NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 0926

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A Phase II Protocol for Patients with Stage T1 Bladder Cancer to Evaluate Selective Bladder Preserving Treatment by Radiation Therapy Concurrent with Radiosensitizing Chemotherapy Following a Thorough Transurethral Surgical Re-Staging

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Informed Consent Template for Cancer Treatment Trials
(English Language)

A Phase II Protocol For Patients With Stage T1 Bladder Cancer To Evaluate Selective Bladder Preserving Treatment By Radiation Therapy Concurrent With Radiosensitizing Chemotherapy Following A Thorough Transurethral Surgical Re-Staging

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have bladder cancer that has not responded to standard treatment.

Why is this study being done? (3/31/14)(3/6/2015)

For patients with your type of bladder cancer (non-muscle invading tumor or tumors with at least one being a Stage T1 tumor) for whom standard treatment (such as BCG therapy) was not successful or for whom BCG treatment is judged unsuitable, the usual next step for treatment in patients that are medically fit and accept this treatment is removal of the bladder (cystectomy). However, recently there have been reports that indicate a good success rate in destroying your type of bladder cancer using a repeat surgical procedure (transurethral resection of the bladder tumor) followed by radiation therapy plus chemotherapy. The majority of patients receiving this treatment did not require cystectomy and were able to maintain very satisfactory bladder function.

The purpose of this study is to find out the effects of transurethral surgery followed by radiation therapy plus chemotherapy. Although the combination of radiation therapy and chemotherapy used in this study is not an experimental treatment because it is used for patients with more advanced bladder cancer (the type that has invaded the bladder muscle), the use of this approach in this study is new for patients like you with either a tumor initially presenting as a non-muscle invading stage T1 tumor that has recurred within 18 months of receiving BCG therapy or with a stage Ta tumor treated by BCG therapy but recurred within 18 months as a T1 tumor.

How many people will take part in the study?

About 37 people will take part in this study

What will happen if I take part in this research study? (4/6/12)(5/15/12)

If you take part in this study, you will have a surgical procedure called a transurethral bladder resection. Under sedation (anesthesia), a lighted tube (fiberoptic scope) 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 around the tumor also will be removed (biopsy).

Before you begin the study:
You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of the regular evaluation of your cancer and are usually done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam, including an assessment of your ability to carry out activities of daily living
- Blood tests
- Pregnancy test for women who are able to have children
- Transurethral bladder tumor resection (TURBT; surgical removal of the tumor)

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Cystoscopic evaluation (cystoscopy: examination of the inside of the bladder using an instrument called a cystoscope)
- Blood tests
- Bone scan if necessary
- CT scan of your abdomen and pelvis: A CT scan is a test using x-rays to look at one part of your body
- An intravenous pyelogram (IVP) if necessary: An x-ray that provides pictures of the kidneys, bladder, the tubes that carry urine from the kidneys to the bladder [ureters], and the urinary tract [urethra].
- Chest x-ray
- You will be asked to fill out a questionnaire on urinary symptoms and function.

There are two types of chemotherapy that may be used in this study. Some patients will receive chemotherapy with a drug called cisplatin. In some instances, your doctor will decide to treat you instead with two chemotherapy drugs called mitomycin and 5FU.

If your treatment includes cisplatin, you will receive radiation therapy once a day, 5 days a week for about 7 weeks. During the first 3 days of week 1, week 3 and week 5, you will also be given chemotherapy (cisplatin) by vein.

If your treatment instead includes mitomycin and 5FU, you will still receive radiation therapy once a day, 5 days a week for about 7 weeks. On the first day of week 1, you will receive a single treatment with mitomycin chemotherapy by vein. In addition, during week 1 and week 4 of chemotherapy, you will receive a continuous infusion of the 5FU chemotherapy through a pump. This pump will be attached to an intravenous line (such as a PICC line or portacath) that you will have placed before starting treatment. You do not have to be in the hospital during this time, but you will have to come to the clinic on the first and last days of those two weeks (weeks 1 and 4) to have the pump attached and then detached. If you have any problems with the pump during the week, you should call the office of your treating physician right away.

