Protocol Title: Pilot Study of Adjuvant Proton Beam Teletherapy for Post-Hysterectomy Cancers of the Uterus and Cervix with Metastases to Regional Lymph Nodes

DF/HCC Principal Research Doctor / Institution:

Andrea Russo, MD / Massachusetts General Hospital

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study. You are invited to take part because you have uterine or cervical cancer that has spread to one or more of your lymph nodes, and have had surgery to remove your uterus. When cancer has spread to lymph nodes, radiation treatment is often recommended post-operatively to reduce the risk of cancer recurrence. This research study is a way of gaining new knowledge about radiation treatment for your cancer. If you decide to take part, you will be known as a "participant" rather than a "patient". This research study is evaluating a type of radiation treatment called proton beam radiation therapy as a possible treatment for uterine and cervical cancer intended to reduce the side effects and potential complications which can result from standard (photon) radiation treatments.

It is expected that about 22 people will take part in this research study.

Some research studies are supported in some way by an outside organization. The Federal Share of program income earned by Massachusetts General Hospital (MGH) is supporting this research study by providing funding for the research study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your regular doctor.

We encourage you to take some time to think this over, to discuss it with other people and your doctor, and to ask questions now and at any time in the future.

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B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a pilot study. Pilot studies are conducted to see if it is practical to do this type of research on a larger scale in the future. Proton beam radiation therapy is an investigational treatment. "Investigational" means that the treatment is still being studied and that research doctors are trying to find out more about it.

Proton beam radiation therapy is known to spare surrounding normal tissues from radiation. Proton beam radiation delivers less radiation beyond the area of the target tissues. This may reduce side effects that patients would normally experience with standard (photon) radiation therapy which tends to unavoidably include more normal tissue along with tumor target tissue.

In this research study, we are looking to determine if proton beam radiation is effective in controlling your cancer growth. We are also looking to see if proton beam radiation can reduce side effects when compared to standard radiation treatment (photon radiation).

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Standard treatment including photon radiation therapy.
- Participate in another research study.
- No therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Before the research starts (screening): After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you

can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Physical exam**, including height and weight.
- **Vital signs**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An assessment of your tumor by CT**(Computerized Tomography) scan, of the chest, abdomen and pelvis
- **Pelvic exam**
- **Routine blood tests** for platelets (blood clotting), blood counts and chemistry. We will take 2 teaspoons of blood.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

After the screening procedures confirm that you are eligible to participate in the research study:

Study treatment (proton beam radiation therapy): You will receive proton beam radiation treatment as an outpatient at the Francis H. Burr Proton Center. This center is located at the Massachusetts General Hospital. All proton beam radiation treatments will be administered 5 days per week (Monday-Friday) over 5 to 6 weeks depending on your type of cancer and how well you tolerate the study treatment.

Tests and procedures during study treatment: In addition to your daily radiation treatments, you will have the following tests every week:

- Questions about your health and current medications
- **Physical exam,** includes height, weight and vital signs
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood test** for complete blood counts and blood clotting**.** We will take 2 teaspoons of blood. These are repeated twice weekly for uterine cancer participants and once weekly for cervix cancer participants during treatment. These tests will be ordered at the discretion of the treating physician.
- **Pelvic exam** (*at Week 6 only*)

- **Questionnaires** about your quality of life

After completion of proton beam radiation treatment : You will be followed for 5 years after completion of your treatment or removal from the study. The follow-up visits will occur every 3 months for 2 years; every 4 months to year 3 and every 6 months there after. At each visit you will receive the following:

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Physical exam,** includes height, weight and vitals
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Pelvic exam**
- **CT**(**Computerized Tomography) scan**, of the chest, abdomen and pelvis twice per year to year 3
- **Questionnaires** about quality of life at 6, 12, 24, 36, 48, and 60 months.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be followed for 5 years after the completion of your treatment in this study.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your regular doctor first.

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F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. Many treatments given for tumors, including proton beam radiation therapy, have side effects, which can range from mild and reversible to severe, long lasting and possibly life threatening. There is a great deal of variability among side effects and between individuals.

You need to tell your doctor or a member of the study team immediately if you experience any side effects.

Since the effect of the study treatment taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Proton Beam Radiation:

Radiation has the capacity to injure all normal tissues unavoidably included in the target volume. Usually radiation effects are divided into acute effects which are experienced during radiation treatment which may temporarily persist for several weeks after completion of treatment, and late or delayed effects which may first be experienced months to years after radiation treatment.

Acute (temporary) effects include:

Likely (more than 50% chance this will happen):

- Fatigue
- Cramps
- Frequent bowel movement
- Diarrhea
- Nausea
- Urinary frequency and urgency
- Burning with urination
- Vaginal irritation with itching and discharge

- Skin reaction (radiation dermatitis)
- Rectal irritation

Frequent (10-50% chance this will occur):

- Nausea (mild) and vomiting (rare) that is treatable with medications.
- Reduction in circulating blood counts including red cells which are important for carrying oxygen, platelets which are important for normal blood coagulation, and white cells which are important in fighting infection. If severe, changes in circulating blood counts may require blood transfusion, hospitalization, and medication intended to bring blood counts to normal levels.

Occasional (Between 1-10% chance this will occur):

- Dehydration and Electrolyte imbalances (changes in body salts) may occur in patients experiencing nausea, vomiting and diarrhea. This may not cause symptoms but sometimes causes fatigue, muscle weakness, muscle cramps, irregular heart beat or seizures. This can be severe and possibly life threatening, and may require hospitalization and intravenous treatment.

Delayed effects which may develop after completion of Proton beam radiation treatment include:

Frequent (10-50% chance this will occur):

- Leg lymphedema (swelling of legs due to a block in lymphatic flow)

Occasional (Between 1-10% chance this will occur):

- Bowel obstruction requiring surgery to repair.
- Bowel injury
- Premature menopause: probable if ovaries have not been conserved surgically and removed to locations remote from the radiation target volumes.
- Bone fractures in the pelvis or spine

Rare (Less than a 1% chance this will occur):

- Appearance of radiation caused cancer in or next to the radiation site: very rare and usually observed 20 or more years after radiation treatment.
- Reduced bladder capacity with urinary frequency and urgency
- Potential injury to any/all normal tissues unavoidably irradiated
- Possible injury to liver and/or kidneys

Risks Associated with Radiological Scans and X-Rays:
While you are in this research study, CT scans may be used to evaluate your disease. The frequency of these exams is about the same as what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

There is a small risk with using the contrast agent that is injected into a vein during the scan. It may worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

Taking part in this research study may or may not make your health better. We hope the information learned from this research study will help doctors learn more about proton beam radiation as a treatment for uterine and cervical cancer in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the treatment. In some cases, the abrupt stopping of a treatment can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid to take part in this research study.

We may use your information to develop a new product or medical test to be sold. The sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your information is used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care, including your radiation therapy. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

We will offer you the care needed to treat injuries directly resulting from taking

part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for Dana-Farber/Partners CancerCare (DF/PCC) on behalf of the Dana-Farber/Harvard Cancer Center (DF/HCC) to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital

- Andrea Russo, MD: 617-219-1200

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

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4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

O. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

_____ _____

Signature of Participant or Legally Authorized Representative — Date

_____

Relationship of Legally Authorized Representative to Participant

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Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

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