Feasibility of 3D Perfusion Ultrasound for Liver Cancer SABR Planning and Response Evaluation

Study Protocol and Statistical Analysis Plan

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STANFORD CANCER INSTITUTE
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eProtocol # **IRB-30071** | OnCore # **HEP-0048**

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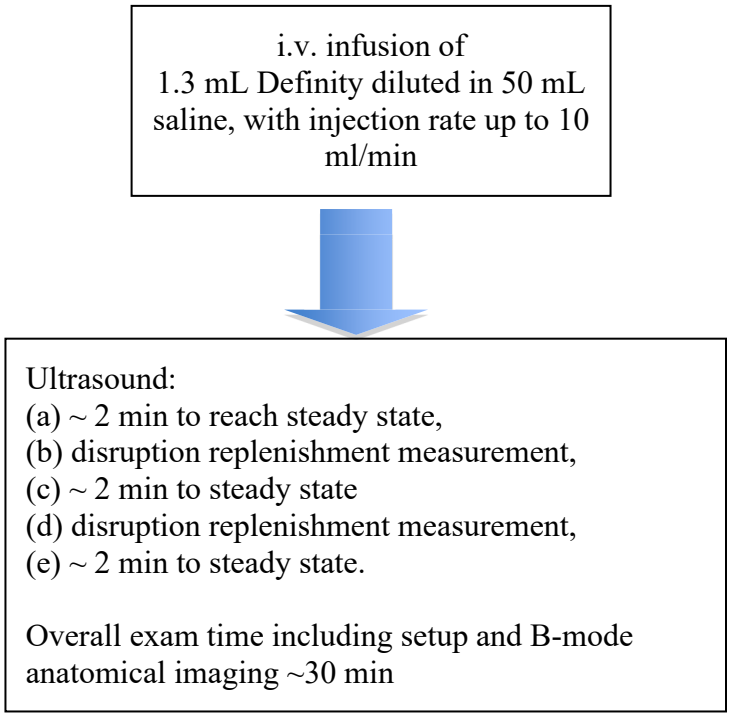
PROTOCOL SYNOPSIS

TITLE	**Feasibility of 3D perfusion ultrasound for liver cancer SABR planning and response evaluation**
STUDY PHASE	Pilot
INDICATION	Evaluation of primary and/or metastatic liver tumor perfusion characteristics before and after Stereotactic Ablative Radiotherapy (SABR).
INVESTIGATIONAL AGENTS	Definity® Contrast Agent (perflutren lipid microspheres) for Ultrasound of the Liver.
PRIMARY OBJECTIVE(S)	The primary objectives of this pilot study is to (1) determine the feasibility and reproducibility of 3D contrast enhanced ultrasound imaging in liver patients undergoing Stereotactic Ablative Radiotherapy and (2) evaluate whether there are treatment induced early changes in imaging metrics derived from 3D contrast enhanced ultrasound. This study will provide valuable insight as to the potential of baseline and/or early post-treatment 3D ultrasound perfusion characteristics (measurements of blood-flow) of primary and metastatic liver tumors to predict tumor response to treatment.
TREATMENT SUMMARY	The study does not modify existing standard of care treatment. It only adds baseline and early contrast-enhanced ultrasound imaging with the DEFINITY® ultrasound contrast agent. DEFINITY® Vial (Perflutren Lipid Microsphere) for Injectable Suspension is Lantheus Medical Imaging Inc.'s non-blood based ultrasound contrast agent approved by the United States Food and Drug Administration (FDA). DEFINITY® is the first approved ultrasound contrast agent in the U.S. that offers flexible dosing and administration through IV bolus injection and continuous IV infusion.
SAMPLE SIZE	20
STATISTICAL CONSIDERATIONS	

SCHEMA

The following 3D Definity-enhanced ultrasound procedure will be performed at three patient visits: once prior to radiotherapy after the simulation CT scan, once at 0-7 days after the first fraction of radiotherapy treatment, and once in 2-4 months following the start of radiotherapy.



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BID	Twice daily
CBC	Complete blood count
CI	Confidence interval
CRF	Case report/Record form
CR	Complete response
CT	Computed Tomography
DCE	Dynamic Contrast Enhanced
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
FDA	Federal Drug Administration
ECOG	Eastern Cooperative Group Performance Status
GI	Gastrointestinal
Hgb	Hemoglobin
HTN	Hypertensions
IND	Investigational New Drug application
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
MR	Magnetic Resonance
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RCC	Renal Cell Carcinoma
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SOP	Standard Operating Procedure
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
US	Ultrasonography, Ultrasound
WBC	White blood cell
3D	Three Dimensional
4D	Four Dimensional

1 OBJECTIVES

1.1 Primary Objective

The primary objectives of this prospective pilot study is to (1) determine the feasibility and reproducibility of 3D contrast enhanced ultrasound imaging in liver cancer patients undergoing Stereotactic Ablative Radiotherapy and (2) evaluate whether there are treatment induced early changes in imaging metrics derived from 3D contrast enhanced ultrasound. This study will provide valuable insight as to the potential of baseline and/or early post-treatment 3D ultrasound perfusion characteristics (measurements of blood-flow) of primary and metastatic liver tumors to predict tumor response to Stereotactic Ablative Radiotherapy. Our underlying goal is to assess whether early perfusion changes at 0-7 days after SABR initiation can be used as a non-invasive early biomarker for treatment response assessment.

