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PRINCIPAL INVESTIGATOR: Goran K. Svensson, Ph.D.

CONTRACTING ORGANIZATION: Beth Israel Deaconess Medical Center
Boston, Massachusetts 02215

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Use of Combination Thermal Therapy and Radiation in Breast-Conserving Treatment of Extensive Intraductal Breast Cancer

Svensson, Goran, Ph.D.

Beth Israel Deaconess Medical Center
Boston, Massachusetts 02215

U.S. Army Medical Research Command
Fort Detrick, Maryland 21702-5012

This research supports the development of a technique for breast cancer treatment using ultrasound hyperthermia (heat treatments produced by sound waves) in addition to standard treatment using radiation therapy. The rationale is that treatment of early stage breast cancer (Ductal Carcinoma in Situ, DCIS, and Extensive Intraductal Carcinoma, EIC) is based on the hypoxic (low oxygen) environment in parts of the tumor region that causes tumor cells to be less sensitive to the killing effects of radiation and more sensitive to the killing effects of hyperthermia. Hyperthermia has the potential of increasing local tumor control and may eliminate the need for disfiguring mastectomy. A breast treatment applicator and the associated instrumentation has been completed. The applicator consists of 384 ultrasound transducers in a cylindrical geometry, specifically designed for hyperthermia of the intact breast. The results of the acceptance testing are presented in this progress report. The breast treatment system allows hyperthermia of a quadrant of the breast, half the breast or the whole breast. A device evaluation with ten patients will test how to operate the therapy machine with minimal toxicity and discomfort to the patients. An Investigational Device Exemption has been approved by the Food and Drug Administration.
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In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Soren Soens 6/30/97
PI - Signature Date
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Page number.

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VIII Appendix. Appendix 1 is a 377 page self-contained document. The PI considered it impractical and confusing to number this document consecutively with the annual report.
IV. Introduction.

1. Clinical problem, background and hypothesis:

Thermal Therapy or Hyperthermia (sustained tissue temperature at 40.5°C - 44°C) adjuvant to radiation has been shown in the laboratory to increase cell killing (1 - 17). Clinical investigations show that the combination of hyperthermia with radiation therapy or with cytotoxic agents improve the complete response rate of many cancers (18 - 20). A large European randomized study with over 300 patients with recurrent or primary inoperable breast cancer showed an overall complete response rate of 60% when using radiation plus hyperthermia as compared to 40% for radiation alone (21). The investigators in that study emphasize that current general purpose hyperthermia treatment devices may be inadequate for the treatment of relatively deep tumors in intact breast. Novel and optimized technology that allows reaching hyperthermic temperatures to the whole breast or to any tumor bearing volume in the breast is thus essential to reach adequate thermal dose and meet the goals of this proposal. We wish to accomplish hyperthermia treatment of the breast by using a multi-frequency high resolution site-specific ultrasound applicator.

Contract DAMD 17-93-C-3098 supports the development of a technique for adjuvant treatment of breast cancer using hyperthermia generated by a site-specific ultrasound device. Ultrasound is capable of penetrating soft tissues to produce deep heating. The research also supports a clinical study of the safety and efficacy of using hyperthermia in combination with radiation for treatment of breast cancer patients with an extensive intraductal component of their infiltrating tumor or patients with pure intraductal carcinoma. Breast cancer patients with these histologies have a higher risk of local recurrence after treatment with radiation alone than patients without these histologies (22 - 32).

Intrahuctal carcinoma is characterized by cancer cells spreading within the lactiferous ducts. It is suggested that intraductal carcinoma is associated with tumor necrosis within the ducts and that the necrotic tumor cells are related to the absence of blood supply with resulting hypoxia (26). It is well known that thermal therapy, in contrast to radiation, is more effective in killing hypoxic cells as compared to well oxygenated cells (33, 34, 35).

The clinical rationale and hypothesis for this work is that patients with infiltrating breast cancer containing an extensive intraductal component or patients with pure intraductal carcinoma will have a reduced risk for local recurrence from a combined and non-disfiguring treatment approach using hyperthermia and irradiation. This will extend the indications for breast conserving therapy and eliminate the need for mastectomy for many patients. There may be a population of patients with early stage breast cancer, where the hyperthermia treatment can replace radiation treatments and eliminate radiation associated toxicities to normal tissues in the treated breast, in the opposite breast, and toxicities to heart and lungs.

The research also postulates that the hyperthermia is most effectively and controllably delivered to the breast tissue using a breast site specific ultrasound applicator.
During year 01 and 02 (April 1, 1993 to March 31, 1995), the breast treatment applicator and the associated complex instrumentation system was designed, fabricated and in part tested. This has been described in detail in previous Annual Progress Reports. The third contract year began on April 1, 1995. Due to unforeseen technical, scientific, and regulatory problems, this research has taken significantly more time than originally anticipated. As a result, I have requested and received a No-Cost extension of this program on two occasions, first from April 1, 1996 to December 31, 1996 and the second time from January 1, 1997 to May 31, 1998. In spite of a delay in progress, the quality of the treatment system is excellent and the hypothesis and goals of this program remain the same.

The technical rationale and criteria for the design of the ultrasound therapy system and applicator are derived from the tissue characteristics and features of the breast:

a. The breast is an external, convex shaped organ. When submerged into a temperature controlled water bath, the temperature boundaries are well defined and the skin temperature can be well controlled.

b. Ultrasound heating is suitable for the breast, because there is no intervening gas or bone in the breast tissue. With the patient in prone position and the breast submerged into a water bath, the breast tissue can be surrounded with an array of ultrasound transducers and achieve tangential incidence of the ultrasound beam relative to the chest wall. Tangential incidence is desired to avoid interaction between the ribcage and the ultrasound pressure wave.

c. There are no major blood vessels that carry away heat from the breast tissue, which can reduce the ability to deliver therapeutic heat.

d. The hyperthermia target volume can be the whole breast, a quadrant of the breast, or even a smaller specific tumor mass. Energy deposition, which may heat sensitive regions, such as a lumpectomy scar must be avoided or minimized. It is therefore essential that the energy deposition be controlled and focused on specific sites within the breast tissue. Ultrasound permits this level of control.

e. Although our initial pilot study will aim for a target temperature of $T_{90} > 40.5^\circ C$ ($T_{90}$ means the temperature reached by 90% of the sensors) and $T_{\text{max}} < 45^\circ C$, the device must be able to heat the breast tissue within an even more narrow temperature range ($42^\circ C - 44^\circ C$) over a reasonable range of tissue perfusion (i.e. 30 to 200 ml, kg$^{-1}$, min$^{-1}$).

2. Specific Research Objectives.

The first research objective is to build a cylindrical, multi-transducer, dual frequency, intensity controlled ultrasound therapy system and applicator for treatment of breast cancer. The device must be capable of delivering controllable energy for the purpose of heating the whole breast or a small volume of breast tissue as defined by the clinical situation and the criteria in section V.2.A. The intensity control of the applicator must permit heating within a narrow temperature range, i.e. $42^\circ C < T_{\text{tissue}} < 44^\circ C$. Many scientific and technical problems associated with the individual subsystems have now been solved and the sophisticated system has been assembled in the laboratories at the Dornier Medical Systems, Inc., Champaign, Illinois.

A second objective is to develop an effective pre-treatment planning and real-time treatment control system. One aspect of this effort is to perform the thermal therapy using dense thermometry. It is essential for the assessment of outcome that
temperatures are measured during thermal therapy in a large number of points throughout the breast tissue volume. The objective is to accomplish this through new technologies using minimally invasive or non-invasive thermometry. The minimally invasive temperature measurements will be achieved by using small multi-sensor thermistor probes (dense thermometry), developed at the Massachusetts Institute for Technology (MIT) under the direction of Dr. F. Bowman, who is a consultant to our contract (36). To augment the dense thermometry mapping, we have implemented a technique for real time imaging of the breast surface. This is important for monitoring of the location of the breast tissue within the treatment cavity and thus for control of power deposition in the breast.

A third objective is to develop ultrasound thermal therapy protocols. These protocols and the investigational device exemption from the food and drug administration are completed and described in the body of the report.

V. BODY OF ANNUAL REPORT

1. Program Organization.

This contract was originally sponsored by the New England Deaconess Hospital (NEDH); a Harvard Medical School (HMS) affiliated hospital in Boston, Massachusetts. In 1996, the NEDH and another HMS affiliated hospital, The Beth Israel Hospital merged into one institution with the name Beth Israel Deaconess Medical Center (BIDMC). BIDMC is now the sponsor of this contract. The program director, Goran K. Svensson, Ph.D. is an Associate Professor at HMS and he is responsible for the progress of the scientific, technical and clinical developments. Dr. Svensson is also the Director of Physics at the Joint Center for Radiation Therapy (JCRT). The JCRT provide radiation therapy and thermal therapy (hyperthermia) services the BIDMC, the Dana Farber Cancer Institute (DFCI), Brigham and Women's Hospital (BWH) and Children's Hospital (CH). These hospitals are all affiliated with Harvard Medical School.

In addition the JCRT provides service to several community hospitals in Boston and the South Eastern part of Massachusetts. An important aspect of this program is that this treatment technology will be available to women in the outreach community where academic medicine is not normally available.

All clinical work will be done at the BIDMC and at DFCI. Clinical research protocols used by the JCRT member hospital network require IRB approval from the participating hospitals. The DFCI has a large Breast Evaluation Center (BEC), which is an important referral base for breast cancer patients. We have therefore chosen to seek IRB approval for hyperthermia, using this device, from DFCI and from the sponsoring hospital BIDMC.

Theoretical simulations and treatment planning require large computational resources. This work will take place at the BIDMC or DFCI using a distributed computer network with a centrally located 60 Gigabyte server.

The electronic design and the fabrication of the ultrasound treatment system and breast applicator is subcontracted to Dornier Medical Systems Inc. (DMSI) with headquarters in Atlanta, Georgia. The actual work has been performed at the DMSI R&D Laboratory in Champaign, Illinois under the direction of Everette C. Burdette, Ph.D. Dr. Burdette directs advanced technology research for DMSI. The breast treatment system has been completed, and is currently awaiting shipment to its clinical site in Boston.

A. Introduction.

Appendix I is the institutional application to the Food and Drug Administration (FDA) for an Investigational Device Exemption (IDE), and associated correspondence with FDA. This document (Appendix I) contains all work performed under this contract related to technical progress, and the clinical protocols approved by the hospital Internal Review Boards (IRB). Appendix I does not include the extensive acceptance testing of the system, which is separately described on page 13 in the progress report. To avoid excessive redundancy between this progress report and Appendix I, frequent reference will be made to this document.

