INFORMED CONSENT FORM – [VOLUNTEER WITH METASTATIC RENAL CELL CARCINOMA]

Official title: A Prospective Study to Evaluate Quantitative Non-Contrast Perfusion using Arterial Spin Labeled MR Imaging for Assessment of Therapy Response in Metastatic Renal Cell Carcinoma

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The University of Texas Southwestern Medical Center
Parkland Health & Hospital System
Children's Medical Center
Retina Foundation of the Southwest
Texas Scottish Rite Hospital for Children
Texas Health Presbyterian Hospital Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: A Prospective Study to Evaluate Quantitative Non-Contrast Perfusion using Arterial Spin Labeled MR Imaging for Assessment of Therapy Response in Metastatic Renal Cell Carcinoma

Funding Agency/Sponsor: National Institutes of Health/National Cancer Institute

Principal Investigator: Dr. Ananth Madhuranthakam

You may call the study doctor or research personnel any time including business hours and outside of business hours at 214-645-1568.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
This study is being done to determine if our own research MR imaging techniques can detect treatment response in patients with your condition better than the standard of care clinical MR imaging. Both the clinical and research MR imaging will involve a contrast agent injection. Gadolinium-based contrast agents, such as Gadavist (generic Gadobutrol) or Dotarem (generic Gadoterate acid), both of which are FDA- approved contrast agents and are routinely used for MR imaging will be used.

Why is this considered research?
This is a research study because we are using our own research MR imaging techniques such as arterial spin labeled (ASL) MRI, in comparison to the standard of care clinical MR imaging. The researchers are interested in learning which imaging technique is more effective in monitoring your condition.

The following definitions may help you understand this study:
- Principal Investigator means the lead researcher on this study.

- Magnetic Resonance Imaging (MRI) means a method to take pictures of inside the body while you lie inside a large magnet (which applies magnetic fields). The scanner processes the response of your body to the magnetic fields into images.
- Arterial Spin Labeled MR Imaging is a way to measure blood flow in your body without using contrast agents.
- Standard medical care means the regular care you would receive from your personal doctor if you choose not to participate in this research.
- Researchers means the study doctor and research personnel at the University of Texas Southwestern Medical Center at Dallas and its affiliated hospitals.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you have been diagnosed with renal cell carcinoma and are scheduled to undergo treatment.

Do I have to take part in this research study?
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at this center.

How many people will take part in this study?
About 40 people will take part in this study at UT Southwestern.

What is involved in the study?
Procedures and Evaluations during the Research

If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. Some of the procedures may be part of your standard medical care, but others are being done solely for the purpose of this study.

Screening Procedures
To help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:

- Physical exam and medical history;
- Vital signs;
- Blood tests; and

- Demographic information (age, sex, ethnic origin).

Both clinically and for the purpose of this study, tumor measurements will be taken from your clinical imaging at baseline. Additionally, the structure and pathology of your tumor may also be analyzed from the clinically collected biopsy or surgical resection tissue samples. Researchers may use this information to assist them with this study.

	Pre-study	Week 0 (T0) (before initiation of anti-angiogenic therapy)	Day 7±2 (T1)	Day 14±2 (T2)	T3	T4	T5	Follow-up (As indicated clinically)
Assessment	X							
Informed Consent	X							
History and PE	X							
Tumor Measurements	X							
Clinical MRI					X	X	X	X
Research MRI		X	X	X	X	X	X	

Clinically, you may be imaged every 2-3 months after the initiation of your treatment. However, with this research imaging technique we are testing, we would like to image you as early as 1-week after initiation of your treatment. You will be having both your clinical imaging and our research imaging, if you choose to participate in this study.

We will be performing our research MR imaging, along with your clinical imaging at the T3, T4, and T5 time points from the start of your treatment, or when progression is clinically indicated. The research MR imaging may take approximately an additional 15 minutes per each imaging session. However, the T0, T1, and T2 MR imaging sessions will be performed additionally for the purpose of this study, with each taking approximately one hour. Ideally, we would like you to participate at both T1 (7±2 days) and T2 (14±2 days) time points after initiating treatment. However, you can also choose to participate at only one of these time points.

The research imaging technique, called Arterial Spin Labeled (ASL) MRI is similar to other standard MR imaging techniques, except that with this technique, the amount of blood flow to your kidney cancer can be measured. With ASL-MRI, we will acquire two images, one similar to other standard MR images (called control image) and the other image, in which we selectively “label” the blood to the cancer using MR principles (called label image). Both control and label images are acquired without using any contrast injection, but using MR principles. During the acquisition of control and label images, you do not experience anything additional except the standard scanner noise and heating (both of which will stay below the FDA guidelines), similar to any other standard MR examination.
Clinically, you will also receive gadolinium based contrast injection for your MRI study to measure the blood flow to the tumors. This is done at your clinical imaging time points

of T3, T4, and T5. Similar to this, we will also administer contrast agent during the research portion of the study at T0, T1 and T2 time points, to compare the blood flow measured with ASL-MRI.

