INFORMED CONSENT AND RESEARCH AUTHORIZATION

A PHASE I/II STUDY OF INTRAOPERATIVE RADIOTHERAPY FOR PATIENTS WITH LARGE BRAIN METASTASES TREATED WITH NEUROSURGICAL RESECTION

Key Summary Information

The purpose of this study is to establish a maximum tolerated dose (MTD) of intraoperative radiotherapy (IORT) following neurosurgical resection for large brain metastases, and to determine the recurrence rate of treated brain metastasis.

Participants in this study will: undergo surgery to remove a brain tumor and receive intraoperative radiotherapy.

There are risks to this study that are described in this document. Some risks include: Scalp redness or soreness, hair loss, which may be temporary or permanent, temporary hearing decrease or loss, tiredness, decrease ability to concentrate, behavior changes, difficulty walking, difficulty talking, hearing decrease or loss, and damage to the brain.

If you are interested in learning more about this study, please continue to read below.

Introduction and Background Information

You are invited to take part in a research study because you have been diagnosed with large brain metastases. The study is being conducted under the direction of Dr. Shiao Woo at the University of Louisville**.** About 50 local subjects total will be invited to take part in this research.

An investigational treatment for brain cancer is intraoperative radiation therapy (IORT). Intraoperative radiation therapy is radiation treatment that takes place in the operating room immediately after tumor removal, while still under anesthesia.
With this technology, radiation is delivered directly to the area of the tumor removal, helping avoid damage to normal structures near the tumor.

Purpose

The purpose of this study is to establish a maximum tolerated dose (MTD) of intraoperative radiotherapy (IORT) following neurosurgical resection for large brain metastases, and to determine the recurrence rate of treated brain metastasis.

Procedures

Your participation in this study will last for 1 year after your surgery with additional survival follow up every six months for the rest of your life. If you consent to participate, you will have the following procedures while you are in this study:

Visit 1: Screening

You will have the following tests and procedures to see if you are eligible to participate in this study:

- Physical exam including vitals, height and weight
- Demographic information about you will be collected
- Your medical history information will be collected
- A complete neurological exam
- Blood tests
- Assessments and questionnaires of how well you can perform daily functions and quality of life. You may decline to answer any questions that make you feel uncomfortable.
- MRI (magnetic resonance imaging) of the brain performed within 28 days of planned surgery

You will then have surgery to remove your brain tumor. The study doctor will place the miniature x-ray source inside the balloon shaped catheter placed inside the tumor cavity. Radiotherapy will be initiated by the study doctor and when the radiotherapy is delivered, the surgeon will remove the balloon applicator and complete the surgery. You will undergo a postoperative brain MRI within 72 hours of your surgery.

Follow up visits

Visit 2, Short Interval Post-Operative Visit (within 4 weeks of IORT):

- Your medical history information will be collected
- A complete neurological and physical exam
- Assessments and questionnaires of how well you can perform daily functions and quality of life. You may decline to answer any questions that make you feel uncomfortable.
- The study doctor will review your postoperative brain MRI and your medications

Visit 3, (3 months after IORT completion)

- Your medical history information will be collected
- A complete neurological and physical exam
- Assessments and questionnaires of how well you can perform daily functions and quality of life. You may decline to answer any questions that make you feel uncomfortable.
- MRI (magnetic resonance imaging) of the brain, both with and without Gadolinium contrast
- Discuss any side effects you are experiencing

Visit 4, 5, and 6: (6 months, 9 months and 12 months after IORT completion)

- Your medical history information will be collected
- A complete neurological and physical exam
- Assessments and questionnaires of how well you can perform daily functions and quality of life. You may decline to answer any questions that make you feel uncomfortable.
- MRI (magnetic resonance imaging) of the brain, both with and without Gadolinium contrast
- Discuss any side effects you are experiencing

Potential Risks

The first human tests of investigational drugs or therapies occur in Phase I trials. Phase I trials are designed to determine the best dose of the investigational treatment and to check for any potential side effects. These trials usually involve small numbers of volunteers. Because some Phase I trials use study treatments that have never been tested in humans, they may involve significant risks.