The clinical rationale and hypothesis for this work is that patients with infiltrating breast cancer containing an extensive intraductal component or patients with pure intraductal carcinoma will have a reduced risk for local recurrence from a combined and non-disfiguring treatment approach using hyperthermia and irradiation. This will extend the indications for breast conserving therapy and eliminate the need for mastectomy for many patients. The hyperthermia treatment is most effectively and controllably delivered to the breast tissue using a site specific ultrasound Breast Therapy System (BTS).

Toxicities associated with hyperthermia are well documented (12, 13, 37). One major concern addressed in the design of the system is that women that have undergone lumpectomy or surgical biopsy are left with a scar cavity within the breast. Scar tissue, in general, has much lower perfusion than surrounding normal tissue. Clinical experience has revealed that the poorly perfused scar tissue can easily over-heat during hyperthermia that can cause a burn or a blister as an undesired toxicity. The BTS must have very accurate temporal and spatial power control to reduce the temperature in and around the scar tissue. To achieve this level of control and spatial resolution, 384, 1.5x1.5 cm² square transducers are incorporated in the cylindrical site-specific applicator. The control of these ultrasound therapy transducers is augmented by minimally invasive thermometry and non-invasive monitoring. The power level to each transducer is independently controlled.

The technical rationale and criteria for the design of the ultrasound therapy system and applicator are derived from the tissue characteristics and features of the breast. These criteria were described in the Introduction on page 6.

B. Completion of the hyperthermia Breast Treatment System (BTS).

To reach the clinical goal, defined on page NN, we have designed, built, and tested a Breast Therapy System (BTS), which now is ready for clinical use. Although the system is described in detail in Appendix I a brief summary is given here. Figure 1 shows the completed BTS.
Figure 1. Completed BTS. All electronics and control computers are mounted in the center column of the machine.

The BTS consists of several subsystems. The major subsystems and their relationships are shown schematically in Figure 2.

Figure 2. Schematic drawing of the BTS subsystems. The individual systems are briefly described below using the terminology from Figure 2.
1. The ultrasound breast applicator consists of the cylindrical transducer array and the treatment cavity (Appendix 1, pages 143 - 148). The cylindrical transducer array surrounds the breast, which is submerged into the treatment cavity. The applicator is schematically illustrated in Figure 3 and a photograph of the completed applicator on the table frame is shown in Figure 4. The array consists of eight individual rings, which are stacked with water-tight seals between each ring. Each ring accommodates 48 transducers. Each transducer has a square emitting face with dimensions of 1.5 cm x 1.5 cm. Computer simulations (38 - 40) show that three different frequencies are needed to achieve sufficient control of the heating pattern. Table 1 shows the number of rings, transducers per ring and the frequencies of the transducers in each ring. Table 2 shows the expected ring activation for the treatment of a large breast and a small breast. Each transducer was fabricated with the crystal mounted in a machined transducer housing, sealed watertight and faced with a matching layer. Each transducer was individually tested to determine operating acoustic efficiency, center frequency and bandwidth. More details are available in the Systems Description Manual (Appendix I page 139).

<table>
<thead>
<tr>
<th>Number of Transducers</th>
<th>Ring Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>6</td>
</tr>
<tr>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>48</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 3. Applicator shown schematically.
Figure 4. Completed applicator transducer array mounted on table frame. The Agar-Graphite breast phantom is submerged into the treatment cavity. Also see figure 5.

Total Cylinder I.D. = 25 cm
Transducers: 15 mm x 15 mm
Rings of Transducers: 10 (numbered from top down)
Each 1/8 ring vertical section driven by RF
Amplifiers whose outputs are multiplexed to step around ring

<table>
<thead>
<tr>
<th>Ring No.</th>
<th>FQ 1 (MHz)/No. XDCRS</th>
<th>FQ 2 (MHz)/No. XDCRS</th>
<th>TOTAL XDCRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.5/24</td>
<td>2.0/24</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>4.5/24</td>
<td>2.0/24</td>
<td>48</td>
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<tr>
<td>6</td>
<td>4.5/24</td>
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<td>48</td>
</tr>
<tr>
<td>7</td>
<td>4.5/24</td>
<td>2.5/24</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>4.5/24</td>
<td>2.5/24</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TOTAL 384</td>
</tr>
</tbody>
</table>

Table I. Description of transducers and frequencies in each ring.
Total Cylinder I.D. = 25 cm  
Transducers: 15 mm x 15 mm  
Rings of Transducers: 8 (numbered from top down)  
Each 1/8 ring vertical section driven by RF amplifiers whose outputs are multiplexed to “step around” ring

<table>
<thead>
<tr>
<th>Ring No.</th>
<th>No. Transducers</th>
<th>Breast Size (cm)</th>
<th>No Transducers in 1/8 of ring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>12</td>
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<td>0</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Illustration of how many rings and transducer elements in each ring that will be activated when treating a large breast and a small breast respectively.

2. Systems control is performed by a control computer and an instrument computer (Appendix 1 pages 172 - 175). When power is turned on to the system, the treatment software initializes automatically so that no interaction is required by the user to start the software. All available options are displayed on the start-up screen, including access to treatment planning software, file handling utilities, diagnostic mode selection, treatment record printing and treatment initiation.

Prior to the beginning of a treatment, the user will be required to complete a treatment plan. The treatment planning software is in graphical form to simplify data entry such as target volume outline, the number and locations of temperature sensors, temperature and thermal dose for each sensor, scar tissue location and patient information. Since the external contour of the breast is monitored in real time prior to and during treatment, the breast contour(s) with sensor location, scar tissue location and thermal dose information is displayed on an operators screen. Guided by this information, the operator may manually select and control the power on any transducer or group of transducers (e.g. reduce power deposition directly over the scar).

Temperatures and thermal dose are determined in two ways. The thermistor thermometry subsystem supports the use of multisensor (14 sensors) temperature probes that are placed in the breast tissue following guidelines from the Radiation Therapy Oncology Group (RTOG) (41 - 43). The thermometry subsystem provides real time temperature information and real time thermal dose data (i.e. CEMT10, which stands for the Cumulative Equivalent Minutes for 10% of the sensors reaching 43°C).

3. The RF power subsystem, the receiver subsystem, and the cooling subsystem
controller are important electronic modules of the system. A description of these systems is available in the Systems Description Manual (Appendix 1 Page 159 and 171).

4. The **patient table assembly** (Appendix 1, pages 148 - 154) is shown in Figures 1. The patient table is designed similar to a stereotactic breast biopsy table, allowing the breast to be suspended through an opening in the table top. Its specifications are described in Appendix 1, Table 3 on page 152. The table top consists of sheet steel with a tubular steel outer frame fabricated to provide for insertion of a 1.5" foam padding.

The central column or “pedestal” beneath the table houses all of the system electronics, and the appearance of the total system is clean, appealing, and without any clutter of cables and instruments.

5. Experimental studies have been performed throughout the whole development phase of the BTS. The studies have demonstrated that the BTS can deliver a power deposition capable of achieving uniform temperatures within $20^\circ$C. This is achieved by using individual amplifier power control and three ultrasound transducer frequencies; 2.0 MHz, 2.5 MHz and 4.5 MHz. The range of power control is expected to be greater than the clinical requirements. Consequently, it will be possible to adequately treat a wide variety of clinical situations and over a large range of breast tissue parameters, such as various perfusion and temperature boundary conditions. These studies also demonstrated the system's ability to control power deposition in each octant, quadrant, half and whole volume of the breast. The experiments also demonstrated deep and shallow heating control and individual transducer control. Our experiments did not show any unpredictable hot or cold areas (38) (Also attached in Appendix 1, Figure 11 on page 123). This demonstrates that there are no constructive or destructive interferences between the ultrasound transducers that would create hot or cold areas. We have therefore concluded that the electronic design and the multiplexer switching arrangements have been successfully implemented.

C. **Acceptance testing of BTS.**

**Experimental methods:**

The hardware and software modules of the BTS were assembled and ready for acceptance testing in February/March 1996. The research team from the JCRT-BIDMC traveled to Champaign, Illinois, where the BTS has been designed and manufactured. The team spent a total of eight days carefully analyzing the system with respect to its ability to safely deliver hyperthermia to breast phantoms. A large number of measurements were performed and later analyzed. However, the system was not accepted by the research team during the February/March visit. There were significant problems with the control algorithm which prevented adequate control of the power deposition, and caused software crashes of the system. The software problems were fixed during the summer of 1996 and the team returned for testing in August of 1996, at which time the system was accepted.

In order to increase the density of temperature sensors available for dense thermometry and mapping of thermal dose distributions, a 32-channel thermometry system was brought from BIDMC supplementing the 84 channel thermometry system built into the BTS.
The BTS was tested using non-perfused phantoms designed to mimic the physical shape and ultrasound properties of the intact female breast. The phantoms were constructed from a latex membrane, shaped like an average breast, filled with an Agar-graphite-alcohol mixture formulated to yield a velocity of sound of 1540 m/sec and an absorption coefficient of 0.75 dB/cm both at 1 MHz. The phantom mixture, which is prepared hot, solidifies after being filled into the latex membrane and being allowed to cool down.

The phantom experiments were primarily designed to test the basic design philosophy of the BTS. The hyperthermia applicator was constructed with half the transducers operating at a low frequency of 2.0 to 2.5 MHz and the other half at a high frequency of 4.5 MHz. The low frequency transducers were designed to deposit energy at the core of the breast, and the high frequency transducers to deposit power at the treatment volume boundaries thereby compensating for thermal conduction to the non-heated surroundings of the breast. During patient treatments, all transducers will be activated initially in order to raise the temperature in all of the target area. When the core of the target area reaches therapeutic levels, the power to the low frequency transducers will be decreased thus lowering the power delivered to the core of the target area. During the remainder of the treatment the power delivered to the high frequency transducers will be controlled to compensate for thermal conduction from the surface of the breast to the coupling water and maintaining therapeutic temperatures in the surface of the breast.

