common bile duct max (0.5 cc) < 70 Gy (even though the bile duct is not often well visualized, it is always within the portal region and may be within high dose volumes for caudate lobe targets, so efforts to reduce hot spots in this region are warranted).

6.6 Compliance Criteria (3/20/17)

The review process for this protocol is aimed at assuring correct contouring of target and critical structures, as well as appropriate planning. These reviews should avoid violations and deviations for this protocol. Each treatment shall be judged according to the protocol guidelines, with variations and deviations defined below:

6.6.1 Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Start date after study entry	within 6 weeks	6-8 weeks	>8 weeks
Total elapsed treatment time to completion	19-26 days	27-34 days	> 34 days
Treatment interruptions	3-4 days	4-7 days	>7 days

6.6.2 GTV Contouring Compliance

Per protocol: No edits required

Variation acceptable: Variations in GTV or CTV other than deviation unacceptable

Deviation unacceptable: Definite HCC or enhancing thrombosis not contoured within GTV

6.6.3 PTV Compliance

PTV Contouring

	Minimum PTV Margin	Maximum PTV Margin
Per Protocol	≥ 4 mm	≤ 20 mm
Variation Acceptable	3 – 4 mm	20 – 25 mm
Deviation Unacceptable	< 3 mm	> 25 mm

PTV Dosimetry

Target coverage for each PTV should be considered on its own. If there are multiple tumors, the primary (dominant) PTV should be labeled #1 (e.g. PTVp 4500).

The intent is for prescription dose to cover 95% of each PTV ($V_{Rx} > 95\%$). If **PTVs are not treated as per guidelines, this is a deviation unacceptable. The PTV should be treated to as high a dose as possible, respecting normal tissue constraints (as per [Section 6.1.5](#)), as a dose response has been observed. Modifying required PTVs due to close proximity of adjacent OARs is not permitted.**

The following table describes variations and deviations in the prescription dose (dose covering 95% of the PTV, $D_{95\%, PTV}$). **Treating “per protocol” should always be the planning intent.**

PTVs (around GTVs)

	Per Protocol	Variation Acceptable	Deviation Unacceptable
$V_{100\%}(\%)$	$\geq 95\%$	$\geq 90\%$	$< 90\%$
$D_{99\%}(\%)*$	$\geq 95\%$	$\geq 90\%$	$< 90\%$
$D_{1\%}(\%)*$	$\leq 130\%$	$\leq 140\%$	$> 140\%$
$D_{0.03cc}(\%)*$	$\leq 150\%$		$\geq 150\%$
Prescription Dose (Gy)	≥ 37.5 Gy		< 37.5 Gy

- * The $D_x(\%)$ criteria are given in terms of % of PTV prescription dose. (e.g. 100% = 45 Gy for a prescription of 45 Gy for PTVp_4500)
- Note: For PTVs < 2cm from the porta-hepatic, the maximum dose is 58.05 Gy
- Note: For nodal PTVs, the dose must be 40.5 Gy unless the prescription dose is 37.5 Gy or if normal tissue constraints require underdosing to 37.5 Gy

Nodal PTVs (around non-GTVs CTVs)

	Per Protocol	Variation Acceptable	Deviation Unacceptable
$V_{100\%}(\%)$	$\geq 95\%$	$\geq 85\%$	$< 85\%$
$D_{99\%}(\%)*$	$\geq 95\%$	$\geq 85\%$	$< 85\%$
$D_{1\%}(\%)*$	$\leq 130\%$	$\leq 140\%$	$> 140\%$
$D_{0.03cc}(\%)*$	$\leq 150\%$		$\geq 150\%$
Prescription Dose (Gy)	≥ 37.5 Gy		< 37.5 Gy

- * The $D_x(\%)$ criteria are given in terms of % of PTV prescription dose. (e.g. 100% = 45 Gy for a prescription of 45 Gy for PTV_45)
- Note: For PTVs < 2cm from the porta-hepatic, the maximum dose is 58.05 Gy
- Note: For nodal PTVs, the dose must be 40.5 Gy unless the prescription dose is 37.5 Gy or if normal tissue constraints require underdosing to 37.5 Gy

Dose values in this section should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).

Note that lower doses than the dose-allocation schedule are acceptable if they are required due to adjacent GI luminal structures that may limit the deliverable dose

6.6.4 Compliance for Critical Structures (organs at risk, OARs)

If non-hepatic OARs limit the prescription dose, the highest dose (from the 5 prescription doses listed in [Section 6.1.5](#)) should be used, while maintaining OAR dose constraints.

