RTOG 0233
A Phase II Randomized Trial for Patients with Muscle-Invading Bladder Cancer
Evaluating Transurethral Surgery and BID Irradiation Plus Either Paclitaxel and Cisplatin or 5-Fluorouracil and Cisplatin Followed by Selective Bladder Preservation and Gemcitabine/Paclitaxel/Cisplatin Adjuvant Chemotherapy

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SPONSOR: Radiation Therapy Oncology Group

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RESEARCH STUDY

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor. You are being asked to take part in this study because you have bladder cancer.

PURPOSE OF THE STUDY

About 96 people will take part in this study. The purpose of this study is to find out what effects (good and bad) chemotherapy combined with twice-daily external radiation therapy and possible removal of your bladder has on you and your cancer. The chemotherapy drugs (paclitaxel, cisplatin, 5-Fluorouracil, and gemcitabine) used in this study are not experimental drugs. These drugs have been used in the treatment of many patients with tumors such as yours. This research is being done because we do not know whether one combination of drugs with radiation is superior to another in the treatment of your disease.

The usual treatment for your type of bladder cancer is surgical removal of the bladder and the surgical construction of an alternative bladder that usually requires a permanent opening (stoma) in your abdomen for urine drainage. Also, with the standard treatment, chemotherapy and radiation therapy may be recommended following surgical removal of the bladder.

This study uses similar therapies to the standard treatment, but chemotherapy and radiation therapy are given before removal of the bladder is considered. In this study, bladder removal is advised if, after chemotherapy and radiation, your tumor has not completely disappeared, if your tumor comes back, or if it gets larger.

UAB – IRB
Consent Form Approval 3-9-06
Expiration Date 3-8-07

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Participant’s Initials _______
You will be in the study for 8 months of treatment. Treatment will begin 4-6 weeks after the transurethral bladder resection and will take about 2 ½ weeks to complete. Three weeks after the completion of the chemotherapy and radiation, the surgeon will reexamine your bladder. If your tumor has completely disappeared, you will receive chemotherapy and radiation therapy for an additional 10 days. Or, if your tumor has not completely disappeared and you are medically fit for surgery, surgical removal of your bladder within two weeks will be recommended. You will then have four months of additional chemotherapy.

Follow-up visits will take place every 3 months after all treatment for the first year, every 4 months for the 2nd year, every 6 months for three years, then annually thereafter.

**EXPLANATION OF PROCEDURES**

If you take part in this study, you will have a surgical procedure called a transurethral bladder resection. Under sedation (anesthesia), a lighted tube is inserted through the urethra (the small tube-like structure that allows urine to empty from the bladder) into the bladder. The surgeon examines your bladder tumor through this fiberoptic scope. The surgeon then will remove your tumor as thoroughly as is safely possible using an electric current. Some of your tissue also will be removed for biopsy.

After this resection, you will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will determine into which group you are placed. Neither you nor the researcher will choose what group you will be in. You will have approximately an equal chance of being placed in one of the two groups below, and you treatment will begin 4-6 weeks after the resection.

**Treatment Arm 1**

If you are randomized to this group, you will receive the drugs cisplatin and paclitaxel. You will receive cisplatin three days a week by injection over one hour into a vein (intravenously) along with special fluid treatment. You will also receive paclitaxel once a week on the same day as your first cisplatin injection. You will receive two radiation treatments each day, Monday through Friday, at least 4 hours apart. The drugs will be given starting approximately one hour before the first daily radiation treatment. The chemotherapy and radiation therapy will take about 2 ½ weeks to complete.

**Treatment Arm 2**

If you are randomized to this group, you will receive the drugs cisplatin and 5-Fluorouracil. You will receive cisplatin three days a week by injection over one hour into a vein (intravenously) along with special fluid treatment. You will also receive 5-Fluorouracil three days a week by injection over 24 hours into a vein (intravenously) during the first and last week of your radiation treatment. You will receive two radiation treatments each day, Monday through Friday, at least 4 hours apart. The drugs will be given starting approximately one hour before the first daily radiation treatment. The chemotherapy and radiation therapy will take about 2 ½ weeks to complete.
Treatments 1 and 2

Three weeks after the completion of the chemotherapy and radiation, the surgeon will reexamine your bladder through the fiberoptic scope, and a biopsy will be done. Depending on the results of these examinations, you will have one of the following treatments:

- If your tumor has completely disappeared, you will receive the chemotherapy and radiation therapy you received before the re-examination of your tumor for an additional 10 days. Also, you then will have four months of additional chemotherapy (with cisplatin, paclitaxel, and gemcitabine) to reduce the chance of cancer spreading to other parts of your body.

- If your tumor has not completely disappeared, and you are medically fit for surgery, surgical removal of your bladder within two weeks will be recommended. After surgery, you then will have four months of additional chemotherapy (with cisplatin, paclitaxel, and gemcitabine) to reduce the chance of cancer spreading to other parts of your body.

If your bladder is not removed, you will undergo careful and frequent evaluations of the bladder through a fiberoptic scope. Should the bladder tumor come back or get bigger, then surgical removal of your bladder may be recommended.

