ID: UMCC 2015.039

NCT02460835

A Pilot Study of Individualized Adaptive Radiation Therapy for Hepatocellular Carcinoma

UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THE STUDY

Study title: A Pilot Study of Individualized Adaptive Radiation Therapy for Hepatocellular Carcinoma 2015.039

Company or agency sponsoring the study: Department of Radiation Oncology

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):
Principal Investigator: Theodore Lawrence, M.D., Ph.D Department of Radiation Oncology

Study Coordinator: Jody Sharp

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research collects protected health information and a blood and tumor tissue to better understand hepatocellular carcinoma (HCC). This research will determine the safety and effectiveness of individualized adaptive Radiation Therapy (RT). Subjects in the study will receive either IC-GREEN (special green dye, for use in assessing liver function) if their doctor chooses to evaluate liver function with ICG, or standard blood tests, and a MRI to see how fluid passes to your tissues then you will have to sets of RT.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include new symptoms from the use of the IC-GREEN and/or RT. More detailed information will be provided later in this document.

This study may offer some benefit to you now or in the future by customizing your radiation treatments to what your liver can safely tolerate and how much your tumor needs to be killed, to maximize both the safety and effectiveness of the therapy. This study may offer some benefit to others in the future. Doctors and researchers may benefit by learning more of this disease and how to treat it. More information will be provided later in this document.

We expect the amount of time you will actively participate in the study will be approximately 2.5 years.

You can decide not to be in this study. Alternatives to joining this study include standard treatment for hepatic tumors. You may have other options including other research studies, or even no treatment except for comfort measures.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The aim of this study is to determine the safety and effectiveness of individualized adaptive Radiation Therapy (RT) in subjects who have hepatocellular carcinoma (HCC). Before you begin treatment, assessments of your liver function will be done using a MRI and a blood test using Indocyanine Green (IC-Green) or using ALBI score. IC-Green is a special green dye, approved by the FDA for use in assessing liver function, and is injected into your body through a vein in your arm over 10-15 seconds to determine how well your liver is working. A perfusion MRI uses injected contrast to see how fluid passes through your tissues. ALBI score is an assessment of liver function based on standard bloodwork that is routinely tested in liver patients. You will have two sets of RT, separated by a 4-week break. During this time, the above tests will be repeated to re-assess your liver function and see if you can safely receive additional treatment. The goal of this study is to customize your radiation treatments to what your liver can safely tolerate and how much your tumor needs to be killed, to maximize both the safety and effectiveness of the therapy. Blood and urine will be used for analyses of liver function and in predicting liver damage during radiation therapy. Any extra will be saved for future analyses.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Every study has strict guidelines for determining which people may participate. These are called eligibility criteria. You will need to meet all of these criteria before you can participate in this study. If you agree to consider participating in this study, you will undergo evaluations to see if you meet the eligibility criteria for this study. Even though you may meet all the criteria for participation, it is possible that you may not be enrolled in this study for other reasons.

You must be over 18 years or older, have biopsy proven hepatocellular carcinoma (HCC) or a liver tumor that has not spread. You cannot be eligible for a liver resection, unless you have refused it. If you have had any other therapy on your liver, a minimum of 4 weeks must have passed before you can start treatment on this study. You cannot be allergic to IV iodine contrast agent.

You must have adequate organ function. Females of childbearing age must not be pregnant or become pregnant during the study. Females and males of reproductive age must agree to use an effective contraceptive method during treatment.

3.2 How many people (subjects) are expected to take part in this study?

Approximately 100 subjects will be enrolled at the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

The study team will explain the research study and answer any questions you have about the study. If you still want to participate in the study, the study team will request you sign the consent form prior to any activities occurring that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Once it is determined you are eligible to enter the study, tests and procedures done at your study visits as part of your regular cancer care will continue, but some may be done more often because you are participating in this research study. Also, some of the tests or procedures may have to be repeated if, for example, they were done too long ago or the results are not normal.

Some tests and procedures may be done that are not part of your regular cancer care and are being done only for this research study. Tests and procedures that are performed more often or are not part of your standard cancer care will be identified below as "Research".

Study Screening

After you agree and sign the informed consent to take part in this research, the study team will perform tests and procedures to see if you are eligible to be part of the study. This is called Screening. The screening will include the following:

- History and physical exam
- Blood tests
- Imaging of your abdomen (MRI or CT scan) and chest (x-ray or CT scan)

These tests and procedures are done as part of a pre-treatment evaluation before you start the study. If any of the imaging tests have been done prior to your enrollment on this study, the results may be used. These are all standard tests for someone with liver cancer. These tests will not be repeated just for the purposes of the research; your physician will decide if your CT or MRI scans need to be repeated. If you have had any of these tests completed somewhere other than the University of Michigan, your doctor may want these repeated at the University of Michigan if the technology here may provide better results. This would be the case whether or not you take part in the research.