<u>Regardless of which chemotherapy you receive, you will need the following assessments during radiation therapy plus chemotherapy</u>:

- Weekly measurement of your weight
- Weekly blood tests
- On your last day of treatment: an assessment of your ability to carry out activities of daily living

When you are finished radiation and chemotherapy*:
<u>You will need these tests and procedures 8-10 weeks after the completion of radiation and chemotherapy</u>

- Cystoscopy (examination of the inside of the bladder using an instrument called a cystoscope)
- Bladder biopsy

- Urine cytology (a series of tests that are done to identify all the different types of cells and other substances in your urine)
- *For patients in whom the tumor has not completely disappeared, surgical removal of the bladder or possibly further treatment by instilling drugs into your bladder, as recommended by your doctor

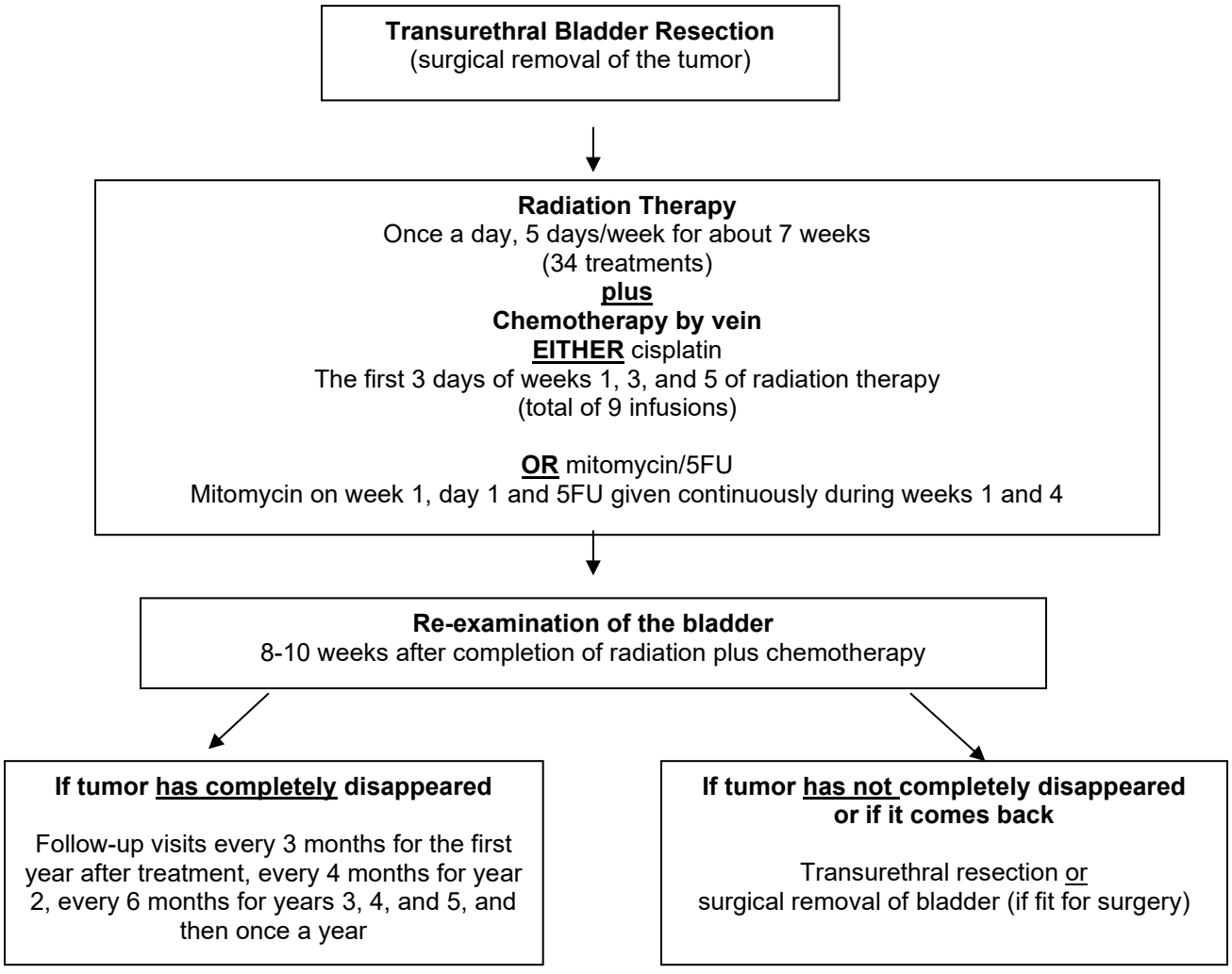
You will need these tests and procedures during follow-up after the completion of radiation and chemotherapy

- History and physical exam, including an assessment of your ability to carry out activities of daily living, blood tests, cystoscopy (for patients who still have their bladder), urine cytology, and bladder biopsy every 3 months after all treatment for the first year, every 4 months during the 2nd year, every 6 months during years 3, 4, and 5, then once a year thereafter
- CT scan and chest x-ray once a year for years 1, 2, and 3
- You will be asked to fill out a questionnaire on urinary symptoms and function during year 3

After you've finished radiation and chemotherapy, if your tumor comes back (recurrence) your doctor may recommend other treatment options (for example, cystectomy – the surgical removal of your bladder). The type of treatment recommended will vary based on the type of tumor you have.