1.2 Secondary Objectives

Evaluate the feasibility of contrast-enhanced ultrasound-to-CT fusion by assisting three-dimensional (3D) perfusion ultrasound (US) imaging with optical and electromagnetic tracking of the ultrasound probe on patients with liver cancer that will undergo CT for treatment planning and/or response evaluation.

2 BACKGROUND

2.1 Study Disease

Vascular damage and response have been implicated in the response to radiotherapy at ablative doses. Perfusion MR, CT, SPECT, and PET can be used to detect therapy-induced changes in tumor vascularity. However, radiation exposure from multiple exams (CT/PET/SPECT), restrictions on the use of contrast in patients with renal insufficiency (MR/CT), limited access (MR/SPECT/PET), and elevated cost render these modalities less practical for frequent routine imaging. Two-dimensional (2D) contrast-enhanced perfusion ultrasound (US) of injected microbubbbles, is non-ionizing, accessible, and relatively inexpensive but fundamentally limited in quantification by the three-dimensional (3D) heterogeneity of tumor perfusion and the 3D nature of tumor motion.

These fundamental limitations of 2D US imaging have been recently overcome by the development of novel real-time 3D US transducers that make 3D dynamic US perfusion imaging in patients possible. Our goal is to assess the utility of 3D US perfusion for liver SABR planning and response evaluation.

2.2 Study Agent/Device/Procedure

DEFINITY® is comprised of lipid-coated microspheres filled with octafluoropropane gas. DEFNITY® does not contain any human or animal materials. The microspheres contained in DEFINITY® have a mean diameter of 1.1 to 3.3 microns (in vitro measurements). The

microspheres are stable and small enough to pass through the pulmonary capillaries. The microbubbles are eliminated via the breath.

For cardiac application, after activation of DEFINITY® and intravenous injection, the physical acoustic properties of activated DEFINITY® provide contrast enhancement of the endocardial borders during echocardiography. The perflutren lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood (21).

In this study it is hoped that perfusion characteristics of the lesion will predict whether a patient will respond to therapy.

For clinicaltrials.gov compliance

This is an FDA approved drug for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

This investigation is proposed to be conducted under IND exemption per 21CFR§312.2(b) and IRB approval.

2.3 Rationale

Medical imaging plays a prominent role in the clinical evaluation of cancer therapies. The Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate anatomic response to treatment were developed to standardize tumor measurements in routine clinical care and in clinical trials (1). With the use of RECIST, patients are classified to either respond, stabilize, or progress, depending on treatment-induced changes in tumor size measured on computed tomographic (CT) scans or magnetic resonance (MR) images. However, cancers treated with the new generation of targeted therapies (e.g., such as anti-angiogenic agents) often show little change in size during the 1st months of therapy despite substantial clinical benefit. Radiologic criteria that additionally take into account functional changes in the enhancement of lesions on contrast material–enhanced CT scans (3,4) or dynamic contrast-enhanced (DCE) MR images (5) have helped to identify patients who went on to show clinical benefit as early as 9 weeks into treatment (6).

DCE ultrasonography (US) can be used to quantify microbubble enhancement and can be used to assess functional change in response to antiangiogenic treatment of patients with metastatic RCC. The advantage of DCE US are the lack of ionizing radiation (as compared to CT) and the relatively low costs and availability (compared to MRI). Furthermore, US contrast agents are not nephrotoxic and, therefore, can be injected with renal insufficiency. Recent research showed feasibility of two-dimensional (2D) DCE US in patients. Lamuraglia et al (7) described DCE US criteria to classify the response to sorafenib (Nexavar; Bayer, West Haven, Conn). Correlations between changes in DCE US parameters, during the first 2 weeks of treatment with sorafenib, and overall survival have also been reported (8), while revascularization of tumors following the cessation of treatment with bevacizumab (Avastin; Hoffmann-La Roche, Basel, Switzerland) has been characterized by using a DCE US–derived perfusion index, which correlates with histologic findings in a murine tumor model (9). Other preclinical studies of antiangiogenic treatments have demonstrated correlations between DCE US and DC CT measurements (10) and among DCE US, DCE MR

imaging, and fluorine 18 fluorodeoxyglucose positron emission tomographic measurements (11).
Dynamic contrast-enhanced ultrasonography (DCE-US) is a technique that can be used to detect microvessels and quantitatively assess solid tumor perfusion using raw linear data (15). It involves Doppler ultrasound after injection with a contrast agent, which enhances the vessel signal (16, 17). Doppler ultrasonography can accurately detect and characterize blood flow in vessels with a diameter as low as 100 μm (14). Doppler signals provide functional information on neovascularity by indicating the maximal velocity in tumor supply vessels (16). The addition of perfusion software and microbubble contrast agents has further improved the technique, enabling the visualization of vessels with a diameter as small as 40 μm (17). To date, DCE-US has been used in a number of clinical trials with receptor tyrosine kinase inhibitors. These studies have indicated that DCE-US parameters may be correlated with tumor responses, for example in RCC with sorafenib (18, 19) or in gastrointestinal stromal tumors (GIST) treated by imatinib (20).

