A PHASE I TRIAL OF HIGHLY CONFORMAL RADIATION THERAPY FOR PATIENTS WITH LIVER METASTASES

Translational Research Co-Chair
Hany Elsaleh, M.D., Ph.D.
UCLA Medical Center
200 UCLA Medical Plaza, Suite B265
Los Angeles, California 90095
(310) 792-2407/Fax# (310) 794-9795
helsaleh@mednet.ucla.edu

Medical Physics Co-Chair
Michael C. Schell, Ph.D.
University of Rochester Medical Center
601 Elmwood Avenue, Box 647
Rochester, New York 14642
(585) 275-5261
Michael_Schell@urmc.rochester.edu

Principal Investigator/Radiation Oncology
Alan W. Katz, M.D., M.P.H.
University of Rochester Medical Center
601 Elmwood Ave, Box 647
Rochester, New York 14642
(585) 275-3913/Fax# (585) 275-1531
Alan_Katz@urmc.rochester.edu

Radiation Oncology Co-Chair (1/10/06)
Laura A. Dawson, M.D., FRCPC
Associate Professor
Dept. of Radiation Oncology
Princess Margaret Hospital
University of Toronto
610 University Ave.
Toronto, Ontario
M5G 2M9
(416) 946-2124/Fax# (416) 946-6566
laura.dawson@rmp.uhn.on.ca

Document History

<table>
<thead>
<tr>
<th>Event</th>
<th>Version/Update Date</th>
<th>Broadcast Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Termination</td>
<td>-</td>
<td>November 5, 2013</td>
</tr>
<tr>
<td>Amendment 3</td>
<td>March 1, 2011</td>
<td>March 8, 2011</td>
</tr>
<tr>
<td>Closure</td>
<td>-</td>
<td>March 12, 2009</td>
</tr>
<tr>
<td>Amendment 2</td>
<td>August 7, 2007</td>
<td>August 28, 2007</td>
</tr>
<tr>
<td>Update</td>
<td>August 28, 2007</td>
<td>August 28, 2007</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>April 21, 2006</td>
<td>June 20, 2006</td>
</tr>
<tr>
<td>Update</td>
<td>January 10, 2006</td>
<td>January 10, 2006</td>
</tr>
<tr>
<td>Update</td>
<td>November 3, 2005</td>
<td>November 3, 2005</td>
</tr>
<tr>
<td>Activation</td>
<td>November 3, 2005</td>
<td>November 3, 2005</td>
</tr>
</tbody>
</table>

RTOG Headquarters/Department of Statistics
215-574-3189
1-800-227-5463, ext. 4189

RTOG 0438
This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
INDEX

Schema

Eligibility Checklist

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Additional Pretreatment Evaluations/Management

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Specimen Submission

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix III - Blood collection kit/shipping procedures

RTOG 0438
RADIATION THERAPY ONCOLOGY GROUP

RTOG 0438

A PHASE I TRIAL OF HIGHLY CONFORMAL RADIATION THERAPY FOR PATIENTS WITH LIVER METASTASES

SCHEMA

All Patients will receive 10 fractions Monday-Friday for 2 weeks at the following levels; Dose escalation by 0.5 Gy to maximum of 50 Gy, as follows:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Level I</th>
<th>†Level II</th>
<th>Level III</th>
<th>Level IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose per fraction</td>
<td>3.5 Gy</td>
<td>4.0 Gy</td>
<td>4.5 Gy</td>
<td>5.0 Gy</td>
</tr>
<tr>
<td>Total dose</td>
<td>35 Gy</td>
<td>40 Gy</td>
<td>45 Gy</td>
<td>50 Gy</td>
</tr>
</tbody>
</table>

†Protocol Treatment Begins at Level II

See Section 6.0 for Radiation Therapy; See Section 5.0 for pre-registration requirements

**Patient Population:** *(See section 3.0 for details)*

- Non-lymphoma liver metastases confirmed pathologically or new radiographic liver lesions most consistent with metastases in a patient with known pathologically proven non-lymphoma cancer and a previously negative contrast CT, MRI or PET/CT of the liver.

**Required Sample Size:** Maximum of 18
The following questions will be asked at Study Registration:

- Name of institutional person registering this case?
- Has the eligibility checklist been completed?
- Is the patient eligible for this study?
- Date the study-specific Consent Form was signed? (must be prior to study entry)
- Patient’s Initials (First Middle Last) [If no middle initial, use hyphen]
- Verifying Physician
- Patient’s ID Number
- Date of Birth
- Race
- Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- Gender
- Patient’s Country of Residence
- Zip Code (U.S. Residents)
- Patient’s Insurance Status
- Will any component of the patient’s care be given at a military or VA facility?
- Treatment Start Date
- Blood kept for cancer research?
- Blood kept for medical research?
- Allow contact for future research?
- Does the patient have either non-lymphoma liver metastases confirmed pathologically or new radiographic liver lesions consistent with metastases from a pathologically proven non-lymphoma cancer with a previously negative contrast CT/MRI/PET-CT of the liver?
- Was a contrast enhanced liver CT, MRI or PET/CT performed?
- Specify the date of CT, MRI or PET/CT (mm-dd-yyyy)
- Number of measurable lesions on the CT, MRI or PET/CT?
- Size of largest lesion?
If there is disease outside the liver, is the liver disease judged to be life-limiting?

Is all intrahepatic disease encompassed within the radiation fields according to protocol criteria? (See Section 6.4.1)?

Is the patient medically unfit for surgery or is the patient’s liver metastases deemed unresectable?

Age?

Zubrod Performance Status?

Results of ANC (cells/mm³)

Date of ANC (mm-dd-yyyy)

Results of platelet count (cells/mm³)

Date of platelet count (mm-dd-yyyy)

Results of hemoglobin (g/dl)

Date of Hemoglobin (mm-dd-yyyy)

Was an INR, total bilirubin, albumin, alkaline phosphatase, ALT and AST drawn within 2 weeks prior to study entry?

Date additional pretreatment labs were drawn? (mm-dd-yyyy)

Was Chest CT or PET/CT performed within 30 days of study entry?

Was a negative serum pregnancy test obtained within 72 hours prior to registration?

Was a CEA drawn and found to be positive?

Was an AFP drawn and found to be positive?

Was a CA19-9 drawn and found to be positive?

Has the patient received prior chemotherapy or targeted agent?

IF YES Completion date of chemotherapy or targeted agent (mm-dd-yyyy)

Has the patient had a prior invasive malignancy, other than liver metastasis primary?

IF YES Date of eradication of prior malignancy (mm-dd-yyyy)

Has the patient received prior RT to the region of the study cancer that would result in overlap of radiation fields?
Has the patient had unstable angina and/or CHF requiring hospitalization within the last 6 months?

Has the patient had a transmural MI within the last 6 months?

Has the patient had an acute bacterial or fungal infection requiring antibiotics at the time of registration?

Has the patient had a COPD exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration?

Does the patient have active hepatitis or clinically significant liver failure?

Is the patient currently receiving anticoagulation treatment with coumadin or IV heparin?