The tests were also designed to test ability of the BTS to treat any part of the breast including any quadrant of the breast, any half of the breast, or the whole breast. Correlation between power deposition fields and temperature fields are dependent upon the exact perfusion (or blood flow) patterns in the breast. Due to the non-perfused nature of the phantom, the main emphasis of these experiments was placed on measuring power deposition field in the phantoms. In hyperthermia, power deposition is commonly measured as Specific Absorption Rate (SAR) with the unit J/kg.sec. If temperature measurements are performed immediately after a power field has been imposed on the phantom, and before any significant temperature gradient has build up, then \( \text{SAR} = \frac{c}{\rho} \times \frac{dT}{dt} \), where \( c \) is the specific heat capacity and \( \rho \) is the specific density of the phantom material. Both these factors are physical constants of the phantom material, which leaves SAR proportional to the rate of temperature rise \( \frac{dT}{dt} \) measured in units of °C per unit time.

During experiments the phantoms were heavily instrumented with temperature probes containing up to 14 temperature sensors each. Up to 5 probes, each with 14 temperature sensors, were carefully implanted in the phantoms for each experiment and their exact position in the phantom determined. Figure 5 shows a photograph of the phantom and the temperature probes, and figure 4 shows the phantom submersed into the cylindrical treatment cavity.
Figure 5. Agar-Graphite phantom with array of 14 sensor probes.

Figure 6 illustrates, a schematic view of the phantom placed in the treatment cavity of the degassed water filled applicator.
Figure 6. The top figure shows a sagittal cut and the figure below is a coronal cut through the applicator-phantom setup. The top schematic drawing shows the breast mimicking phantom submerged in the ultrasound transducer cylinder. The cylinder is filled with degassed coupling water. Below, the heavy circle indicates the transducer array, where all transducers are engaged, and the thin circle indicates the breast phantom outline. This probe configuration is one of several used for whole breast exposure experiment. The probe marked A was implanted in a position of the phantom, where the diameter is 12.7 cm.

As an example of our results, we will analyze four different sets of data shown in figures 7 - 14. Many different treatment geometries were measured, and the results below represent about 10% of the total number of data sets.

Results and discussion:

Figure 7 shows a family of relative power deposition (SAR) profiles as measured by probe A. The rate of temperature rise was determined by monitoring the temperature at each sensor point during application of a power field. This experiment was subdivided into 3 power applications. In the first application (shown as filled diamonds), all the high frequency transducers were engaged to assess the ability to deposit power in the surface of the phantom in order to compensate for thermal conduction to the coupling water. It is clear from the "diamond" curve that most power is deposited at the surface of the breast phantom leaving less power deposition in the center (about 6 cm deep). In the second application (shown as filled squares), all the low frequency transducers were engaged to assess the ability to deposit power to the core of the phantom. This is also evident from the curve showing a power deposition peak in the center of the phantom at about 6 cm. In the third measurements (shown as filled triangles), all transducers were engaged at a ration of two parts power to the high frequency transducers and one part power to the low frequency transducers with the purpose of testing the ability to deposit power (SAR) both at the surface and at depth in the phantom. If this ratio of power deposition is retained for about 10 minutes, the thermal conduction will generate a relatively uniform temperature distribution reaching a quasi steady state condition. Figure 8 shows the temperature rise in the breast phantom resulting from the non-uniform power deposition (SAR) shown in Figure 7.
Figure 7. This figure shows a family of relative power deposition profiles measured by probe A in figure 6. This profile is measured through the center of the breast phantom at a position where the diameter of the phantom is 12.7 cm. The diamonds indicate the power being mostly deposited at the surface (edge) of the phantom due to the 4.5 MHz high frequency, the squares indicate that the 2.0 MHz low frequency mostly deposits power at the core of the phantom, and the triangles shows the ability to combine the low and high frequencies in order to achieve a more uniform power deposition profile.

Figure 8. This figure show the steady state temperature profile achieved during the experiment in shown in figure 7. Initially power (SAR) was delivered to both the low and high frequency transducers. After the temperature had increased by 4°C at the center of the phantom, the low frequency transducers were decreased and controlled for maximum uniformity of the temperature profile.
Figure 8 demonstrates that the system is capable of delivering uniform temperature distribution to within +/- 0.5°C in this plane throughout the breast phantom.

Figures 9 and 10 show the results of insonating half the breast phantom. Figure 9 shows two cuts through the phantom setup as in Figure 6. On the right, this figure indicates that temperature sensors in probe B are distributed differently than the sensors in probe A (Figure 6) in that it has temperature sensors concentrated in the left part of the phantom where the power deposition is expected. The heavy semi-circle indicated the part of the transducer array that is engaged for this experiment.

Figure 10 shows the resulting family of relative power deposition curves. Again, the high frequency transducers preferentially deposit power at the edge of the phantom (left part of diamond symbols), the low frequency transducers mostly at the center of the phantom (right part of square symbols). A combination of frequencies can be employed to deposit even amount of power at the surface and to the core of the phantom (circular symbols).

Figure 11 shows the phantom setup for insonating a quadrant of the breast. Temperature sensor B is utilized and the heavy quarter circle indicates which transducers that are engaged. Figure 12 shows the resulting power deposition profiles. The selective heating to the surface and the core of the phantom is now much less pronounced due to the fewer transducers and therefore lower geometrical gain of the setup. It is however still possible to selectively heat the surface or the core of the phantom.

Figure 9 shows cuts through the applicator-phantom setup as in Figure 6. The temperature probe shown on the right drawing is placed through the center of the phantom, with the sensors distributed through the left part of the phantom. The heavy semicircle on the right schematic drawing indicated that the left half of the transducer array is engaged.
Figure 10. This figure shows a family of relative power deposition profiles measured by probe B in figure 9. This profile is measured through the center of the breast phantom at a position where the diameter of the phantom is 12.7 cm. The diamonds indicates the power being mostly deposited at the surface (edge) of the phantom due to the 4.5 MHz high frequency, the squares indicate that the 2.0 MHz low frequency mostly deposits power at the core of the phantom, and the circles shows the ability to combine the low and high frequencies in order to achieve a more uniform power deposition profile.

Figure 11. This figure shows a coronal cut of the experimental setup where one quadrant of the ultrasound transducers is engaged. Temperature probe B is placed as in figure 9, and the quadrant of transducers engaged is highlighted on the left of the schematic.
Figure 12 shows the relative power deposition profiles through the center of the irradiated quadrant of the breast. The diamonds indicate the power deposition profile when the high frequency transducers are engaged. The squares show the same properties for the low frequency transducers, and the triangles show the power deposition pattern when the transducers are engaged with a power ratio of 1:4 high to low frequency.

An experiment was performed to assess the deposition of power along the central axis of the breast phantom. Figure 13 shows the position of temperature probe C for this experiment. Figure 14 shows the resulting relative power deposition profile. The sensors at the apex (or tip) of the breast phantom is to the left, and the base of the phantom is to the right. As expected, the power deposition on the central axis close to the apex is highest due to a smaller diameter of the phantom at this position. This can easily be compensated by increasing the power to the rings closer to the base of the phantom.

Figure 13. This figure shows the position of temperature probe C placed to demonstrate the uniformity of relative power deposition (SAR) along the central axis of the breast phantom. In this experiment the phantom was insonated with uniform power applied to the upper 5 rings.
Figure 14. The relative power deposition profile resulting from supplying uniform power to all transducers in the upper 5 rings. The power delivered to each of the rings can be adjusted in order to achieve improved uniformity in the power deposition profile.

The temperature distributions have been measured in many coronal and sagittal planes in the breast phantom with the conclusion that the system has enough power output and control capability to achieve a uniform three dimensional temperature distribution throughout the breast phantom.

D. Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA), and Clinical Protocols.

The clinical study of the capability, limitations, and safety the BTS is planned (device evaluation). Clinical research protocols for cancer treatments using new devices are subject to increasingly rigorous scrutiny by the hospital IRB and the U.S. FDA branch that issues the IDE. Recent federal regulations require the hospital to have an IDE for any new device used in therapy before the IRB approval. In addition the US Army Human Use Review and Regulatory Affairs Division require an institutional IDE before approving the protocol and before granting permission to proceed with the clinical trial. The process of receiving an IDE and approval of protocols by the hospitals and the Army, has been very lengthy. As a result, we have received a No-Cost extension of this program to May 31, 1998.

The progress is as follows:

$\Rightarrow$ The IDE application was completed during the fall of 1996. The first submission included a pre-IDE visit to the FDA in Rockville, Maryland. Dr. Bornstein from the
JCRT, Dr. Burdette from DMSI, Mr. Hansen from JCRT, and Dr. Svensson (PI) from JCRT gave a presentation of this program to FDA officials on October 4th, 1996. We received important feedback to the IDE application. In particular, the wording of our consent form was significantly changed. The feedback from this meeting was incorporated into a new version of the IDE application, and was submitted on December 16, 1996 (Appendix 1, pages 17 - 377). The response from FDA (Appendix 1 pages 14 - 15) required additional clarification of the IDE application (Appendix 1, pages 2 - 13), which was submitted on March 7, 1997. The approval from FDA to begin the clinical study and treat 10 patients was received on March 27, 1997.

- The clinical protocol previously submitted and approved by the hospital IRB had to be resubmitted because of the changes in the consent form required by FDA. The protocols are now approved by both the BIDMC and the DFCI. See Appendix 1, pages 52 - 103.

- The approved clinical protocol was submitted to the US Army Human Use Review and Regulatory Affairs Division for approval. We received a lengthy response requiring several additional changes. Unfortunately, some of the requested changes were in direct conflict with the internal policies at the DFCI and could not be immediately implemented. The proposed changes are now being reviewed by the General Counsel of the hospital. The clinical trial cannot begin until the changes requested by the Army are either implemented or withdrawn. This process has significantly delayed the patient studies for which we have requested a No-Cost extension to May 31st, 1998.

VI. Conclusion and importance:

This report demonstrates that the technical component of the Contract DAMD17-93-C3098 has been completed. A site-specific hyperthermia breast treatment system (BTS) has been built and accepted for clinical use. The system is capable of delivering hyperthermia as an adjuvant modality to the whole breast volume, and to a portion of the breast which can be as small as a quadrant of the breast.

During the design, building and testing of the system, we experienced difficult technical, scientific, and regulatory challenges requiring complex solutions before the system could be completed and accepted. This has resulted in delays in the program and we have been approved for a No-Cost extension to May 31st, 1998, to be able to begin the clinical studies. The process to acquire an Institutional IDE was very lengthy, but finally we were approved in March 1997. One remaining problem is that the US Army Human Use Review and Regulatory Affairs Division has requested changes in our IDE and hospital approved treatment protocols that are inconsistent with our hospital protocol policies, and a legal review of the Army requirements are currently underway. As soon as these issues are resolved, we will start patient accrual for a device evaluation and Phase I study.