Dynamic US can be used to quantify dynamic changes in tumor vascularity as early as 3 days after bevacizumab administration in patients with HCC. These early changes in tumor perfusion may be predictive of tumor response at 2 months, progression-free survival, and overall survival, and they may be potential surrogate measures of the effectiveness of antiangiogenic therapy in patients with HCC (13).

However, a major limitation of current perfusion US studies is that all imaging is performed in a limited two-dimensional (2D) field-of-view which cannot capture the heterogeneity of tumor perfusion throughput its volume. Recent animal studies have shown that a 2D sampling of tumor perfusion may be highly biased by the position of the US transducer placement over the tumor and that entire-tumor three-dimensional (3D) imaging approaches are of paramount importance to translate non-invasive perfusion US into a clinical applications (12).

Through our research collaboration with Philips, we have acquired a new FDA approved 3D US transducer that allows 3D DCE-US perfusion imaging of an extended field-of-view. This allows for the first time to quantify tumor perfusion of the entire volumetric extent of a liver metastasis and will likely substantially improve reliability and accuracy of US perfusion imaging in the clinical arena.

In this pilot study, we will assess performance of 3D US perfusion imaging in patients with liver tumors undergoing SABR to evaluate the feasibility of performing 3D perfusion CEUS in this patient population and understand whether early changes in perfusion parameters are introduced as a result of the SABR treatment.

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

This is a pilot, single-center study in subjects with liver tumors. The primary objectives of this prospective pilot study is to (1) determine the feasibility and reproducibility of 3D contrast

enhanced ultrasound imaging in liver cancer patients undergoing Stereotactic Ablative Radiotherapy and (2) evaluate whether there are treatment induced early changes in imaging metrics derived from 3D contrast enhanced ultrasound. This study will provide valuable insight as to the potential of baseline and/or early post-treatment 3D ultrasound perfusion characteristics (measurements of blood-flow) of primary and metastatic liver tumors to predict tumor response to Stereotactic Ablative Radiotherapy.

The target lesion will be located at the simulation CT scan for treatment planning. Prior to Definity® administration, gray scale and Doppler (color or power imaging) ultrasound investigations of the target lesion will be performed using commercially available ultrasound equipment and standard techniques (B-mode or Harmonic imaging) to study the anatomy of the target lesion and surrounding parenchyma.

Immediately after the unenhanced ultrasound evaluation, contrast-enhanced ultrasound will be performed, according to the procedures described to study the lesion vascularity in comparison to the surrounding parenchyma. Definity® will be administered intravenously through a central line or in a peripheral vein.

Unenhanced ultrasound and Definity®-enhanced ultrasound images will be recorded and stored anonymously.

The primary analysis will be based on comparison of the readout (perfusion parameters of the lesion) at baseline, at 0-7 days after the first fraction of radiotherapy treatment, 2-4 months following the start of radiotherapy, and the clinical outcome of the patient, including findings on routine CT and PET-CT imaging.

This is a Single Group, Open Label Study designed to evaluate to evaluate as a primary outcome feasibility and efficacy.

2.5 Correlative Studies Background

Correlative studies background is not provided, as there are no correlative studies planned.

3 PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

All patients consulted for Stereotactic Ablative Radiotherapy (SABR) treatment of primary or metastatic liver tumors will be considered for this study.

3.1 Inclusion Criteria

3.1.1 Ability to understand and willingness to sign the written informed consent document

3.1.2 Patient with primary liver tumor or metastasis scheduled for Stereotactic Ablative Radiotherapy (SABR)

3.1.3 Patient is at least 18 years of age. No gender/race-ethnic restrictions.

3.1.4 Performance status (ECOG) between 0-3

3.1.5 History and Physical done within 4 weeks of enrollment.

3.2 Exclusion Criteria

3.2.1 Patient has previously been enrolled in and completed this study.

3.2.2 Known right to left cardiac shunt, bidirectional or transient.

3.2.3 Patient has any medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data, achieving study objectives, or completing the study and/or post-dose follow-up examinations.

3.2.4 History of hypersensitivity to perflutren

3.2.5 History of pulmonary hypertension

3.2.6 Patients who are pregnant or are trying to become pregnant

3.3 Informed Consent Process

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.

3.4 Randomization Procedures

This is an open label study.

3.5 Study Timeline

Definity®-enhanced ultrasound at baseline will be completed prior to delivery of SABR treatment. The patient will then be re-scanned 0-7 days post their first fraction of radiation treatment. An additional US scan will be performed 2-4 months (when patient comes to routine follow-up CT and PET-CT imaging).

Primary Completion:

The expected study completion timeline is within 24 months from when the study opens.

Study Completion:

The expected study completion timeline is within 24 months and 1 day from when the study opens.

4 TREATMENT PLAN

Pregnancy Test

If the subject is female and of child-bearing potential, exclude the possibility of pregnancy by:

- testing serum βHCG or urine pregnancy test prior to the start of Definity® administration (the local laboratory may be used)
- obtaining surgical history (e.g., tubal ligation or hysterectomy)
- obtaining medical history (post-menopausal with a minimum of 1 year without menses). See Appendix B.

Safety Assessments Adverse Events

We will record all untoward medical events in the Adverse Event section of the CRF. Only post-dose untoward medical occurrences will be tabulated as adverse events.

