INSTITUTE: National Cancer Institute

STUDY NUMBER: 05-C-0191 PRINCIPAL INVESTIGATOR: Aradhana Kaushal, M.D.

STUDY TITLE: A Phase I Study of Image Guided Dose Escalation with Intensity Modulated Radiation Therapy (IMRT) to Histologically Confirmed Regions of Prostate Cancer

Continuing Review Approved by the IRB on 1/12/09
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Description of Research Study

You are being asked to take part in this study because you have cancer of the prostate and will be receiving radiation therapy. The purpose of this study is to deliver higher doses of radiation just to the areas of your prostate that have the cancer without increasing the damage to the normal tissues. To do this we will use an MRI scan (Magnetic Resonance Imaging) that can better detect and localize cancer within your prostate gland. We may also perform a special MRI scan, called Dynamic Contrast Enhanced MRI (DCE-MRI), a medicine is injected into your veins and the MRI can measure how the medicine flows through your prostate gland. These measurements can tell us about the blood vessels in your prostate gland, which can also provide information about the cancer. In this study, you will undergo a procedure where needle biopsies from different parts of your prostate gland will be obtained during the MRI. The biopsy results will then be compared with the measurements from the MRI. This information will tell us where in

the prostate gland your cancer is located. We will use this information to plan and deliver your radiation therapy. About 36 men will take part in this study.

Before you can start this procedure, we will do an evaluation to see if you are eligible to participate in this study. This will include a physical examination and blood laboratory studies. The day before the procedure you will take an antibiotic, called Levofloxacin. Some antacids or other drugs may interfere with this antibiotic; please discuss this with your doctor. The morning of the procedure, you will have another dose of antibiotic and a small enema. We will place a needle in a vein in your arm to inject the MRI medicine.

The doctor will give you some local anesthetic into the area around the prostate to numb the tissues in that area and decrease any discomfort from the procedure. This may be done just before, or at the beginning the MRI procedure before the biopsies are obtained from your prostate. You will be taken to the MRI scanner and an antenna shaped like a tube will be placed in your rectum. The antenna provides a channel to take needle biopsies and obtain better pictures of your prostate gland. During the procedure you will need to lie very still on your stomach while MRI images are taken. During the scan, you may be asked to breathe carbogen air through a tube placed in your mouth. Carbogen contains high concentrations of both oxygen and carbon dioxide compared to room air. The doctor will use these scans to decide where to take the biopsies. . The scans using carbogen, are optional scans and you may elect not to participate in these procedures. For each of the biopsies, a needle will be placed through your rectum into your prostate gland while you lie in the MRI. Once the needle is in place, a small biopsy will be taken through the needle. This procedure will be repeated until 4-10 biopsies are taken. You will be lying still on your stomach for approximately one hour, but the entire biopsy procedure may take approximately 2 hours. The equipment, including the endorectal coil, used is investigational and has been specially made for this procedure and has been tested for safety. We will also observe you for any problems you might be having and will ask you to report any symptoms.

It is possible that up to four non-reactive gold markers may be placed in the prostate gland during this procedure. These markers are about 1mm in diameter and are left in place. The markers will help us target the radiation treatments better and also will help us know where the biopsies were taken from if the prostate is removed.

When you are finished, you will be moved to a stretcher and transferred to a bed to recover. You will be able to get up in about 30 – 60 minutes and will be able to walk and urinate as your medication wears off. We will observe you for any problems you might have and you will be asked to report any symptoms. You will be able to go home the same day of the procedure, and may need Tylenol or Motrin if you have any pain. You will need to take another dose of antibiotic the day after the procedure.

Some patients may choose to repeat this biopsy procedure in the MRI during or after their treatment for prostate cancer. This step will help us find out whether the MRI test is still helpful after treatment. Any repeat biopsies will only be performed for clinical reasons.

Radiation therapy is usually given once a day, Monday through Friday, except for holidays. You will be lying on your back and each treatment takes about 10 minutes. You will then receive a 8 and half week course of standard external beam radiation therapy using a newer form of radiation delivery called "intensity modulated radiation therapy" (IMRT). The use of IMRT will allow your doctor to increase the dose of radiation just to the areas of the prostate that appear on MRI and/or biopsy to have the cancer. During the course of this study the amount of radiation dose will be increased and it is possible that areas of your prostate may be receiving more radiation than usually given as a standard dose. We will be closely monitoring you for any side effects that may tell us if this is harming your normal tissues and you will be asked to

report any bowel symptoms and to fill out a questionnaire. Each week of your radiation treatment, we will also take an x-ray to check the position of the prostate and fiducial markers.