Non-liver OARs	Per Protocol	Variation Acceptable	Deviation Unacceptable
Esophagus max (to 0.5 cc)	$D_{0.5cc} \leq 45 \text{ Gy}$	$D_{0.5cc} \leq 48 \text{ Gy}$	$D_{0.5cc} > 48 \text{ Gy}$
Stomach max (to 0.5 cc)	$D_{0.5cc} \leq 40 \text{ Gy}$	$D_{0.5cc} \leq 45 \text{ Gy}$	$D_{0.5cc} > 45 \text{ Gy}$
Duodenum max (to 0.5 cc)	$D_{0.5cc} \leq 45 \text{ Gy}$	$D_{0.5cc} \leq 48 \text{ Gy}$	$D_{0.5cc} > 48 \text{ Gy}$
Small bowel max (to 0.5 cc)	$D_{0.5cc} \leq 45 \text{ Gy}$	$D_{0.5cc} \leq 48 \text{ Gy}$	$D_{0.5cc} > 48 \text{ Gy}$
Large bowel max (to 0.5 cc)	$D_{0.5cc} \leq 48 \text{ Gy}$	$D_{0.5cc} \leq 51 \text{ Gy}$	$D_{0.5cc} > 51 \text{ Gy}$
Cord + 5 mm max (0.5cc)	$D_{0.5cc} \leq 37.5 \text{ Gy}$	$D_{0.5cc} \leq 40 \text{ Gy}$	$D_{0.5cc} > 40 \text{ Gy}$
Kidneys: Bilateral mean dose	$D_{\text{mean}} \leq 12 \text{ Gy}$	$D_{\text{mean}} \leq 15 \text{ Gy}$	$D_{\text{mean}} > 15 \text{ Gy}$
Note 1: Dose distributions not meeting the “Variation Acceptable” dose limits will be scored at Deviation Unacceptable			
Note 2: Dose values in these tables should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).			

Prescription dose	Liver (minus GTV) mean dose, D_{mean}		
	Per protocol	Variation acceptable	Deviation acceptable
67.5 Gy	22 Gy	$\leq 22.2 \text{ Gy}$	$> 22.2 \text{ Gy}$
58.05 Gy	24 Gy	$\leq 24.2 \text{ Gy}$	$> 24.2 \text{ Gy}$
52.5 Gy	24 Gy	$\leq 24.2 \text{ Gy}$	$> 24.2 \text{ Gy}$
45 Gy	24 Gy	$\leq 24.2 \text{ Gy}$	$> 24.2 \text{ Gy}$
37.5 Gy	27 Gy	$\leq 27.2 \text{ Gy}$	$> 27.2 \text{ Gy}$
Dose values in these tables should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).			

6.7 Documentation and RT Quality Assurance Requirements (5/7/15)

All digital data submission will be uploaded using TRIAD (see [Section 12.2](#)).

6.7.1 Pre-Randomization Imaging Submission for All Patients (including non-radiation patients)

For all patients randomized, submission of IV contrast CT or MR must be submitted **within one day of registration**. This imaging may be done in radiation planning CT and/or may be done on diagnostic CT or MR imported to a radiation planning system or any platform that allows organ segmentation and data transfer. The liver volume and the IHC and/or vascular thrombosis should be contoured. Any differences in the segmentation of tumor or liver or in the tumor: liver volume calculation will be recorded.

6.7.2 Pre-Treatment and Timely Review of RT Plans (5/7/15)

The first two photon and/or proton cases to be treated at the site on this protocol will have a pre-treatment review of their plans, i.e. the individual plan needs to be approved PRIOR to delivering any protocol RT treatment for patient or subsequent patients. These pre-treatment reviews are aimed at providing feedback from the co-chairs and IROC Philadelphia on the institution's imaging, contours and treatment plan. After a pre-treatment review by the PI, suggestions regarding protocol RT compliance will be forwarded to the participating institution.

In order to accomplish these reviews, digital data must be submitted in a rapid fashion. Three business days are required to complete a pre-treatment review. Feedback for the first registered patient must be received before the second patient is registered, and feedback for the second patient must be approved before the third patient is registered. Following approval of a minimum of two cases, all subsequent cases will undergo a timely review. More pre-treatment reviews will be required if deviations are seen in these reviewed plans. Thus, complete digital data must be submitted in a timely manner– at least 3 (business) days prior to planned start of therapy for pre-treatment reviews and within 5 (business) days post RT completion for timely reviews. All subsequent plans are reviewed in a timely review. Based on the results of any of the reviews described above, a request for additional pre-approval reviews might be necessary.

Liver protocol CT scan and/or MR showing the extent of the tumor with contrast is required to be submitted. If multiple phases of CT and/or MR imaging, and/or if diagnostic CTs or MR imaging, are helpful for target delineation, multiple phase imaging datasets should be submitted. A maximum of three datasets per patient is to be submitted. These datasets should be submitted, registered as they were used for target delineation, which should be with the best fit liver-to-liver image registration, focusing on the region of the PTVs if deformation or rotation occurs between scans.

6.7.3 IGRT Data Review (5/7/15)

IGRT images in treatment position for every fraction (and a table of subsequent “shifts”) are required to be archived at the site for possible future evaluation.

6.7.4 Treatment Interruptions

Treatment interruptions should be clearly documented in the patient’s treatment record. Total treatment time is recommended to be 19 days, with allowable total duration between 19 days and 26 days (see [Section 6.6.1](#)).

6.7.5 Quality Assurance Documentation For Patients Not Treated

In patients randomized to the RT arm who do not receive radiation, the intended and/or best treatment plan should be submitted with an explanation for why the patient did not start radiation therapy.

6.7.6 Planned Interim Analyses of Quality Assurance

After the first 50 patients are enrolled and/or 25 patients are randomized to the RT arm (whichever comes first), the Radiation Oncology Chair and Co-Chair, along with a delegated team from IROC Houston, will summarize all QA results. All submitted imaging datasets for both arms of the study will be reviewed as well as imaging, contouring and IHC liver strata determination. Following this analysis, modifications to education material and/or the protocol to help prevent violations and deviation for future patients, may be recommended.