The importance of this work is our attempt to address two of the goals suggested by the 1993 Institute of Medicine Report, that was used by the USAMRMC to formulate its Broad Agency Announcements (BAA).

One of the goals is to identify new biologically based therapies to move away from today's relatively toxic treatments, and to offer more precise intervention that can eradicate the cancer, perhaps at its earliest stage, to improve local control, conserve
the breast and reduce toxicity. The rationale for choosing adjuvant hyperthermia treatment of early stage breast cancer (DCIS and EIC) is based on the hypoxic environment in the target region that causes tumor cells to be less sensitive to the killing effects of radiation and more sensitive to the killing effects of hyperthermia. Therefore, hyperthermia has the potential of increasing local control without adding toxicity and may eliminate in many cases the need for disfiguring mastectomy. There may in fact be a population of patients with early stage breast cancer, where the hyperthermia can replace radiation treatments and eliminate radiation associated toxicities to normal tissues in the treated breast, in the opposite breast, and toxicities to heart and lungs.

The second goal relates to the mission of the Joint Center for Radiation Therapy (JCRT) to reach out beyond its academic headquarters at Harvard Medical School and provide cancer management in community hospitals that were previously under serviced. One objective of the USAMRMC breast research program is to support efforts to disseminate novel treatment approaches to women who are older, less affluent and more diverse than those women who normally enroll in academically based trials. We intend to make the hyperthermia treatment facility a regional resource that will include at least five community hospitals in a more ethnically diverse environment outside of Boston. Hyperthermia is particularly suitable for a regional approach, since only two treatment visits are needed for each patient.

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Dear Dr. Svensson:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application. You have corrected the deficiencies cited in our January 17, 1997 conditional approval letter. Therefore, your application is approved and you may continue your investigation at the institution enrolled in your investigation where you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA. Your investigation is limited to 1 institution and 15 subjects.

If you have any questions, please contact John C. Monahan at 301) 594-1212.

Sincerely yours,

Lillian Yin, Ph.D.
Director, Division of Reproductive, Abdominal, Ear, Nose and Throat, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
IDE Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

RE: Amendment to IDE G970001  
Breast Ultrasound Therapy System

Dear Madame/Sir:

This amendment to IDE #G970001 is in response to your letter of January 1997. All changes requested to the informed consent form have been executed. Please find appended 3 copies of the updated patient consent form with the requested changes highlighted and letters confirming IRB approval.

Sincerely yours,

Goran K. Svensson

Enclosures: Updated Informed Consent Form  
IRB Confirmation from Dana-Farber Cancer Institute
Jorgen Hansen, M.D., Physicians and Administrators

Richard D’Augusta, R.Ph., M.P.A. - IRB Chair

March 7, 1997

SUBJECT:

Revisions - Major Changes -- (Revision date 2/10/97)

95-006 Radiation and Thermal Therapy for Extensive Intraductal Carcinoma

Please be advised that "major changes" with the current issue date of 02/10/97 have been made to the above mentioned protocol. These revisions were reviewed by the Human Protection Committee (HPC) on 03/06/97 and now have IRB approval.

Please note that the existing protocol will be updated with the appropriate replacement pages.

If there are any questions, please contact me at 2-3029.

Attachments

CC: Carol A. Moyer, Ph.D. - PAO
    Bruce Bornstein, MD

CHHPAPP
RADIATION AND THERMAL THERAPY FOR EXTENSIVE INTRADUCTAL CARCINOMA OF THE BREAST

INTRODUCTION

Your physician has determined that you either have, invasive breast cancer that contains an extensive amount of intraductal carcinoma (non-invasive cancer), or that your have pure intraductal carcinoma without any associated invasion. Local recurrence of breast cancer following breast conserving treatment with lumpectomy and radiation therapy is seen in 10-15% of cases. However, breast cancers such as yours, with an extensive intraductal component may have a higher risk of local recurrence in the breast than cancers without an extensive intraductal component when treated with breast conservative therapy. For patients with an extensive intraductal component, the option of mastectomy may have a lower risk of breast recurrence, but many patients prefer breast conservation.
Intraductal carcinoma may be more resistant to radiation therapy and this may account for the poor results seen with irradiation in these patients. Thermal therapy or hyperthermia refers to the use of temperatures 42°C (107.6°F) or higher to treat malignant tumors. Laboratory and clinical reports have demonstrated that heat kills tumors, if tumors are heated to 43°C (109°F) for 30-60 minutes. Many studies suggest that the addition of heat may also improve upon the usual results of radiation therapy for many tumors, including recurrent invasive breast cancer, bladder cancer, and tumors of the head and neck region. Investigators have found an improvement in tumor response rates and a lengthened duration of response. This is the first study to attempt to treat non-invasive breast tumors.

You are being asked to participate in a research project to study the use of thermal therapy (heat treatments produced by sound waves) for the treatment of breast cancer with extensive intraductal carcinoma. We have developed the thermal therapy technologies required to make use of the positive interaction between heat and radiation. The specific clinical study we propose is a study to optimize and establish our ability to safely deliver heat to the breast using a new breast thermal therapy device. The purpose is to determine if we can control heat delivery.

OBJECTIVE

The purpose of this research study is to determine the safety and effectiveness of generating, and delivering, heat to the breast in combination with radiation therapy. We want to evaluate what side effects are associated with this treatment. Fifteen patients will be treated in this research study.
TREATMENT DESCRIPTION

Your radiation oncologist will schedule a radiation therapy treatment planning and an initial thermal therapy planning session. Both of these are conducted at the Dana Farber Cancer Institute even though the radiation therapy is carried out at another hospital. Photographs of the treatment site will be taken during the planning and at each of the thermal therapy sessions.

**Thermal Therapy:** At the Radiation Therapy Planning Department at the Dana Farber Cancer Institute you will receive two thermal therapy treatments. Each treatment will require at least two hours of preparation time prior to treatment. The heat treatment requires you to lay on your stomach on a soft flat table for approximately two hours. Therefore, on the day of thermal therapy you must plan for a total of approximately 5 hours from the time you arrive for therapy to the time you are ready to leave. The device used to generate heat produces ultrasonic sound waves to heat the breast. This device was developed under contract with the U.S. Army Medical Research & Development Command. This is a new heat treatment device. Your breast will fall through a cut-out (hole) in the table and rest in a tank of water for the heat treatment. The ultrasound energy waves enter the quadrant or half of the breast containing the original lump (tumor) region. The goal will be to reach 40 to 43 °C (104 to 109 °F) in the breast for 45 minutes. During heat treatments you will experience warmth and occasionally discomfort or pain. The level of discomfort or pain is currently unknown and may be mild, moderate, or severe. If you experience any intolerable discomfort or pain we will modify or stop the treatment to attempt to relieve your symptoms. You
will have an intravenous line inserted prior to treatment that may be used to give pain medications if needed. A technologist will be with you during treatment.

During the heat treatment, temperatures will be measured. Prior to each heat treatment at least two metal thermometer needle probes will be inserted into the breast. The thermometer probes help control the temperature in the breast and avoid burns. A Radiation Oncologist and Diagnostic Radiologist will place the small needle probes into the breast through numbed skin under sterile conditions using local anesthesia. The temperature measuring probes will be removed after each thermal therapy treatment. The total time for each treatment session will be at least three hours.

**Radiation Therapy:** In addition to the heat treatments, you will receive radiation therapy to your breast. Your radiation oncologist will decide what radiation dose you receive. On the basis of experience, we believe that the effectiveness of the radiation may be improved with heat. On days when both radiation and thermal therapy are given, radiation will follow thermal therapy by 30-60 minutes. Radiation will be given daily, five days a week, for 6 to 6 1/2 weeks.

After the treatment course is completed you will be asked to return at regular intervals for follow-up visits to evaluate the results of treatment and the potential long-term side effects. In order to assess your response to treatment certain diagnostic tests will be done prior to beginning treatment and at intervals following treatment. This may include blood tests, mammography, breast ultrasound, breast magnetic resonance imaging (MRI), and other tests determined to be necessary by your physician. They will be explained to you at the time of your initial evaluation and at follow-up visits.
POTENTIAL BENEFITS

The potential benefits associated with the treatment include a possible reduced risk of tumor recurrence. Heat appears to increase the effectiveness of radiation therapy. However, no guarantee or assurance can be made regarding the results, if any, that may be obtained since research results cannot be foreseen. Your participation will contribute to the development of medical knowledge about the treatment of breast cancer and the use of this thermal therapy device.

If new information develops during the course of your treatment that may be related to the efficacy or risks of your treatment, you will be informed and options will be discussed.

POTENTIAL SIDE EFFECTS

Although hyperthermia has the potential to produce beneficial results, it may be of no benefit and may have injurious effects.

Thermometer probe placement: Despite local anesthesia to diminish pain during thermometer probe insertion, you may experience pain at the time of probe placement. When local anesthesia is given, you will experience a momentary stinging sensation. As with any invasive procedure, there is a risk of bleeding, infection, or perforation of normal structures in or near the region of treatment. There is the small risk of a permanent scar at the point where the thermometry probe enters the skin of the breast, but this risk should be small. There is a minor risk that tumor cells could track along
the thermometry probe path in the breast, but this would be rare, and be included in the field receiving radiation therapy treatment.

**Radiation Therapy:** Your radiation oncologist will describe the possible side effects to you, and you will be asked to sign a separate consent form for the delivery of the radiation therapy. However, common immediate side effects include fatigue and skin redness and irritation in the treated breast. Thermal therapy may also make the normal tissues more sensitive to the toxic effects of radiation. Thus, all of the tissues that receive radiation therapy and heat are potentially more prone to radiation injury. Since this treatment is investigational, it is possible that unforeseen side effects could occur.

**Thermal Therapy (heat treatment):** Is associated with possible pain, burns, blisters, nausea, itching, or fever during the treatment session. If any of these is observed, it may be possible to change the heating pattern to eliminate them. You may also become uncomfortable from lying on your stomach, in the treatment position. We will attempt to make you comfortable.

During treatment, your heart may beat faster and you will probably feel warm and begin to sweat. Your heart’s electrical pulses and your blood pressure will be monitored during therapy. You may choose to stop receiving the study treatment at any time if any of the related side effects is intolerable. In addition if you experience dizziness, shortness of breath, or chest pain, you must notify your physician immediately, so that the treatment can be modified or stopped. We expect most acute (short-term) side effects associated with the use of thermal therapy and radiation therapy to be controllable and reversible. We do, however, emphasize that we cannot
rule out any unsuspected short-term or long-term side effect. During this study, provisions and precautions will be taken to insure your safety throughout the course of treatment.