If you take part in this study, you also will have the following tests and procedures:

- A physical exam, a bladder exam through a fiberoptic scope, and bladder biopsy prior to study entry, 3 weeks after chemoradiotherapy, and at follow-up visits, if you have not had your bladder removed. Follow up visits will be every 3 months after all treatment for the first year, every 4 months for the 2nd year, every 6 months for three years, then annually thereafter.
- Measurement of your weight weekly during chemoradiotherapy.
- Blood tests prior to study entry, weekly during chemoradiotherapy, 3 weeks after chemoradiotherapy, then weekly during additional chemoradiotherapy, if you have not had your bladder removed.
- Prior to study entry, if recommended by your doctor: a bone scan and an intravenous pyelogram (IVP); the IVP is an x-ray in which dye, which is put into your vein, is used to outline the kidneys, the tubes that carry urine from the kidneys to the bladder, and the bladder on an x-ray.
- CT scan of your pelvic area prior to study entry and at follow-up visits for the first and second year after treatment.
- A chest x-ray prior to study entry and at follow-up visits for the first and second year after treatment.
- For patients who still have their bladder, a test of bladder function in the third post-treatment year.
- For women who are able to have children, a test prior to study entry to see if you are pregnant.

RISKS AND DISCOMFORTS

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many
side effects go away shortly after the chemotherapy drugs and radiation therapy are stopped, but in some cases side effects can be serious or long lasting or permanent.

**Risks associated with Radiation Therapy to the Pelvis**
A small risk of cancer, cataracts, and other radiation effects, which may not be known at this time, may develop from this therapy.

*Very Likely*
- Loss of pubic hair
- Reddening and irritation of the skin in the treatment area
- Diarrhea
- Urinary frequency, possibly with pain and/or blood
- Tiredness near the end of treatment
- Nausea and/or vomiting
- Poor digestion of food
- Rectal irritation
- Pain with sexual intercourse
- Shortening and narrowing of the vagina
- Low blood counts causing easy bruising

*Less Likely But Serious*
- Weight loss; if this severe, you may need a tube placed into your stomach to provide nutrition
- Rectal ulcer
- Bleeding or narrowing of the rectum
- Bleeding, and/or blockage of the bowel, which may require surgery
- Ureteral (tube connecting kidneys to the bladder) obstruction
- Fistula (opening) forming between pelvic tissues

Radiation to the pelvis will cause sterility. Women of childbearing potential will go through menopause and may require the use of hormones given orally to replace the hormones normally produced by the ovaries.

**Risks Associated with Cisplatin**

*Very Likely*
- Nausea and/or vomiting
- Tiredness, weakness
- Hearing loss or ringing in the ears
- Loss of appetite and/or taste; metallic taste in your mouth
- Numbness or tingling in the hands or feet
- Decrease in blood counts that can lead to a risk of infection and bleeding

*Less Likely*
- Restlessness
- Muscle cramps or spasm
Loss of coordination
Involuntary movements or shaking
Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet
Facial swelling

*Less Likely, But Serious*
A decrease in the kidneys' ability to handle the body's waste, which may be permanent
Allergic reactions, which can cause difficulty breathing, fast heartbeat, and sweating
Decrease in liver function
Another cancer called Acute Leukemia

**Risks Associated with Paclitaxel**

*Very Likely*
Decrease in blood counts that can lead to a risk of infection and bleeding
Hair loss
Fatigue
Mouth sores
Numbness, tingling, or burning in the hands or feet
Skin redness or rash

*Less Likely*
Muscle aches and/or joint pains
Nausea and/or vomiting
Headaches
Skin or nail darkening
Skin ulcers

*Less Likely, But Serious*
Changes in vision
Decrease in blood pressure
Allergic reaction, which can cause difficulty breathing, irregular heartbeat, low blood pressure, and even be life threatening
Continuing, long-lasting numbness, tingling, or burning in the hands or feet
Severe rash called Stevens-Johnson syndrome, which can cause fever and red sores in your mouth and eyes

**Risks Associated with 5-FU (5-Fluorouracil)**

*Very Likely*
Loss of appetite
Nausea and/or vomiting
Diarrhea with cramping or bleeding
Skin rash
Fatigue
Headaches
Hair loss, which is temporary
Mouth sores and/or sore throat, which may require medication to decrease discomfort
Decrease in blood counts that can lead to a risk of infection and bleeding

Less Likely
Confusion
Inflammation of the fingers and toes
Increased sensitivity to sunlight
Darkening of the skin, nails, or veins
Loss of coordination

Less Likely, But Serious
Chest pain
Infection at the puncture site

Risks Associated with Gemcitabine

Very Likely
Lower blood counts, which can lead to a risk of infection and bleeding
Nausea and/or vomiting
Fatigue

Less Likely
Skin rash
Constipation
Diarrhea
Fever
Hair loss
Pain
Swelling
Shortness of breath
Sores in the mouth

Less Likely, But Serious
Change in liver function
Decrease in kidney function
Pneumonia

Risks of Surgery

If removal of your bladder is necessary: In men, the operation includes removal of the bladder, the pelvic lymph nodes, the seminal vesicles, and the prostate. As a result, there is loss of sexual function. In women, the operation includes removal of the bladder, vagina, uterus, tubes, and ovaries. As a result, women cannot have children and may find intercourse difficult. Also during surgery, a urinary diversion procedure is necessary; this probably will include placement
of a permanent opening (stoma) created in the abdomen and a bag placed over it to collect the urine.

