

Lipiodol as an imaging biomarker of tumor necrosis after transcatheter chemoembolization therapy in patients with primary and metastatic liver cancer

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**COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH
PROJECT
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YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Lipiodol as an imaging biomarker of tumor necrosis after transcatheter chemoembolization therapy in patients with primary and metastatic liver cancer

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Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at using Lipiodol (an oily substance used as a carrier to transport chemotherapy drugs) as a biomarker (or indicator) of response to therapy. You have been asked to take part because you are eligible to receive conventional (Lipiodol-based) transarterial chemoembolization (cTACE) therapy for cancer that has started in the liver, or cancer that started elsewhere and has spread to the liver. We plan to enroll 21 patients on this study at the Yale School of Medicine.

The goal of Lipiodol based TACE is to deliver highly concentrated doses of chemotherapy to the tumor in order to maximize tumor kill and to minimize the release of the chemotherapy drug outside of the liver (thereby reducing the chemotherapy side effects). We believe that use of Lipiodol can be expanded into that of a marker of response (biomarker) to the TACE therapy. When Lipiodol is delivered to the tumor during TACE, it is generally retained within the tumor for many weeks to months. The radiopacity of Lipiodol (being easily seen on x-ray imaging) makes it very easy to track. If it is proven true that the amount of Lipiodol remaining in the treated tumor is equal to tumor death, then Lipiodol may be considered as a valid marker of successful tumor treatment.

Lipiodol has been approved since 1954 for use in patients undergoing hysterosalpingography (x-ray pictures of the female reproductive system) or lymphography (x-ray pictures of the lymph nodes). In 2014, Lipiodol was approved for selective liver use for imaging tumors in adults with known hepatocellular carcinoma (a type of cancer that originates from liver cells), and has been used off-label for cancer in the liver that originated elsewhere. Lipiodol is commonly used in TACE as a carrier of chemotherapeutic drugs to the tumor. The effectiveness of combined Lipiodol and TACE procedures has been generally recognized for more than 2 decades. The use of Lipiodol as a biomarker in this study is investigational. The word “investigational” means that Lipiodol is not approved by the U.S. Food and Drug Administration (FDA) to be used as a biomarker of response to TACE therapy and is still being tested in research studies, but the FDA is allowing the use of Lipiodol in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information

about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to take part in this study, you will be asked to do the following things (please note that some of these procedures are part of your clinical care but are identified here to avoid confusion):

Initial screening visits:

The initial evaluation and screening procedures are standard clinical care (would be done regardless of your participation in this study), and will include the following: physical examination, medical history, blood tests requiring about 4 tablespoons of blood, and an MRI imaging study of your abdomen to look at your liver.

Additionally, A CT scan and PET-CT scan of your abdomen will be done for the research study, unless you have recently had one. See details below.

These procedures may require one or two visits, depending on your schedule and the appointments available for the necessary studies.

CT scan with contrast

A CT (computerized tomography) scan uses x-rays and a computer to produce a 3-dimensional image of your body. The CT scan takes about 30-60 minutes. During the test you will lie on your back on a padded table. A strap will be placed across your body to prevent movement so that the x-ray pictures will be clear. The table will slide into a large, donut-shaped machine. An X-ray tube will slowly move across your body, taking many pictures from all directions.

When you have contrast: You will have a contrast material (dye) inserted through a needle (IV) into a vein in your arm or hand. The contrast material is used to improve the images of certain parts of your body.

PET-CT scan

A PET-CT scanner combines two scanners – PET (Positron Emission Tomography), and CT (Computed Tomography). A PET scan uses very small amounts of radioactive material injected into the blood to show the internal workings of your body. A CT scan uses x-rays and a computer to produce a 3-dimensional image of your body. Combining the two scans can help the researcher better understand the extent and the exact location of the disease. Before the PET-CT scan, you will be asked to limit the amount and type of food you eat. The procedure itself will take about 2-4 hours. A plastic tube (catheter) will be placed in a vein in your forearm to inject a small amount of the radiotracer. You will need to wait about 1-3 hours to allow the radiotracer to be absorbed into your tissue. The scan takes about 30-60 minutes. During the scan you will lie on your back on a padded table. A strap will be placed across your body to prevent movement so that the x-ray pictures will be clear. The table will slide into a large, donut-shaped machine. An X-ray tube will slowly move around your body, taking many pictures from all directions.

Summary of procedures for screening visits:

- Standard of care: Physical examination, medical history, laboratory tests, electrocardiogram (if applicable), and MRI scan of the liver.
- Research related (paid for by the study): CT scan of the liver, PET/CT scan.

TACE (Day 0): As part of your clinical care you will be treated with Lipiodol based TACE (cTACE).

After you have undergone TACE (standard of care therapy):

The following day, before you are discharged from the hospital, a CT scan (part of your clinical care) will be done to check the placement and distribution of the Lipiodol.