Imaging Procedures

The unenhanced ultrasound and Definity®-enhanced images will be performed, in the same session, using commercially available (FDA-approved) ultrasound systems with appropriate contrast-specific capabilities. The ultrasound examination, both unenhanced and contrast-enhanced should be performed by qualified personnel with at least 3 years of experience in liver ultrasound or Fellows with appointment in Stanford Radiology

Definity® will be administered intravenously into a central line or port or an upper extremity vein (e.g., a vein in the cubital fossa or dorsal aspect of the wrist or hand) using a catheter while observing aseptic technique. Immediately following the Definity® injection, 5 mL to 10 mL of saline will be administered to flush the intravenous line of any remaining contrast agent. Subjects will be monitored for any untoward medical occurrences listed in a study case report form or note for 30-60 min after Definity® injection is initiated.

Imaging parameters:

Contrast-specific imaging will be performed with an abdominal matrix-array transducer (PM mode, Philips iU22 with X6–1; Philips Ultrasound, Bothell Wash) which is a low-mechanical-index (MI) nonlinear imaging (MI, 0.06) that allows visualization of the micro-bubbles nondestructively Time-gain controls will be aligned to the center line. Receive gain, dynamic range, image depth, and transmit focus will be optimized for each patient at the baseline examination, and then identical settings will be used at follow-up. Disruption-replenishment data will be collected for approximately 30 seconds following 1-second, 8-frame flash at an MI of 1.3.

Unenhanced Ultrasound

During the unenhanced ultrasound examination, the morphology and localization of the target FLL will be evaluated using gray scale ultrasound and color/power Doppler modes. The target lesion will be identified using gray scale ultrasound and its location will be identified using Coineaud's system. Then, either color Doppler imaging or power Doppler imaging should be used to study the morphology/vascularity of the target lesion and surrounding parenchyma. Specific measurements with Spectral Doppler may be used depending on the presence and/or visualization of vessels.

Contrast-Enhanced Ultrasound Examination
The following protocol will be used, according to published literature (23):

An infusion of 1.3 mL of Definity diluted in 50 mL of saline will be administered using an injection pump. Two minutes will be allowed for the infusion to reach a steady level before disruption-replenishment. Measurements will be performed two times (to assess reproducibility of the replenishment curves analysis following microbubble destruction and replenishment of microbubbles into the US field-of-view).

4.1 General Concomitant Medication and Supportive Care Guidelines

Concomitant Medications
Given that concomitant meds are neither indicated nor no counter-indicated as per the Definity Prescription Information the Concomitant Medication section of the Case Report Form (CRF) will not be filled.

4.2 Criteria for Removal from Study

Subject will be discontinued from the study if the subject:

- withdraws consent.
- during the course of the study manifests condition matching exclusion criteria.
- will not be able to adhere to protocol timeline due to scheduling or other conflict
- has an adverse event that, in the opinion of the Investigator, requires the subject's Discontinuation.

5 INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

DEFINITY® Vial for (Perflutren Lipid Microsphere) Injectable Suspension is Lantheus Medical Imaging Inc.'s non-blood based ultrasound contrast agent approved by the United States Food and Drug Administration (FDA). DEFINITY® is the first approved ultrasound contrast agent in the U.S. that offers flexible dosing and administration through IV bolus injection or continuous IV infusion. (21)

The FDA has approved activated DEFINITY® for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

DEFINITY® is comprised of lipid-coated microspheres filled with octafluoropropane gas. DEFNITY® does not contain any human or animal materials. The microspheres contained in DEFINITY® have a mean diameter of 1.1 to 3.3 microns (in vitro measurements). The microspheres are stable and small enough to pass through the pulmonary capillaries. (21,22, 23)
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%

In clinical trials, serious cardiopulmonary events occurred in 19 (1.1%) patients. None of these events, which included 8 deaths and 11 other serious adverse events, was attributed to DEFINITY®, but to progression of underlying disease.

CONTRAINDICATIONS
DEFINITY® is not to be administered in patients with known or suspected right-to-left, bi-directional or transient right-to-left cardiac shunts, by intra-arterial injection, or to patients with known hypersensitivity to perflutren. In post marketing use, rare but serious cardiopulmonary or anaphylactoid reactions have been reported during or shortly following perflutren-containing microsphere administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions. It is not always possible to reliably establish a causal relationship to drug exposure due to the presence of underlying cardiopulmonary disease. Thus all patients need to be assessed for the presence of any condition that precludes DEFINITY® administration and it is recommended that resuscitation equipment and trained personnel are readily available.

Devices:
In addition, there will be an Optical and 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 (Optical tracking ony) if the patient has an implantable medical device to eliminate risk from electromagnetic interference.

5.2 Availability

Definity is available from the Hospital Pharmacy.

5.3 Agent Ordering

Definity® is FDA approved and routinely used for patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. It may be requested from the central hospital pharmacy with a signed physician order for the subject with the quantity to dispense. It may also be bought from the central hospital pharmacy for storage within the department of Radiation Oncology.

5.4 Agent Accountability

Central pharmacy will deliver Definity® to the Department of Radiation Oncology, where it will be stored in a temperature controlled refrigerator in the locked office of Protocol Director, Dr. Daniel Chang. The study coordinator (ACRC) will keep both a temperature log and dispensing log according to IDS standards next to the refrigerator. All subjects will be entered into OnCore.

6 DOSE MODIFICATIONS

There are no dose modifications planned for this study.