After these screening tests confirm that you are able to take part in this research, you will begin preparation for your radiation treatments.

Fiducial Markers

If your doctor believes they are necessary for accurate targeting of your tumor, fiducial markers (tiny metal or carbon pieces about the size of a grain of rice) may be placed through the skin close to your tumor(s). Placement of markers is considered standard of care. If these markers are placed, you will be asked to participate in an

additional research process. The process would be obtaining a biopsy of your tumor and, typically, it would be performed during the placement of fiducial markers.

Treatment plan

The treatment planning involves getting a CT scan. The information from this scan will be put into a computer and your radiation plan will be based on this. You will then undergo your radiation treatment planning.

IC-GREEN & ALBI SCORE

Before you begin your first phase of radiation treatment, your liver function will need to be tested. Your doctor can choose a procedure called Indocyanine Green (IC-GREEN) blood test or use ALBI score to evaluate liver function.

For ALBI score you will have some standard bloodwork drawn that you would have had even if you were not on the study. The doctors use the values from this lab work to calculate the function of your liver.

For the IC-GREEN blood test, you will have IC-GREEN administered into one of your veins through an IV. The amount of IC-GREEN you will receive will be based on your body weight. You will need to have a second line in another place (if you don't already have one) that will be used for the blood draws. You will have blood drawn just before you are injected with IC-GREEN and approximately 5, 10, 15 and 20 minutes after you are injected with the IC-GREEN.

After each blood draw, the line will be flushed out with a little saline solution. Each blood draw will be a small amount of blood (slightly more than a teaspoon); the total amount of blood drawn for the ICG testing is approximately 5 teaspoons. If you are enrolled in more than one study, some of the blood drawn at visits could be shared between the studies, to minimize blood draw procedures for you.

The IC-GREEN test will be completed in the Michigan Clinical Research Unit (located in the University of Michigan Cardiovascular Center), which is a clinic dedicated to research studies. These blood samples are used to determine your liver function at the time of the test.

Prior to the IC-GREEN test, you will be required to fast for at least four (4) hours. You can have coffee or water up to two hours before the test. After this time, you should not have anything. You should take all of your medications as usual.

Optional Research Biopsy

One extra needle will be inserted into the tumor to collect a tiny sample. This sample will be used to test if we can predict, in the future, how tumors will respond to treatment- even before we start. The samples will be used for the study of substances such as microRNA and Cytokines (substances secreted or produced to help cells communicate with each other and may control the behavior of other cells). This can also help to predict potential toxicity. The optional tumor biopsy tissue will be labeled with a code and will be processed for analysis of RNA, DNA, and proteins. This analysis will be correlated with the patient treatment outcomes and treatment toxicities experienced by the patient.

The optional tumor biopsy tissue samples will not contain your name or other identifying information. The code that will link you to the sample will be securely stored and safely destroyed when the study is complete. The specimens will be kept for a period of 10 years, until the study is complete or that sample is used up.

See Section 5.1 of this consent for risks related to the tumor biopsy procedure. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

For information about how these samples will be stored and used for unspecified future research see "Unspecified future research" Section below.

You can make your choice whether or not to participate in this optional portion of this study in Section 12 of this consent form.

Other tests

While on study, you will have blood and urine collected prior to treatment, during the evaluation period between the RT phases, and afterward. Researchers will use the blood and urine to determine whether any chemicals are related to side effects of treatment (biomarker analysis). The total amount of blood collected for this part of the study will be approximately 18-30 teaspoons (approximately 6-10 teaspoons at each time), and the total amount of urine is 12-24 teaspoons (approximately 4-8 teaspoons at each time).

Blood and urine not immediately used for biomarker analysis will be stored for future biomarker analysis. The samples will not contain your name or other identifying information. The code that will link you to the sample will be securely stored and viewable only by members of the study team. The specimens will be kept for a period of 10 years, or until the study is complete or that sample is used up.

For information about how these samples will be stored and used for unspecified future research see "Unspecified future research" Section below.