Summary of procedures for TACE visits:

- Standard of care: TACE procedures, associated labwork and imaging scans including a CT scan of the liver post-treatment.

Follow-up visits:

The time points below will begin after the TACE procedure. If multiple TACE procedures are required, then the time points below will begin after the TACE treatment is complete for a particular lesion in the liver. Note that the lab work, clinical exam, and MRI during these visits are part of the standard clinical care for treatment with TACE.

- Day 30:
 - Standard of care: Clinical visit, labwork, MRI of the liver
 - Research related: CT scan of the abdomen
- Day 90
 - Standard of care: Clinical visit, labwork, MRI of the liver
 - Research related: CT scan of the abdomen, PET/CT scan
- Day 180
 - Standard of care: Clinical visit, labwork, MRI of the liver
 - Research related: CT scan of the abdomen, PET/CT scan
- Labwork will include: comprehensive metabolic panel, hematology, coagulation panel, and tumor markers as standard of care

How long will you be in the study?

You will be in the study for 6 months (180 days) from the date of your last TACE procedure.

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.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences of the Research Procedures

Lipiodol (used in TACE procedures, also being tested as a biomarker):

Possible side effects of Lipiodol are transient fever post-procedure, abdominal pain, and gastrointestinal disorders (nausea, vomiting, or diarrhea). Other side effects include hepatic ischemia (low blood or oxygen supply to the liver), elevated liver enzymes, transient decrease in liver function, liver decompensation, and renal insufficiency. Pulmonary and cerebral embolism (a sudden blocking of the blood flow to your lungs or brain) can occur if Lipiodol is inadvertently injected to a nontarget location.

In patients with an iodine deficiency, there is a risk of hyperthyroidism (symptoms include weight loss, accelerated heart rate, increased intestinal transit rate, anxiety, insomnia, etc). Additionally, there is a risk of an

allergic reaction. Patients with a history of allergic reactions to iodinated products are premedicated prior to a TACE procedure as per standard of care.

Risks Associated with Radiation

This research study involves exposure to radiation from eight helical liver CT scans and three F-18 Fluorodeoxyglucose liver PET/CT scans. Please note that this radiation exposure is **not** necessary for your medical care and is for research purposes only.

The total amount of radiation that you will receive in this study is about 92.19 mSv or 9,219 mrem. The Yale-New Haven Hospital Human Use Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired. To give you an idea about how much radiation you will get, we will make a comparison with an every day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 31 extra years' of this natural radiation.

Please tell your doctor if you have taken part in other research studies or received any other medical care recently involving radiation. If you are pregnant or breast feeding, you **SHOULD NOT** participate in this research study.

Having an intravenous (IV) line placed is a very safe procedure. There is a slight chance that multiple needle-sticks will be needed to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or a minor infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary.

The FDA approves the contrast agents Omnipaque and Visipaque for use with human participants. You need to know that there are certain risks associated with the use of contrast. Some healthy subjects (fewer than 3%) may experience mild nausea, headache or dizziness after the injection. These side effects usually go away themselves without need for treatment. There is also a risk of allergic reaction (less than 1%). An allergic reaction can cause hives and itching or difficulty breathing. Individuals with severe kidney dysfunction may suffer adverse effects if receiving contrast, and will only receive contrast if the possibility of benefit clearly outweighs the risk. This is why prior to your CT study you will have to undergo blood work to make sure that your kidney function is normal. Detailed information on the contrast agents Omnipaque and Visipaque can be provided to you at your request.

You should tell your principal investigator: (1) if you are pregnant or breast feeding, (2) if you have a history of allergic reactions to MR or CT contrast agents, (3) if you have a history of kidney disease, seizure, asthma, or allergic respiratory disorders, and (4) if you have anemia or disease that affects red blood cells.

Incidental Findings:

The CT scan and PET-CT scan you are having as part of this research study will be reviewed by a qualified person just as it would be if you were having the CT scan and PET-CT scan as part of your routine medical care. There is a possibility that while reviewing your CT scan or PET-CT scan we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding." We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home. A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an

option to decline information about an incidental finding. If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

Risks associated with standard of care TACE:

Serious side effects occur after approximately 5% of chemoembolization procedures. The most common serious side effects are liver abscess (a collection of pus in the liver) or liver infarction (interruption of blood flow to the liver), which occur in about 2% of cases each.

Constitutional symptoms: The post embolization syndrome consisting of temporary abdominal pain, ileus (lack of digestive movement in the intestines), fever, and a general feeling of discomfort affects 60% to 80% of patients receiving TACE.

Gastrointestinal symptoms: Liver enzymes are commonly elevated following a TACE procedure. Patients may develop inflammation of the gallbladder, liver abscess, narrowing of the bile duct, nausea or vomiting, or ascites (collection of fluid in the peritoneal cavity).

Endocrine symptoms: Some patients may develop symptoms of an underactive thyroid as a result of TACE therapy.