Risks and side effects related to the radiation include those which are:

Possible Side Effects of Brain Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 may have:
• Scalp redness or soreness • Hair loss, which may be temporary or permanent • Temporary hearing decrease or loss • Tiredness • Temporary increase of brain tumor symptoms such as headaches, seizures, or weakness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Changes in thinking patterns, decreased ability to concentrate, behavior changes, difficulty walking, difficulty talking • Permanent hearing decrease or loss • Cataracts • Nausea, Vomiting • Dry mouth, changes in taste • Loss of appetite • Abnormal hormone levels related to changes to the pituitary gland may cause symptoms such as low blood sugar, low blood pressure, and fatigue which may require hormone replacement.

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Damage to the brain • Swelling of the brain • Blurred vision with chance of blindness • A new cancer resulting from treatment of earlier cancer

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

There may also be other procedures required as part of the study. The risks associated with these procedures are:

Risks of MRI Scans:

MRI scans do not usually have bad effects unless you have metal in your body. Do not take part in this test if you have any pieces of metal in your body because of earlier injury or surgery. Some older tattoo ink may contain metal, so you should also tell the study doctor or MRI staff if you have any tattoos.
People who do not like to be in small spaces (claustrophobia) might feel confined by an MRI. You may be bothered by the noise the scanner makes. You may be given earplugs or headphones to reduce the noise of the scanner.

In addition, you may suffer harms that we have not seen before.

Possible Pregnancy Risks

You should discuss pregnancy risks with your doctor before signing this consent form. Women who are pregnant or breast feeding may not participate in this research study. If you are pregnant or become pregnant, your unborn child may suffer harms that we have not seen before. If you (or your partner) become pregnant while in this study, the study doctor may ask to follow the outcome of the pregnancy. If you agree to allow the study doctor to follow your pregnancy, you will be asked to read and sign a separate consent form for permission to follow the outcome of your pregnancy.

If you are a man taking part in the study and your partner becomes pregnant, the study doctor may ask you to ask your partner for permission to follow her pregnancy. If she agrees, she will be asked to sign a separate consent form mentioned above.

Before starting this research study, females able to have children will have a pregnancy test. Talk to your doctor about the best method of birth control to use while you are in this study. It is important that you call your study doctor at (502) 562-4360 right away if you become pregnant or father a child during the course of this study. If you or your partner becomes pregnant, a decision may have to be made whether or not to end the pregnancy.

We do not know all of the effects of radiotherapy on an unborn baby. There is a risk that your unborn baby could be harmed if you become pregnant during your treatment in the study. (If you ask, your study doctor will discuss the possible risks to your unborn child and your options should you become pregnant while in this study.)

Benefits

You may not benefit by participating in this study. The information collected may not benefit you directly; however, the information may be helpful to others.

Alternatives

It is your choice whether or not to be a part of this research study.
If you decide not to join this study, you may be able to receive:

- Treatment without participating in a research study

- No medical treatments at all
- If you decide that you do not want any more active treatment, one of your options is called "comfort best supportive care." This includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you have questions about alternative treatments and their potential benefits and risks, ask the study doctor for additional information. You do not need to participate in this study to be treated for your cancer.

Research Related Injury

If you are injured by being in this research study, the study doctor will arrange for you to get medical treatment. The study site, or your study doctor has not set aside money to pay for treatment of any injury. You and your insurance will be billed for the treatment of these injuries. Before you agree to take part in this research study you should find out whether your insurance will cover an injury in this kind of research. You should talk to the study doctor or staff about this. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call your study doctor at (502) 562-4360.

Payment

You will not be paid for your time, inconvenience, or expenses while you are in this study.