7 ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

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%
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Nausea	1.0%

In clinical trials, serious cardiopulmonary events occurred in 19 (1.1%) patients. None of these events, which included 8 deaths and 11 other serious adverse events, was attributed to DEFINITY®, but to progression of underlying cardiovascular disease.

7.2 Adverse Event Reporting

7.2.1 Adverse Events

Adverse events will be assessed for 30-60 minutes after each injection of Definity®.

Adverse events will be graded according to CTCAE v4.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution. SAEs must be reported while on study and up to 30 days after the last dose of the study treatment is given.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

7.2.2 AE Definition

An adverse event (AE) is any untoward medical occurrence in a subject or a clinical trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with the use of the product.

Any untoward medical occurrence that occurs outside the period of subject follow-up defined in the protocol is not required to be collected in the AE section of the CRF.

An existing condition, which is detected by the diagnostic procedure conducted to test the efficacy of an investigational contrast agent, is not considered an AE.

Symptoms or medically significant laboratory or instrumental (e.g., electrocardiographic) abnormalities of a pre-existing condition, such as cancer or other disease, should not be considered an AE. However, occurrence of new symptoms, laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, are considered AEs.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e., the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgment),
- is a congenital anomaly/birth defect,
- is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.
- A non-serious adverse event is any adverse event that does not meet the criteria listed above for a SAE.

7.2.3 Unanticipated Problem (UP)

Per Stanford IRB, UPs are events involving risks to participants or others and must meet ALL 3 criteria below:

1. Unexpected: in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents, and (b) the characteristics of the subject population being studies; AND

2. Related to participation in the research: or there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; or if a device is involved, probably caused by, or associated with the device; AND

3. Harmful: suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

UPs generally will warrant consideration of substantive changes in the research protocol or informed consent process/document, or other corrective actions, in order to protect the safety, welfare, or rights of subjects or others.(27) Due to this, UPs will be reported promptly to Stanford IRB following the below guidelines.

A UP may also be an AE or SAE and can be noted as both on CRFs and in OnCore.

Reporting UPs
UPs should be entered into OnCore and reported within 24 hours of learning of the event.

7.2.4 AE Relationship to the Investigational Product:

Every effort will be made to determine the cause of each adverse event. The correlation between the investigational product and the adverse event will be classified as follows:

1. **Probable**

a) The event follows a reasonable temporal sequence from administration of the investigational product;

b) The event follows a known response pattern to the investigational product;

c) The event cannot be reasonably explained by any of the following features:

- the known characteristics of the subject's clinical state, or
- other therapy administered
- or the diagnostic/interventional procedure;

d) There is evidence of partial or complete disappearance of the event after withdrawal of the product (positive challenge).

e) The event follows a known response pattern to the investigational product but the event could have been produced by any of the following features:

- the subject's clinical state, or
- other therapy administered, or
- the diagnostic/interventional procedure.

f) The event does not meet any of the above criteria because of:

- conflicting data and/or
- dubious or insufficient/poor evidence, or
- the event is not judged as related or not related.

g) The event is either a pre-dose event or is definitely due to causes separate from the administration of the investigational product, i.e.

- documented pre-existing condition
- technical and manual procedural problems
- concomitant medication
- the subject's clinical state
- the event is judged as not related and does not fall under any of the above points.

2. **Possible**
3. **Not Related**
4. **Unknown**

7.2.5 AE Action Taken:

0. None

1. Change in the investigational product administration (including brief interruption of administration of total dose and early termination of administration, i.e., dose reduction)
2. Drug treatment required (a medication was prescribed or changed; record in the Concomitant Medication section of the CRF)
3. Non-drug treatment required (a non-drug treatment was prescribed or changed, record under "Comments" in the Adverse Event section of the CRF)
4. Hospitalization or prolonged hospitalization
5. Diagnostic or clinical test(s) conducted (attach a copy of the results to the CRF)
6. Subject discontinued from the study

7.2.6 AE Subject Outcome:

1. Recovered without sequelae.
2. Recovered with sequelae (describe the sequelae under "Comments" in the Adverse Event section of the CRF)
3. Not Recovered, event on-going (follow the subject until a definite outcome can be determined. When follow-up data are collected, report follow-up information under "Comments" in the Adverse Event section of the CRF; if the event is serious, fill in a follow-up SAER)
4. Died (list primary cause of death under "Event Description" in the Adverse Event section of the CRF)

8 CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

There are no Laboratory Correlative Studies

9 STUDY CALENDAR

	Enrollment	Baseline	0-7Days after the first fraction of radiotherapy treatment	2-4 Months from starting SABR
Informed consent	X[a]			
H&P	X[a,f]			
Eligibility	X[a]			
Documentation of Consent	X[a]			
ECOG PS	X[a,e]			
Study Registration	X[a]			
Simulation CT		X		
AE Evaluation		X[b,d]	X[b,d]	X[b,d]
Definity® /Ultrasound		X	X	X
B-HCG or urine pregnancy test	X[a,c]			

a. Prior to study procedures.
b. Baseline assessment prior to Definity© injection .
c. Required for women who are not post-menopausal as defined in Appendix B and who are not excluded from possibility of pregnancy by a physician.
d. Documented 30-60 minutes after Definity © injection
e. ECOG specified in medical note prior to eligibility confirmation, defined in Appendix C.
f. H&P done within 4 weeks of enrollment.