Secondary reviews will occur after the first 100 and after all patients are enrolled, again with a plan to improve education material and/or the study if needed, with individual feedback to participating institutions.

6.8 **Radiation Therapy Adverse Event Reporting**

See [Section 7.6](#) for details on adverse event reporting.

6.9 **Radiation Therapy Toxicity Assessment During Therapy**

The criteria used for grading toxicities that occur on this study is the Common Toxicity Criteria (CTC) version 4.0.

Common (20-100%)

- Fatigue (which generally goes away after the radiation therapy is completed)
- Skin irritation, redness, itchiness, discomfort

Occasional (4-20%)

- Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated
- Gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes)
- Chest wall pain, rib fracture (< 10%)
- Non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease.

Rare, but serious (<3%)

- Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver.
- Permanent thrombocytopenia (<1%); this may lead to bleeding
- Kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

Patients will be assessed at least once during radiation therapy for toxicity (as per [Appendix I](#)). Radiation therapy will continue as planned as long as there is no grade 3 or 4 toxicity, bilirubin is <3 mg/dL, Child score is Child Pugh ≤7 and the treating physician recommends continuation. Otherwise, a delay in radiation therapy should occur with possible continuation of radiation if toxicity resolves as per [Section 6.10](#).

6.10 Radiation Modification Table

TOXICITY	MODIFICATION
<u>Hematologic Toxicities</u>	
grade 1 or 2	Continue radiation
grade 3	Hold radiation until ≤ grade 2, then continue
grade 4	Hold radiation 1 week and until ≤ grade 2, then continue
<u>Gastrointestinal Toxicities</u>	
grade 1 or 2 diarrhea	Continue radiation
grade ≥ 3 diarrhea	Hold radiation until improves to ≤ grade 2, then resume
grade 1 or 2 nausea or vomiting	Initiate anti-emetics prior to radiation and as needed and continue radiation
grade 3 nausea or vomiting	Hold radiation until improves to ≤ grade 2, then resume with anti-emetics prior to radiation and as needed
<u>Hepatic Dysfunction</u>	
bilirubin 1.3-3.0 mg/dL	Continue radiation
bilirubin > 3.0 mg/dL	Hold radiation until improves to ≤ 3.0, then resume
grade 1 or 2 AST or ALT	Continue radiation

grade 3, < 10x ULN AST or ALT	Continue radiation
grade 3, > 10x ULN AST or ALT	Hold radiation until improves to ≤ grade 2, then resume
grade 4 AST and ALT	Hold radiation for one week and until improves to ≤ grade 2, then resume
<u>Other non-hematologic Toxicities</u>	
grade 1, 2	Continue radiation
grade 3	Hold radiation until improves to ≤ grade 2, then resume
grade 4	Discontinue radiation

7.0 ADVERSE EVENT REPORTING REQUIREMENTS (3/20/17)

7.1 Adverse Events (3/20/17)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

All adverse events (AEs) as defined in the tables below will be reported via the CTEP Adverse Event Reporting System (CTEP-AERS) application accessed via the CTEP web site <https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865>

7.1.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

7.1.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in [section 7.6](#) will be reported in the CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in [section 7.6](#). **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.1.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.2 **CTEP-AERS Expedited Reporting Requirements (3/20/17)**

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported in CTEP-AERS, [https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Operations Center at 215-574-3191, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number

on each page. Contact the NRG Operations Center for submission details at **215-574-3191**.

- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see [Section 12.1](#)).

Arm 1 during RT: Any Phase Study Utilizing Radiation Therapy (including chemoRT studies)¹

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require

reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials:

For Arm 2, expedited adverse event reporting is not applicable; routine adverse event reporting on the case report form fulfills safety reporting requirements for all adverse events.

8.0 SURGERY

Not applicable to this trial.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy (3/20/17)

All supportive therapy for optimal medical care will be given per institutional standards

9.2 Non-permitted Supportive Therapy

None

10.0 TISSUE/SPECIMEN SUBMISSION (3/20/17)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment.

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in [Section 10.1](#) of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank – San Francisco provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue banking and translational research (recommended).

For patients who have consented to participate in the tissue/blood component of the study (See sample informed consent).

10.2 Specimen Collection for Tissue Banking and Translational Research (3/20/17)

The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Bank – San Francisco:

- 10.2.1** One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block); it does not have to be the diagnostic slide itself.)
- 10.2.2** A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block number that correspond to the Pathology Report.
 - The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- 10.2.3** A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and date of procedure information must NOT be removed from the report.
- 10.2.4** A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG protocol number and patient's case number.

Serum, plasma, whole blood, and urine will be collected at study entry. In addition Serum and Plasma should be collected at 2 months from randomization and at documented progression. The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

See Appendix VI for processing and shipping instructions

10.2.5 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.2.6 Specimen Collection Summary (3/20/17)

Specimens for Tissue Banking for Translational Research			
Specimens taken from patient:	Collected when:	Submitted as:	Shipped:
Representative H&E stained slides of the primary tumor	At study entry	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the	At study entry	Paraffin-embedded tissue block or punch	Block or punch shipped ambient

primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool		biopsy (must match the H&E slide being submitted)	
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	1) At study entry 2) At 2 months from randomization 3) At documented progression	Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	1) At study entry 2) At 2 months from randomization 3) At documented progression	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Plasma sent frozen on dry ice via overnight carrier
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	At study entry <u>Note:</u> If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note this on the ST Form.	Frozen whole blood samples containing 1 mL per aliquot in 1ml cryovials (three-five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	At study entry	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20°C or -80°C	Urine sent frozen on dry ice via overnight carrier

10.2.7 Submit materials for Tissue Banking and Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco- Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.3 Reimbursement

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program

10.4 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx> for further details.)