Costs

You or your insurance company will be billed for all office visits, tests, medications and procedures that are part of your routine medical care and this research study. You will be responsible for paying your co-pay that is associated with any office visit, test, medication or procedure. Some insurance companies will not pay for medical bills for people who participate in a research study.
It is your responsibility to find out what costs, if any, your insurance company will cover before taking part in the study. If you need help finding out what your insurance company will cover, please ask your study doctor for assistance. If your insurance company does not pay for your bills associated with this study, you will be responsible for paying them.

According to Kentucky State Law (KRS Chapter 304.17A-136, Coverage for Cancer Clinical Trials) insurance plans may not deny coverage for routine treatment costs incurred during your participation in a cancer study if your insurance plan would have covered those costs had you not been in the study. This law is for your protection. For more information about this law, ask your study doctor.

HIPAA Research Authorization

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides federal safeguards for your protected health information (PHI). State and federal privacy laws also may also require your health information to be protected. By signing this form you provide your permission, called your "authorization," for the use and disclosure of PHI.

If you sign this form, the research team working on this study will use and share your health information to answer the research questions described in this document, and to make sure that the research was done correctly. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, medical history, and other information from your medical records from this institution and other institutions involved with this research, as well as from your other healthcare providers (which may include information about HIV status, drug, alcohol or sexually transmitted disease treatment, genetic test results, or mental health treatment). Those persons who receive your health information may not be required by Federal privacy laws (such as the HIPAA Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

In most cases, the health information that identifies you can be used or shared by the research team only if you give your permission by signing this form. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations or interventions.

The time period when information can be used or shared ends when all activities related to this study are completed.

You do not have to sign this form. If you do not sign this form, you may not participate in the study and health information that identifies you will not be shared for research purposes.

Revocation of Research Authorization

You may withdraw the authorization you have given to use and share your protected health information at any time. This means you can tell us to stop using and sharing your protected health information. If you cancel your permission:

- We will stop collecting information about you.
- You may not withdraw information that we had before you told us to stop.
    - We may already have used it or shared it.
    - We may need it to complete the research.
    - We may need it to search records that are available to the public.
    - We may need it to search records that are available to the public.
- Staff may ask your permission to follow-up with you if there is a medical reason to do so.

To cancel your permission, you will be requested to complete a written “Revocation of Research Authorization” form located at the end of this document. You may also obtain a copy from your study doctor, designated personnel or from the Human Subjects Protections Program Office website (https://louisville.edu/research/humansubjects/templates/biomedical-forms).

Information Available on ClinicalTrials.gov

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

Confidentiality

Total privacy cannot be guaranteed. We will protect your privacy to the extent permitted by law. If the results from this study are published, your name will not be made public. Once your information leaves our institution, we cannot promise that others will keep it private.

Your information may be shared with the following:

- Organizations that provide funding at any time for the conduct of the research.
- The University of Louisville Institutional Review Board, Human Subjects Protection Program Office, Privacy Office, others involved in research administration and compliance at the University, and others contracted by the University for ensuring human subjects safety or research compliance
- The local research team
- People who are responsible for research, compliance and HIPAA oversight at the institutions where the research is conducted
- People responsible for billing, sending and receiving payments related to your participation in the study
- Government agencies, such as:
    - Office for Human Research Protections
    - Office of Civil Rights
    - Food and Drug Administration
- Those responsible for data safety monitoring related to the study

Security

Your information will be kept private by password protected computers and storage in limited access, locked areas.

Voluntary Participation

Taking part in this study is completely voluntary. You may choose not to take part at all. If you decide not to be in this study, you won't be penalized or lose any benefits for which you qualify. If you decide to be in this study, you may change your mind and stop taking part at any time. If you decide to stop taking part, you won't be penalized or lose any benefits for which you qualify. You will be told about any new information learned during the study that could affect your decision to continue in the study.

Termination

Your study doctor has the right to stop this study at any point. Your study doctor may take you out of this study with or without your okay. Reasons why this may occur include:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

Participation in Other Research Studies

You may not take part in this study if you are currently in another therapeutic research study. It is important to let your study doctor know if you are in another research study.