Study Plan (4/6/12)(5/15/12)

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study? (4/20/15)

Radiotherapy and chemotherapy will begin within 15 weeks after the transurethral bladder resection and will take 6 to 8 weeks to complete.

Eight to 10 weeks after the completion of the radiation and chemotherapy, the study doctor will re-examine your bladder. If your tumor has completely disappeared, you will be seen during follow-up visits every 3 months after completion of treatment for the first year, every 4 months during the 2nd year, every 6 months for years 3, 4, and 5, then once a year thereafter. If your tumor has not completely disappeared or if it comes back (recurrence) and you are medically fit for surgery, surgical removal of your bladder will be recommended at this time.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the radiation and chemotherapy (cisplatin) can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study? (4/6/12)(3/6/2015)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop radiation and chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the radiation therapy to the pelvis in this study include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving pelvis radiation, more than 20 and up to 100 may have:
• Hair loss in the treatment area, may be permanent • Diarrhea • Need to urinate often • Urgency with urination • Slower urinary flow • Tiredness • Pain, including with urination and/or bowel movements • Nausea, vomiting • Painful sexual intercourse (women) • Abnormal sexual function, may be permanent (men)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving pelvis radiation, from 4 to 20 may have:
• Chronic bowel/bladder symptoms as described above • Blood in urine • Inability to control urine, inability to control bowel movements • Mucous-like stools • Bleeding of the rectum • Swelling, redness, rash, skin changes, or itching in the area of radiation

RARE, AND SERIOUS In 100 people receiving pelvis radiation, 3 or fewer may have:
• Weight loss • Blockage of internal organs that may require surgery • A tear or hole in internal organs that may require surgery • Bladder shrinkage, discomfort, or bleeding which may require medication or surgery, including removal of the bladder. • Internal bleeding which may cause bleeding of the rectum, black tarry stool, blood in vomit, blood in urine, and may require surgery. • Infection which may cause painful and frequent urination • A new cancer resulting from treatment of earlier cancer

Radiation to the pelvis will cause sterility (inability to father children or become pregnant). 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 and side effects related to chemotherapy include:

Possible Side Effects of Cisplatin (Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Nausea, vomiting • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require blood transfusions • Bruising, bleeding • Kidney damage which may cause swelling, may require dialysis • Hearing loss including ringing in ears

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Difficulty with balance

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy later in life • Seizure

Possible Side Effects of 5-Fluorouracil (Table Version Date: October 24, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil, more than 20 and up to 100 may have:
• Hair loss • Redness, pain or peeling of palms and soles • Rash, increased risk of sunburn, itching • Diarrhea, nausea, vomiting, loss of appetite • Difficulty swallowing • Sores in mouth • Heartburn • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil, from 4 to 20 may have:
• Chest pain • Blood clot • Belly pain • Internal bleeding which may cause black tarry stools • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Cough, hoarseness • Bruising, bleeding • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Abnormal eye movement, blurred vision, watering eyes • Discomfort from light

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil, from 4 to 20 may have:
• Swelling, redness, tingling and pain of hands and feet • Difficulty with balancing

RARE, AND SERIOUS In 100 people receiving 5-Fluorouracil, 3 or fewer may have:
• Damage to the heart which may cause shortness of breath • A new cancer resulting from treatment of earlier cancer

Possible Side Effects of Mitomycin (Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Mitomycin, more than 20 and up to 100 may have:
• Infection, particularly when white blood cell counts are low • Anemia which might require blood transfusion • Tiredness • Nausea, vomiting, diarrhea • Swelling of the body • Difficult, painful or frequent urination (when the drug is administered into the bladder)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Mitomycin, from 4 to 20 may have:
• Loss of appetite • Sores in the mouth • Rash • Hair loss • Loss of fertility

RARE, AND SERIOUS In 100 people receiving Mitomycin, 3 or fewer may have:
• Scarring of the lungs • Kidney failure that could require treatment with dialysis

Risks of Surgery:

If removal of your bladder is necessary

In men, after radiation, the operation generally includes removal of the bladder, the pelvic lymph nodes, the seminal vesicles, and the prostate. As a result, there is likely to be loss of sexual function. In women, the operation may include removal of the bladder, vagina, uterus, tubes, and ovaries. As a result, women may not be able to 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. In some circumstances other types of urinary diversion may be possible, based on the judgment of your surgeon.