10 MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

10.1 Primary and Secondary Outcome measures

10.1.1 Relevant Subset

All patients will be considered for the secondary outcome.

10.1.2 Measurement Definition

Primary Objective:

The primary objectives of this pilot study is to (1) determine the feasibility and reproducibility of 3D contrast enhanced ultrasound imaging in liver patients undergoing Stereotactic Ablative Radiotherapy and (2) evaluate whether there are treatment induced early changes in imaging metrics derived from 3D contrast enhanced ultrasound.

10.1.3 Measurement Methods

Contrast Agent Administration

The US contrast agent will be perflutren lipid microspheres (Definity; Lantheus Medical Imaging, North Billerica, Mass). Patients will receive an infusion of 1.3 mL of perflutren lipid microspheres diluted in 50 mL of saline delivered up to 10 mL/min by using an injection pump (Medfusion 3500; Smiths Medical, Dublin Ohio). Two minutes will be allowed for the infusion to reach a steady level before disruption-replenishment measurements were performed.

Imaging System Parameters

Contrast-specific imaging will be performed with an abdominal matrix-array transducer (PMPI mode, Philips iU22 with X6–1; Philips Ultrasound, Bothell Wash). Low-mechanical-index (MI) nonlinear imaging (MI, 0.06) will allow visualization of the microbubbles nondestructively. Persistence and other post-processing will be disabled to minimize temporal and spatial averaging. Time-gain controls will be aligned to the center line. Receive gain, dynamic range, image depth, and transmit focus will be optimized for each patient at the baseline examination, and then identical settings will be used at follow-up. Disruption-replenishment data will be collected for approximately 30 seconds following each 1-second, 8-frame flash at an MI of 1.3. Frame rates ranged from 7 to 12 Hz. Data will be stored in a compressed "native" format to allow linearization.

10.1.4 Measurement Time Points

The probe will be held steady throughout each acquisition. During the infusion, continuous 3D data will be collected and two disruption-replenishment acquisitions will be performed.

10.1.5 Image analysis and derived measures

Volume of interest (VOIs) encompassing the lesions will be defined on the 3D DCE-US. After linearization of the 3D DCE-US signal (to make it proportional to contrast concentration), time intensity curves (TIC) will be generated for the mean contrast concentration within the VOI. After standard TIC fit curve parameters will be extracted to serve as measures that describe perfusion. These measures include: relative blood volume, mean flow velocity, and relative blood flow = relative blood volume x mean flow velocity.

10.2 Secondary Outcome

In this pilot study of 20 patients, we will focus on the primary objective: feasibility, reproducibility and assessment of changes in metrics (indices) derived from 3D contrast enhanced ultrasound. Our secondary objective is to evaluate the feasibility of contrast-enhanced ultrasound-to-CT fusion by *assisting three-dimensional (3D) perfusion ultrasound (US) imaging with optical and electromagnetic tracking of the ultrasound probe* on patients with liver cancer that will undergo CT for treatment planning and/or response evaluation. Thus the secondary outcome will be the relative number of ultrasound examinations in which fusion to CT was possible.

11 REGULATORY CONSIDERATIONS

11.1 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.2 Data Management Plan

Case Report Forms (CRFs) are printed or electronic documents designed to record all protocol-related information on each trial participant. CRFs should summarize the clinical findings and observations necessary to ensure safety of participants on the study, and to document the study outcomes. CRFs are required by the SRC for all Interventional studies. Study-specific CRFs will document treatment outcomes for data analysis. CRFs will be developed manually and will be maintained by the study coordinator.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical Design

The primary objectives of this pilot study is to (1) determine the feasibility and

reproducibility of 3D contrast enhanced ultrasound imaging in liver patients undergoing Stereotactic Ablative Radiotherapy and (2) evaluate whether there are treatment induced early changes in imaging metrics derived from 3D contrast enhanced ultrasound. Specifically, we will perform exploratory analysis for testing the following hypotheses:

12.2 Outcome Measurements:

Primary endpoints:

- To characterize the reproducibility of 3D DCE-US by estimating the concordance correlation coefficient (30,31) for repeated 3D DCE-US measures (see Section 10.1.6, Image analysis and derived measures).
- To determine the variance in the relative changes of repeated 3D DCE-US measures.
- To provide summary statistics of the relative changes in 3D DCE-US measures before and after SABR.

Secondary endpoint:

- To provide relative number of 3D DCE-US examinations in which fusion to CT is possible with tracking of the ultrasound transducer.

12.3 Analysis plan:

This is an exploratory pilot study designed with a primary objective to evaluate (1) the feasibility and reproducibility of 3D DCE-US in cancer patients undergoing SABR for liver lesions and (2) the magnitude of the differences in perfusion measures before and after SABR. Future studies will seek to understand if 3D DCE-US perfusion baseline values or changes have predictive power for clinical endpoints in SABR treatments. The knowledge gained from this study will aid in calculating the appropriate sample size for such studies. The main focus here is on understanding the discrepancies in measures from repeated acquisitions and differences in measures before and after SABR. Thus the data will be analyzed as follows:

- Estimation the concordance correlation coefficient (30, 31) for repeated 3D DCE-US measures (see Section 10.1.6, Image analysis and derived measures) as a measure of reproducibility. Concordance correlation values between 0.9 and 0.95 will be interpreted as moderate reproducibility and values between 0.95 and 0.99 will be interpreted as substantial reproducibility based on the following scale for the concordance correlation coefficient: Poor, < 0.9; moderate, 0.9 – 0.95; substantial 0.95 – 0.99, nearly perfect >0.99.
- Histogram analysis and summary statistics (mean, median, variance, and maximum) of the relative changes (difference/average) of repeated 3D DCE-US measures. (Small variance and zero mean of the relative changes will be indicative of highly reproducible 3D DCE-US measures).
- Histogram analysis and summary statistics (mean, median, variance, and maximum) of the relative changes (difference/baseline) in 3D DCE-US measures before and after SABR. Large mean differences will be indicative of treatment (SABR) effect.