Unspecified future research

Besides the information about the main study, the following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your required samples (see "other tests" Section above) or if applicable optional tumor sample so that we may study them in future research. We will also like your permission to keep some of your medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

If you give us your permission, we will use your required and (if applicable) optional samples and medical information for future research. Even if you give us permission now to keep some of your required and (if applicable) optional samples and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your required and (if applicable) optional samples, we may not be able to take the information out of our research.

We may share your required and (if applicable) optional samples and medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your required and (if applicable) optional samples and medical information with other researchers, we will not be able to get it back.

There are no physical risks associated with future research testing on samples that were already collected.

There are non-physical risks associated with taking part in future research, such as the risks of genetic testing and the risks associated with the loss of privacy or confidentiality. See Section 5.1 and 9.1 of this consent form for more information about these risks. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your required and (if applicable) optional samples. Allowing us to do future research on your blood or tumor and medical information will not benefit you directly.

With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

Radiation Treatment

There are two phases of radiation treatment in this study and, depending on how well your liver tolerates the initial phase, you may not qualify for the final phase. In the first phase, you will receive three (3) treatments, which take about an hour for each session. Depending on your physician's judgment of what would be safest and most effective for you, these treatments are usually daily, but could be every other day.

After you finish the initial phase of treatment, you will have approximately a one-month break. After your break, your liver function will be re-assessed by a second IC-GREEN blood test or ALBI Score and MRI. Based on these results, your doctor will adjust the radiation dose for your final phase of radiation treatment, which will consist of two (2) treatments, similar to those in the first phase. If it will not be safe to deliver the final phase of radiation treatment, then your physicians will switch to the standard monitoring schedule of clinical visits, scans, and blood tests described below.

Follow Up

After you finish treatment, you will be followed on a regular basis. You will be seen during a clinic visit by a member of the research team at approximately 1 month after treatment, then at 3 to 6 month intervals until 2 years have passed, as is standard of care. MRI and IC-GREEN or ALBI score blood tests will be repeated at approximately 1 month and you will have an additional IC-GREEN or ALBI score blood test 3 months after treatment. During your clinic visits, you will have standard blood tests (typically about 9 teaspoons of blood) and monitoring of your disease with MRI or CT, as would any subject who receives treatment for your type of cancer, to monitor your response to treatment to make sure your tumor goes away and you do not have long-standing effects.

4.2 How much of my time will be needed to take part in this study?

IC-GREEN tests will take approximately 1.5 hours. Blood collection for the ALBI test will take only a few minutes. The MRIs will take approximately 1.5 hours. The treatments will take approximately 1 hour each. We will make

every effort to minimize the number of times you need to travel to the University of Michigan Hospital for treatments and testing. Typically, there is only one extra trip you would make beyond what would happen if you did not participate in this study.

4.3 When will my participation in the study be over?

Your active participation in both phases of the study will last the duration of your radiation planning and treatment (typically about 1.5-3 months) in addition to 2-years of post- treatment follow-up visits, which are standard of care and not any different than we monitor all of our subjects.

4.4 What will happen with my information and/or biospecimens used in this study?
Your collected information and biospecimens may be shared with the department of radiation oncology at the University of Michigan.

Your collected information and biospecimens may also be shared with other researchers, both here or around the world, or with companies. Any sharing is subject to contractual obligations with the Sponsor. Additionally:

- With appropriate permissions, your identifiable collected information and biospecimens may be shared, and/or,
- Without your additional consent, your identifiable private information and identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Your study doctor and study staff will monitor you closely for side effects. Even with frequent blood tests and other examinations, participation in this study involves risks, and some side effects cannot be predicted. Side effects can range from mild to severe and life-threatening. Many side effects will get better when you stop the study intervention, but some may be long lasting or may never go away. Side effects may even cause death. You should tell your study doctor immediately about any side effects that you have or any change in how you feel while on this study.

The known or expected risks are:

Stereotactic Body Radiation Therapy (SBRT): You should be aware that significant risks are associated with Stereotactic Body Radiation Therapy, although they are rare. Most subjects experience mild fatigue during treatment, relieved by rest. Radiation therapy may cause or aggravate nausea or vomiting in less than 1 of 10 subjects. It can cause stomach or intestinal ulcer and possibly scarring of intestine that could narrow the passage that food passes through in less than 1 in 100 subjects. You may also experience skin irritation (less than 1 in 100 subjects). It is possible that the very top of your right kidney could be exposed to radiation, which could produce a decrease in your kidney function, but we will carefully sculpt the radiation away from your kidney as much as possible. Radiation can damage the liver and decrease your liver function. This could be severe enough to result in liver failure, which could lead to death. Even though this risk is extremely small, we are working toward making this treatment even safer. The purpose of this study is to minimize this risk by customizing radiation to your body and liver function. Your radiation treatment will be carefully planned to minimize these risks.