Once your radiation treatment is completed, you will return to the Radiation Oncology Clinic for follow-up visits after your radiation treatment at 2, 4 8, and 12 weeks and then at 6, 9, 12,18 and every 6 months for up to 36 months. At these times you will have a PSA blood test, a physical examination and will also be asked to report any bowel symptoms and to fill out a questionnaire. It is possible, but not guaranteed that you may be eligible for other protocols in the future. Your physician will discuss this with you.

Alternative Approaches or Treatments

You may choose to not participate in this study. Alternatives to this study include receiving the appropriate standard treatment for your prostate cancer or to receive no treatment other than watchful waiting. Standard treatments for your condition may include the following: 1) external beam radiation, 2) brachytherapy, 3) surgery, or 4) hormones. These treatments could be given either alone or in combination with each other. You may also choose to be treated at another facility.

Risks or Discomforts of Participation

Treatments often have side effects. It is possible that you may experience some, all, or none of the side effects described below. It is also possible that this combination treatment may cause some side effects that we cannot anticipate. For that reason, you will be watched closely while you are receiving treatment for any signs of unexpected side effects. The risks and discomforts of this research protocol are related to the normally expected risks associated with external radiation therapy for prostate cancer, and those expected for the placement of needles into the prostate through the rectum.

Biopsies can cause pain and bleeding. There is also a small risk (<0.5%) of developing an infection or complication requiring hospitalization although you will be receiving an antibiotic to prevent this. The tissue sample that we get from the biopsy will be used for experiments in the laboratory, and portions will be stored and used later. Tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this protocol. If there are any risks to you or your family associated with these scientific studies which are not covered in this consent form, your consent will be obtained before such studies are performed. You should ask your physician any questions that you have concerning this program.

Local Anesthesia for the procedure is provided with Bupivacaine, which is a medicine that is used routinely for prostate biopsies and rarely causes adverse reactions. At much higher doses this drug can cause restlessness, anxiety, dizziness, hearing changes, blurred vision and tremors, convulsions, seizures, decreased cardiac output, heart block, low blood pressure, heart arrhythmias, and cardiac arrest. You will have a chance to discuss these risks with your doctor.

MRI scans cannot be done on people who have a cardiac pacemaker, neural pacemaker, surgical metal clips in the brain or on blood vessels, cochlear implants, or foreign metal objects within the eye. At the time of your MRI, you will be asked about these things. When you are in the scanning machine, a feeling of claustrophobia may come over you, and there will be a repetitive thumping noise. Cool air will surround you, and the room is lit so you will not feel like you are in a cave or underground. It is important to remain still during the MRI scan. You may have some discomfort or feeling of heat from the tube placed in the rectum. If you are very claustrophobic in MRI scanners you may ask your physician for a mild sedative for the procedure. If you do this you must not drive a vehicle after the MRI. You can notify the MRI

technologist of any discomfort you feel. The medicine that is used for the injection may rarely (1:2000) cause an allergic reaction such as hives, shortness of breath, or low blood pressure. The medical personnel in the MRI room are prepared to treat you for this kind of reaction. If you participate in carbogen breathing during the MRI scan, a tube will be placed in your mouth that contains high concentrations of oxygen, called carbogen, and a clamp will be placed over your nose. Because the oxygen-risk gas (carbogen) contains carbon dioxide some people may feel short of breath while they breathe it. They are actually getting much more oxygen than is usually present in room air. We will monitor the blood oxygen with "pulse oximetry," which is a small device that clips over your finger, to make sure you are getting enough oxygen. If you feel you cannot tolerate breathing the gas you can simply spit out the mouthpiece and begin breathing room air. The feeling of shortness of breath will stop in a few seconds. The MRI study will be stopped any time you request.

Antibiotic therapy with Levofloxacin can cause nausea, diarrhea, vomiting, and abdominal pain. Bad taste in the mouth, restlessness, rash, sensitivity to sunlight and seizures are other possible side effects. If you are known to be allergic to this antibiotic or if you have a reaction to it, please let us know and a different one, such as Bactrim, will be prescribed.