Research Subject's Rights

If you have any questions about your rights as a research subject, you may call the Human Subjects Protection Program Office at (502) 852-5188. You may discuss any questions about your rights as a research subject, in private, with a member of the Institutional Review Board (IRB). You may also call this number if you have other questions about the research, and you cannot reach the study doctor, or want to talk to someone else. The IRB is an independent committee made up of people from the University community, staff of the institutions, as well as people from the community not connected with these institutions. The IRB has approved the participation of human subjects in this research study.

Questions, Concerns and Complaints

If you have any questions about the research study, please contact (502) 562-4360.

If you have concerns or complaints about the research or research staff and you do not wish to give your name, you may call the toll free number 1-877-852-1167. This is a 24-hour hot line answered by people who do not work at the University of Louisville.

Acknowledgment and Signatures

This document tells you what will happen during the study if you choose to take part. Your signature and date indicates that this study has been explained to you, that your questions have been answered, and that you agree to take part in the study. You are not giving up any legal rights to which you are entitled by signing this informed consent document though you are providing your authorization as outlined in this informed consent document. You will be given a copy of this consent form to keep for your records.

_____	_____
Subject Name (Please Print)	Signature of Subject Date Signed
_____	_____
Printed Name of Legally Authorized Representative (if applicable)	Signature of Legally Authorized Representative Date Signed

_____
Authority of Legally Authorized Representative to act on behalf of Subject

*Authority to act on behalf of another includes, but is not limited to parent, guardian, or durable power of attorney for health care.

_____	_____
Printed Name of Person Explaining Consent Form	Signature of Person Explaining Consent Form (if other than the Investigator) Date Signed
_____	_____
Printed Name of Investigator	Signature of Investigator Date Signed

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24 hour phone number for subjects to call for questions: (502) 562-4360
Clinicaltrials.gov identifier: NCT04040400
Investigator(s) name, degree, phone number, University Department, & address:
Shaio Woo MD, FACR
University of Louisville, James Graham Brown Cancer Center
529 South Jackson Street, Louisville, KY 40202, USA
Site(s) where study is to be conducted:
University of Louisville, James Graham Brown Cancer Center and University of Louisville Hospital
529-530 South Jackson Street, Louisville, KY 40202, USA

REVOCATION OF AUTHORIZATION FOR USE AND DISCLOSURE OF YOUR HEALTH INFORMATION FOR RESEARCH

Return To:

PI Address: University of Louisville J.G. Brown Cancer Center
529 S. Jackson Street, Louisville, KY 40202
PI Phone: (502) 562-4360

OR

Institutional Review Board
MedCenter One, Suite 200
501 E. Broadway
Louisville, KY 40202

Do not sign this letter unless you are withdrawing from this research. You will be sent confirmation that this notice was received.

To Whom It May Concern:

I would like to discontinue my participation in the research study noted above. I understand that health information already collected will continue to be used as discussed in the Authorization I signed when joining the study.

Your options are:

☐ **Withdraw from Study & Discontinue Authorization:**
Discontinue my authorization for the future use and disclosure of protected health information. In some instances, the research team may need to use your information even after you discontinue your authorization, for example, to notify you or government agencies of any health or safety concerns that were identified as part of your study participation.

☐ **Withdraw from Study Treatment, but Continue Authorization:**
Allow the research team to continue collecting information from me and my personal health information. This would be done only as needed to support the goals of the study and would not be used for purposes other than those already described in the research authorization.

_____ _____
Printed Name and Signature of Subject Date Signed

_____ _____
Signature of Subject's Legal Representative (if subject is unable to sign) Date Signed

_____ _____
Printed Name of Subject's Legal Representative Birthdate of Subject

_____
Relationship of Legal Representative to Subject

_____ _____
Subject's Address Subject's Phone Number

Optional:
I am ending my participation in this study because:

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