The research MR imaging in this study is designed for research, not for medical purposes. Even though the researchers are not looking at your condition to treat a medical problem, you will be told if they notice something unusual other than the renal cell carcinoma. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the research MR imaging done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

How long can I expect to be in this study?
MRI including ASL will be performed before, during and after your treatment, in a total of 6 MRI sessions until 7 months after the first session. After the research imaging sessions are completed, you will be followed clinically.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?
As a result of your participation in this study, you are at risk for side effects listed in this section. You should discuss these with the investigator and with your regular doctor if you choose.

Females**:** Because being a part of this study while pregnant or breast-feeding may expose an unborn child or infant to risks, pregnant and breast-feeding females cannot participate in this study. If you can become pregnant, a urine pregnancy test will be done and it must be negative before you participate. You may have a urine pregnancy test prior to each imaging session.

If you do become pregnant during this study, you must tell the researchers immediately.

MRI: We will ask you a series of questions prior to the study to make sure that there is nothing that would preclude an MRI study (such as pacemaker, electronic implants, shrapnel in the eye, certain intracranial aneurysm clips). Some subjects may experience claustrophobia or a “closed-in” feeling and some subjects could experience a “warm heating” sensation. When very high-speed methods are used for imaging, some people experience a mild twitching sensation. This should not be uncomfortable; but let us know if you experience this sensation since we can modify the imaging method to eliminate it. Fast imaging has been done for several years and no serious side effects have been encountered. There is a purely theoretical risk of causing an irregular heartbeat at the highest possible scan speeds. However, the system will be operated well below the threshold of potential ill effects in the heart. When the research MRI

techniques are added to the clinical protocol, there is a minimal although potential risk of affecting the way the images are acquired for the entire exam. The researchers will test these MRI methods prior to using them in patients to ensure the image quality of your clinical MRI exam is not affected by this research and that the FDA safety guidelines for MRI are not exceeded. The ASL-MRI research imaging technique will also follow these FDA safety guidelines. There are no additional risks associated with the ASL-MRI research imaging technique, compared to standard MRI examination.

Contrast Agents: You will be asked to receive an IV contrast agent for both your clinical and research imaging. Specifically, you will be given a group II gadolinium based contrast agent (GBCA), such as Gadavist or Dotarem. A systemic disorder called Nephrogenic Systemic Fibrosis (NSF) has been associated with the IV administration of some MRI gadolinium-based contrast agents in patients with renal dysfunction (meaning the kidneys do not work properly). However, the risk of NSF for group II GBCA (such as Gadavist and Dotarem) is so low that the current clinical guidelines from the American College of Radiology (ACR) for use of these agents consider optional the screening of patient renal function – updated in 2017 (https://www.acr.org/Clinical-Resources/Contrast-Manual). The concern for gadolinium deposition is also lower for Group II agents and not related to renal function. Accordingly, patients receiving group II GBCA for clinical MRI are no longer screened for renal function impairment at UT Southwestern.

Hemolysis (breakdown of blood cells) has been reported following IV contrast administration in patients with sickle cell disease and patients with other hemolytic anemias (low red blood count in body). This will preclude you from the study, if you have either of these conditions. Specific adverse reactions and their frequency for each contrast agent used for this study are listed below:

Gadavist™ (Gadolinium-based contrast agent)
The most common adverse reactions are: headache (1.5%), nausea (1.2%), injection site reactions (0.6%), dysgeusia (0.5%), feeling hot (0.5%), dizziness (0.4%), vomiting (0.4%), rash (0.3%), pruritus (0.2%), erythema (0.2%), dyspnea (0.2%), paresthesia (0.1%). Adverse reactions occurring in less than 0.1% of patients include: hypersensitivity/anaphylactoid reactions (hypotension, urticaria, flushing, and pallor), loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise and feeling cold.

Dotarem® (Gadolinium-based contrast agent)
Overall, approximately 4% of patients report at least one adverse reaction, primarily occurring immediately or several days following administration. The most common reactions are nausea (0.6%), headache (0.5%), injection site pain (0.4%) or coldness (0.2%), and burning sensation (0.2%). Adverse reactions that occur with a frequency < 0.2% of patients include: feeling cold, rash, somnolence, fatigue, dizziness, vomiting, pruritus, paresthesia, dysgeusia, pain in extremity, anxiety, hypertension, palpitations,

oropharyngeal discomfort, serum creatinine increased and injection site reactions, including site inflammation, extravasation, pruritus, and warmth.

