

Kansas City Clinical Oncology Program

N0574, Phase III Randomized Trial of the Role of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with One to Three Cerebral Metastases

WHO IS CONDUCTING THIS STUDY?

This study is a clinical trial conducted by the North Central Cancer Treatment Group (NCCTG). Clinical trials are research studies designed to find better ways to treat diseases like cancer.

You are being asked to take part in this research study because you have cancer somewhere else in your body that has metastasized (spread) to your brain. You have one to three metastases in your brain. It is up to you to decide whether or not to take part in this study.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please read this consent form carefully and take your time making your decision. We encourage you to talk with your doctor, family and friends before you decide to take part in this research study.

WHY IS THIS STUDY BEING DONE?

- The purpose of this research study is to compare overall survival and to compare the effects (good and bad) of stereotactic radiosurgery (SRS) to stereotactic radiosurgery plus whole brain radiation therapy (WBRT) on you and your brain metastases.
- There may be microscopic tumor deposits that are not yet visible on imaging (the MRI scan) that may appear at some point in the future. This research study is being done to find out if adding WBRT to stereotactic radiosurgery (SRS) will offer any additional benefit to receiving stereotactic radiosurgery alone in treating these possible microscopic tumor deposits in the brain since it is not known whether more treatment will be better or worse.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 238 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

As part of the evaluation of your eligibility to take part in this research study, your study doctor will do a MRI that needs to be done within 3 weeks prior to signing up for the study. To be eligible, the results of the MRI must show that you have at least one but no more than three brain metastases and that none are more than approximately one inch in size (a little larger than a quarter). Your study doctor must also verify that you meet other study requirements, such as not being pregnant and not having uncontrolled growth of cancer that is outside of your brain. If you are eligible and agree to participate, you will be randomized into one of the two treatment groups. The two treatment groups are described by the procedures that will be tested in this study: (Group A) radiosurgery and (Group B) radiosurgery plus whole brain radiation therapy. Everyone in this research study will have radiosurgery.

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Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor your study doctor will choose what group you will be in. The group you are put in is chosen by a computer. You will have a 50-50 chance of being in one of the two treatment groups (Group A or Group B).

If there are more than three brain metastases or if any of the brain metastases are larger than approximately one inch in size on your pre-treatment/planning MRI, you will not be eligible for this research study.

There are procedures that are part of regular cancer care that may be done even if you do not join the study. If you participate in this research study, some of these tests may be done more frequently than if you were not taking part in this research study.

Radiosurgery (SRS)

Radiosurgery utilizes immobilization (a head frame or a soft plastic mask that forms to the shape of your face that helps hold the head in place during treatment) to allow very precise targeting of tumors. Radiosurgery is a single treatment and will be done as an outpatient procedure in most cases. A high dose of radiation will be delivered to a small, focused area of your brain. One technique, called the 'gamma knife,' uses gamma rays. Other systems use a specially designed x-ray machine called a linear accelerator. This machine works much like a regular x-ray machine, but the x-ray dose is much higher and the machine will target the tumor. Either a gamma knife or a linear accelerator can be used in this research study.

If a head frame is used you will be given a local anesthesia to numb your skin and make it easier to position the special head frame. The head frame must be fixed in place with pins partially extending into your skull. The head frame holds your head to prevent it from moving and to focus the gamma rays or x-rays and aim them at the tumor(s) in your brain. To plan the procedure, a MRI is done while you are wearing the head frame. You may be given a steroid medicine through a needle into a vein in your arm before the radiosurgery to prevent swelling. For most patients, the actual time on the radiosurgery treatment machine is in the range of 30 to 90 minutes. The head frame will be removed after the treatment and the frame attachment sites on your head will be cleaned.

If a facemask is used, this will be placed over your face to keep your head from moving during the procedure. During the procedure, they will also confirm the exact location that needs to be treated using x-rays. For most patients, the actual time on the radiosurgery treatment machine is in the range of 30 to 90 minutes. The facemask will be removed after the treatment.

Whole Brain Radiation Therapy (WBRT)

Whole brain radiation therapy will be given to you as an outpatient for 5 days a week for approximately 2 ½ weeks (about 12 treatments). The treatments will deliver small doses of radiation to the whole brain each treatment day. The treatments typically last anywhere from 10 to 20 minutes (and part of this time includes making adjustments to accurately target the whole brain). The treatment will use a specially designed x-ray machine called a linear accelerator. This machine works much like a regular x-ray machine, but the targeting is more specific and the x-ray dosage is much higher. The linear accelerator will deliver the radiation with x-ray beams on each side of your head. The treatment is painless and bloodless, and there is no danger of infection. No head frame is used for whole brain radiotherapy although a soft plastic mask that helps hold the head in place during treatment may be utilized.

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Follow-up Visits

Regardless of which treatment group you are in (Group A or Group B), you will be asked to visit your study doctor for follow-up visits after your radiosurgery treatment is completed. These follow-up visits will be at 6 weeks, 12 weeks, 6 months, 9 months, 12 months, 16 months, 24 months and then every year until it has been 5 years since you started the study. During these visits your study doctor or a member of the research team will talk with you about your symptoms, give you a physical and neurological examination and you will have an MRI scan. You will be asked questions to determine your ability to think and remember, and you will be asked questions about your daily living activities. These questions will take approximately 20 to 30 minutes to complete.

In addition to the questions that your study doctor will ask you, you will be asked to complete a questionnaire that will take an additional 10-15 minutes before your treatment and at each follow-up visit after your treatment. The questionnaire asks how you feel physically, socially, emotionally and functionally.