Is there CNS metastasis?

Is there liver cirrhosis?

Is there clinical ascites?

Is the patient, male or female, of reproductive potential?

Will a medically acceptable form of contraception be used?
1.0 INTRODUCTION

1.1 Background
Liver metastases cause substantial morbidity in an increasing number of patients primarily due to the fact that only a minority of patients are suitable for surgery. Metastatic colorectal cancer to the liver is a common pattern of spread, sometimes as the only site of metastatic disease. Colorectal cancer deaths (57,000 per year in the USA) are second only to lung cancer and are commonly associated with liver metastases, often as the only site of metastatic disease. Approximately 50% of metastatic deaths from breast and prostate cancers are associated with liver metastases: 43,000 women and 34,000 men per year. Hence, the potential gains in survival and palliation are substantial if high-dose focal liver radiation can control liver metastases safely.

Autopsy studies have shown that 40% of colon cancer patients fail with disease confined to the liver. This has led to the hypothesis that not all metastases are diffuse and that “oligometastasis” can occur where aggressive local therapy to the oligometastasis may lead to long-term control of disease. This hypothesis is gaining support over the currently held belief that metastases are always systemic. Evidence for the oligometastasis theory is found in surgical series of treated oligometastases of the colon, sarcoma, melanoma and breast. If metastases were truly confined to the liver, and if effective therapy for the localized intrahepatic disease existed, aggressive local therapy may lead to improved survival in some patients.

Conventional intravenous chemotherapy for hepatic metastases, and intrahepatic chemotherapy via infusion pump have demonstrated high transient response rates, however, with no chance for long-term cure. Palliative whole liver radiation for hepatic capsular pain may be effective in relieving symptoms, but with no increase in survival. Thus chemotherapy and palliative whole liver radiation are unsatisfactory therapies.

Surgical resection of hepatic metastasis can improve survival of patients with isolated liver disease. Fong, et al demonstrated a 30% five-year survival in patients with colorectal cancer who had their liver lesions resected. Another study by Scheele demonstrated a 40% five-year survival and 30% five-year freedom from disease following curative resection of colorectal liver metastasis. Other studies confirm the survival benefit to patients with resectable disease.

Unfortunately, most patients with liver metastases are not surgical candidates due to anatomic location or size of the tumor or medical inoperability. Therefore an important role exists for a treatment that can provide the equivalent of tumor excision, but with minimal morbidity.

Recent technological advances have made it possible to deliver high doses of radiation therapy precisely to small tumors while preserving function in critical structures surrounding the lesion. Stereotactic conformal radiotherapy is commonly used to treat small metastatic lesions in the brain. With these techniques, control rates in excess of 80% have been achieved in patients with metastasis from lung, breast, renal, and other cancers. We hypothesize that similar control rates may be feasible using stereotactic radiotherapy for metastatic liver cancer. If this strategy is safe, we hypothesis that stereotactic liver radiation may be able to cure some patients unsuitable for resection.

The liver tolerance to external beam irradiation depends on the volume treated and the fractionation schedule. Lawrence, et al found that patients who developed grade III or IV radiation induced liver disease (RILD) tended to receive a higher mean dose and have less sparing of normal liver than those who did not. In the original analysis, none of the 45 patients who received a mean dose to the whole liver of less than 37 Gy (in 1.5 Gy per fraction bid) developed RILD, while 9 of 34 patients who received a mean dose of more than 37 Gy developed this complication. Another study from the University of Michigan looked at 26 patients with hepatobiliary cancer treated with radiation doses up to 72.6 Gy, in 1.5 Gy bid and concurrent intrahepatic fluorodeoxyuridine administration. Patients treated with a component of 36 Gy whole liver radiation were more likely to develop RILD compared to those treated with focal high-dose radiation with no whole liver radiation. These studies indicate that by using modern conformal radiation planning it is possible to deliver tumoricidal doses of radiation. More recently, we have developed a better understanding of the relationship between dose, volume of liver irradiated and RILD, based on an analysis of over 200 patients with hepatic malignancies treated...
at the University of Michigan. This analysis demonstrates that for a small effective liver volume irradiated, far higher doses of radiation can be prescribed than previously estimated. In addition to the dose and volume irradiated, several other factors were significantly associated with increased the risk of RILD, including use of BuDR chemotherapy (versus FuDR), primary hepatobiliary cancer diagnosis (versus metastatic cancer diagnosis) and male sex. In this study, we will exclude patients with underlying liver disease or primary hepatobiliary cancer. For patients with metastases, the mean liver dose associated with a 5% risk of RILD is 33 Gy in 2 Gy per fraction and 28 Gy in 10 fractions (assuming an alpha/beta ratio of 2.5 for the liver).  

It is well known that only a portion of the normal liver is required to sustain life. A surgical rule of thumb suggests that 25-40% of the normal liver must be spared during a resection. The Dose Volume Histogram (DVH) for the liver can be useful in quantifying the amount of liver receiving a “toxic” dose of radiation. At the University of Rochester, 17 initial patients were treated with 3D Conformal Therapy for primary or metastatic disease in the liver. The hepatic lesions ranged in size from 1-9.5 cm. Dose to the lesions ranged from 40-54 Gy using an average dose per fraction of 286 cGy (range 150-540 cGy). 60-70% of the non-tumor containing liver received a dose under 27-30 Gy. At six month’s follow-up, only three in-field failures were observed. CT scans one month following radiation demonstrated focal liver changes within the treatment fields. Repeat CT scans three to six months later revealed measurable liver regeneration. None of the patients developed signs of liver failure or jaundice.

In patients with metastatic liver disease, aggressive local therapy using modern radiotherapy techniques should be studied in a multi-institutional setting to confirm safety and feasibility. In the long-term, we hypothesize that radiation therapy will have a substantial role in the treatment of metastatic liver cancer to eradicate unresectable disease. Although ablative techniques such as radiofrequency ablation compete with radiation therapy, they are invasive and most appropriate for small lesions (less than 4 cm) away from large vessels. There is a need for improved local therapies for liver metastases. We thus propose a phase I study to determine the feasibility and safety of this strategy in patients with liver metastases.