10.4.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank – San Francisco database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See [Appendix I](#)

11.2 Evaluation During Treatment

11.2.1 Once PD has occurred, patients need to follow the study on-treatment calendar. Documentation of all subsequent therapies should occur. The follow-up schedule post-treatment is outlined in [Appendix I](#).

11.3 Measurement of Response/Definition of Response

11.3.1 [See Appendix I](#) (Study Parameter Table). Note, response in the irradiated volume is challenging to assess before 3 months post radiation therapy due to radiation change in the surrounding liver. Even at 3 months, changes in the surrounding liver around the IHC may represent radiation treatment change, rather than tumor progression. Thus, review of images by experienced radiologists is required, as is importance of relaying radiation information to the radiologists, to avoid inaccurate labeling of progression when liver changes are due to radiation effect on the liver.

It is strongly recommended to use the same method of assessment (i.e. comparable scanners and imaging techniques) from one scan to the subsequent scans. For example, multi-phasic CT scans should be used with the same slice thickness for each follow-up scan. It would not be appropriate to compare a pre-treatment non-contrast liver MRI on a 0.5T scanner with 0.5 cm slice thickness to a post-treatment gadolinium enhanced MRI on a 3T scanner with 0.2 cm slice thickness (nor vice versa). If a patient develops a contraindication to CT IV contrast, then contrast MR may be used to follow the patient. If a patient develops a contraindication to MR IV contrast, then non-contrast MR and/or US is recommended for follow-up. Imaging details are outlined in [Appendix IV](#).

11.3.2 Response will be evaluated in this study using the international criteria proposed in the Reviewed Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 (Eur J Cancer: 2009; 45:228-247). Response will be assessed locally, with no planned central review.

Overall response will be measured (based on assessment of target lesions), as well as irradiated lesion response (defined as response of the target measurable disease included in the radiation volume).

Measurable disease is defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded), e.g. liver lesions ≥ 10 mm by CT scan with slice thickness no greater than 5 mm, nodes ≥ 15 mm in short axis by CT. All tumor measurements should be recorded in millimeters.

Non-measurable disease is defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathologic lymph node ≥ 10 mm and ≤ 15 mm) and any vascular thrombosis. Other non-measurable disease includes ascites, pleural effusions.

11.3.3 Response criteria: Evaluation of target lesions

Target lesions: All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (longest diameters).

Target irradiated lesions (for Radiation arm only): All measurable lesions up to a maximum of two lesions in the liver (including satellite), within the irradiated volume. Target lesions should be selected on the basis of their size (longest diameters) and their suitability for accurate repeated measurements. The sum of longest diameters (in any dimension) of target lesions will be used to characterize the objective tumor response.

Complete response (CR): Disappearance of all measurable target lesions. Any pathological nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least 30% decrease in the sum of the longest diameters of the target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD): At least 20% increase in sum of the longest 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. The appearance of one or more new lesions is also considered progression. Unequivocal, unambiguous progression of non-measurable disease is included as PD. Because of radiation changes may be confused for local progression, local progression of the irradiated must be seen on two consecutive scans, for a minimum total relative increase of 20% AND a minimum of 5 mm.

11.4 **Criteria for Discontinuation of Protocol Treatment (3/20/17)**

- Progression of disease as defined in [Section 11.3.3](#);
- Unacceptable adverse events, as specified in [Sections 6.0](#) and/or [7.0](#).
- Pregnancy
- Interruption in Radiation therapy ≥ 14 days

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

This study will utilize Medidata Rave® for remote data capture (RDC) of all data. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave see [Section 5.0](#) of the protocol.

Each person responsible for data entry must be on the NRG Oncology roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (elearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1 Summary of Data Submission (3/20/17)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See section 7.5 and 7.6 for information about expedited and routine reporting.

Summary of Data Submission: Refer to the CTSU website.

12.2 Summary of Dosimetry Digital Data Submission (5/7/15)

(Submit to TRIAD; see [Section 5.1](#) for account access and installation instructions)

<u>Item</u>	<u>Due</u>
Preliminary Dosimetry Information (DD) ALL CASES	
Digital Data Submission – Baseline Diagnostic CT/MRI or <u>Treatment Planning CT with IV contrast</u> submitted to TRIAD	Within 1 day of randomization
Digital data submission includes the following:	
<ul style="list-style-type: none">• Contours of Liver and IHC and /or vascular thrombosis	
ARM 1 ONLY	
<u>ITEM</u>	
<ul style="list-style-type: none">• Preliminary Dosimetry Information (DD)	
<ul style="list-style-type: none">• Digital Data Submission – Treatment Plan submitted to TRIAD exported from treatment planning machine by Physicist	
<ul style="list-style-type: none">• CT data, critical normal structures, all GTV, CTV, and PTV contours	