Should any of the above side effects appear, your physician(s) will take steps to reduce or eliminate these effects by whatever means are necessary, but there can be no assurance that such effects can be reduced or eliminated.

In the long-term, after the thermal therapy session it is possible to develop pain, burns, or blisters that might persist. In addition, infection or ulceration may occur. If persistent pain should develop, this may represent muscle or nerve injury. You will be evaluated by your physician and further heat treatment sessions will be stopped until such problems have resolved.

In addition, in the future, tissue changes, such as fibrosis (scar tissue), necrosis (dead tissue), and ulceration, in the treated breast could happen at any time following treatment, be permanent and require additional surgery. Some of these long-term effects such as fibrosis could make follow-up examinations of your breast by you or your physician more difficult. In addition, thermal therapy may make follow-up mammograms of the breast more difficult to interpret.

This is a new deep-heating device and with all investigational treatments, it is possible that unforeseen complications could occur.
ALTERNATIVE TREATMENTS.

The alternative treatment is mastectomy with or without reconstruction of the breast. Reconstruction can be done at the time of the mastectomy or at a later time. Another alternative treatment would be conventional radiation therapy alone. Your physician has explained these procedures and both their advantages and their disadvantages to you.

CONTRAINDICATIONS

Thermal therapy is not to be given to patients whose sensitivity to heat sensation has been significantly decreased in the area to be treated by any means (previous treatment, anesthesia, diabetic nerve damage, etc.), patients with cardiac pacemakers, and patients having a known decrease in circulation in the area to be heated. General or regional anesthetic must not be given with thermal therapy and will not be used in your treatments. Pain-medication, sedatives, or tranquilizers may be used in your treatments as long as they do not significantly decrease your awareness of pain sensation in the treatment area.

FOR WOMEN OF CHILDBEARING POTENTIAL

Radiation therapy may have an adverse effect on an unborn child and should not be performed during pregnancy. You are advised NOT to become pregnant before or during this study. If you become pregnant, you would automatically be excluded from radiation therapy and this protocol study.
PARTICIPATION

Your participation is voluntary and you may refuse to participate and/or withdraw your consent and discontinue participation in the project at any time without penalty, loss of benefits to which you are otherwise entitled, or penalty of prejudice in your future treatment.

Also, your physician can terminate your participation without your consent at any time in the event of physical injury or other condition that makes further treatment an unnecessary risk in the medical opinion of your physician.

CHARGES

You will not be charged for the hyperthermia treatment. However, you will be charged for the ultrasound examination of the breast that will occur at the time of thermometer probe placement. You will be charged in the usual fashion for radiation therapy, doctors visits, and any other portion of your care that is considered standard care. You are also responsible for payment of all charges for medical procedures to treat conditions resulting from adverse outcomes related to the study treatment.

CONTACT PERSONS

For more information concerning the research and research-related risks or injuries, you can contact Dr. Bruce Bornstein, the investigator in charge, at (617) 632-3591.
INFORMED CONSENT FOR RESEARCH

You may receive care or have studies performed at either the Brigham & Women's Hospital ("BWH") or the Dana-Farber Cancer Institute, Inc. ("DFCI"), collectively, the Hospitals. Your medical record may be made available to health care professionals at the Hospitals and may be reviewed by Hospital staff members. Except as provided below, information in your medical record will be kept confidential. The results of the study, coded so that only those affiliated with the Hospitals will know which patient the data represents, will be reported to the study sponsor (and/or its agent), to regulatory agencies such as the FDA, and in scientific presentations and publications. It is also possible that your medical and research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the FDA, other federal or state government agencies, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agent), or by any of these agencies, the Hospitals will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

If you are injured as a result of this study, you will be provided with the necessary care. This care does not imply negligence on the part of the Hospitals. Where applicable, the Hospitals reserve the right to bill third-party payors for services rendered. The Hospitals will not provide you with any additional compensation as a result of such injuries.

If you have questions about your treatment, the research, your rights, injuries which occur, if you believe you have not been adequately informed of the risks, benefits, or alternative treatment options, or if you feel any pressure to enroll in this research study or continue to participate against your wishes, please speak to a representative of the Human Protection Committee at the DFCI (617-632-3022).

I have been fully informed of the purpose of the research, the expected duration of my participation, the procedures to be followed, and which procedures are investigational and which are standard. I have been given a description of the expected discomforts, risks, and benefits of the alternative procedures available, and the risks and benefits of those alternative procedures. I voluntarily agree to participate in this research study and understand that I am free to withdraw my consent and end my participation at any time, without prejudice of any kind. I understand that if I have questions at any time, they will be answered. I have been given a copy of the informed consent document describing the protocol.

SIGNATURE OF PATIENT/RESEARCH SUBJECT OR PERSON LEGALLY AUTHORIZED TO CONSENT FOR PATIENT/RESEARCH SUBJECT

PRINTED NAME AND RELATIONSHIP TO PATIENT/RESEARCH SUBJECT

SIGNATURE OF WITNESS PRINTED NAME DATE

I have fully explained to the patient/research subject (or the person named above authorized to consent for the patient/research subject) the purpose of this research study, the expected duration of his or her participation, the procedures to be followed, and which procedures are investigational and which are standard. I have given the patient/research subject a description of the expected discomforts, risks, and benefits, the alternative procedures available, and the risks and benefits of those alternative procedures. I have asked whether any questions have arisen regarding the procedures and have answered those questions to the best of my ability.

PHYSICIAN'S SIGNATURE AND PRINTED NAME

(If Non-Treatment: Researcher's or Approved Designee's Signature and Printed Name)

DATE
Dear Dr. Svensson:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. Your application is conditionally approved, and you may begin your investigation at the Joint Center for Radiation Therapy, Boston Massachusetts, using a revised informed consent document which corrects deficiency numbers 1, 2, and 3 after you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA. Your investigation is limited to 1 institution and 15 subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

1. Please revise page 1 of the informed consent document to remove the statement comparing breast conservation to mastectomy with respect to survival. Since the treatment being used in this study has not been established as an alternative for this particular subset of patients the above statement could give the subjects an unrealistic impression of the risks involved in not undergoing standard surgical treatment.

2. Please revise the following statement on page 3-4 that states "during heat treatments you will experience warmth and occasionally mild discomfort." This statement should be revised to more accurately reflect the fact that the extent to which patients will experience discomfort or pain is currently unknown and may be mild, moderate or severe.

3. Your statement on page 7 that most side effects associated with thermal therapy and radiation are expected to be "controllable and reversible" is inconsistent with the potential long-term tissue damage described on the next page. Please revise this statement to indicate that a real potential for severe and permanent damage does exist and that additional surgery could be necessary to treat such injuries.
This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device Investigation" which you should provide to participating investigators.

If you have any questions, please contact John C. Monahan at (301) 594-1212.

Sincerely yours,

Lillian Yin, Ph.D.
Director, Division of Reproductive, Abdominal, Ear, Nose and Throat, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosures

(1) Sponsor's Responsibilities for a Significant Risk Device Investigation
(2) Guideline for the Monitoring of Clinical Investigations
Dear Sir/Madame:

Please find enclosed three copies of an institutional IDE application for the use of an ultrasound device for hyperthermia of breast cancer. On October 4, 1996, the research team from Dana Farber Cancer Institute traveled to FDA for a Pre-IDE visit to review the application. The enclosed IDE application includes all the very useful advice received during the Pre-IDE visit.

Thank you for your attention to this matter.

Yours Sincerely

Goran K Svensson, Ph.D.
PI for this project.
Application for an Investigational Device Exemption for a Significant Risk Device

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-470)
9200 Corporate Blvd.
Rockville, MD 20850

Project: Use of Combination Thermal Therapy and Radiation in Breast Conserving Treatment of Breast Cancer
Device: Breast Ultrasound Therapy System

Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115

Sponsor: B.W. Janicki, Ph.D.
Director of Research

Date: December 16, 1996
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I. Introduction

Dana-Farber Cancer Institute (DFCI) is requesting an institutional Investigational Device Exemption (IDE) for the ultrasound Breast Therapy System (BTS), a computerized cylindrical multi-element ultrasonic hyperthermia system. This system is a custom-built device fabricated to DFCI specifications by Dornier Medical Systems, Inc.

I.a. Background

Heat has the ability to kill cancer cells as does ionizing radiation and chemotherapeutic drugs. Studies of the safety and the efficacy of using hyperthermia in combination with radiation for treatment of breast cancer patients with an extensive intraductal component of their infiltrating tumor or patients with pure intraductal carcinoma will be conducted. This IDE application focuses on a Device Evaluation to determine if the custom built BTS can heat to the desired thermal dose without causing local pain and heat related toxicities [14]. We will also evaluate the user interaction with the BTS, the thermometry system and the ability to control the local energy deposition.

Intraductal carcinoma is characterized by cancer cells spreading within the lactiferous ducts. It is suggested that intraductal carcinoma is associated with tumor necrosis within the ducts and that the necrotic tumor cells are related to the absence of blood supply with resulting hypoxia. It has been demonstrated [4] that thermal therapy, in contrast to radiation, is more effective in killing hypoxic cells as compared to well oxygenated cells. Breast cancer patients with these histologies have a higher risk of local recurrence [10].

The clinical rationale and hypothesis for treating intraductal carcinoma is that patients with infiltrating breast cancer containing an extensive intraductal component or patients with pure intraductal carcinoma will have a reduced risk for local recurrence from a combined and non-disfiguring treatment approach using thermal therapy and irradiation. This will extend the indications for breast conserving therapy and may eliminate the need for mastectomy for many patients.

In the future we may also treat non-inflammatory stage III patients and patient with ipsilateral local recurrence after radiation therapy. A European phase III study with over 300 patients randomizing to radiation alone or radiation and hyperthermia shows an overall complete response rate of 60% for the combined treatments as compared to 40% for radiation therapy alone [29].

Ultrasound hyperthermia is a common method of heat delivery. High power ultrasound devices have the ability to deliver heat down to 7 cm depth for planar non-focused transducers and to 10-15 cm depth for focused devices [3]. A device using ultrasound generated by arrays of planar non-focused transducers received a PMA from the FDA in 1989 (Sonotherm 1000; Labthermics Technologies). This device has been successful in tumor therapy of many types of solid tumor cancers. Several ultrasound systems for deep-seated tumor therapy have been designed and reported in the literature [7,9,11,12,13,16,17,18,20,21,27,28]. However, it is often difficult to find suitable treatment insonation portals with available general purpose heating devices. This is due to limitations in the use of ultrasound including the presence of intervening critical organs and other tissue heterogeneities, such as muscle-bone interfaces, which can create painful overheating or sheer stresses. In addition, air cavities do not conduct the ultrasonic wave energy and thus present another obstacle to heat delivery in some anatomical locations.