Loss of Confidentiality: There is the potential for loss of confidentiality by participating in this study. Every effort will be made to protect the confidentiality of your identifiable information. However, if your participation becomes known, it could create a problem or hardship for you depending upon the type of information disclosed. Your anonymized study data may be shared with MR equipment manufacturers for the purposes of product development, training, education, display at scientific meetings and trade shows, and product literature development. Your anonymized study data may also be submitted to National Cancer Institute (NCI) of National Institutes of Health (NIH), who may make these anonymized data publicly available for future research and development.

Psychological Stress: Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. MRI machines are long, narrow, cylindrical tubes which can cause a feeling of claustrophobia or panic in some patients. While you are in the scanner, we will be in constant two-way contact with you and will remove you immediately from the magnet at your request. You may stop your participation in the study at any time.

Other Risks: There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?
We will review your medical history with you and complete a MRI Screening Form and complete urine and/or blood labs as needed before receiving any MR imaging procedures, contrast agents and entering the MR magnet. Procedures are in place to prevent the danger of metal objects becoming deadly airborne projectiles when in the magnetic field of the scanner. Safety rules are strictly enforced and followed by the research study team, MRI technologists, and the study participants themselves.

During the MRI scanning process, the study team is in constant two-way communication with you and can remove you from the magnet immediately. The MRI scanners are served by the Rapid Response Team should an adverse event arise during your study visit. All individuals involved with this study must have proof on file that they are up-to-date with their Patient Oriented Research and HIPAA training as required by the institution’s IRB and other governing bodies.

We protect your confidentiality and private information by storing electronic data in password-protected computers and paper source documents (e.g., signed consent forms, screening results, etc.) are kept in a locked file cabinet accessible to the PI and

those designated as needing access. MRI images will be digitally stored in a password-protected computer in the Radiology Department at UT Southwestern Medical Center, also with limited access to the principal investigator and his designates. Any data that are shared with MRI manufacturers or NIH will not contain personally identifiable information, it will be labeled with a study ID number. All electronic data will be encrypted and/or stored on a secure server. When you are consented, adequate time will be provided to address any questions or concerns. You will be provided HIPAA and Consent forms to review and you may discuss with other individuals before participating in the study. The researchers will be available to answer any questions and/or concerns.

What will my responsibilities be during the study?
While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or illnesses while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking.

What are the possible benefits of this study?
If you agree to take part in this study, there may not be direct benefits to you. The researchers cannot guarantee that you will benefit from participation in this research.

We hope the information learned from this study will benefit others with renal cell carcinoma in the future. Information gained from this research could lead to better diagnostic techniques.

What options are available if I decide not to take part in this research study?
This is not a treatment study. You do not have to be part of it to get treatment for your condition.

Will I be paid if I take part in this research study?
Yes. $100 each will be paid after completing the research-only scans and $25 each will be paid when your research scan is performed in conjunction with the clinical scan.

You will be issued a UT Southwestern Greenphire ClinCard, which can be used as a credit or debit card. You will also receive instructions on how to use the card. In order to receive study payments, your name, address, date of birth and Social Security Number (SSN) will be collected from you by the research staff. All information will be stored in a secure fashion and will be deleted from the UT Southwestern Greenphire ClinCard system once the study has been completed.

Important Information about Study Payments

1. Your SSN is needed in order to process your payments. Should you decide not to provide your SSN, your study participation payment will be decreased at the current IRS tax rate. Study payments are considered taxable income and are reportable to the IRS.
2. An IRS Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.
3. Your ClinCard payment information will not be shared with any third parties and will be kept completely confidential

This information will remain confidential unless you give your permission to share it with others, or if we are required by law to release it.

You will be reimbursed for your parking expenses for the T2 and T6 research appointment only.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures or Experimental Procedures including MR imaging described above).

However, the standard medical care for your condition (care you would have received whether or not you were in this study) is your responsibility (or the responsibility of your insurance provider or governmental program). You will be charged, in the standard

manner, for any procedures performed for your standard medical care.

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.

Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- Your medical problem remains unchanged or becomes worse.
- The researchers believe that participation in the research is no longer safe for you.
- The researchers believe that other treatment may be more helpful.
- The PI or the FDA stops the research for the safety of the participants.
- The PI cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?
Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Nation Cancer Institute/Nation Institutes of Health;
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people; and
- The UT Southwestern Institutional Review Board.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Whom do I call if I have questions or problems?
For questions about the study, contact Dr. Ananth Madhuranthakam at 214-645-2717.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.

_____

Name of Participant (Printed)

_____ _____ _____ AM / PM

Signature of Participant Date Time

_____

Name of Person Obtaining Consent (Printed)

_____ _____ _____ AM / PM

Signature of Person Obtaining Consent Date Time