CT and MRI Scans: There is an extremely small risk of developing an allergic reaction to the contrast material used for the scanning procedure. Most subjects with your type of cancer have already had a CT and/or MRI scan, so you probably know if you have an allergy. Be sure to tell your study doctor if you have allergies of any kind, such as hay fever, iodine allergy, eczema, hives, and food (including seafood) allergies. If you have a history of kidney problems, blood tests may be done to check that your kidneys are healthy enough for this test. There is always a slight risk from being exposed to any radiation, including the low levels of X-rays used for a CT scan. The main potential risk from exposure to radiation is cancer. As the amount of radiation increases, so does the potential risk of cancer. Thus, with minimal radiation from the CT scans required to plan treatment for your cancer, the risk is negligible. MRI scans do not use radiation so there is no risk from radiation with MRI scans. However, it is important that you tell the technician if you have any metal in your body, because MRI uses a very strong magnetic field and powerful radio waves. We will also follow standard procedures and ask you to fill out a questionnaire to make sure performing an MRI would be safe for you.

MRIs done for research that use IV contrast have risks similar to MRIs done for clinical care. Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation. The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF) is a thickening of the skin, organs and other tissues, is a rare complication in patients with kidney disease that undergo an MR with contrast material. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

IC-GREEN blood test: You may experience bruising, swelling, or infection where you are injected with the IC-GREEN, and where you have blood drawn. In rare cases, some subjects may experience a severe allergic reaction to the iodine in IC-GREEN, which is why subjects who have an iodine allergy are not allowed to participate in this study and why we only perform the test under close monitoring. Although it is unlikely, this allergic reaction could be severe enough to cause death. Any side effects you experience from the injection of the IC-GREEN or blood draws will be treated as medically appropriate. You may also experience pain, bruising, redness, itching, soreness, infection and swelling where the I.V.s were placed. Sometimes the I.V. may move and may not work properly. Because of this, the results from these draws may not be accurate.

Tumor Biopsy: A tumor biopsy is a minor procedure that uses a thin and hollow needle to extract a few cells from a tumor**.** This piece of a tumor will be removed for testing. Potential risks and discomforts that you may experience as a result of the procedure depend upon the location of the tumor. The more common risks/discomforts include pain, bleeding, infection, damage to tissues, and healing complications. Your doctor will further explain any specific risks that may apply based on the procedure, and you will sign a separate consent for the procedure which will provide risk information in more detail. In order to make the procedure more comfortable, you will get a local anesthetic to numb the area. A mild sedative may also be given to you.

Pregnancy Risk:

<u>Women</u>

You should be aware that if you are or may become pregnant, radiation may involve unforeseeable risks to the embryo, fetus, or you.

If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or must use at least TWO types of birth control (one from each list below) AT THE SAME TIME.

These birth control methods must be used all during treatment including during temporary breaks from therapy, and for at least 28 days after treatment has stopped. The following methods are considered acceptable birth control methods:

Primary forms	**Secondary forms**
tubal sterilization (tubes tied)	male latex condom with or without spermicide
partner's vasectomy	diaphragm with spermicide
intrauterine device	cervical cap with sperm
Hormonal contraceptives (includes Transdermal patch, injectables, implantables)	vaginal sponge (contains spermicide)

Any birth control method can fail. The reports of birth control failing are more frequent for female subjects who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

Men

Men must agree to either abstain from sexual activities that could result in pregnancy or use an acceptable form of birth control while taking part in the study. Acceptable forms of birth control are male latex condom (with or without spermicide) or vasectomy.

You will notify your doctors immediately if you think you may be pregnant while you are taking part in this research.

To minimize the risks of radiation therapy, all subjects undergo frequent examination and laboratory tests to detect the early signs of toxicity. You will be followed closely, so that your treatment can be adjusted, both as a part of this research study and your routine clinical care. Follow-up procedures for all radiation therapy subjects include the following:

Hematologic: You will be monitored for symptoms of decreased blood counts.

Gastrointestinal: If necessary, you will be treated with anti-nausea (antiemetic) medications for nausea and vomiting. The risk of ulcers will be decreased by the use of anti-ulcer therapy as necessary.

Hepatologic: You will be monitored for changes in your liver function by the IC-GREEN test or ALBI score described above, and your treatment may be altered as appropriate.