The experience using these general purpose devices is therefore mixed, especially with respect to
the patients' sense of discomfort and pain during therapy. For example, a six-transducer fixed beam ultrasound system, developed by the group at Stanford University, has been reported [9]. This device has transducers mounted on a spherical shell with a 26 cm radius of curvature. The device is capable of heating a therapeutic volume approximately 8 cm wide and 6 cm deep located at 10 cm depth. Almost 50% of the patients treated reported some degree of pain. The level of pain was related to anatomical site, power level, frequency, and geometric arrangement of the transducers.

In another report, a commercial diagnostic ultrasound scanner was modified for hyperthermia therapy [11,12]. The system uses four large focused ultrasound transducers operating at 1 MHz and scanned under computer control. Test results from this device show that it can heat perfused tissue down to depth of at least 10 cm, and that uniform temperature can be produced in volumes up to 5 cm in diameter.

The team that presents this IDE application has worked on hyperthermia devices since approximately 1987. Dr. Burdette developed the Sonotherm-1000 when he was the president of Labthermics Inc. Dr. Burdette in collaboration with the research team at Dana-Farber Cancer Institute developed the Focused Segmented Ultrasound Machine (FSUM) for delivering hyperthermia to deep tumors at maximum depth of 15 cm. The system consists of 56, 1 MHz transducers mounted on a spherical shell focused at 24 cm radius. This development was sponsored by NCI and the device received an Investigational Device Exemption in February of 1994. The FSUM is a general purpose device which has been used for the treatment of various abdominal and axillary tumors.

Treatment of breast cancer (intact breast) using hyperthermia cannot be adequately done with FSUM or any other general purpose device. The main problem is effective coupling of the FSUM applicator to the breast and the anteriorly directed ultrasound beam which will cause undesirable interaction in the bony ribcage. Also, the spherical geometry used in this applicator is not suitable for heating the whole breast.

We therefore postulated that hyperthermia is most effectively and controllably delivered to the breast tissue using a breast site specific ultrasound applicator where the ultrasound transducers are arranged in a cylindrical geometry, thus completely covering the breast tissue when the patient is placed in a prone position.

We proposed the site specific BTS to, and received funding from, the U.S. Army Medical Research and Material Command (USAMRMC).

The technical rationale and criteria for the design of the ultrasound applicator are derived from the specific tissue characteristics and features of the female breast:

a. The breast is an external, convex shaped organ. When submerged into a temperature controlled water bath, the temperature boundaries are well defined and the skin temperature can be well controlled.

b. Ultrasound heating is suitable for the breast, because there is no intervening air cavities or bone in the breast tissue. With the patient in the prone position and the breast submerged into a water bath, the breast tissue can be surrounded with an array of ultrasound transducers and achieve tangential incidence of the ultrasound beam relative to the chest wall. Tangential incidence (relative to the chest wall) is desired to avoid interaction between the ribcage and the ultrasound pressure wave.

c. There are no major blood vessels that carry away heat from the breast tissue, which could reduce the ability to deliver uniform therapeutic heat.
d. The hyperthermia target volume can be the whole breast, a quadrant of the breast, or even a smaller specific tumor mass. Energy deposition, which may heat sensitive regions such as a lumpectomy scar, must be minimized or avoided. It is therefore essential that the energy deposition be controlled and focused on specific sites within the breast tissue. Ultrasound permitting this level of control is achieved by the cylindrical applicator design of the BTS.

The work so far has been focused on the specifications, design, fabrication, and phantom testing of the BTS. With this IDE application we propose proceeding to a device evaluation on human subjects.

Dr. Göran K. Svensson, Director of Physics at the Harvard Joint Center for Radiation Therapy (JCRT) is available to answer questions in reference to this IDE application. Dr. Svensson can be reached by telephone at (617) 667-9570, by fax at (617) 667-9599, or by mail at JCRT, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215.

II. Name and address of sponsor.

Bernard W. Janicki, Ph.D.
Director of Research
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115
(617) 632-3488

III. Report of Prior Investigation

The BTS incorporates a cylindrically mounted transducer array applicator which provides accurate computer-assisted control of the energy deposition and a therapeutic temperature distribution for hyperthermia therapy. Preliminary results illustrate an advantage for this system over other clinical systems currently available. The experimental data to support this conclusion are reported herein. The work to date has included the design, modeling, fabrication, and laboratory testing of the BTS for hyperthermia therapy.

III.a. Bibliography

Published articles and abstracts pertaining to the Breast Ultrasound Therapy System:


III.b. Published and unpublished adverse information

None.

III.c. Other unpublished information

None.

III.d. Non clinical laboratory data

The performance of the system was evaluated in the laboratory by thoroughly testing the electronics components, by extensive computer modeling of the therapy applicator, in vitro by insonating into absorbing AGAR-graphite breast phantoms, and through dynamic thermal modeling of the breast over a wide range of perfusion values.

III.d.1. Laboratory Experimental Studies

Each electronic system component was individually tested to verify adherence to design specifications, sub-system assemblies were tested, and finally, complete system performance tests were conducted.

III.d.1.i. RF Generator and Amplifier Tests

A block diagram of the RF Generator-Amplifier is shown in Figure 1. The design consists of an onboard VCO connected through an on/off channel gate to a driver stage which is in turn connected to the output driver (amplifier) stage. The design operates in Class D-E using a bipolar driver and dual switched FETs in the output stage. The output power is variable from 0 watts to approximately 10 watts and is controlled by a linear voltage regulator circuit. The linear voltage regulator and on/off gate are controlled via an onboard micro-controller which is controlled by the system computer. Each RF Generator-Amplifier in the breast therapy system is individually controlled.

The RF Generator-Amplifier design has been developed with numerous design variations and board configurations being tested. The final configuration incorporates 4 channels per circuit.
A total of 24 cards provide 96 channels which are multiplexed 1:4 to drive the individual array transducers (384 total). The RF system is described in detail in Section IV.d.2.v.

Operating specifications and test results for the RF Generator-Amplifier are consistent with design criteria. These are summarized as follows:

Specifications:
- Square wave generator consisting of a computer controlled Voltage Controlled Oscillators (Frequency range 1 to 5 MHz)
- On/Off gating
- 10 Watt continuous power output computer controlled with a DC/DC linear voltage regulator.
- Short circuit current limiting

Test results:
- Frequency range of 0.8 to 6.2 MHz with little signal degradation
- 10 to 15 Watt output over full frequency range
- 12 Watt continuous at 2.0 MHz
- 10 Watt continuous at 4.5 MHz

Gating and current limiting function operating as designed.

Figure 1. RF Generator-Amplifier block diagram.
III.d.1.ii. Multiplexer-Transmit-Receive Switch Tests

The multiplexer switches the RF Generator-Amplifier outputs among different transducers and also selects transducers in the "receive" mode through the multiplexer's transmit-receive select function. Each multiplexer-transmit-receive switch connects to four transducers. Test results for the transmit-receive switch function are shown in Figure 2. Note there is minimal power output attenuation through the switch.

---

Figure 2. Multiplex-Transmit-Receive switch function test results. Top oscilloscope trace shows the input signal to the T/R switch, and the bottom trace the output signal in transmit position.

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III.d.1.iii. 16-Channel Transmit-Multiplex-Receive Board

Boards were constructed and tested which integrate control of 16 transducers into a single circuit card, which is designated the Transmit-Multiplex-Receive (TMR) board. On these cards are 4 RF Generator-Amplifier channels, 4 separate 4-channel multiplexer/transmit-receive switches, and a receiver section. These are illustrated in the block diagram of Figure 3.

The receivers are used for monitoring tissue attenuation and for measuring reflected signals for determination of the breast contours. The TMR board is used to acquire acoustic information regarding the breast tissue during therapy. This information will be used as a real-time monitor of the treatment.
III.d.2. Theoretical Simulation of the Breast Ultrasound Applicator

The cylindrical ultrasound applicator has been extensively characterized by using a validated computer model to optimize the physical size of the transducers and the excitation frequencies (references C, D, E, and Appendix C). The specific design of the applicator (number and frequency of transducers) is a direct result of this extensive modeling effort.

III.d.2.i. Methodology

The thermal treatment of the breast will be done with the patient in prone position. The breast is submerged through a hole in the treatment table into a water filled cylindrical applicator housing as shown in Figure 4. A cylindrical array of individually controlled ultrasound transducers surround the breast (Figure 5). The ultrasound wave enters the breast tissue tangential to the chest wall to eliminate or minimize the interaction with the ribs. To accommodate a large sized breast, the diameter of the cylindrical array is 25 cm. This is enough of a margin to accommodate asymmetry in the breast contour and alignment of the breast in the cylinder. The cylindrical applicator consists of a stack of 8 rings, each being approximately 1.7 cm high. Each ring contains 48 transducers, alternating between low frequency and high frequency transducers. Each ring deposits power in a plane parallel to the chest wall and the heating effect of each ring is relatively independent of adjacent rings. This property facilitates local control of the heating pattern.
Figure 4. Schematic drawing of the treatment couch with the applicator positioned under the opening in the table top.

Figure 5. Schematic diagram of the cylindrical applicator. The applicator is constructed from 8 rings, each containing 48 transducers alternating between high and low frequency.
The clinical specifications and capabilities of the breast applicator are listed in Section IV.d.1. The technical specifications and operating parameters for the cylindrical array were determined by computer simulations using several common treatment conditions. A Hewlett-Packard 9000/735 workstation made these complex and lengthy calculations practical. A detailed description of the three-dimensional acoustic and thermal computer model and the results of this simulation are found in reference C and in Appendix C.

III.d.2.ii. Conclusions

There is a significant normal variation in the numerical values of ultrasound interaction parameters and heat transfer parameters in tissue. There are also uncertainties in these values. A range of operating characteristics of the breast applicator accounting for these variations and uncertainties has been determined by computer simulations. We concluded that to achieve the therapeutic goals, we need to build a multiple frequency transducer array. A low ultrasound frequency, in the range of 1.5 - 2.5 MHz, is needed to compensate for the heat removed by the blood flow and permits an initial quick temperature elevation at depth in the breast tissue. Due to variations in the breast tissue attenuation, a broad frequency band for the low frequency transducers is desired. High frequency ultrasound, in the range of 4 - 4.7 MHz, is needed to maintain a steep temperature gradient near the surface of the target volume. The high and low frequency transducers are mounted alternately in each ring. Each ring offers power and frequency control sufficient to heat the whole breast or a quadrant of the breast to a minimum of 42°C without exceeding 44°C.