<ul style="list-style-type: none"> • Digital beam geometry for composite beam sets 	
<ul style="list-style-type: none"> • Doses for composite sets of concurrently treated beams 	
<ul style="list-style-type: none"> • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures MUST be labeled per the Table in Section 6.4.4 • <i>The “NRG-GI001 Datasheet” is available in the Forms section of the web site</i> http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1320. Submit via TRIAD with the digital data listed above. 	
<p>Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DDSI) located in the Core Lab Tab on the web site at http://www.rtog.org/CoreLab/TRIAD.aspx</p>	
<p><u>Note:</u> All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.</p>	
<p>Final Dosimetry Information</p>	Within 1 week of RT end
Radiotherapy Form	
Daily Treatment Record	
<p>NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.</p>	

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints (3/20/17)

13.1.1 Primary Endpoint

Overall survival (*failure: death due to any cause*)

13.1.2 Secondary Endpoints

- Local progression (*failure: per definition in [Section 11.3.3](#)*)
- Regional progression (*failure: progression of existing or appearance of new nodal disease, per definition in [Appendix V](#)*)
- Distant metastases (*failure: appearance of distant metastases*)
- Progression-free survival (*failure: local, regional, and/or distant progression, and death due to any cause*)
- Adverse events (*evaluated using CTCAE v 4.0*)

13.2 Stratification (3/20/17)

Patients will be stratified before randomization with respect to maximum tumor size (≤ 6 cm vs. >6 cm), presence of satellite lesions (yes vs. no), and months of chemotherapy completed (4-5 vs. 6). The permuted block randomization treatment allocation schema described by Zelen (1974) will be used because it balances patient factors other than institution.

13.3 Sample Size and Power Justification (3/20/17)

13.3.1 The primary hypothesis of the study is to determine if liver-directed radiation therapy results in a change in OS in patients with unresectable, localized intrahepatic cholangiocarcinoma. Patients who have received 4-6 months of gem/cis will be randomized between the radiation and no radiation treatment arms in a 2:1 fashion respectively.

The required sample size for the primary endpoint of OS is based on the following conditions:

- OS times are exponentially distributed with (at least approximately) constant hazards in both treatment arms
- The control arm will have a 2-year OS of 18% (monthly hazard of 0.0714)
- The experimental arm will have a 2-year OS of 40% (monthly hazard of 0.0382)
- Hazard ratio (experimental/control) = 0.53
- Two-sided test at $\alpha=0.05$
- Statistical power of 85%
- 4 years of accrual and 1 year of follow-up
- Two interim significance tests and a final test based on the Lan DeMets alpha/beta spending functions [Lan 1983]

Based on the conditions above and using the group sequential design method (Pocock 1977) with two interim analyses, 134 randomized patients are needed to obtain the 102 OS events required to detect the hypothesized increase in OS. Guarding against ineligibility or lack-of-data rate of up to 8%, the targeted accrual of randomized patients is 146.

13.3.2 Treatment other than the treatment arm to which the patient was randomized is not permitted per the protocol and will be considered non-compliant. However, as this will not prevent treatment crossovers (patients receiving the treatment to which they were not randomized) from occurring and the primary endpoint analyses will be done based on the arm to which the patient was randomized and the rate of treatment crossovers will be closely monitored.

Table 1 shows the impact for 5%, 10%, and 15% crossover from the control arm to the experimental arm. If the crossover rate falls between 5% and 15%, NRG Oncology will discuss with NCI the potential of amending the trial in order to adjust for this crossover, so as to maintain the original study parameters. If the crossover rate reaches or exceeds 15%, NRG Oncology will discuss with NCI the feasibility of continuing the trial.

Table 1: Impact of Crossover from control arm to experimental arm

Crossover Rate	Adjusted 5-yr Experimental Rate	Type I Error (0.05 by Design)	Increase in Accrual Time to Maintain Original Parameters
5%	0.389	0.072	4 mths
10%	0.378	0.10	8 mths
15%	0.367	0.12	14 mths

13.3.3 Patient Accrual

Patient accrual is projected to be 3 randomized cases per month, with a ramp-up period in the first 6 months. The expected monthly accrual in months 1 through 3 and months 4 through 6 following amendment activation are 0 and 1, respectively. Assessment of accrual compliance will be based on the NCI Ph III accrual rules and will be monitored by the NRG Oncology Data Monitoring Committee (DMC). If the total accrual during months 13 through 18 of the study is $\leq 20\%$ of the targeted accrual (< 4 cases in total), then the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual during months 13 through 18 is between 21% and 49% (4 to 8 cases), then the protocol will continue to accrue subjects and will be evaluated again at the end of month 24. If the accrual during months 22 through 24 is at least 50% of the targeted accrual (≥ 5 cases in total), the NCI-CTEP accrual guidelines for phase III studies will have been met and the study will continue accrual; otherwise, the study will be discontinued.

13.4 Analysis Plan (3/20/17)

13.4.1 Statistical Methods:

Overall survival (OS) and progression-free survival (PFS) will be estimated by the Kaplan-Meier method [Kaplan 1958]. The distributions of OS and PFS estimates between the two arms will be compared using the log rank test [Mantel 1966]. OS and PFS times will be measured from the date of randomization to the date of death or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, which may be associated with OS or PFS. Local, regional, and distant failures will be estimated by the cumulative incidence method (Kalbfleisch 1980) and the comparison of these endpoints between and experimental arm and the control arm will be done use Gray's test (Gray1988).

13.4.2 Interim Analysis to Monitor the Study Progress:

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pretreatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm.
- compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint (OS), or any secondary endpoints, with the exception of reporting of adverse events.