2.0 OBJECTIVES
2.1 Primary
2.1.1 To identify the maximally tolerated dose (up to 50 Gy in 5 Gy per fraction) of high dose per fraction, highly conformal radiation therapy in patients with metastatic liver cancer.
2.2 Secondary
2.2.1 To evaluate local control rate within the irradiated fields.
2.2.2 To assess failure patterns and survival of patients treated with highly conformal liver radiation therapy.
2.2.3 To analyze the dose volume characteristics that influence whether RILD or other toxicities occur.
2.2.3 To collect blood samples for translational research.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility (4/21/06, 8/7/07)
3.1.1 Eligible patients include patients with any of the following:
3.1.1.1 Non-lymphoma liver metastases confirmed pathologically or,
3.1.1.2 New radiographic liver lesions most consistent with metastases, in a patient with known, pathologically proven non-lymphoma cancer and a previously negative contrast CT, MRI or PET/CT of the liver.
3.1.2 ≤ 5 liver lesions measurable on a contrast-enhanced liver CT, MRI or PET/CT performed within 6 weeks prior to study entry.
3.1.3 Liver metastases measuring ≤ 8 cm.
3.1.4 Extrahepatic disease outside the liver is permitted if the hepatic disease is judged to be life-limiting.
3.1.5 All intrahepatic disease must be encompassed within the radiation fields according to protocol criteria. See Section 6.4.1.
3.1.6 Patient is medically unfit for surgery or patient is deemed surgically unresectable.
3.1.7 Zubrod Performance Scale = 0-1.
3.1.8 Age ≥ 18.
3.1.9 Adequate bone marrow function, defined as follows:
- Absolute neutrophil count (ANC) > 1,800 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study
- Platelets > 100,000 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study
- Hemoglobin ≥ 8.0 g/dl based upon CBC/differential obtained within 2 weeks prior to registration on study (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

3.1.10 Previous liver resection or ablative therapy is permitted.
3.1.11 Chemotherapy and/or targeted agent therapy must be completed at least 2 weeks prior to radiation.
3.1.12 Women of childbearing potential and male participants must practice adequate contraception.
3.1.13 Patient must sign study specific informed consent prior to study entry.
3.1.14 Pretreatment Evaluations Required for Eligibility include:
  - A complete history and general physical examination
  - For women of childbearing potential, a serum or urine pregnancy test must be performed within 72 hours prior to registration
  - INR, total bilirubin, albumin, alkaline phosphatase, ALT, AST within 2 weeks prior to study entry

3.2 Conditions for Patient Ineligibility (4/21/06, 8/7/07)
3.2.1 Prior invasive malignancy, other than liver metastasis primary, (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible).
3.2.2 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.
3.2.3 Severe, active co-morbidity, defined as follows:
  - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
  - Transmural myocardial infarction within the last 6 months
  - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
  - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
  - Active hepatitis or clinically significant liver failure
3.2.4 Patients currently receiving anticoagulation treatment with coumadin or IV heparin.
3.2.5 CNS metastases.
3.2.6 Underlying liver cirrhosis.
3.2.7 Clinical ascites.
3.2.8 Pregnancy, nursing women, 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.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT
Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient’s eligibility for this study, please contact RTOG HQ immediately (215) 574-3189.
4.1 Additional Recommended Pre-treatment Evaluations
4.1.1 CT or PET/CT scan of chest within 30 days from study entry.
4.1.2 Baseline tumor appropriate markers – CEA, AFP, CA19-9.

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements (8/7/07)
Institutions must be credentialed by the Advanced Technology Consortium (ATC) prior to enrolling patients into this study. As it pertains to this study, the ATC includes the Image-Guided Therapy Center (ITC) at Washington University, St. Louis; the Radiological Physics Center (RPC) at MD Anderson Cancer Center; and RTOG RT Quality Assurance. Credentialing includes the following four steps (Sections 5.1.1-5.1.4):
5.1.1 Each institution must complete the 3D QA Facility Questionnaire for Stereotactic Body Radiation Therapy (SBRT) available on the ATC web site, http://atc.wustl.edu. Each institution must submit the completed Facility Questionnaire by email, fax, or mail to:

Image-Guided Therapy Center (ITC)
Attn: Roxana Haynes
4511 Forest Park Avenue, Suite 200
St. Louis, MO 63108
E-mail: itc@castor.wustl.edu
Phone: 314-747-5415
FAX: 314-747-5423

The Facility Questionnaire requires the following:
Institutional and/or peer-reviewed documentation of accountability for internal organ motion, including compensation for respiratory movement by one of the following methods:
- Inhibition of diaphragmatic movement by abdominal compression or equivalent;
- Active breath holding techniques synchronized to radiation delivery;
- Respiratory gating monitoring consistent breathing patterns synchronized to radiation delivery;
- Dynamic tumor tracking with collimator or machine movement synchronized to radiation delivery.

Institutional and/or peer-reviewed documentation of target position reproducibility (gross tumor volume within planning treatment volume) must be consistent with Section 6.4.

Documented ability to transfer patient specific material and treatment planning parameters including CT-based dose deposition representations, dose-volume matrices and parameters, and stereotactic targeting representations to the ITC.

5.1.2 Each institution must contact the ITC (itc@castor.wustl.edu) and request an SFTP account for digital data submission.

5.1.3 Each institution must successfully irradiate a standardized phantom provided by the Radiological Physics Center (RPC) at MD Anderson Cancer Center. Instructions for requesting and irradiating the phantom are available at the RPC web site, http://rpc.mdanderson.org/rpc/ by selecting “Credentialing” and “RTOG”. The phantom simulates a tumor within liver tissue. The irradiation must be within tolerances specified in Section 6.0. The treatment plan for irradiation of the phantom must be submitted electronically to the ITC (see Section 5.1.2).

5.1.4 PRIOR TO DELIVERING ANY PROTOCOL TREATMENT each institution must successfully complete and submit a protocol-specific Dry-Run Test, for more information please refer to: http://atc.wustl.edu. If a prior CT simulation dataset is not available for a patient with liver cancer, a simulated liver tumor Dry-Run will be submitted as per protocol treatment. For example, an upper abdominal CT planning dataset for a non-liver cancer patient can be used for the Dry-Run by placing a “simulated 4 cm diameter tumor” anywhere within the liver. This “simulated tumor” should then be treated per protocol, at a dose of 40 Gy in 4 Gy per fraction. The plan will be reviewed centrally at the ITC, and suggestions regarding protocol compliance will be forwarded to the participating institution. If the plan is fully compliant, the treatment plan for subsequent patients enrolled at a site will not be required to be centrally reviewed prior to treatment, but will be reviewed for protocol compliance at a later date. If the Dry-Run plan is not fully compliant, there may be a request for the first plan for a patient enrolled at a site on protocol to be rapidly reviewed real time by ITC. All patients’ plans not reviewed in real time will be centrally reviewed at a later date.

5.2 Registration
5.2.1 Online Registration
Online (versus Dial-in) registration is mandatory for this study. Patients can be registered only after eligibility criteria are met. The RA will register the patient by logging onto the RTOG Web Site (www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. A user name and password are
required. The system triggers a program that verifies that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the identification of the person who completed the checklist and the date the study-specific informed consent form was signed.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

### 6.0 RADIATION THERAPY:

**Note:** Intensity Modulated RT (IMRT) is Not Allowed. 
H2 blockers or proton pump inhibitors will be required in an attempt to decrease the chance of late GI bleeding. 
Radiation Therapy must start within 4 weeks of patient registration.  (1/10/06)

#### 6.1 Dose Specification (8/7/07)

6.1.1 The target dose is determined based on the study dose level and the volume of normal liver excluded from radiation (using the liver DVH) see Section 6.5. Treatment at the allocated dose level is only permitted if the normal tissue criteria in Section 6.5 are maintained. If the normal tissue criteria are not met at that dose, treatment at a lower dose level is permitted, as long as the normal tissue constraints are met at the lower dose level.