III.d.3. Breast Phantom Studies

The BTS was tested, under a variety of different transducer emission conditions, to evaluate design performance of the treatment applicator. The ultrasound field was measured by heating ultrasound absorbing graphite-AGAR breast phantoms using built-in thermocouple sensors (Reference B).

These tests permitted critical examination of the hardware and software design, including temporal multiplexing of the therapy transducers. A schematic drawing depicting the setup for these tests is shown in Figure 6. Equipment utilized in the testing includes the treatment applicator, RF generating and multiplexing circuitry, T/R switching circuitry, and Instrument Computer system.

The system's Instrument Computer controlled the excitation of consecutive ultrasound transducers to "sweep around" the ring at least once per two second interval. The same interval applies when multiple rings are excited (i.e. time is not extended). Heating of phantoms has been studied with extensive invasive thermometry used to characterize performance. Conditions as close as possible to modeled parameters from the simulation studies were created and comparisons made between the simulation study results and measured results in phantoms.
III.d.3.i Phantom Construction

Several breast tissue mimicking phantoms were manufactured from breast shaped latex membranes salvaged from ultrasound guided biopsy phantoms. The membranes were mounted in a sturdy frame, and a mixture of heated distilled water, agar, powdered graphite, and n-Propanol was poured into the membrane [19]. When returned to room temperature the phantoms solidifies. The composition of the phantom materials was chosen to yield an ultrasound attenuation of 0.75 dB/cm/MHz, a specific density of 1.076 g/cm$^2$, specific heat capacity of 0.776 calories/g/°C, and thermal conductivity of 0.015 calories/cm/MHz [6,15].

The phantoms were instrumented in several patterns to test different aspects of the applicators heating capabilities. 18 gauge temperature probes, each containing 14 thermistor temperature sensors, were placed in different planes parallel to the base of the phantom (where the chest wall would be located in a patient). Following instrumentation, the phantom was placed in the center of the treatment cylinder.

Experimental studies were conducted to determine if temperature uniformity could be expected to within a 2°C variation throughout a 12.7 cm diameter breast tissue-equivalent phantom. In each experiment, temperatures were recorded from 6 probes each containing 14 sensors. The positioning of the sensors is indicated in Figure 6.

III.d.3.ii Results

Predicting the temperature field in a blood perfused breast from the measurements in a non-perfused phantom is very complex. For this reason we decided primarily to investigate the power deposition or Specific Absorption Rate (SAR) patterns in the phantom. SAR is deduced from the temperature rise $dT/dt$ (measured immediately after the power is engaged and before significant
thermal gradients can develop in the phantom) multiplied by the specific density and the heat
capacity of the phantom material. Computer models indicates that to produce a uniform
temperature distribution, initially a uniform SAR distribution is required. However, after
therapeutic temperatures have been reached, the power delivered to the core of the breast has to
be decreased to prevent overheating. Therefore, the measurements were performed in 3 steps: 1)
the low frequency transducers were engaged to quantify the power deposition at the core; 2) the
high frequency transducers were engaged to quantify the power deposition at the surface; 3) both
low and high frequency transducers were engaged and adjusted to create a variable power
deposition profile over the extent of the breast phantom. All measurements were repeated for one
quadrant, one half, and the whole breast.

Figure 7 shows the SAR profile through the center of the breast at a level where the phantom
diameter is 8.7 cm (also see figure 6). The schematic indicates the placement of the temperature
probe, and the graph shows the individual SAR profile for high frequency, low frequency, and a
2 : 1 combination of high and low frequency. The low frequency profile demonstrated, that we
are able to preferentially deposit posit power at the core of the breast, the high frequency profile
demonstrates the ability to preferentially deposit power at the surface of the phantom, and the
combination profile shows the ability to combine the two frequencies to achieve a balance
between depositing power at the core and the surface.

Figure 7. SAR profiles through the breast phantom close to the center of the breast. The
schematic drawing to the left indicates the experimental setup. The heavy circle indicated the
position of the transducer array with all transducers engaged, the thin circle in the center indicates
the outline of the breast phantom, and the temperature probe is indicated by a line with circles
indicating temperature measurement points.
The graph on the right shows a family of curves representing the profile of the temperature rise
(and by inference power deposition) as a function of ultrasound frequency combinations. The
diamond symbols shows the power deposition profile when the 2.0 MHz low frequency
transducers are engaged, the triangular symbols the profile when the 4.5 MHz high frequency
transducers are engaged, and the squares the profile with a high to low frequency ratio of 2:1.
Figure 8 demonstrates the system's ability to achieve the same features at a position in the breast closer to the chest wall, where the phantom has a diameter of 12.7 cm. Again we are able to selectively deposit power at the surface of the breast, at the core, or to balance out the power deposition between these locations. Figure 9 shows the steady state temperature profile (in the non-perfused phantom) achieved by combining the SAR profiles in figure 8. Please note that the temperature goal in phantom experiments is different from 42-44°C. Here we try to achieve a uniform temperature distribution approximately 6°C above the baseline temperature of the phantom.

![Diagram of breast and phantom with temperature probe](image)

**Figure 8.** The ability to heat a large diameter breast is demonstrated. On the schematic drawing on the left, the temperature probe is shown placed through the center of the phantom at a level where the phantom has a diameter of 12.7 cm. The heavy circle indicates that the full transducer array is engaged.

In the graph on the right are shown a family of SAR curves. The diamond symbols represent the profile when the 4.5 MHz high frequency transducers are engaged, the squares the profile when the 2.0 MHz low frequency transducers are engaged, and the crosses are measurements of a high frequency to low frequency power ratio of 2:1.

The ability to heat half of a breast is demonstrated in figure 10. Again the SAR profiles achieved with the different frequency combinations are separated, and the graph indicates the ability to selectively heat the surface of the breast, the center of the breast, or any combination of the two.

One comparison of phantom measurements to computer models is shown in figure 11. The measurement was taken at a location where the phantom diameter is 9.7 cm, and the computer simulation was set up to dissemble the geometrical parameters and physical properties of the phantom experiment. The computer simulation is indicated in a solid line, and the phantom measurements are indicated by diamond symbols. In this figure all modeled and measured data has been calculated to absolute SAR values. The most prominent reason for the discrepancy between the modeled and the measured data is due to the limitation in the spatial resolution of the measured data. Any measurement records the temperature rise in a volume of finite size, whereas the computer model can calculate the temperature variation in much smaller volumes.

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Steady State Temperature

Figure 9. Temperature profile (in a non-perfused breast phantom) after a steady state has been reached with the power deposition pattern indicated in figure 8.

Figure 10. A schematic drawing of the phantom setup is shown on the left. The heavy semi circle indicates that half the transducer array is engaged for insonation into the thin circle representation of the breast phantom. Probe 1 is placed through the center of the phantom at the level of ring 3. The graph on the right shows the corresponding temperature rise profiles. The diamonds shows the profile when the 4.5 MHz high frequency transducers are engaged, the squares when the 2.0 MHz low frequency transducers are engaged, and the circles when the transducers are engaged with a ration of 2 parts high to 1 part low frequency.

### III.d.3.iii Conclusion

From these studies, it has been demonstrated, that the BTS can deposit the required ultrasound power profiles throughout the central region of a female breast, and that the BTS can deliver power to the surface of the breast to compensate for thermal conduction to the ultrasound coupling medium without overheating the core of the breast. We feel confident that the BTS will be able to raise the breast target volume temperature to 42-44 °C with relative uniformity, and maintain this temperature.
Figure 11 show a graph comparing computer model with phantom experiments. The power deposition profiles are calculated and measured through the center of the phantom where all transducers are engaged at a ratio of 8 parts high frequency to 1 part low frequency. All data are absolute and true specific absorption rate power deposition values.

III.d.4. Animal Tests

None. In consultation with Robert Hopkins, III, D.V.M. we have concluded that there is no meaningful animal breast model available to test the cylindrical applicator. However, under an approved DFCI animal protocol, and under the supervision of Dr. Hopkins, we have used 8 pigs over the last three to four years in terminal animal tests of the FSUM device. The FSUM is a spherically focused device with planar transducers as compared to the BTS, which is a cylindrically focused device with planar transducers. In these tests, we have validated the accuracy of the thermometry system and the computer models being used for the planning of the breast system. We believe that the experiences from the numerous FSUM animal studies can safely be extrapolated to the breast treatment system.

IV. Investigational plan.

IV.a. Purpose

The ultrasound Breast Therapy System is intended for use in thermal therapy of breast cancer. It is engineered and designed to provide precise application of ultrasound energy to induce local hyperthermia in tumor sites within breasts up to 15 cm diameter and 13 cm or less "length". Once the machine is proven to provide sufficient and safe control capabilities in the Phase I Device Evaluation and toxicity study, we expect to move to a Phase I/II study of the potential efficacy of this device.
The objectives of this investigation are:

1. Establish criteria for clinical operation and therapeutic application of the BTS.
2. Demonstrate the safety of the BTS for thermal therapy when used in accordance with operating instructions, and clinical protocol guidelines.
3. Determine site-specific normal tissue toxicities of hyperthermia induced with the BTS used in conjunction with radiation therapy.
4. Demonstrate efficacy of breast thermal therapy as an adjuvant therapy in combination with radiation therapy in a phase II clinical study protocol (second stage of study after completion of initial device evaluation).

**IV.b. Protocol**

The clinical protocol is a Phase I (toxicity/feasibility) study combining ultrasound hyperthermia and radiation therapy. The complete clinical protocol as approved by the Institutional Review Board of the DFCI is provided in Appendix A.

The investigator will keep the following information on each patient:

1. Past medical history.
2. The result of diagnostic tests.
3. Documents evidencing informed consent.
4. Records detailing other concurrent therapies or corrective therapy for device-related adverse effects for each patient.
5. Therapy observations on each patient noting general condition, condition prior to each therapy session, during session, and after the sessions.
6. Therapy record including the date, time and length of each therapy session along with any observed complaints or adverse effects of therapy.
7. Documents specifying the nature of and reason for any and all deviations from the protocol.