The major complications that can occur include infection, heart attack, severe bleeding, and blood clots. After the chemotherapy and radiation therapy treatment, surgery is likely to be more difficult for the urologic surgeon.

Also, there is a somewhat higher risk of complications for you when surgery follows radiation and chemotherapy. Surgery and bladder reconstruction can be more difficult after receiving radiation therapy. If chemotherapy fails to decrease the size of the tumor, your cancer can be more advanced at the time of surgery.

**Reproductive Risks**

The chemotherapy drugs and radiation in this study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. Reliable methods of birth control are considered to be: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), Depo Provera, Norplant, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. If you should become pregnant while on study, you must tell your doctor immediately.

As described above, radiation therapy to the pelvis will result in sterility. Surgery to remove the bladder and other organs also will result in loss of sexual function for men, and women will not be able to bear children.

**BENEFITS**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with bladder cancer in the future. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival, but these benefits are not certain or guaranteed. It is a possibility that your condition may become worse.

**ALTERNATIVES**

You may choose not to participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.
Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law. The UAB Institutional Review Board (IRB) could review your records.

ECOG Patients
Records of patient progress while on the study will be kept in a confidential file at both the Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG).

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, and other groups or organizations that have a role in this study.

Information relating to this study, including your name, medical record number, date of birth, and social security number may be shared with the billing office of UAB and UAB Health System-affiliated entities so that claims may be appropriately submitted to either the study sponsor or your insurance company for clinical services and procedures provided to you during the course of this study.

If you receive services in University Hospital as part of this trial, this informed consent document will be placed in and made part of your permanent medical record at this facility.

WITHDRAWAL FROM STUDY

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest, if funding for this study is stopped, or if your condition worsens. You may also be taken off this study if new information becomes available about how to better prevent growth of bladder cancer.

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Participant’s Initials ________
You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**COSTS TO SUBJECT**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems. The cost of your standard medical care will be billed to you and/or insurance company in the usual manner.

**PAYMENT FOR PARTICIPATION IN THIS RESEARCH**

You will receive no payment for taking part in this study.

**PAYMENTS FOR RESEARCH RELATED INJURIES**

UAB and RTOG have made no provision for monetary compensation in the event of injury resulting from this research. In the event of injury, treatment will be provided but is not provided free of charge.

**SIGNIFICANT NEW FINDINGS**

Any significant new findings that develop during the course of the study, which may affect your willingness to continue in the research, will be provided to you by the study physician. We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

**QUESTIONS**

For more information concerning any of the procedures, you may contact Lisa Clemons, RN at (205) 975-2880. If you have any questions about the research, you may contact the principal investigator, Dr. Ruby Meredith at (205) 934-2760.

If you have any questions about your rights as a research subject, you may contact Ms. Sheila Moore, Director of the Office of Institutional Review Board for Human Use (IRB). Ms. Moore can be reached at (205) 934-3789 or 1-800-822-8816, press the option for an operator/attendant and ask for an extension 4-3789 between the hours of 8:00a.m. and 5:00p.m. CT, Monday through Friday. Do not sign and date this form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

**LEGAL RIGHTS**

You are not waiving any of your legal rights by signing this consent form.
STORAGE OF SPECIMENS

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue/blood before it is given to a researcher. The tissue/blood samples will be stored safely at RTOG. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care. Please initial your choice below.

__________ I agree to allow my samples stored for future cancer research.

__________ I do not agree to allow my samples to be stored for future research.

SIGNATURES

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study and that you have read, or had read to you, all the information on this form. You will be given a signed copy of this form.

__________________________
Signature of Participant

__________________________
Signature of Physician or Investigator

__________________________
Signature of Witness

__________________________
Signature of person obtaining consent
(If other than Investigator)

__________________________
Date

__________________________
Date

__________________________
Date
University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION
FOR RESEARCH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant name: ____________________________
Research Protocol: A Phase II Randomized Trial for
Patients with Muscle-Invasive Bladder Cancer Evaluating
Transurethral Surgery and BID Irradiation Plus Either
Paclitaxel and Cisplatin or 5-Fluorouracil and Cisplatin
Followed by Selective Bladder Preservation and Gemcitabine/
Paclitaxel/Cisplatin Adjuvant Chemotherapy
UAB IRB Protocol Number: F030312014
Principal Investigator: Ruby F. Meredith, MD
Sponsor: Radiation Therapy Oncology Group

What health information do the researchers want to use? All medical information and personal identifiers including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: ____________________________ Date: _________________
or participants’ legally authorized representative: ____________________________ Date: _________________
Printed Name of participant’s representative: ____________________________
Relationship to the participant: ____________________________

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