6.1.2 The dose per fraction to the PTV will start at dose level II (4.0 Gy), but may vary from 3.5 Gy to 5.0 Gy, in 10 fractions, Monday through Friday, in 0.5 Gy increments, as described in Section 13.0. The starting level will be Level II, 4.0 Gy per fraction.

6.1.3 **Doses will be prescribed to a peripheral covering isodose covering the PTV.** Assuming dose is normalized to this isodose at 100%, the maximal dose can be 120% and the minimum PTV dose 90%. Any dose > 110% must be within the PTV (except for adjacent tumors, in which the maximum dose outside the PTV must be < 115%). Minor variation is defined as minimum PTV dose falling between 85 and 90% (of the required 100% isodose prescription). Major variation (unacceptable) is defined as minimum PTV dose < 85 % (for the required 100% isodose prescription).

6.1.4 Maximum doses described in Section 6.1.3 are defined at 1 cc of volume. Minimum dose to the PTV is defined as minimum dose to 99.0% of the PTV.
6.1.5 Table of permitted doses (in Gy)

<table>
<thead>
<tr>
<th>Level</th>
<th>Total Dose (Gy)</th>
<th>Dose/fraction (100%)</th>
<th>PTV dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Maximum (120%)</td>
<td>Minimum (90%)</td>
</tr>
<tr>
<td>I</td>
<td>35</td>
<td>3.5</td>
<td>4.2</td>
</tr>
<tr>
<td>II†</td>
<td>40</td>
<td>4.0</td>
<td>4.8</td>
</tr>
<tr>
<td>III</td>
<td>45</td>
<td>4.5</td>
<td>5.4</td>
</tr>
<tr>
<td>IV</td>
<td>50</td>
<td>5.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

† Protocol treatment begins at level II

6.1.6 All separate lesions with different isocenters must achieve the above rules. In a single patient all PTVs are in the same dose escalation category.

6.1.7 The minimum, maximum, and mean dose to the PTV is to be recorded for each GTV.

6.2 Technical Factors

6.2.1 External Beam Equipment

Treatment will be delivered with 6 - 25 MV photons, with selection of appropriate energies to optimize the radiotherapy dose distribution within the target volume and minimize the dose to non-target tissues.

6.2.2 3D conformal radiation therapy capabilities as defined by the ATC can be accessed via, http://atc.wustl.edu/. The ability to plan and deliver non-coplanar fields is necessary.

6.3 Localization, Simulation and Immobilization (8/7/07)

For specific questions or concerns regarding this section please contact Dr. Michael C. Schell at University of Rochester Medical Center by email: Michael_Schell@urmc.rochester.edu, or telephone: 585-275-5261.

6.3.1 Patient positioning will be based on clinical judgment to best achieve the ideal dose distribution (supine position is preferred). Credentialing is required for SBRT.

6.3.2 The target volume will be identified on an IV contrast CT scan and/or MRI that is registered to the planning CT dataset. The planning CT and all subsequent CT studies will be obtained using the identical immobilization technique used for treatment.

6.3.3 An immobilization frame may be used, but is not required.

6.3.4 Immobilization: A variety of immobilization methods may be utilized for planning and treatment, including active breathing control (ABC), voluntary breath hold, gating, shallow breathing, or abdominal compression. For free breathing, 4D-CT can be used to aid in PTV definition. The maximal extent of tumor motion must be less than 20 mm.

6.3.5 Institutional reproducibility data regarding patient setup and tumor targeting must be provided to the physics and image guidance committees. Details of this procedure can be found on the ATC web site (http://atc.wustl.edu/).

6.4 Treatment Planning/Volume Definitions (8/7/07)

6.4.1 CT-based 3D treatment planning shall be used for all patients.

6.4.2 The gross tumor volume (GTV) will be defined by IV contrast CT or MRI. If defined on MRI, the study must be obtained using the same breath hold technique as the planning CT, and registered to the planning CT dataset.

6.4.3 The clinical target volume (CTV) will be the GTV + 5 mm, within the liver.

6.4.4 The planning target volume (PTV) will be determined by the immobilization device used and/or the individual patient breathing motion. The minimal and maximal PTV margins permitted are 4 mm and 30 mm, respectively, dependent on the immobilization method used and breathing motion.

6.4.5 Dose volume histogram (DVH) shall be calculated for the liver (liver minus the GTVs), both kidneys, the spinal cord, small bowel and stomach as well as the target lesions (GTVs. CTVs, and PTVs). The maximum, minimum, and mean dose and dose per fraction must be documented.
6.4.6 All volumes delineated on the CT and the entire plan should be sent for QA. Digital data transfer of the plan, including target GTV, CTV and PTVs, normal tissue volumes, the 3D dose distribution and DVHs of all structures defined, is required.

1. Beam verification imaging or films are required prior to every radiation fraction. A minimum of one pair of angled verification images or film must be acquired to confirm the position of at least one isocenter. CT scans (e.g. cone beam, tomotherapy, etc.) obtained in the treatment room are recommended if possible. If not, then verification of the treatment isocenter can be performed by one of the following methods. For a conventional linear accelerator, standard port film or portal imaging verification techniques are acceptable (preferably demonstrating soft tissue, e.g., diaphragm)

2. For the BrainLAB Novalis units with first generation Novalis Body systems, the use of a virtual treatment isocenter with a radiopaque marker is recommended.

6.4.7 At least two repeat CTs must be performed in the treatment position to assure that repositioning of the PTVs are consistent with the certification tests. These images/films will not be submitted but should be available if requested.

6.4.8 As multiple tumors may be treated, the respective volumes will be labeled as follows: GTV1, CTV1 and PTV1 for the first tumor; GTV2, CTV2 and PTV2 for the second; etc. for all tumors treated (the maximal number of tumors is five).

6.5 Critical Structures

6.5.1 Normal Liver: The normal liver is defined as that portion of liver not radiographically involved by gross tumor (Normal liver volume minus GTV). In all patients, it is required that there is at least 1000 cc of normal liver. No more than 30% of the normal liver may receive more than 27 Gy, and no more than 50% of normal liver may receive over 24 Gy. See figure below:
6.5.2 **Kidney**: For patients with only one functioning kidney or creatinine > 2.0 mg/dl, no more than 10% of the functioning kidney(s) may receive 10 Gy or more. For patients with normal creatinine and two functioning kidneys, no more than 33% of the combined renal volume may receive 18 Gy or more.

6.5.3 **Spinal Cord**: Maximal permitted dose to spinal cord is 34 Gy.

6.5.4 **Small Bowel**: Maximal permitted dose to small bowel is 37 Gy for any 1cc volume.

6.5.5 **Stomach**: Maximal permitted dose to stomach is 37 Gy for any 1cc of volume.

6.5.6 **All doses are physical doses (not biologically corrected)**. Note that 37 Gy is biologically equivalent to 50 Gy in 2Gy/fraction using an \(\alpha/\beta\) of 3.