Blood drawing may include pain, swelling, or bruising at the needle puncture site. These are expected and temporary. In addition, there is a very small risk of fainting or of infection at the needle entry site.

Fiducial Maker Placement can cause pain and bleeding. There is also a small risk of developing and infection although you will be receiving an antibiotic to prevent this.

Radiation Therapy can cause tiredness, skin reddening, and inflammation. The most common side effects of radiation to the prostate are cystitis (an inflammation of the urine system or bladder) causing frequent, painful, or urgent urination, and proctitis (an inflammation of the rectum) causing diarrhea, painful bowel movements, bleeding or increased gas. These side effects can be treated with medications and comfort measures if they occur and usually resolve over time after the radiation therapy is finished.

Long-term or chronic side effects from radiation for prostate cancer do not usually occur, but they may include: increased gas, frequent urination, difficulty urinating, impotence, and infertility. Less common long term side effects can include discomfort in the prostate area, bleeding from the rectum or bladder, leakage of urine or bowel movements. Rare or extremely rare long-term side effects can include swelling of the legs and genital organs, injury to the hips or other bones, or new tumors caused by radiation.

The side effects listed above are the same as those for standard external beam radiation therapy for prostate cancer. However, because we will be using larger doses to parts of the prostate that actually have cancer, it is possible that the side effects listed here may occur more frequently or be worse than they would be with standard external beam therapy.

Potential Benefits of Participation

If you agree to take part in this study there may or may not be direct medical benefit to you, but you will be receiving treatment for your prostate cancer. By placing the fiducial markers into your prostate gland, we hope that the radiation can be better aimed at your prostate. In addition, the information learned from this study may benefit other patients with prostate cancer in the future.

Research Subject's Rights

Participation in this research study is voluntary and you can withdraw at any time. We encourage you to ask questions so you can make the most informed decisions during your participation in this study. Refusal to participate will not result in penalty or less benefits to which you are otherwise entitled.

It is important to stress that being in this protocol does not promise long-term medical care here at the NIH Clinical Center. If there is no further research study that is suitable for you and your state of disease, or if you are not currently on another research study, you will be returned to the care of your referring doctor or institution, or alternative sources of care closer to your home. If you have any questions about your treatment at NIH, you can contact the Principal Investigator, Dr Aradhana Kaushal(301-496-5457), the study chairperson, Dr. Peter Pinto (301-496-6353), or the patient care representative (301-496-2626).

All possible attempts will be made to maintain confidentiality of information concerning participants on this research study. Names of participants or material identifying participants will not be released without permission except as required by law. Patient medical records related to this research may be reviewed by qualified representatives of the National Cancer Institute or the Food and Drug Administration. Information regarding the safety and efficacy of the results of this study may also be published in scientific journals. It will not be possible to identify you specifically in any publication that results from this study.

Associate Investigators of the research team have developed the device being used in this research and hold a patent on it. This means that it is possible that the results of this study could lead to payments to an NIH or non- NIH scientist involved in the research. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from development of the device.

Optional Studies

We would like to keep some of the biopsy specimen (s) that is collected for future research. These specimen(s) will be identified by a number and not your name. The use of your specimen(s) will be for research purposes only and will not benefit you. It is also possible that the stored specimen(s) may never be used. Results of research done on your specimen(s) will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your biopsy specimen(s) can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimen(s). Then any biopsy specimen(s) that remain will be destroyed.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial each answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My biopsy tissue may be kept for use in research to learn about, prevent, or treat cancer.

_____Initials Yes No

2. My biopsy tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease or heart disease).

   _____Initials Yes No

3. Someone may contact me in the future to ask permission to use my biopsy tissue in new research not included in this consent.

   _____Initials Yes No

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions If you have/your child has any problems or questions about this study, or about your/your child's rights as a research participant, or about any research-related injury, contact the Principal Investigator: Aradhana Kaushal, M.D.; Building 10, Room B3B69, Telephone: (301) 496-5457 or the NCI Clinical Director at (301) 496-4251.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE
FROM JANUARY 12, 2009 THROUGH JANUARY 11, 2010.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____