

INFORMED CONSENT
1B-04-4

TITLE: An International Randomized Controlled Trial to Compare Targeted Intra-operative Radiotherapy with Conventional Post-operative Radiotherapy after Conservative Breast Surgery for Women with Early Stage Breast Cancer

DEPARTMENTS: **Surgery and Radiation Oncology**

PRINCIPAL INVESTIGATOR: Dennis R. Holmes, MD

24-HOUR PHONE (EMERGENCY): (323)-865-3000

You have been asked to participate as a subject in a medical experiment. Before you decide whether you want to participate in the experimental procedure, you have a right to the following information:

CALIFORNIA LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. The nature and purpose of the study.
2. The procedures in the study and any drug or device to be used.
3. Discomforts and risks to be expected from the study.
4. Benefits to be expected from the study.
5. Alternative procedures, drugs or devices that might be helpful and their risks and benefits.
6. Availability of medical treatment should complications occur.
7. The opportunity to ask questions about the study or the procedure.
8. The opportunity to withdraw at any time without affecting your future care at this institution.
9. A copy of the written consent form for the study.
10. The opportunity to consent freely to the study without the use of coercion.
11. Statement regarding liability for research-related injury, if applicable.

I have carefully read the information contained above and I understand fully my rights as a potential subject in a medical experimentation involving people as subjects.

Date: _____ Time _____

Signature: _____
(patient)

Signature: _____
(parent/legally authorized representative)

If signed by other than patient, indicate relationship: _____

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WHY IS THIS STUDY BEING DONE?

You are invited to take part in a research study. Treatment for the type of breast cancer you have has traditionally been mastectomy (removal of the whole breast). However, it has now been clearly shown that removal of only the lump and the lymph nodes under the armpit, followed by radiotherapy after surgery, is equally effective, and has the benefit of preserving the breast. Conventional radiotherapy is given to the whole breast. This can take up to 6 weeks of daily (Monday through Friday) visits to hospital. Although this is known to considerably reduce the risk of breast cancer recurrence, over a ten-year period, a few patients in every hundred will have a recurrence of the tumor in the treated breast. Over the last few years, a new device has been developed that delivers the radiotherapy accurately targeted to the tumor bed immediately after the tumor is removed in the operating room. It has been tested in a pilot study with 25 subjects.

This device, the Intrabeam Photon Radiosurgery System, will provide a means to position a radioactive source within the cavity created by the lumpectomy (See Figure 1). This radioactive source will deliver the radiation therapy to the breast tissue over a 30-35 minute period.

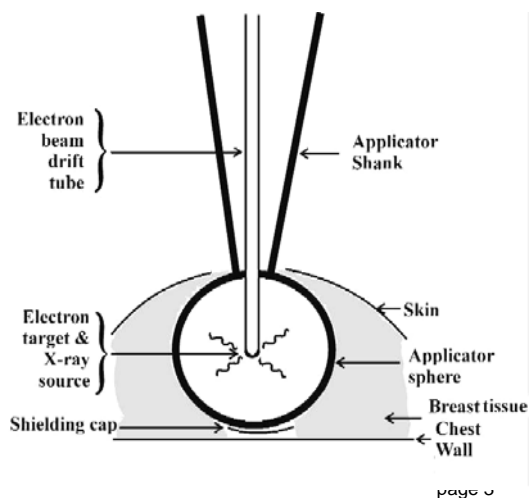


Figure 1.

Drawing showing the Intrabeam Photon-Radiosurgery System positioned within the breast at the time of surgery. Applicator containing X-ray source is inserted into biopsy cavity. X-rays are released to treat the surrounding breast tissue. Shielding cap used to minimize exposure of underlying chest to X-rays.

The purpose of this study is to assess whether Targeted Intraoperative Radiotherapy is as effective as the standard 6-week course of radiotherapy after surgery (which we will now call Conventional Radiotherapy). If you agree to participate, you will have an equal chance of receiving either Conventional Radiotherapy (up to six weeks of treatment) or Targeted Intraoperative Radiotherapy (done only at the time of surgery). This study is designed to enroll 2400 patients internationally. Half of the patients will receive Targeted Intraoperative Radiotherapy and half will receive Conventional Radiotherapy. About 100 patients from USC will participate.

The study is being done to find out whether there is any difference between the treatments in reducing the risk of the cancer returning in the affected breast and in the long-term changes to the breast tissue.

WHAT IS INVOLVED IN THE STUDY?