6.6 **Documentation Requirements**

6.6.1 In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.7 **Compliance Criteria**

6.7.1 See 6.1.4 Table of permitted and violation actual doses (in Gy).

6.8 **R.T. Quality Assurance Reviews**

The Radiation Oncology Co-Chairs, Alan W. Katz, M.D., M.P.H. and Laura A. Dawson, M.D. will remotely perform an RT Quality Assurance Review for each dose level after complete data for each given dose level has been received. These reviews will be ongoing and performed remotely and at the RTOG semi-annual meetings.

6.9 **Radiation Adverse Events (4/21/06)**

6.9.1 **Hepatic**: Radiation therapy should be held at any point in the protocol for CTCAE v3.0 hepatic adverse event Grade 4. It is expected that a proportion of patients will have transient elevation of liver enzymes following treatment (possibly up to Grade 3 CTCAE levels). If elevation of liver enzymes is observed up to Grade 3 levels, more frequent measurements (at least twice weekly) of the liver enzymes are recommended until the enzymes stabilize or return to baseline levels. Repeat of all Grade 4 blood work is required at least 5 days following the first abnormal lab value to determine if the Grade 4 levels are transient (defined here as < 5 days) or persistent.

Patients will be evaluated at 1-month and 3-month follow-up visits for symptoms and signs of Radiation Induced Liver Disease (RILD). RILD is a clinical syndrome of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase (ALP) relative to other transaminases that may occur 2 weeks to 3 months following radiation to the liver. ALP must be at least 2-fold increased above the baseline ALP. In this setting, due to the difficulty in distinguishing RILD from disease progression, if ascites develops at any time within 3 months following treatment, an abdominal CT and paracentesis with pathological evaluation of the ascitic fluid is required. If the ascitic fluid does not reveal malignancy and there is no evidence of disease progression in the liver or abdomen, it will be assumed that RILD has occurred. If disease progression in the liver or abdomen has occurred, no diagnosis of RILD can be made. Treatment for RILD with repeat paracenteses, diuretics (Spironolactone), and close follow-up is recommended. For ease of reporting, any patient with a Grade 3 or higher ALP (5-fold increase above upper limit of normal) in the presence of ascites and absence of disease progression will be labeled as having RILD. In patients who have elevation of liver enzymes near Grade 4 levels and/or in patients with early non-specific signs or symptoms of liver injury, close follow-up is required with repeat blood work. If no tumor progression is documented in these patients, liver injury will be presumed to be treatment related.

6.9.2 **Gastrointestinal**: The dose constraints required for the normal stomach and small intestine should limit the GI toxicity observed and it is not expected that GI toxicity will be dose limiting. However, if a portion of the stomach or small intestine is treated (> 30 Gy), H2 blockers or proton pump inhibitors will be required to attempt to decrease the chance of late GI bleeding. Patients will be followed for GI toxicity at each follow up visit.
6.9.3 **Thrombocytopenia:** Transient thrombocytopenia may occur following radiation. If the platelets drop to 50,000 cells/mm$^3$ during radiation, radiation should be held until they are over 80,000 cells/mm$^3$.

6.9.4 **Other:** The occurrence of Grade 4 adverse events, related to protocol treatment, in any organ system will prompt discontinuance of protocol therapy while appropriate physical examination, laboratory, and imaging assessments are undertaken. Protocol treatment will not be resumed in the absence of recovery from adverse events of this magnitude. Once recovery to grade 1 has occurred, treatment may continue at the discretion of the treating physician.

6.10 **Radiation Adverse Event Reporting (3/1/11)**

6.10.1 **Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements**

Adverse events (AEs) and serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application AND to the Radiation Therapy Oncology Group (RTOG) as directed in this section.

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

**Definition of an SAE:** Any adverse experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not 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.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

**AdEERS REPORTING REQUIREMENTS**

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

**Beginning April 1, 2011,** this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE v4.0. All AE reporting on the study case report forms will continue to use CTCAE version 3.0.
Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Use the patient’s case number as the patient ID when reporting via AdEERS. AEs and SAEs reported using AdEERS must also be reported to RTOG on the AE case report form (see Section 12.1).

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.

---

### CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

<table>
<thead>
<tr>
<th>3 Unexpected</th>
<th>3 Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td></td>
</tr>
<tr>
<td>24 Hour: 5 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

<table>
<thead>
<tr>
<th>3 Unexpected</th>
<th>3 Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not Required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Probable</td>
<td>Definite</td>
<td></td>
</tr>
<tr>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Hour: 5 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

- **Expedited AE reporting timelines defined:**
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
  - Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
• Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.

• Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

Beginning April 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

All appropriate treatment areas should have access to a copy of the CTCAE v4.0. All AE reporting on the study case report forms will continue to use CTCAE version 3.0.

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported as indicated in the following tables to: RTOG AE/SAE PHONE: 215-717-2762; 800-227-5463 ext. 4189 (available 24 hours/day). SAEs must be reported to RTOG within 24 hours of discovery of the event.

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event. The Data Manager will also inform the caller whether the AdEERS report must be submitted within 5 or 10 days of the initial phone report.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

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

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system. If you are reporting in CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or, 3) Treatment related secondary malignancy.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.2 Treatment for RILD with repeat paracenteses, diuretics (Spironolactone), and close follow-up is recommended.

9.1.3 H2 blockers or proton pump inhibitors are required. See Section 6.9.2

9.2 Non-Permitted Supportive Therapy (8/7/07)

9.2.1 Coumadin and IV heparin are not allowed.

9.2.2 No chemotherapy and/or targeted agents within 2 weeks prior to start of RT, during RT, and/or within 7 days of RT completion.

9.2.3 No anthracyclines within 4 weeks of RT completion.

10.0 SPECIMEN SUBMISSION

10.1 Blood Submission

In this study, a portion of the blood/serum submitted for the translational research will be banked at the RTOG Tissue Bank. The RTOG Tissue Bank at LDS Hospital in Utah acquires and maintains high quality specimens from RTOG trials. The RTOG encourages participants in protocol studies to consent to the banking of their blood (and tissue if applicable). The RTOG Tissue Bank provides specimens to investigators for future translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions including markers for response to therapy and/or predictors of toxicity.

10.2 Specimen Collection for Translational Research (4/21/06, 8/7/07)

10.2.1 A Pathology Report of the patient’s cancer diagnosis should be submitted with the blood/serum. The report must include the protocol number (RTOG 0438) and patient’s case number. The patient’s name and/or other identifying information should be removed from the report.

10.2.2 A Specimen Transmittal Form clearly stating that blood/serum is being submitted for the RTOG Tissue Bank; documenting the date of collection of serum; the protocol number (0438) and the patient’s case number; and method of storage (for example, stored at -70° C) must be included. The form can be accessed at http://www.rtog.org/pdf_forms.html?members/forms=specimen.pdf; no password required. The form must include the RTOG protocol number (0438) and the patient’s case number.

