CONSENT FORM

Are you participating in any other research studies? ____ Yes _____ No

PURPOSE OF RESEARCH

You are invited to participate in a research study of liver perfusion (how blood flows to the liver over time). We hope to learn whether perfusion characteristics of liver metastases may be predictive of response to treatment and whether liver perfusion characteristics can be used to follow response to treatment. You were selected as a possible participant in this study because you are identified as having liver metastases.

If you decide to terminate your participation in this study, you should notify Daniel Chang, M.D. at 650-724-3547.

This research study is looking for 20 people with a primary or metastatic liver tumor, which can be imaged with Contrast 3D Ultrasound. Stanford University expects to enroll 20 research study participants.

DURATION OF STUDY INVOLVEMENT

This study will take approximately sixty minutes of your time for each Ultrasound scan. There will be 3 ultrasound scans, one prior to your scheduled Stereotactic Ablative Radiotherapy (SABR) treatment, one 0-7 days after your first fraction of radiotherapy treatment, and one 2-4 months from the start of your treatment.

PROCEDURES

If you choose to participate, Daniel Chang and his research study staff will ask you to participate in this study by undergoing an Ultrasound scan prior to your first Stereotactic Ablative Radiotherapy (SABR) treatment, one 0-7 days after your first fraction of radiotherapy treatment, and once in 2-4 months from the start of your treatment. These Ultrasound scans will be compared to the CT or MRI scans that will be done at approximately 2-4 months after the start of the SABR as part of routine care. They will be done in addition to and not instead of these routine scans. Each scan will be performed with an electromagnetic or optical tracking device attached to the Ultrasound probe.

Definity will be administered through an IV (intravenously) into a central line or port or an upper extremity vein (wrist, hand, arm) using an IV catheter. 1.3mL of Definity will then be injected for 6-8 minutes. The contrast-enhanced ultrasound will be performed within these 8 minutes.

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants will sign an IRB approved informed consent prior to participation in any study specific procedure. The participant will receive a copy of the signed and dated consent document. The original signed copy of the consent document will be retained in the medical record or research file.

If the subject is female and of child-bearing potential, pregnancy will be tested by:

- Serum βHCG or urine pregnancy test within 24 hours prior to the start of Definity® administration (the local laboratory may be used)
- Surgical history (e.g., tubal ligation or hysterectomy)
- Medical history (post-menopausal with a minimum of 1 year without menses).

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast-feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast feeding during this study, you or your child may be exposed to extra radiation.

If you have had a previous reaction to contrast agents or a history of severe allergies, please notify the operator/investigator. If you have kidney problems, please tell the operator.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.

- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Tell the Protocol Director or research staff if wear any implantable medical devices such as pacemakers, etc.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time.

Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent, to participate in this study, you should notify Daniel Chang, M.D. at 650-724-3547.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff
- Pregnancy
- The study is cancelled
- Other administrative reasons
- Unanticipated circumstances

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

You will undergo 3 additional Ultrasound scans which will take up to 1 hour of your time in total each session. Unlike CT scans, the Ultrasound Imaging does not require radiation. The contrast should not be administered to patients with blood flow shunting from one to the other heart chamber; also, in patients with known allergies to perflutren (Definity), the agent should not be administered.

DEFINITY®

The safety of DEFINITY® is well documented in multiple clinical trials involving over 1,700 patients at more than 20 U.S. medical centers. Age, gender, race and ethnicity did not affect the overall incidence of adverse events.

The overall incidence of treatment-related adverse events was 8.4%. The most frequently reported treatment-related adverse experiences were in the Central and Peripheral nervous system (3.1%), Body as a Whole (2.4%) and Gastrointestinal system (1.8%). The most frequently reported treatment-related adverse experiences were:

Headache 2.3%

Back/renal pain 1.2%

Flushing 1.1%

Nausea 1.0%

Follow Definity administration, there have been reported adverse reactions involving the heart and the lungs. Most serious reactions occur within 30 minutes of administration; however, you will be in the care of the physician performing the scan and the hospital staff for greater than 30 minutes post Definity injection.

You should not participate in this study if you have a history of hypersensitivity to Definity, have a history of pulmonary hypertension (increased pressure in the pulmonary arteries), if you are pregnant or trying to become pregnant, or if you have other any other medical conditions which would prevent you from participating in this study.

The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

There will be an Optical and/or Electromagnetic tracking tools attached to the Ultrasound Transducer that will not be in contact with the patient. There is very little risk to the patient associated with optical tracking as there is no transfer of energy to the patient. With electromagnetic tracking there may be electromagnetic interference with implantable devices such as pacemakers, etc. Electromagnetic tracking will not be used (powered off) if you have told the Program Director that you are wearing any implantable medical device to eliminate risk from electromagnetic interference.

POTENTIAL BENEFITS

Although there will be no direct benefit at the time of the study, the knowledge we gain may provide future benefit to subjects who are diagnosed primary liver metastases and need to be monitored for treatment response.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

The alternative is not to participate. Your treatment and care will not be affected by your decision to participate or not participate. Participation/non-participation will not affect the routine radiologic evaluation of studies and clinical care of the patients.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

If you decide not to participate, tell the Protocol Director. You will still receive care for your disease and will not lose any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The purpose of this study is to test the feasibility of contrast enhanced 3D Ultrasound of the liver to evaluate whether perfusion characteristics (measurement of blood flow) of primary or metastatic liver tumors can predict tumor response to treatment. You were selected as a possible participant in this study because you are identified as having primary liver tumor metastases and you are scheduled to be treated with Stereotactic Ablative Radiotherapy (SABR) for the first time. Your liver perfusion data will be deidentified and then analyzed. Images without any identification may be used in clinical presentations or publications.

Do I have to sign this authorization form?
Signing this form is not a condition for receiving any medical care outside of this study. You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

Dr. Daniel Chang
Associate Professor
Department of Radiation Oncology
Stanford University Medical Center
875 Blake Wilbur Drive CC-G231
Stanford, California 94305-5105

What Personal Information Will Be Used or Disclosed?

Your health information related to this study may be used or disclosed in connection with this research study which may include MRN, age at onset of disease, extent of disease, current age, weight, height, therapies to date (e.g. medications, interventions), imaging information and any other information related to primary liver tumor metastases.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director (Dr. Daniel Chang)
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on January 1, 2059, or when the research project ends, whichever is earlier.

_____ _____

Signature of Adult Participant Date

_____

Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment: You will not be paid to participate in this research study.

Costs: If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed. Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.** If costs of care related to such an injury are not covered by your insurer,

managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital. You do not waive any liability rights for personal injury by signing this form.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONTACT INFORMATION

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask Daniel Chang, M.D. at 650-724-3547. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;

- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ☐ Yes ☐ No

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of Witness *Date*
(e.g., staff, translator/interpreter, family member)

_____
Print Name of Witness

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*

- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - Must be signed by the witness AND the Person Obtaining Consent (POC).
  - The non-English speaking participant/LAR does not sign the English consent.
  - The non-English speaking participant/LAR should not sign the HIPAA participant line
  - If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.