If you are willing to join the study, your doctor will contact the research center where the study computer will assign one of the two treatments to you by a process similar to tossing a coin. This is the best scientific way to obtain results that are not biased in any way. Your doctor will then let you know whether you will receive the Conventional Radiotherapy or the Targeted Intraoperative Radiotherapy. If you are going to receive Conventional Radiotherapy, you will have your operation and be discharged from the hospital. The radiation oncologist will then arrange for you to receive Conventional Radiotherapy at USC or at a treatment center near your home. After Conventional Radiotherapy is completed, you will be asked to attend the clinic at USC for routine check up visits.

If you are going to receive Targeted Intraoperative Radiotherapy you will be given treatment while still under anesthesia in the operating room. This treatment will last 30-45 minutes. This means that you will complete your radiotherapy during surgery, and then be discharged from the hospital when you are well enough. You will be asked to return for routine check up visits.

Prior to your surgery, a series of tests will be performed to determine if you qualify for participation in the clinical study, including additional imaging studies (mammograms, ultrasounds or breast MRI) to fully understand the extent of cancer within your breast. Your physician will ask you a series of questions regarding your medical history. Your temperature, blood pressure and pulse will be taken. Standard physical exams will be performed. If you are a woman of childbearing age, you will be asked to give a urine specimen so that a pregnancy test can be performed.

After seeing the pathology report (the detailed examination of the removed tissue) there is a small chance that your surgeon will want to re-operate because he is not completely sure that he has removed all the affected tissue or because it is an unusual type of breast cancer. All breast cancers are reviewed in this way-it is not just because you are in the study. If further surgery is necessary, he will talk to you about it. If you are in the group treated with Targeted Intraoperative Radiotherapy, you will receive radiotherapy at the time of surgery. If a second surgery is needed, but you have already received Targeted Intraoperative Radiotherapy at the time of your first operation, your doctor will recommend that you undergo Conventional Radiotherapy after the second operation, since re-treatment with Targeted Intraoperative Radiotherapy may cause increased wound complications. If you receive Targeted Intraoperative Radiotherapy, but are found to have extensive cancer affecting your lymph

nodes, your doctor will recommend that you undergo Conventional Radiotherapy because patients with extensive cancer affecting the lymph nodes respond better to Conventional Radiotherapy.

If you are in the Conventional Radiotherapy group, then the radiotherapy will be given after you have completed all surgery. If your doctors recommend chemotherapy to treat your breast cancer, then the chemotherapy will be given after surgery, followed by Conventional Radiotherapy given after chemotherapy.

If you have undergone surgery at another hospital for breast cancer, you may still participate in this study. To determine if you qualify for this study, your doctors might request that you undergo additional studies (for example, mammogram, ultrasound or breast MRI) to ensure that your original surgery was adequate. If the doctors decide that your original surgery was inadequate, you will be advised to have additional biopsies or surgery to remove affected breast tissue. If you are placed in the group receiving Targeted Intraoperative Radiotherapy, the radiotherapy will be given at the time of this second operation. Even if your first surgery was successful, you will still need to undergo a second operation in order for the Targeted Intraoperative Radiotherapy to be given. Also, at the time you receive Targeted Intraoperative Radiotherapy, the surgeon might need to remove additional breast tissue or re-shape your breast tissue so that the radiotherapy may be given properly. The surgeon will discuss this with you prior to surgery.

If you have undergone surgery at another hospital for breast cancer and have been placed in the Conventional Radiotherapy group, your doctors might request that you undergo additional studies (for example, mammogram, ultrasound or breast MRI) to ensure that your original operation was successful. If your doctors decide that your original surgery was inadequate, you will be advised to have additional biopsies or surgery before being allowed to remain in this study. Once you have received permission to remain in this study, the radiation oncologist will arrange for you to receive Conventional Radiotherapy at USC or at a treatment center near your home. After Conventional Radiotherapy is completed, you will be asked to return to USC for routine check up visits.

Most patients with breast cancer are recommended to take additional treatment (adjuvant therapy) to try to stop the cancer from coming back. This may be chemotherapy or hormone therapy. These treatments are not part of the study. If you are in the Targeted Intraoperative Radiotherapy group and have been advised to receive chemotherapy, your radiotherapy will be given at the time of surgery and chemotherapy will be given after surgery. If you are in the Conventional Radiotherapy group and have been advised to receive chemotherapy, you will be given chemotherapy after surgery followed by Conventional Radiotherapy after completing chemotherapy. If hormone therapy is recommended, it is usually started after the completion of surgery, chemotherapy, and radiotherapy.