10.2.3 Blood Collection: A Specimen Collection/Shipping Kit with instructions and all required supplies can be obtained from the RTOG Tissue Bank (see Appendix III, Section A). Please request the specimen collection kit from the RTOG Tissue bank. Do not collect blood until you have received the specimen collection kit. This will require the use of a centrifuge, pipette and -70° C freezer for storage, and dry ice for shipping if sending immediately. Sites will collect blood at 1 time point: pre-treatment or during the first two weeks of treatment. At the pre-treatment or during the first two weeks, 14 ml of blood will be collected from each patient: one 5ml red top tube for serum extraction, and two 4.5 ml purple EDTA tubes for plasma extraction and DNA analysis. Carefully label each cryovial with specimen type (serum, plasma, buffy coat, etc.) and date and time collected.

Peripheral Blood Collection: Collection kits and detailed instructions for obtaining blood specimens can be obtained by contacting the RTOG Tissue bank. A brief explanation of collection requirements is found below.

Preparation of Plasma and Buffy coat:

1) Collect 5-10 mL of anticoagulated blood (EDTA). Invert tube several times to assure blood is mixed thoroughly with anticoagulant.

For a visual explanation of Buffy coat, please refer to diagram below:
2) Using three (3) 1mL cryovials, label them with the RTOG study, and patient’s case number, procedure date, and clearly mark cryovials “plasma”. Similarly, label three (3) 1mL cryovials and mark as “buffy coat”.

Process:
1. Centrifuge specimens within one hour of collection. EDTA (purple top) tubes should be centrifuged in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Remove plasma close to the buffy coat taking care not to disturb the white cell layer. Aliquot plasma into three 1mL cryovials labeled with the RTOG study and case numbers, procedure date, and clearly mark as “plasma”.
4. Remove the buffy coat cells carefully and place into the 1mL cryovials labeled “buffy coat” (it is okay if a few packed red cells below the buffy coat layer are inadvertently collected in the process).
5. Place cryovials into biohazard bag.
6. Store plasma and buffy coat specimens frozen. Buffy coat samples must be shipped to the tissue bank within one (1) week of collection.

Preparation of Serum:
1) Collect one 5-10 mL red-topped tube. Allow 30 minutes for clotting at room temperature before processing.

2) Using four (4) 1ml cryovials, label them with the RTOG study, and patient’s case number, procedure date, and clearly mark cryovials as “serum”.

Process:
1. Allow one 5ml red top tube to clot for 30 minutes at room temperature.
2. Spin red-topped tube in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
3. Aliquot serum into the four 1mL cryovials labeled with the RTOG study and case numbers, procedure date, and marked “serum”.
4. Place cryovials into biohazard bag.
5. Store serum frozen (at –80°C Celsius) until ready to ship

Specimens must be sent by overnight express to the RTOG Tissue Bank. Specimens should be sent only Monday through Wednesday. Saturday deliveries will not be accepted. Please notify the RTOG tissue bank that you are sending the specimens (801-408-5626; 801-408-2035).

Specimen Shipping: Serum, Plasma, and Buffy Coat Cells. Tubes with serum, plasma, and the buffy coat cells must be wrapped in an absorbable material (i.e., paper towels) and placed in an airtight plastic biohazard bag (i.e., resealable bag). Serum, plasma, or
buffy coat specimens requiring specific infectious precautions should be indicated clearly, with the specific source of infectious concern listed, if known. Place the biohazard bag into the Styrofoam shipping container and fill the container with a generous amount of dry ice and place the Styrofoam lid. All pertinent paperwork as described in Sections 10.2.1 and 10.2.2 should be placed on top of the Styrofoam container, but within the cardboard shipping box. Seal the outer cardboard container with plastic tape. Specimens should be sent only Monday through Wednesday due to shipping, delivery and time required for processing. Saturday deliveries will not be accepted. Be cautious to avoid shipping close to holidays as well.

Blood Samples that are received thawed or unfrozen will be discarded and a notification will be sent immediately to the Principal Investigator and Clinical Research Associate of the submitting institution. A subsequent specimen obtained as close as possible to the original planned collection date should be submitted.

10.2.5 Submit materials for Translational Research to:

LDS Hospital  
RTOG Tissue Bank, 1st Floor North  
8th Avenue and C Street  
Salt Lake City, UT 84143  
(801) 408-5626; (801) 408-2035  
FAX (801) 408-5020  
RTOG@intermountainmail.org

10.3 Reimbursement (4/21/06)
Only as specimens are requested by the protocol, or as defined for tissue banking, RTOG will reimburse submitting institutions $300 per case for buffy coat specimens and/or $100 per case for serum, or plasma. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement

10.4 Confidentiality/Storage
The RTOG Tissue Bank is approved by LDS Hospital’s IRB and meets all tissue bank regulations. (For more details visit the RTOG Patient Tissue Consent Frequently Asked Questions page at, http://www.rtog.org/tissuebank/tissuefaq.html.)

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Tissue Bank 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 Serum/blood will be analyzed for the translational research component of this protocol and 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.
# Patient Assessments

## Study Parameters

<table>
<thead>
<tr>
<th></th>
<th>Pre Treatment</th>
<th>Weekly during Tx</th>
<th>1 month F/U</th>
<th>3 Month F/U</th>
<th>Q 3 month F/U&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy test&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA, AFP, CA19-9&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>INR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Albumin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AST, ALT, ALP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with differential, platelets</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT, MRI or PET/CT of Liver</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>CT or PET/CT Chest</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup> Q 4 months for year 2, Q 6 months for year 3  
<sup>b</sup> CT of liver required Q 3 months until CR or stable residual mass or intrahepatic progression. If intrahepatic progression is documented on imaging, subsequent scans are not required. CT scans after 12 months in patients without intrahepatic progression may be done every 3 –4 months, at the treating MD’s discretion.  
<sup>c</sup> Within 72 hours prior to registration  
<sup>d</sup> Optional at the discretion of treating physician  
<sup>e</sup> If positive at baseline

## 11.2 Many of the expected biochemical and imaging changes seen after irradiation can mimic tumor progression. It is expected that patients will have an area of hypo-vascularization on CT scan that is within the high dose treated portion of the liver, larger than the original tumor, 1 month following radiation. It is also expected that an elevation of alkaline phosphatase and other liver enzymes may persist for 3 months in many patients. Most of these patients, however, will be asymptomatic. Evaluation of partial and complete response will be based on the 3-month follow-up CT scan. Only very gross increase in tumor size seen in less than that time will be scored as progressive disease. Response to radiation may continue up to 12 months follow-up and time of maximal response will be recorded. Tumor markers such as CEA can be obtained at follow up at the discretion of the treating physician.

## 11.3 Measurement of Response

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

Response Criteria: Evaluation of target lesions

*Complete Response (CR): Disappearance of all target lesions
*Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
*Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
*Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

*In-field local control
For this study, local control is defined as the lack of progressive disease in the treated fields. Hepatic failure, by contrast, is progressive disease within or outside of the irradiated fields. Hepatic failure will also be reported.