Phase III trials are required by NCI Cooperative Group Program Guidelines to be reviewed by a Data and Safety Monitoring Committee (DSMC). To monitor the safety of this study, the NRG Oncology DMC will officially review this study twice per year and on an “as needed” basis in between Committee meetings.

13.4.3 CDUS Reports

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.4 Significance Testing for Early Termination and/or Reporting

Primary Endpoint: Overall Survival (OS)

Two interim significance test of treatment difference for the primary endpoint of OS are planned based on the Lan DeMets alpha/beta spending functions [Lan 1983]. The timing of the interim analysis will be based on OS failure events (death due to any cause). The maximum number of OS events required for the study is 102. Under the alternative hypothesis of a 20% difference in OS, the projected number of events and the nominal significance levels for rejecting the H₀ or the H₁ for this interim analysis are shown in the table below:

Table 2: Nominal Significance Levels for Interim Analyses

Interim Analysis	Number of Events	Reject H ₀ if p ≤	Reject H ₁ if p ≥
#1	34	≤ 0.0002	0.98
#2	68	≤ 0.012	0.36

At each planned interim analysis, the p-value from the log-rank test assessing treatment differences with respect to OS will be compared to the nominal significance levels in Table 2 above. If the computed p-value is less than or equal to the nominal significance level boundary for rejecting the H₀, then accrual to the trial will be stopped (if applicable) and it will be concluded that the OS with radiation (Arm 1) is significantly different than

without radiation (Arm 2) and the results will be reported. If the computed p-value is greater than or equal to the nominal significance level boundary for rejecting the H_1 , then accrual to the trial will be stopped (if applicable) and the fact that it cannot be concluded that the OS with radiation (Arm 1) is significantly different than without radiation (Arm 2) will be reported. Otherwise, if neither boundary is crossed, accrual to the trial and/or follow-up (as applicable) will continue until the next/final analysis.

In addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events, and compliance with protocol treatment blinded efficacy results will be reported to the oversight NRG Oncology DMC, following the required number of events for the planned interim analysis.

13.4.5 Analysis for Reporting the Initial Treatment Results

The primary hypothesis of the study is to determine if liver-directed radiation therapy results in a change in OS in patients with unresectable, localized intrahepatic cholangiocarcinoma. This major analysis will occur after at least 102 OS events (deaths) have occurred. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm.
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment difference in OS, assuming both interim analyses have been carried out, will be tested with a 2-sided significance level of 0.0463. Additional analyses of treatment effect will be performed using the logistic regression model with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms (e.g. age, gender, race, etc.). Where feasible, treatment comparisons with respect to the primary endpoint (OS) will be compared within each ethnic and racial category.

13.5 **Gender and Minorities**

Both men and women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interactions between race/ethnicity and treatment have been considered. It is projected that 80% of the patients will be men and 20% women; 2% will be of Hispanic or Latino ethnicity; racial distribution will be 74% white, 20% Asian, 5% black or African American, and 1% across the other racial categories. Assuming no differences between the ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference in the randomized patients is 78% for males. The projected female, Hispanic/Latino and non-White accrual rates are too low for any meaningful treatment comparisons.

The following table lists the projected randomized accrual by gender, ethnic, and racial categories.

Projected Distribution of Gender and Minorities

Ethnic Category	Gender		
	Females	Males	Total

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	1	2	3
Not Hispanic or Latino	29	114	143
Ethnic Category: Total of all subjects	30	116	146
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	0	0	0
Asian	6	23	29
Black or African American	2	5	7
Native Hawaiian or other Pacific Islander	1	1	2
White	21	87	108
Racial Category: Total of all subjects	30	116	146

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APPENDIX I (3/20/17)
STUDY PARAMETER TABLE: STUDY ENTRY ASSESSMENTS

Assessments	prior to study entry	≤30 days prior to study entry	≤21 days prior to study entry	AT Study Entry
Biopsy or cytology confirmed IHC	X			
Performance Status	X			
Height/Weight		X		
CT Chest/Abdomen/ Pelvis w multiphasic liver CT OR CT chest without contrast and MRI of abdomen and pelvis		X		
CBC w/ diff, ANC, platelets			X	
Serum creatinine or creatinine clearance, ALT, AST, Bilirubin, Albumin			X	
Alkaline phosphatase, phosphate, sodium, potassium, chloride, magnesium, calcium			X	
CA 19-9, CEA			X	
bHCG test (if applicable)	X			
Urine sample (for consenting patients)				X (See Section 10.2.6 for details)
Blood collection (plasma and whole blood for DNA for consenting patients)				X (See section 10.2.6 for details)
Tissue banking (for consenting patients)				X (See section 10.2.6 for details)
Informed consent		X		

APPENDIX I (3/20/17)

(continued)

STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

Assessments	During RT (Arm 1 patients only)
History/physical	X per institutional standard
Vital Signs	X per institutional standard
Weight	X per institutional standard
CBC w/diff, ANC, platelets	X per institutional standard
Alkaline phosphatase, phosphate, sodium, potassium, chloride, magnesium, calcium, Serum creatinine or creatinine clearance	X per institutional standard
ALT, AST, Bilirubin,	X (Day 1, 8, and 15)
Toxicity Assessment	X per institutional standard
Blood collection (for consenting patients)	X (see Section 10.2.6 for details)

APPENDIX I (3/20/17)

(continued)

STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW-UP

Assessments	At end of treatment	Every 3 months from study entry for 3 years, then every 6 months for 2 years (Arms 1 and 2)
History/physical		X
Vital Signs and Performance status		X
Weight		X
CBC w/diff, ANC, platelets		X
ALP, phosphate, sodium, potassium, chloride, magnesium, calcium		X
CA 19-9, CEA	X	X
Toxicity Assessment		X
CT Chest/ Abdomen/Pelvis OR CT chest without contrast and MRI of the abdomen and pelvis if contrast is contraindicated		X*
Multi-phase liver CT or MRI		X*

* If the metastatic and liver specific assessments are encompassed within one test, that is acceptable.