HOW LONG WILL I BE IN THE STUDY?

We would like to keep track of your medical condition as long as you are alive or for a maximum of five years after you begin this study to look for any long-term effects of the treatment in this study.

Your study doctor may decide to take you off this study if your medical condition changes, or if NCCTG finds it must limit or stop the study. You may stop participating at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the study doctor or your own doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with your study doctor. There also may be other side effects that we cannot predict. Your study doctor may be able to offer medical treatment to decrease your side effects and make you more comfortable. Some side effects go away after the treatment, but in some cases side effects can be serious, long lasting, or permanent.

The following list of long-term side effects can occur with either treatment (SRS or WBRT) and the risks may be increased if the patient receives both SRS and WBRT (i.e., patients on Group B).

Risks and Side Effects of Radiosurgery:

<i>Very Likely</i>	<i>Less Likely</i>
<ul style="list-style-type: none"> • Temporary pain associated with the head frame placement • Headache • Localized hair loss 	<ul style="list-style-type: none"> • Nausea • Vomiting • Allergic reaction to the local anesthesia (rash, itching, nausea, or difficulty breathing) • Bleeding and/or infection around the head frame (if a head frame is used)

Risks and Side Effects of Whole Brain Radiation:

<i>Very Likely</i>	<i>Less Likely</i>

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<ul style="list-style-type: none"> • Hair loss • Temporary scalp redness and drying • Fatigue (tiredness) 	<ul style="list-style-type: none"> • Nausea • Decreased mental capacity • Decreased motor function (coordination/ movement) • Cataract formation • Dry mouth • Taste changes • Temporary ear and ear canal redness
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Expected Long-Term Serious Side Effects of SRS and WBRT Include:

<i>Less Likely</i>	<i>Rare, but serious</i>
<ul style="list-style-type: none"> • Nausea • Permanent hair loss 	<ul style="list-style-type: none"> • Vomiting • Seizures • Weakness, paralysis, loss of sensation • Loss of vision or hearing • Difficulty with speech. • Decreased mental abilities • Radiation necrosis (brain tissue death which may require surgery or steroid therapy) • Death

Reproductive risks: Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women may not participate in the study. If you are a woman who can become pregnant, a urine or blood pregnancy test will be done within 7 days prior to randomization. If the pregnancy test is done using blood, approximately 1 teaspoon of blood will be drawn from a vein by needle-stick. The pregnancy test must be negative before you can enter this study. If you are sexually active, you must agree to use birth control measures for the duration of the radiation treatment (SRS Group A or Group B WBRT + SRS). If you are a man, the treatment used in this study could affect your sperm and could potentially harm a child that you may father while on this study. If you are sexually active, you must agree to use birth control measures for the duration of the radiation treatment (Group A SRS or Group B SRS + WBRT) and for three months following the completion of the radiation treatment.

Medically acceptable birth control includes: (1) surgical sterilization, (2) approved hormonal contraceptives (such as birth control pills, Depo-Provera, or Lupron Depot), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). If you do become pregnant during this study, you must inform your study doctor immediately

For more information about risks and side effects, ask the study doctor (*NAME*) _____ at _____ or contact (*NAME*) _____ at _____.

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ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be a direct medical benefit to you. The treatments in this study have been given before to people with brain metastases, but it is not known which of these treatments works the best. We hope that information learned from this study will help people who have brain metastases in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, some of the following options may be available to you:

- Whole brain radiation therapy
- Radiosurgery
- Radiosurgery + Whole brain radiation therapy
- Surgery
- Surgery + Whole brain radiation therapy
- Surgery + Radiosurgery
- Steroids
- Chemotherapy
- Biological response modifier therapy or immunotherapy
- No therapy at this time, but care that will help you feel more comfortable

You may get radiosurgery and/ or whole brain radiation therapy even if you do not take part in the study.

Please talk to your doctor about these and other options.

In addition, if after treatment, brain metastases come back or new brain metastases develop, some of the above treatment options may be available for you. Please talk to your doctor about these and other options and your doctor will help you decide what is best for your situation.

WHAT ABOUT CONFIDENTIALITY?

Your medical records and study records are confidential but they may be disclosed if required by law.

If the study results are published, no personal information will be identified. This is to ensure that no one will be able to tell that you took part in this study. Records of your progress on the study will be kept in a confidential form at this institution and also in a computer file at the North Central Cancer Treatment Center (NCCTG). The confidentiality of the central computer record is carefully guarded. Your research records will include your medical history, results of your exams, reports from your treatment, and reports of your office visits. Some of the information collected as part of the research also may be included in your medical records.

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Organizations that may look at and/or copy your research records for quality assurance and data analysis include:

- North Central Cancer Treatment Group (NCCTG);
- Radiological Physics Center (RPC);
- Local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and
- Government agencies including the Office for Human Research Protections (OHRP) and the National Cancer Institute (NCI).
- Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- Food and Drug Administration (FDA)

These agencies may look to see that the study is being done safely and correctly.

WHAT ARE THE COSTS?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in research studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice and does not take away any of your rights. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury, you will need to report them to your study doctor and you will be treated as needed.

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WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

You can talk to your study doctor about any study-related injury, questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the Kansas City Clinical Oncology Program Institutional Review Board (a group of people who review the research to protect your rights) at 816-823-0555.

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- **For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>**
- **For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

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Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

Signature of person obtaining informed consent:

Date _____

Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be randomized to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Release

By signing this form you authorize KCCOP to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

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You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all 9 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent:

Date: _____

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