Hematologic symptoms: Some patients may develop a temporary increase in the white blood cell count. Side effects as a result of bone marrow toxicity are uncommon, occurring in less than 4% of patients, and includes neutropenia (reduced neutrophil count) and thrombocytopenia (reduced platelet count). A small portion of patients have developed gastrointestinal bleeding as a result of TACE therapy.

Other Risks:

There is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Because the regimen given during the conventional TACE may harm an embryo or fetus, you cannot take part in this study if you are pregnant. Chemotherapy can cause severe malformation (teratogenicity), failure to thrive and fetal death (embryotoxicity).

If you are a woman who can have children, you will have a pregnancy test at the start of the study. The results of this test must show that you are not pregnant for you to continue in this study.

You should not become pregnant while on this study. You must agree to use a reliable form of birth control during the study. Check with the study doctors to find out what forms of birth control you may use and how long to use them. If you become pregnant during the study, you must tell the study doctor immediately. This research may hurt an embryo or fetus in ways we do not know.

Benefits

There is no direct benefit to you, which we are currently aware of, for participation in the study. If you take part in the study, you may help other liver cancer patients in the future by improving treatment options and guidelines.

Economic Considerations

Research-related procedures will be supplied free of charge by the study, and include:

- CT's (abdomen) with and without contrast
- PET-CT scans of the liver
- Image assessments performed for research
- Pathology (for Lipiodol)

The following procedures are performed as standard of care, and would occur whether or not you choose to participate in the study. You and/or your health insurer will be responsible for procedures, tests, drugs, or devices such as the following (as applicable):

- Physical exam
- Hematology labs
- Chemistry/Electrolyte labs
- PT/INR labs
- Serum/urine pregnancy test
- Electrocardiogram
- Tumor Marker (AFP, CEA, Chromogranin A, or other appropriate marker)
- TACE (trans arterial chemoembolization) procedure, with Lipiodol
- CT scan (abdomen) without contrast (Day prior if necessary and after TACE procedure)
- DCE-MRI (Dynamic contrast enhanced – and diffusion MRI) of liver. CT (abdomen) with and without contrast (if MRI cannot be done)

You will still be responsible for any co-pays required by your insurance company for standard of care treatment.

Treatment Alternatives

Participation in this study is voluntary. You do not have to join this study to receive treatment. If you do not join, your care at Yale will not be affected.

If you decide to not participate in this study, you can still receive your conventional TACE treatment as planned. Alternative treatments may include:

- Liver-directed treatments (treatments confined to the liver)
 - Treatment with TACE, radioembolization, or other intra-arterial therapies.
 - Other research studies for patients with your disease profile.
- Systemic treatments (treatments that affect the whole body)
 - Treatment with chemotherapy
 - External radiation therapy
- Liver transplantation if you are a candidate
- Surgical resection if you are a candidate

Finally, some patients choose to focus their treatments on the symptoms of the cancer and not the cancer directly. You will be given information about alternative and supportive treatments by your doctor. Your doctor will explain the advantages and disadvantages of alternative treatments that are being used.

Confidentiality and Privacy

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)

Authorized representatives of the Food and Drug Administration (FDA), the manufacturer of the drug being tested (Guerbet), and funding source Philips Healthcare may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Collected research data will be kept in a locked and secured environment, and the data that links your identity will be kept on an encrypted and password-protected drive. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and medical record number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for a minimum of 5 years after termination of the study, at which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Research study records
- Medical, imaging, laboratory records, and other test results of only those services provided in connection with this Study.

Information about you and your health which might identify you may be used by or given to:

- *The U.S. Department of Health and Human Services (DHHS) agencies*
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.

- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator, Dr. Todd Schlachter.
- Funding companies (Guerbet and Philips Healthcare)
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Health care providers who provide services to you in connection with this study.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

This study is financially sponsored by the companies Guerbet and Philips Healthcare. The funding sponsors will see the research information (data) we collect about you when they come to Yale to monitor the conduct of this research study. Yale University is also a sponsor for this study. Yale researchers will send the sponsor your health information during the study or at the end of the study. When Yale researchers send information to the sponsors, they will not send information that directly identifies you. Any data sent will be de-identified, and any information that identifies you (such as your name and your address) will be removed before being sent. The sponsors and funding company may use data gained from this study for other research purposes or for similar research studies.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. No further research procedures will be performed and no further research data collected.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. These reasons may include:

- Staying in the study would be harmful
- You need treatment not allowed in this study.
- You fail to follow instructions.
- You become pregnant.
- The study is closed.
- There may be other reasons that we don't know at this time to take you out of the study.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Todd Schlachter, MD at Yale University, 333 Cedar St, PO Box 208042, New Haven CT 06520-8042.

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: _____

Signature: _____

Date: _____

Signature of Principal Investigator
or

Date

Signature of Person Obtaining Consent

Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator: Todd Schlachter, MD: Phone (203) 785-5885.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.