- Calculation of proportion of 3D DCE-US examinations in which fusion to CT is possible with tracking of the ultrasound transducer. Calculation of proportion of 3D DCE-US examination in which repeated scans is successful. These proportions are metrics of feasibility (target 80%-90%). Successful fusion to CT in particular is important metric is 3D DCE-US is to be explored as add-on imaging for treatment planning in further studies.

12.4 Sample Size

20 patients.

12.5 Sample size justification

This study is an exploratory study and there is currently not sufficient information to perform a sample size calculation.

13 REFERENCES

1. Therasse P , Arbuck SG , Eisenhauer EA , et al . New guidelines to evaluate the response to treatment in solid tumors: European Organizationfor Research and Treatment of Cancer, National Cancer Institute of the United States,National Cancer Institute of Canada . J Natl Cancer Inst 2000;92 (3): 205 – 216 .

2. Choi H , Charnsangavej C , Faria SC , et al .Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria . J Clin Oncol 2007 ; 25 (13): 1753 – 1759 .

3. Nathan PD , Vinayan A , Stott D , Juttla J ,Goh V . CT response assessment combining reduction in both size and arterial phase density correlates with time to progression in metastatic renal cancer patients treated with targeted therapies . Cancer Biol Ther 2010 ; 9 (1): 15 – 19 .

4. Hahn OM , Yang C , Medved M , et al . Dynamic contrast-enhanced magnetic resonance imaging pharmacodynamic biomarker study of sorafenib in metastatic renal carcinoma . J Clin Oncol 2008 ; 26 (28): 4572 – 4578 .

5. Smith AD , Lieber ML , Shah SN . Assessing tumor response and detecting recurrence in metastatic renal cell carcinoma on targeted therapy: importance of size and attenuation on contrast-enhanced CT . AJR Am J Roentgenol 2010 ; 194 (1): 157 – 165 .

6. Lamuraglia M , Escudier B , Chami L , et al . To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: pilot study using dynamic contrast-enhanced Doppler ultrasound . EurJ Cancer 2006 ; 42 (15): 2472 – 2479 .

7. Albiges L , et al .Metastatic renal cell carcinoma treated with sunitinib: early evaluation of treatment response using dynamic contrast-enhanced ultrasonography. Clin Cancer Res 2010 ; 16 (4):1216 – 1225 .

8. Guibal A , Taillade L , Mulé S , et al . Noninvasive contrast-enhanced US quantitative assessment of tumor microcirculation in a murine model: effect of discontinuing anti-VEGF

therapy . Radiology 2010 ; 254 (2): 420 – 429 .

9. Pollard RE , Broumas AR , Wisner ER , Vekich SV , Ferrara KW . Quantitative contrast enhanced ultrasound and CT assessment of tumor response to antiangiogenic therapy in rats . Ultrasound Med Biol 2007 ; 33 (2): 235 – 245 .

10 . Niermann KJ , Fleischer AC , Huamani J , et al. Measuring tumor perfusion in control and treated murine tumors: correlation of microbubble contrast-enhanced sonography to dynamic contrast-enhanced magnetic resonance imaging and fluorodeoxyglucose positron emission tomography . J Ultrasound Med 2007 ; 26 (6): 749 – 756 .

11. Quantitative Mapping of Tumor Vascularity Using Volumetric Contrast-Enhanced Ultrasound Hoyt, Kenneth; Sorace, Anna; Saini, Reshu Investigative Radiology. 47(3):167-174, March 2012.

12. Advanced hepatocellular carcinoma: early evaluation of response to bevacizumab therapy at dynamic contrast-enhanced US with quantification--preliminary results. **Lassau N**, Koscielny S, Chami L, Chebil M, Benatsou B, Roche A, Ducreux M, Malka D, Boige V. Radiology. 2011 Jan;6 8(1):291-300. Epub 2010 Oct 27.

13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

14. Lassau N, Chami L, Benatsou B, Peronneau P, Roche A. Dynamic contrast-enhanced ultrasonography (DCE-US) with quantification of tumor perfusion: a new diagnostic tool to evaluate the early effects of antiangiogenic treatment. Eur Radiol 2007;17 Suppl 6:F89–98.

15. Cosgrove D. Angiogenesis imaging-ultrasound. Br J Radiol 2003;76: Spec No 1:S43–9.

16. Lassau N, Koscielny S, Opolon P, et al. Evaluation of contrast enhanced color Doppler ultrasound for the quantification of angiogenesis in vivo. Invest Radiol 2001;36:50–5.

17. Lamuraglia M, Escudier B, Chami L, et al. To predict progression-free survival and overall survival in metastatic renal cancer treated with sorafenib: pilot study using dynamic contrast-enhanced Doppler ultrasound. Eur J Cancer 2006;42:2472–9.