APPENDIX II

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction**
- 1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
- 4 Completely disabled. Cannot carry on self-care. Totally confined to bed**
- 5 Death**

APPENDIX III

AJCC Staging System

Edge SB, ed. AJCC Cancer Staging Manual 7th ed. New York, NY, 2010

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ (intraductal tumor)

T1 Solitary tumor without vascular invasion

T2a Solitary tumor with vascular invasion

T2b Multiple tumor with vascular invasion

T3 Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion

T4 Tumor(s) with periductal invasion*

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Regional lymph node metastases

Distant Metastases (M)

M0 No distant metastases

M1 Distant metastases

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

* The pathologic definition of periductal invasion is the finding of a longitudinal growth pattern along the intrahepatic bile ducts on both gross and microscopic examination.

APPENDIX IV

Multi-Phase Intrahepatic Cholangiocarcinoma Imaging Protocol

Recommended imaging for CT simulation and follow-up

Multi-phase liver CT protocol using iodinated intravenous (IV) contrast will be obtained at 2.5 or 3 mm slice thickness. The four phase HCC protocol includes a non-contrast CT, arterial (A) phase imaging, portal venous (V) phase imaging and delayed (D) phase imaging. The A phase of imaging demonstrates hypervascularity of HCC. The V phase is often best for visualization of vascular thrombi. The D phase imaging demonstrates washout of HCC. All four phases are recommended for use at baseline diagnosis for HCC; A/V/D phase imaging is recommended for follow-up of HCC patients, with all phases including the whole liver and V or D phase including the entire abdomen. For CT simulation, at least 2 phases of imaging are recommended (A/V or A/D), with all phases including the whole liver and one phase including enough of the abdomen to develop a patient model for radiation planning.

All multi-phase imaging is recommended to be obtained in breath hold, with the arms up when possible.

The timing of imaging after IV contrast administration: Bolus Tracking technique

The timing varies between 16 and 64 detector scanners (with image acquisition occurring faster on a 64 detector CT scanner). It is recommended that IV contrast (e.g. Visipaque) 2cc/kg to a max of 180cc be injected @ 5cc/second using a minimum of 20G antecubital. IV bolus tracking, a commercially available technique, is recommended for use to control for variations in cardiac circulation time, to ensure the images are obtained during the correct phases of contrast enhancement. As is standard practice, a cursor is placed in the aorta at the level of the origin of the celiac axis and is used to detect when contrast arrives in the abdominal aorta and raises the attenuation value to 100 Hounsfield Units. For a 64 detector scanner, A, V and D phase scanning occurs 20, 60 and 180 seconds, respectively, after the 100HU threshold is reached.

MR imaging

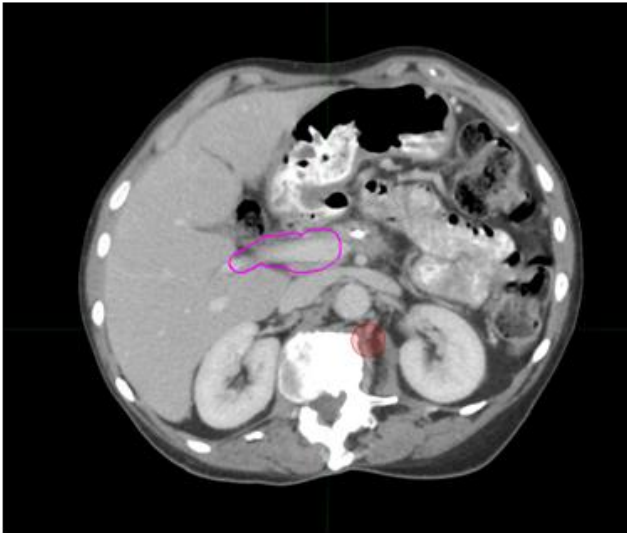
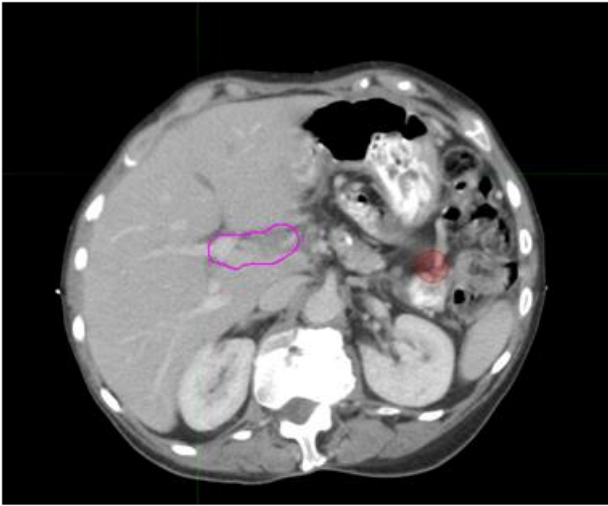
If CT cannot be obtained due to contraindication, a non-contrast CT scan will be obtained, and gadolinium or Primovist/Eovist (Gd-EOB-DTPA) enhanced MRI will be utilized to facilitate target delineation. It is suggested that non-contrast and dynamically obtained T1 weighted sequences at a slice thickness of 7mm at maximum be used. Details of the imaging protocol should be developed in collaboration with the diagnostic radiology department.