The primary purpose of this research is to customize the total radiation dose for your tumor. The risk from the study radiation therapy is minimal.

You should not take any new medications, including over-the-counter drugs, without the knowledge of your radiation oncologist while you are taking part in this research study.

Additionally, there may be a risk of loss to confidentiality or privacy. For example, if your identity as a participant in this research or your identifiable genetic or health information were disclosed to unauthorized persons, there is the possible risk of discrimination by employers or insurance providers. The researchers believe that the risks of such improper disclosure are very small because strict privacy and confidentiality procedures for this research have been adopted. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

If you think you have an injury or illness that is related to your participation in this clinical trial, it is important that you tell your study doctor immediately. If you have a clinical trial related injury or accident, the study staff will make sure that you get medical treatment.

You will receive appropriate medical care for any side effects you have while participating in this study.

You must inform your study doctor immediately if there are any changes in your health/condition, or if you have any concerns regarding the study. If for any reason you are seen by another healthcare provider or admitted to another hospital, you should make known your participation in this research study. These healthcare providers may wish to contact your study doctor to discuss your condition. Your study doctor may need to contact your other doctors if you develop any potentially significant, unexpected diseases or conditions that may have been caused by the study intervention or procedures or are discovered during the study.

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any direct personal benefits from being in this study. The information gathered from this study will be used to improve treatment for subjects with liver cancer in the future. Others may benefit from the knowledge gained from this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

Standard treatment for hepatic tumors could involve radiofrequency ablation, transcatheter arterial chemo-embolization, surgery, or chemotherapy. You may have other options including standard of care radiation, other research studies, or even no treatment except for comfort measures. Ask your doctor about other options you may have.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

You are free to partially or completely end your participation in the study. An example of partially ending your participation would be to discontinue receiving study intervention, while still allowing continuation of study follow-up procedures.

Please note that any information collected before you withdraw will be kept and used to complete the research.

Please note that even if you withdraw consent for further follow-up or contacts, if the study doctor becomes aware of additional safety information this will be reported to the sponsor in order to comply with legal or regulatory requirements.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

Tell the study doctor if you are thinking about stopping or decide to stop. It is important to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. The study doctor will also tell you how to stop safely and discuss what follow-up care and testing could be most helpful for you. If you decide to leave the study before it is finished, please tell your study doctor or one of the researchers listed in Section 10 "Contact Information" (below).

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researcher's number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Treatment of complications
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you or your insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

8.2 Will I be paid or given anything for taking part in this study?

No, there is no compensation of any type for participating in this study.

8.3 Who could profit or financially benefit from the study results?

Neither the researchers conducting the study or the University of Michigan will benefit or profit financially.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my privacy?

Subjects' privacy will be kept confidential, to the extent permitted by applicable laws, in the following manner:

- Subject names will not be used in any reports about the study
- Subjects will be identified only by a study code: a subject ID number and initials
- Identifying information will be kept behind locked doors with restricted access

The investigators will assign a code number to the study data/samples and may use subject initials. Some study data may contain information that could be used (perhaps in combination with other information) to identify the subject (e.g., initials, date of birth).

The information collected about you during the study will be placed into a research record and will not be made a part of your regular medical record. The research record will be linkable to you, but it will be kept in a secure, non-public location in the Department of Radiation Oncology. The research record will be kept confidential to the extent provided by federal, state and local laws. Only authorized personnel will have access to the research records. You will not be identified in any reporting of this study.

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.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan Notice of Privacy Practices. This information is also available on the web at http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researcher listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	Theodore Lawrence, MD, PhD
Mailing Address:	Radiation Oncology 1500 E. Medical Center Drive SPC 5010, UH B2C507 Ann Arbor, MI 48109-5010
Telephone:	734-647-9955

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)

2800 Plymouth Rd

Building 520, Room 3214

Ann Arbor, MI 48109-2800

Telephone: 734-763-4768

Fax: 734-615-1622

e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy, contact the University of Michigan Health System Privacy Officer at 1-888-296-2481.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with_____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent for Participating in an Optional Sub-Study (Tumor Biopsy)

This project involves optional participation in a sub-study. I understand that it is my choice whether or not to take part in the sub-study and have my tumor biopsied. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to have a tumor biopsy.

_____ No, I do not agree to have a tumor biopsy.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

PERSONAL CENSUS FORM

UMCC # 2015.039

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]

2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as "Haitian" or "Negro" are sometimes used in addition to "Black" or "African American.")

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" is sometimes used in addition to "Hispanic" or "Latino."