*Cause of Death
The treating physician will evaluate whether the cause of death was hepatic or non-hepatic, and/or due to tumor or due to toxicity

12.0 DATA COLLECTION
12.1 Data Submission to ITC (8/7/07)
12.1.1 Digital Data Submission may be accomplished using magnetic tape or the Internet. For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@castor.wustl.edu

For tape submission: Please contact the ITC about acceptable tape types and formats. Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

12.1.2 Data Submission to ITC Prior to Treatment of First Patient (Also see Section 5.1)
- Study-specific Facility Questionnaire relating to capabilities and QA programs;
- Treatment plan for irradiation of standardized phantom;
- Dry Run Test.

12.1.3 Data Submission to ITC for Patient Treatment (11/3/05)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>†Digital Data Submission Form (DDSI)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>CT treatment planning images, dosimetry information</td>
<td></td>
</tr>
<tr>
<td>(in 3-D) according to RTOG guidelines</td>
<td></td>
</tr>
<tr>
<td>AP and Lateral Isocenter Setup Films</td>
<td></td>
</tr>
<tr>
<td>Daily Orthogonal Isocenter Localization Films</td>
<td></td>
</tr>
<tr>
<td>*Radiotherapy Form (T1)</td>
<td></td>
</tr>
<tr>
<td>Complete Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Follow-up CT or MRI or PET/CT scans</td>
<td></td>
</tr>
<tr>
<td>†Available on the ATC web site, <a href="http://atc.wustl.edu/">http://atc.wustl.edu/</a></td>
<td></td>
</tr>
</tbody>
</table>

*Send copy to RTOG Headquarters

†Available on the ATC web site, http://atc.wustl.edu/
12.2 Summary of Data Submission (1/10/06)
Data should be submitted to:
RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>4 weeks post RT, then q3 months for the first year; q4 months for the second year; q6 months for the third year</td>
</tr>
<tr>
<td>Adverse Event form (AE) (if corresponding F1 indicates occurrence of AE(Q8))</td>
<td></td>
</tr>
</tbody>
</table>

*NOTE: There is no I1 form for this study; eligibility will be confirmed at the time of registration.

13.0 STATISTICAL CONSIDERATIONS
13.1 Study Endpoints
13.1.1 The primary endpoint of this study is to determine the maximally tolerated dose of highly conformal radiation therapy in patients with metastatic liver cancer.

13.2 Sample Size
13.2.1 Evaluation of Adverse Events
Adverse events will be graded according to the CTCAE v. 3.0 criteria. Dose limiting toxicity (DLT) is defined as any of the following occurring within 90 days from the start of treatment:

- grade 4 or 5 hepatic
- grade 4 or 5 gastrointestinal
- grade 4 or 5 thrombocytopenia
- Radiation Induced Liver Disease (RILD) requiring treatment (including diuretics).
  - RILD will be defined using the following adverse events:
    - grade 3 or higher alkaline phosphatase (ALP) in the presence of ascites occurring in the absence of disease progression
    - grade 4 hepatic liver enzyme elevations persisting for ≥ 5 days
  - any adverse event requiring interruption of therapy by ≥ 2 weeks (14 calendar days). This does not include patient desire to discontinue therapy. It does include failure for thrombocytopenia to improve to a level of 80 requiring interruption of therapy.
  - Any grade 5 treatment-related adverse event
The goal of this study is to determine the maximally tolerated dose (MTD) for patients with liver metastases, such that the rate of DLT is less than 35%.

13.2.2 Dose Escalation
The following are the four possible dose levels for his study:
- Dose Level I: 3.5 Gy for 10 fractions (35 Gy total)
- Dose Level II: 4.0 Gy for 10 fractions (40 Gy total)
- Dose Level III: 4.5 Gy for 10 fractions (45 Gy total)
- Dose Level VI: 5.0 Gy for 10 fractions (50 Gy total)

Patients will be receiving highly conformal radiotherapy starting at Dose Level II. Dose levels will be escalated by 0.5 Gy per fraction for an overall 5 Gy increase per level up to 5 Gy per fraction and a total dose of 50 Gy. Evaluable patients will be defined as any eligible patient that begins treatment. After 6 evaluable patients have been followed for a minimum of 90 days from the start of treatment, if there are 0 or 1 DLT (as defined in section 13.2.1), the dose level will be judged to be acceptable. If this occurs, then patients will begin to be accrued at the next higher dose level. Otherwise, with the exception of Dose Level II, the preceding dose level will be declared to be the MTD. If there are 2 or more DLT (as defined in section 13.2.1) at the starting dose level (Dose Level II), then the dose will be de-escalated to Dose Level I. If this occurs, then after 6 evaluable patients have been followed for a minimum of 90 days from the start of
treatment at Dose Level I, if there are 0 or 1 DLT (as defined in section 13.2.1), the 3.5 Gy per fraction for a total of 35 Gy will be declared to be the MTD. If at any time a grade 5 treatment related adverse event is observed, the study chairs will review the event.

The number of evaluable patients that will be needed depends on the number of times the dose is escalated or possibly de-escalated. If the escalation continues up through Dose Level IV, 18 evaluable patients will be required. If the dose is de-escalated after Dose Level II, then a maximum of 12 evaluable patients will be required.

With 6 evaluable patients, the probability of not escalating when the true DLT rate is 35% or higher is at least 68%. If the true DLT rate is 20%, the probability that the dose will be escalated is 66%.

13.3 Patient Accrual

This study requires extensive credentialing. Allowing time for institutions to get this protocol through their IRB and be approved through the credentialing process, accrual will begin approximately 6-9 months from the date of activation. Patient accrual is projected to be four patients per month. Accrual and evaluation of a given dose level will take approximately 5 months.

13.4 Analysis Plan

13.4.1 Interim Reporting

Interim reports with statistical analyses are prepared every six months until the primary endpoint results have been presented. In general, the interim reports will contain information about:

• the patient accrual rate with a projected completion date for open dose levels
• distribution of important prognostic baseline variables
• the frequency and severity of reported adverse events

13.4.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when the MTD has been established and each patient has been potentially followed for a minimum of 3 months following the start of radiotherapy. The usual components of the analysis are:

• tabulation of all cases entered and those excluded from the analysis, with reasons for the exclusion
• reporting institutional accrual
• distribution of important prognostic baseline variables
• observed results with respect to the endpoint described in Section 13.1
13.5 Gender and Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender and treatments and race and treatments. Due to the small sample sizes within dose levels, subgroup analyses will not be performed.

The following table gives the projected number of patients in each race and gender group.

<table>
<thead>
<tr>
<th>Ethnic Category: Total of all subjects*</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects*</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category: Total of all subjects*</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>6</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects*</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>
REFERENCES


7. Fong Y, Blumgart LH, Cohen AM. Surgical treatment of colorectal metastases to the liver. CA Cancer J Clin.


9. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of
fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma: a randomized trial. Ann Intern

10. Chang FE, Schneider PD, Sugarbaker PH, Simpson C, Culnane M, Steinberg SM. A prospective randomized
trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal

11. Carducci MA, Abrams RA, Yeo CJ, et al. Early evaluation of abdominal/hepatic irradiation and 5-
fluouracil/leucovorin infusion after pancreaticoduodenectomy. Int J Radiat Oncol Biol Phys. 1996;35:143-
50.