In order for the international research center to analyze the results of this study, data on you, your treatment and how you do afterwards will be sent from USC. This will be done in a secure way and all data referring to you will be kept private.

The data may not be analyzed for several years, following strict scientific guidelines as to when this should be done. During this period, the data from the study will be regularly reviewed by a small

group of international experts not directly involved in the study (called the Data Monitoring and Safety Committee). They will advise and make recommendations on the safety and conduct of the study. They are independent and ensure that the study is run to the highest ethical and scientific standards.

When the results have been analyzed, your doctor will be informed so that he can pass on the information to you. A paper will also be published in a scientific journal so that doctors all over the world can read the results. Individual patients will not be identifiable from the information in any publication.

In order to produce reliable results, the research center would like to receive information on you for at least ten years following completion of your treatment. Therefore, if you move and will no longer be able to attend your original treating hospital, please let your doctor know.

If you agree, we would like to collect a small piece of the tissue removed at operation but currently stored in your local hospital. There are now a number of ways we could use this tissue to learn more about breast cancer. There will be no results from this that will affect you or your treatment in any way but we hope that we might be able to learn more about the disease. If you are willing to donate your tissue as a gift to be used in this way please check the appropriate box below:

My tissue samples stored after surgery may be used in future research as described above.

Yes _____ No _____ Initials _____

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

You may experience no side effects, some of them or most of them. Although you will be closely monitored, not all side effects can be predicted and unforeseen problems can arise. There may be some unknown or unanticipated risks or discomforts in addition to those specified here. If you experience any discomfort or side effects following your study participation, please report these to your doctor.

Surgery: Complications associated with the surgery are similar to any tumor removal surgery. These possible complications include, but are not limited to: infection, bleeding, loss or reduced nerve function, swelling (edema), blood clotting, fluid accumulation, wound breakdown, bruising, skin ulceration, scarring, and allergic reactions.

Conventional Radiotherapy: Just as with patients not in the study, Conventional Radiotherapy may cause side effects such as reddening and soreness of the skin, feeling sick (nausea) and tiredness. These side effects gradually disappear once your course of treatment has finished, though the tiredness may continue for some months. Complications arising from Conventional Radiotherapy include, but are not limited to infection, loss or impairment of nerve function, swelling (edema), scarring, rib fracture, chest wall pain, skin ulceration and radiation induced tissue death. Scarring may be a long-term complication of radiation treatment and some firmness, tenderness, pain or deformity in the treated area of the breast may develop in the future.

Targeted Intraoperative Radiotherapy: Complications arising from Targeted Intraoperative Radiotherapy include, but are not limited to infection, loss or impairment of nerve function, swelling (edema), scarring, rib fracture, chest wall pain, skin ulceration and radiation induced tissue death. Scarring may be a long-term complication of radiation treatment and some firmness, tenderness, pain or deformity in the treated area of the breast may develop in the future. Since Targeted Intraoperative Radiotherapy gives radiotherapy to only a portion of the breast, there is a risk that the untreated portions of the breast will be at greater risk of a breast cancer recurrence. This is the main question that this study is trying to answer. For your protection, your doctors will make every reasonable effort to ensure that you are a good candidate for Targeted Intraoperative Radiotherapy. One possible problem with the new treatment may be delayed wound healing.

Chemotherapy: If chemotherapy is needed to treat your cancer, some patients undergoing chemotherapy after radiation therapy may experience a radiation recall reaction that may cause redness, blistering, or peeling of the skin of the breast.

Pathology: If you have received Targeted Intraoperative Radiotherapy at the time of surgery, but are found after surgery to have a tumor greater than 3 centimeters (1 inches), extensive non-invasive cancer, or cancer involving four (4) or more lymph nodes, you will be advised to undergo Conventional Radiotherapy, and possibly more surgery.

WHAT ABOUT PREGNANCY?

Radiotherapy is harmful to an unborn child. If you are pregnant, you may not take part in this study. If you are a woman who could become pregnant, you must have a pregnancy test to make sure you are not pregnant prior to receiving either Targeted Intraoperative Radiotherapy or Conventional Radiotherapy. You must use birth control while receiving radiotherapy.

If you are breastfeeding and do not want to stop, you may not join this study. The only way you can take part in this study is to stop breastfeeding and not use your breast milk to feed your child until your doctor tells you it is safe.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

Patients receiving Targeted Intraoperative Radiotherapy will avoid up to 30 visits to the radiotherapy department for post-operative radiotherapy. The entire breast treatment, including radiotherapy, will have been completed at the time of surgery. Also, because of the way the intraoperative radiotherapy is given, the tissues at greatest risk receive the maximum dose.