18. Escudier B, Lassau N, Angevin E, et al. Phase I trial of sorafenib in combination with IFN-α-2a in patients with unresectable and/or metastatic renal cell carcinoma or malignant melanoma. Clin Cancer Res 2007;13:1801–9.

19. Lassau N, Lamuraglia M, Chami L, et al. Gastrointestinal stromal tumours treated with imatinib: monitoring response with contrastenhanced sonography. AJR Am J Roentgenol 2006;187:1267–3.

20. Ross Williams , BASc John M. Hudson , MSc , PhD, Peter N. Burns , PhD. Dynamic Microbubble Contrast enhanced US to Measure Tumor Response to Targeted Therapy: A Proposed Clinical Protocol with Results from Renal Cell Carcinoma Patients Receiving Antiangiogenic Therapy. Radiology: Volume 260: Number 2—August 2011;page: 581-591.

21. DEFINITY® Prescribing Information: http://www.definityimaging.com

22. McCulloch M et al Ultrasound contrast physics: A series on contrast echocardiography. article

J Am Soc Echocardiogr 2000: 13: 959-67.

23. Lindner JR et al. Microvascular rheology of Definity microbubbles after intra-arterial and intravenous administration *J Am Soc Echocardiogr* 2002; 15(5): 396-403.

24. Pysz MA, Foygel K, Panje CM, Needles A, Tian L, Willmann JK. Assessment and monitoring tumor vascularity with contrast-enhanced ultrasound maximum intensity persistence imaging. Investigative Radiology. 2011 Mar.;46(3):187–95.

25. Lefort T, Pilleul F, Mulé S, Bridal SL, Frouin F, Lombard-Bohas C, et al. Correlation and Agreement Between Contrast-Enhanced Ultrasonography and Perfusion Computed Tomography for Assessment of Liver Metastases from Endocrine Tumors: Normalization Enhances Correlation. Ultrasound Med Biol. 2012 Jun.;38(6):953–61.

26. Meijerink MR, van Waesberghe JHTM, van Schaik C, Boven E, van der Veldt AAM, van den Tol P, et al. Perfusion CT and US of colorectal cancer liver metastases: a correlative study of two dynamic imaging modalities. Ultrasound Med Biol. 2010 Oct.;36(10):1626–36.

27. Rognin N , Frinking P , Costa M , Arditi M .In-vivo perfusion quantifi cation by contrastultrasound: validation of the use of linearized video data vs. raw RF data. In: Proceedings of the IEEE Ultrasonics Symposium. Piscataway, NJ: Institute of Electrical and Electronics Engineers, 2008 ;1690–1693.

28. . Bogaard JM , Smith SJ , Versprille A , Wise ME , Hagemeijer F . Physiological interpretation of the skewness of indicator-dilution curves: theoretical considerations and a practical application . Basic Res Cardiol 1984 ; 79 (4): 479 – 493.

29. Mischi M , den Boer JA , Korsten HH . On the physical and stochastic representation of an indicator dilution curve as a gamma variate .PhysiolMeas2008;29(3):281–294 .

30. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics. 1989 Mar;45(1):255-68. PubMed PMID: 2720055.

31. Carol A. E. Nickerson. A Note On "A Concordance Correlation Coefficient to Evaluate Reproducibility". Biometrics, Vol. 53, No. 4 (Dec., 1997), pp. 1503-1507

14 APPENDICES

14.1 APPENDIX A: **Participant Eligibility Checklist**

I. Protocol Information

Protocol Title:	**Feasibility of 3D perfusion ultrasound of liver cancer SABR planning and response evaluation**
Protocol Number:	**IRB-30071 / HEP0048**
Principal Investigator:	**Dr. Daniel Chang**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria	Yes	No	15 Supporting Documentation*
1. Ability to understand and willingness to sign the written informed consent document.	☐	☐	
2. Patient with primary liver tumor or metastasis scheduled for Stereotactic Ablative Radiotherapy (SABR)	☐	☐	
3. Patient is at least 18 years of age. No gender/race-ethnic restrictions.	☐	☐	
4. Performance status (ECOG) between 0-3	☐	☐	
5. History and Physical done within 4 weeks of enrollment.	☐	☐	
Exclusion Criteria			
1. Patient has previously been enrolled in and completed this study.	☐	☐	
2. Known right to left cardiac shunt, bidirectional or transient.	☐	☐	
3. Patient has any medical condition or other circumstances which would significantly decrease the chances of obtaining reliable data, achieving study objectives, or completing the study and/or post-dose follow-up examinations.	☐	☐	

4. History of hypersensitivity perflutren	☐	☐	
5. History of pulmonary hypertension	☐	☐	
6. Patients who are pregnant or are trying to become pregnant	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial, I verify that this subject is [☐**eligible** / ☐**ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Signature:	Date:
Treating Physician Printed Name:	

Signature:	Date:
Study Coordinator Printed Name:	

Signature:	Date:
Secondary Reviewer Printed Name:	

14.2 Appendix B

Definition of Menopausal Status:

Menopausal will be defined according to the following criteria:

Post-menopausal:

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)
- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4 IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

Pre- or peri-menopausal: Not meeting definition for postmenopausal outlined above

14.3 Appendix C

ECOG Performance Status*

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.