12. Coia LR, Aaronson N, Liggood R, Loeffler J, Priestman TJ. A report of the consensus workshop panel on the


14. Lawrence TS, Haken RKT, Kessler ML, et al. The use of 3-D dose volume analysis to predict radiation


APPENDIX I

RTOG 0438

Informed Consent for Cancer Treatment Trial

A Phase I Trial of Highly Conformal Radiation Therapy for Patients with Liver Metastases

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have liver cancer and cannot have surgery.

Why is this study being done?

The usual treatment for liver metastases is chemotherapy and sometimes surgery. Radiation therapy uses high-energy x-rays to kill cancer cells. The purpose of this study is to evaluate the use of highly conformal radiation therapy at different dose levels. This newer treatment technique delivers a high dose of radiation precisely to the cancer, with the surrounding, normal liver receiving a low enough dose that this tissue should remain free from injury. We want to find out what effects, good and/or bad, it has on you and your type of liver cancer. If this therapy can be delivered safely, we will test whether if can be used to improve survival and quality of life in future patients.

How many people will take part in the study? (1/10/06)

About 18 people will take part in this study.

What will happen if I take part in this research study?

If you agree to participate in this study, you will receive highly conformal radiation therapy to the liver. This treatment will be given once a day, 5 times a week (Monday through Friday) for two weeks.

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated.

- Physical exam
- Blood Tests
- Abdominal CT/MRI scan
- CT scan of the chest

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Physical Exams Weekly during radiation therapy
- Blood Tests Weekly during radiation therapy
Procedures being done because you are in this study include the following:

- If you agree to take part in the blood banking part of this study, a blood sample will be taken within the first two weeks that you are on the study. This blood will be used for future testing.
- You may still participate in the main part of this study without taking part in the blood part of this study. You can let us know if you agree to participate in the blood part of this study by checking the appropriate boxes at the end of this consent form.

After radiation therapy is complete you will need the following tests and procedures. They are part of regular cancer care:

- Physical exams
  - One month after treatment
  - every three months for the first year,
  - every four months for the second year
  - and then every six months for another 3 years while you are on the study.

- Blood tests
  - One month after treatment
  - every three months for the first year,
  - every four months for the second year
  - and then every six months for another 3 years while you are on the study.

- CT scan of liver
  - One month after treatment
  - every three months for the first year,
  - every four months for the second year
  - and then every six months for another 3 years while you are on the study.

How long will I be in the study? (1/10/06)

You will receive highly conformal radiation therapy to the liver. This treatment will be given once a day, 5 times a week (Monday through Friday) for two weeks. After you are finished with the radiation treatments, the study doctor will ask you to visit the office for follow-up exams and laboratory tests for at least 3 years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from stopping the radiation can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.
What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop the radiation. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to radiation therapy include those which are:

**Likely**
- Redness, dryness, or itching of the skin within the treatment area.
- Hair loss in the treatment area, which may be permanent.
- Fatigue
- Nausea
- Loss of appetite and weight loss,
- Diarrhea,
- Indigestion-type pain during treatment, which disappears after radiation treatment has ended.

**Less Likely**
- Low blood counts which can increase the risk of infection or bleeding
- Change in liver function blood tests that may indicate problems with your liver. This would usually not give any symptoms but could cause jaundice (the skin to become yellow).

**Rare but Serious**
- Inflammation of the liver which may cause fever, swelling of the abdomen and in some cases death.
- Intestinal blockage requiring surgery.
- Change in kidney function

**Reproductive risks**

You should not become pregnant or father a baby while on this study because the radiation in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Women must have a pregnancy test before participating in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that highly conformal radiation will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about highly conformal radiation as a treatment for cancer. This information could help future cancer patients.
What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting radiation treatment or care for your cancer without being in a study
- Chemotherapy
- Other treatments to eliminate the tumor by applying cold (cryotherapy) or heat (radiofrequency ablation).
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at __________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.
What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.*]
CONSENT FOR USE OF BLOOD FOR RESEARCH

ABOUT USING BLOOD FOR RESEARCH
We would like to send a small amount of your blood to a central office for future research. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases. About 3 teaspoons of your blood will be drawn once before or during the first two weeks of treatment. These samples of your blood will be sent to the central office and may be used to learn more about cancer and other diseases. Please read the information sheet called “How is Tissue Used for Research” at http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf to learn more about this research.

Your blood may be helpful for research. The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

THINGS TO THINK ABOUT
The choice to let us keep the left over blood for future research is up to you. **No matter what you decide to do, it will not affect your care.** You will continue to receive high quality treatment and supportive care. If you decide now that your tissue/blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and then any tissue/blood that remains will no longer be used for research; or, you may request that your blood be returned to you or your designee.

While _______________ [treating physician/institution] may give them reports about your health, your name, address, phone number, or any other information will not be given out; researchers will **not** know who you are. Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health record.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

BENEFITS
The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

RISKS
The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

MAKING YOUR CHOICE
Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call our research review board at _______________ [IRB’s phone number].
1. My blood may be kept for use in research to learn about, prevent or treat cancer.
   Yes    No

2. My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   Yes    No

3. Someone may contact me in the future to ask me to take part in more research.
   Yes    No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

   1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

   • For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
   • For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date _____________________________________
APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death (Karnofsky 0).</td>
</tr>
</tbody>
</table>
Instructions for use of serum, plasma, or buffy coat collection kit:

This kit includes:
- Ten (10) 1ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

Preparation of Serum:
- Using four (4) 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
1. Allow one 5ml red top tube to clot for 30 minutes at room temperature.
2. Spin red top tube in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
3. Aliquot serum into the four 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as “serum”.
4. Place cryovials into biohazard bag.
5. Use RTOG labels* to label bag.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Preparation of Plasma:
- Using three (3) 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

Process:
1. Centrifuge specimen within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully pipette and aliquot plasma into the 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as “plasma”.
4. Place cryovials into biohazard bag.
5. Use RTOG labels* to label bag.
6. Store plasma at a minimum –80°C Celsius until ready to ship.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Preparation of Buffy coat:

For a visual explanation of Buffy coat, please refer to diagram below.
Using three (3) 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “buffy coat”.

Process:
1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (can be used to send plasma samples – see above instructions).
4. Remove the buffy coat cells carefully and place into the 1ml cryovials labeled “buffy coat” (it is okay if a few packed red cells are inadvertently collected in the process). Clearly mark the tubes with date and time of collection.
5. Place cryovials into biohazard bag.
6. Use RTOG labels* to label bag
7. Store buffy coat refrigerated until shipped (shipped ambient). Buffy coat samples must be shipped to the tissue bank within one (1) week of collection.

*RTOG labels are obtained at the time of patient registration. PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:
- Include all RTOG paperwork in pocket of biohazard bag.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.
- Notify Tissue Bank personnel at LDS Hospital before you send specimens
- For Questions regarding collection/shipping please contact the Tissue Bank by phone (801) 408-5626 or (801) 408-2035; Fax at (801) 408-5020; Email holly.goold@intermountainmail.org or justin.bryner@intermountainmail.org