Except for shortening the duration of your radiation therapy, you will not receive additional benefit if you are in the group treated with Targeted Intraoperative Radiotherapy. The potential benefit to society is the development of a new way of getting radiation to the tumor cells in the area where the tumor was and kill those tumor cells. This new method is designed to spare normal tissue from radiation effects and to reduce the total duration of therapy. The information obtained from this study may be used scientifically and may possibly be helpful to others in the future.

WHAT OTHER OPTIONS ARE THERE?

Other treatment options include mastectomy, Conventional Radiotherapy, chemotherapy or other methods of partial breast irradiation or experimental agents to make you feel better. Another option is no further therapy. Your doctor can provide information about your disease and the benefits of the different treatments for you. You should feel free to talk with your doctor about your disease and expected outcomes. The doctor involved in your care will be available to answer any questions you have about this program. You are free to ask your doctor any question concerning this program now or in the future.

WILL YOUR INFORMATION BE KEPT PRIVATE?

Every effort will be made to maintain the confidentiality of your medical records for this study by the investigators and the Institutional Review Board (IRB). However, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Specific study-related information will be made available to Zeiss, Inc., the manufacturer of the IntraBeam Photon Radiosurgery System. The Food and Drug Administration (FDA) will be allowed access to your medical records. Unless required by law, the FDA will maintain the confidentiality of your medical records. If results of this study are published in medical literature, you will not be identified by name.

WHAT ARE THE COSTS?

If you take part in this study, your insurance company may not pay for some or all of the procedures, treatments and tests. If that happens, you need to pay for these procedures, treatments and tests yourself.

ARE THERE ANY PAYMENTS TO YOU FOR TAKING PART IN THE STUDY?

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

WHAT HAPPENS IF YOU GET INJURED OR NEED EMERGENCY CARE?

If you require medical treatment as a result of injury arising from your participation in this study, emergency medical care required to treat the injury will be provided. However, the financial responsibility for such care will be yours. No compensation will be provided for any injury you may suffer as a direct consequence of non-negligent performance of the procedures described above.

WILL YOU RECEIVE NEW INFORMATION ABOUT THIS STUDY?

During the study, we may learn new things about the risks or benefits of being in the study. If we do, we will share this with you. You might change your mind about being in the study based on this information. If new information is provided to you, we will ask for your agreement to continue taking part in this study.

UNDER WHAT CIRCUMSTANCES CAN YOUR PARTICIPATION BE TERMINATED?

If you do not follow your doctor's instructions, if your disease gets worse, or if the sponsor closes the study, you may be removed from this study. If this happens, your doctor will discuss other options with you.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT AND WHAT WILL HAPPEN IF YOU DECIDE NOT TO PARTICIPATE?

Your participation in this study is voluntary. Your decision whether or not to take part will not affect your current or future care at this institution. You are not waiving any legal claims or rights. If you do decide to take part in this study, you are free to change your mind and stop being in the study at any time.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

Your participation will be under the care of _____, MD at _____. You may contact your doctor with any questions about your care. If you have any questions about problems related to this study, you should contact the Principal Investigator, Dr. Dennis Holmes at 323-865-3000. If you have any questions about your rights as a study subject, you may contact the Institutional Review Board Office at LAC+USC Medical Center, IRD Building, 2020 Zonal Ave., Suite 425, Los Angeles, CA 90033 (Telephone number: 323-223-2340). You will be given a copy of this consent form.

AGREEMENT: I have read (or someone has read to me) the information provided above. I have been given a chance to ask questions. All my questions were answered. I have decided to sign this form in order to take part in this study.

_____ Name of Subject	_____ Signature	_____ Date Signed	_____ Time (if consented on same day as treatment)
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_____ Name of Witness	_____ Signature	_____ Date Signed	_____ Time (if consented on same day as treatment)
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If applicable:
I have verbally translated this informed consent document to the study subject.

_____ Name of Translator	_____ Signature	_____ Date Signed	_____ Time (if consented on same day as treatment)
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I have personally explained the research to the subject and answered all questions. I believe that he/she understands the information described in this informed consent and freely consents to participate.

_____ Name of Investigator/Person Obtaining Informed Consent	_____ Signature	_____ Date Signed	_____ Time (if consented on same day as treatment)
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