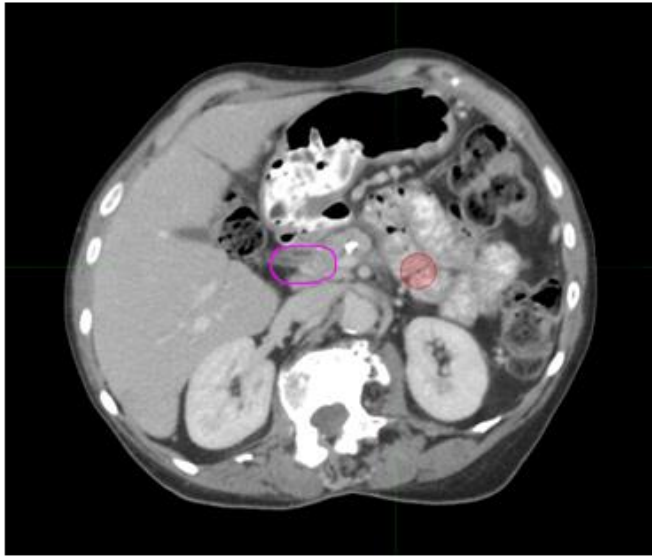
If a patient has contraindications to CT and MR IV contrast, then non-contrast T1 weighted images may be used for target delineation, only if T1 weighted images demonstrate the HCC with clearly defined edges.

APPENDIX V (5/7/15)

Example of the porta hepatis

Only lymph nodes in the vicinity of this structure are considered regional lymph nodes. No celiac, SMA, mesenteric, gastro-hepatic, or pancreaticoduodenal lymphadenopathy is permitted. Please contact Dr. Hong or Dawson if there is any question.





APPENDIX VI (3/20/17)

Appendices for NRG Oncology Biospecimen Collection *(as specified by the protocol)*.

NRG Oncology FFPE Specimen Plug Kit Collection NRG Oncology Blood Collection Kit Instructions NRG Oncology Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco- Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
 - Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
 - FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking might break during shipping.
 - Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice.**

- ❑ **Frozen Specimens:**
 - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep Serum, Plasma, and Whole Bloods in separate bags.
 - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
 - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
 - Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank – San Francisco by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.

NRG ONCOLOGY FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank – San Francisco. The plug kit contains a shipping tube and a punch tool.



Step 1

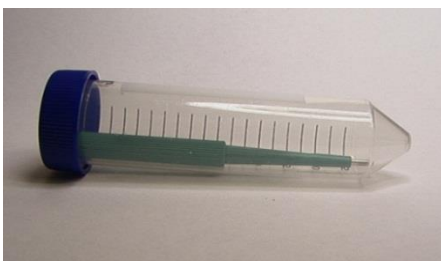
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2

Label the punch tool with the proper specimen ID and block number. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3

Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank – San Francisco and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank – San Francisco by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco- Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143

Courier Address (FedEx, UPS, etc.):
For ALL Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood

Kit contents: Sites are required to provide their own blood draw tubes for this study.

Each kit includes supplies for all time points and one return shipping label for batch shipping of frozen samples from each case.

- Thirty-five (35) 1 ml cryovials
- Biohazard bags (7) and Absorbent shipping material (7)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum: Red Top Tube (One ten ml or two 5ml red top tubes)

- Label five 1ml cryovials for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot a minimum of 0.5 ml serum into five (5) cryovials as are necessary for the serum collected labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

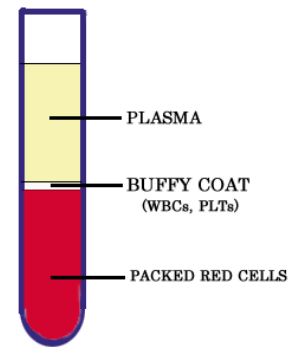
(B) Plasma: Purple Top EDTA tube #1 (one 10 ml or Two 5ml EDTA Tubes)

- Label five (5) 1ml cryovials for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma into each of five (5) cryovials as necessary for the plasma collected labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90°C and store frozen until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.



(C) Whole Blood for DNA: Purple Top EDTA tube #2 (one 10 ml, or two 5ml EDTA tubes)

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials “blood”.

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
3. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

Freezing and Storage:

- ❑ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
 - If a -80°C Freezer is not available,
 - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
 - OR:**
 - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).
 - OR:**
 - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.

- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). **Add padding to avoid the dry ice from breaking the tubes.**
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.*
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.

Shipping Address:

**Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu**

NRG ONCOLOGY URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
 - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
 - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
 - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
 - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the NRG Oncology study and case number, collection date and time, time point of collection, and clearly mark specimens as "urine".
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with study number, case number, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
 - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

OR:

- Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). **Add padding to avoid the dry ice from breaking the tubes.**
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. **Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.

(continued on next page)

- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: 415-476-7864