In general, there is a higher risk of complications for you when surgery follows radiation and chemotherapy. Surgery and bladder reconstruction can be more difficult and the choices for bladder reconstruction are limited. In addition, if chemotherapy fails to decrease the size of the tumor, your cancer can be more advanced at the time of surgery.

After bladder removal, the major complications that can occur include infection, heart attack, stroke, severe bleeding, blood clots in the legs or the lung and injury to the rectum or other areas of the intestine. This type of injury may require a second temporary stoma to allow the intestine to heal. Injury to the intestine may also lead to abnormal connections (fistulas) between the intestines and other organs. Minor complications include wound infection and delayed hospital stay due to intestinal inactivity (ileus).

Reproductive Risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Radiation to the pelvis will cause sterility (inability to father children or become pregnant). 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.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study? (3/31/14)

Taking part in this study may or may not make your health better. While researchers hope that radiation plus chemotherapy will remove all the cancer in your bladder so that surgical removal of the bladder itself (cystectomy) is not necessary, there is no guarantee that a cystectomy will not need to be done.

One of the risks of undergoing the radiation plus chemotherapy in this study is that if a cystectomy is needed, the radiation plus chemotherapy might make the surgery more difficult and make it less likely that the surgeon would judge it safely possible to carry out all aspects of the procedure without needing to create a permanent opening in the abdomen (a type of “urinary diversion” procedure).

We do know that information from this study will help us learn more about the advantages of the treatment used in the study and will help researchers learn more about the use of radiation and chemotherapy for patients with this type of bladder cancer. This information could help future cancer patients who have non-muscle invading bladder cancer.

What other choices do I have if I do not take part in this study? (3/31/14)(3/6/2015)

Your other choices may include:

- Removal of the bladder (radical cystectomy) and a urinary diversion procedure. This is the standard approach for patients with non-muscle invading tumor or tumors with at least one being Stage T1 who have failed BCG therapy within 18 months of this treatment with a Ta or a T1 tumor and those patients who may have failed other forms of injection of drugs into their bladder, or patients who were initially diagnosed with a T1 tumor but who were unsuited to receive BCG therapy.
- Newer forms of intravesical (within the bladder) chemotherapy with previously untested and non standard drugs as part of another study
- Radiation therapy alone
- Receiving no additional treatment other than repeat transurethral resections (with this choice, your tumor could continue to grow and your disease could spread)

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (4/6/12) (3/31/14)

Data are housed at NRG Oncology Statistics and Data Management Center in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- NRG Oncology
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

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

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

What are the costs of taking part in this study? (3/31/14)

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 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.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study? (3/6/2015)

Taking part in this study is your choice. 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.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II NRG Oncology clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any 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 _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

You can say "yes" or "no" to [each of] the following study[ies]. Below, please mark your choice [for each study].

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue, Blood, and Urine for Research (4/20/15)

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. You may also have two additional biopsies.

We would like to keep some of the tissue from the biopsies for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases.

In addition, if you agree to participate in this part of the study, you will have blood drawn and urine collected before you start chemoradiation therapy. We would like to keep about 2 tablespoons of blood and 5 tablespoons of urine at this time for future research. If you agree, this blood and urine will be kept to be used in research to learn more about cancer and other diseases.

Your tissue, blood, and urine may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue, blood, and urine 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.

Things to Think About

The choice to let us keep the left over tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine 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 tissue, blood, and urine. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it. Any remaining blood and/or urine will be destroyed.

In the future, people who do research may need to know more about your health. While the study doctor/ institution may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research (about diseases that are passed on in families). Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records.

Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new treatments for cancer and other diseases in the future.

Benefits

The benefits of research using tissue, blood, and urine include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ [IRB's phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

2. My specimens 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), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

Where can I get more information? (4/6/12)

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

1-800-4-CANCER (1-800-422-6237)

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.

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.

Participant _____

Date _____