**IV.c. Risk analysis**

1. Description and analysis of the nature and incidence of increased risk to subjects:

   Foreseeable risks are:
   
   a) excessive localized heating of normal tissue located adjacent to the treatment volume,
   
   b) potential for blisters or burns of the skin surface.

   As with all ultrasound hyperthermia devices, the BTS could produce localized pain or discomfort. The pain usually is relieved as soon as the applicator power is reduced or turned off.

2. Means by which these risks will be minimized and corrective therapy for anticipated adverse effects:

   Careful pre-planning of the treatment to optimize the insonation pattern, as well as
operator training will minimize the risks to therapy. Control of the insonation pattern
during treatment will minimize risks by:

a) intensity distribution control,

b) interactive monitoring of temperatures at multiple sites in tumor and normal tissue, and

c) independent control of power in each of the transducers comprising the applicator
array.

3. Justification and benefits of the investigation:

Studies involving hyperthermia in conjunction with conventional therapies for cancer have
consistently reported a significant increase in one tumor response rate over the rate for a single
therapy administered alone [1,5,22]. In some cases, complete regression of the tumor and
remission of the disease has been reported, in others, formerly inoperable tumors have regressed
and were rendered operable as a result of the combined therapies. In addition several authors
reported an improved duration of response with the combination of hyperthermia and radiation
therapy. It is possible that the radiation therapy dose may be reduced when given in combination
with hyperthermia, which is especially useful in patients that have previously been treated with
radiation therapy to that location.

The national collaborative RTOG Study 84-01 and various institutional studies [3,8,13,23,
24,25,26,28] have demonstrated the feasibility and safety of regional deep hyperthermia using a
variety of heating devices. Acceptable acute normal tissue side effects have been reported and
continue to be reported in the preliminary analysis of RTOG Study 89-08 evaluating radiation and
deep hyperthermia. These studies have also demonstrated that it is very difficult to achieve
temperature elevation objectives. The first clinical protocol designed to prospectively evaluate
the toxicity of radiation therapy and deep hyperthermia induced by the FSUM. It was fashioned
after the current RTOG Study 89-08 and incorporates many of its features to allow ready
comparison of this device to those already in Phase II use [26]. The BTS is a new apparatus
which is breast site-specific, that can be controlled and is able to preferentially heat sub-regions of
the breast, while hopefully avoiding the heating of surrounding normal tissue. Once the system is
proven safe in this Phase I toxicity and feasibility evaluation, we plan to move to a Phase I/II
study of the potential feasibility and efficacy of this promising new technology.

IV.d. Description of the device.

IV.d.1. Specifications

Design specifications for the breast therapy applicator include the ability to treat a wide range
of breast sizes while providing control of power deposition in a manner which permits therapy of
the entire breast or of a pre-defined sub-region, such as a quadrant of the breast. The applicator
must be able to accommodate sizes of the breast ranging from a few cm diameter up to a
maximum of about 15 cm at the base and still provide control of treatment within a narrow
temperature range (42°C - 44°C) over a reasonably wide range of tissue perfusion, i.e. 30 to 200
ml, kg⁻¹, min⁻¹. The breast system includes the ability to monitor temperature and other vital
tissue characteristics by using minimally invasive techniques, later to be extended to non-invasive
monitoring techniques.
Based on these requirements, design specifications were developed for the breast therapy applicator. Included in the criteria is the patient positioning specification, which is essential in defining the applicator geometry.

Design Specifications:

- Prone patient position with breast extended downward.
- Cylindrical applicator geometry surrounding breast target.
- Ability to accommodate breast diameters of 15 cm or less, measured at the chest wall.
- Ability to accommodate treatment of breast length between 3 cm and 13 cm.
- Spatial resolution control of therapy field to within 1.5 cm vertically and to within one quadrant of the breast.
- Optimize temperature distribution and minimize any potential toxicity to the breast by:
  a. providing temperature control of the breast surface using the surrounding temperature controlled water bath.
  b. provide means for monitoring of the operation of the applicator using opposing pairs of transducers to measure the energy transmitted through the breast.
  c. provide means for accommodating probes for invasive measurements of temperature during therapy.
  d. provide means for using reflected ultrasound energy to define the contour of the breast and determine its position within the applicator.

IV.d.2. Device Description

IV.d.2.i. General System Description and Intended Use

The BTS is intended for use in thermal therapy of breast cancer. Thermal therapy is attained by means of a breast site-specific ultrasound applicator coupled with minimally-invasive and non-invasive thermometry.

The device consists of the hardware components illustrated in Figure 12. A breast site-specific cylindrical array applicator of ultrasound transducers is used for thermal therapy induction and for multiple monitoring functions. The "heart" of the hardware consists of the cylindrical array of transducers which both deposit power into the breast tissue for therapy and monitor the dynamic course of the treatment. The ultrasound array is described in more detail in IV.d.2.ii. The ultrasound transducers are geometrically arranged and operated to provide several monitoring functions. The monitoring functions are comprised of:

1. Diagnostic pulse-echo monitoring to determine breast contour and location within the treatment cylinder.
2. Through-transmission monitoring of power during therapy for determination of absorbed power distribution (SAR) in the breast tissue being monitored.
3. Measurement of "time-of-flight" throughout regions of the target breast tissue referenced to a limited number of invasive temperature measurements for non-invasive mapping of temperatures throughout the treatment volume.

The system consists of an Instrument Computer which provides all direct control and data...
interaction with the RF Power Subsystem, Receiver Subsystem, Transmit/Receive/Multiplexing Modules, Thermistor Thermometry Subsystem, and Cooling Subsystem. The system electronics, Instrument Computer, and Cylindrical Transducer Array/Treatment Cavity are integrated into a Patient Table Assembly/Subsystem, which provides a comfortable treatment support for the patient, accurate positioning of the breast within the treatment cavity, and a convenient means for consolidating system components and functions.

The Patient Table subsystem is discussed further in subsection IV.d.2.iii. The RF Power Subsystem generates the drive power for the transducers during therapy and is used for pulse-echo imaging of the breast contour. The T/R MUX Modules select which transducers are active for receiving or transmitting at any given moment during therapy. The Thermometry Subsystem is used to provide relatively high density (14 sensors in each of 5 needles) invasive thermistor thermometry information within the breast regions of interest. The Cooling Subsystem consists of thermoelectric coolers connected to the cylinder cavity and a temperature controller interfaced to the Instrument Computer. The Control Computer, including all operator interfaces, display and treatment recording functions, is located separately in the Operator Console.

![System hardware block diagram](image-url)

Figure 12. System hardware block diagram
IV.d.2.ii. Transducer Array Applicator Subsystem

The Transducer Array Subsystem is illustrated schematically in Figure 5 and photographically in figure 13. The array consists of 8 individual rings which are "stacked" with water-tight seals between rings. Each ring accommodates 48 transducers. The exact configuration and operating characteristics of the cylindrical transducer array has been extensively studied using theoretical computer simulations described in section III.d.2. Each transducer is square having dimensions of 1.5cm x 1.5cm on a side. Spacing between transducers along vertical dimension of the cylinder is 2.4mm. Therefore, 8 rings accommodates breast "lengths" of 13 cm or less.

Figure 13. A photograph of the un-shrouded ultrasound transducer array. 384 transducer surfaces are mounted on the inside of a 25 cm diameter cylinder. Visible are the external electrical connections and the coaxial cables supplying RF power to the transducers.

IV.d.2.iii. Patient Table Subsystem

The patient table subsystem is shown in the two perspective illustrations in Figures 14 and a photograph is shown in Figure 15. The patient table is designed to maximize utilization of symmetry of the breast by positioning the patient in a prone position with the breast suspended through an opening in the table top. The table top consists of sheet steel with a tubular steel outer
frame fabricated to provide for a 1.5" foam padding insert. The foam is sealed and the entire table top covered with a Naugahyde covering which is stretched tight and snapped into place, and is easily removed for cleaning. The foam insert (and Naugahyde) taper near the hole through which the breast is suspended in order to ensure that the entire breast can be extended beneath the table top for treatment if indicated.

Specifications for the patient table subsystem are indicated in Table 1.

![Perspective drawings of the patient table subsystem.](image)

**Table 1. Treatment table specifications:**

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<tr>
<td>Table top overall length</td>
<td>78&quot;</td>
</tr>
<tr>
<td>Table top height</td>
<td>37&quot;</td>
</tr>
<tr>
<td>Load capacity</td>
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</tr>
<tr>
<td>Table top hole size</td>
<td>10&quot; diameter (25.4 cm)</td>
</tr>
<tr>
<td>X-Y Applicator positioning:</td>
<td>± 2.5&quot; Vernier drive</td>
</tr>
<tr>
<td></td>
<td>± 6.0&quot; Vernier drive</td>
</tr>
<tr>
<td></td>
<td>180° Vernier drive</td>
</tr>
<tr>
<td>Structure material</td>
<td>Stainless steel</td>
</tr>
<tr>
<td>Paint</td>
<td>Non-toxic texture</td>
</tr>
<tr>
<td>Table top cover</td>
<td>1 ¼&quot; foam with Naugahyde cover</td>
</tr>
</tbody>
</table>
Figure 15 shows a photograph of the table top system mounted on the instrument stand. The shrouded transducer array is visible below an opening in the right side of the table top.

IV.d.2.iv. System Control and Computer Subsystems

Upon power up of the system, the treatment software will execute automatically so that no interaction is required by the user to start the software. All available options are displayed to the user in a graphical format. Options that are available at the startup screen include access to the treatment planning software, file handling utilities, diagnostic mode selections, treatment record printing, and treatment initiation. The user makes requests of the system via the computer keyboard, computer mouse, or a mechanical pause switch during all phases of the treatment. A hardware pause switch is provided that guarantees no output power can be delivered in case of an emergency.

Prior to initiation of a treatment, the user will be required to complete a treatment plan. The treatment planning software is in graphical form to simplify data entry, such as target volume locations, the number and location of temperature sensors, target temperatures for each sensor, scar tissue locations, and patient information.

The BTS will perform the treatment in a computer-assisted manual mode. The user selects different target tissue regions on the computer screen and sets a new target temperature value for each region. The computer system will then recommend which ultrasound transducers output power needs to be adjusted to accommodate the users request. The operator makes the actual transducer and power selections.
Treatment progress and status information will be available to the user via a graphical user interface that provides treatment information such as temperature distribution, power absorption distribution, thermal dose distribution, target contour information, and treatment time information. The user will not be required to determine power levels for the individual transducers since temperature distribution information is continually available on a graphics screen. The user will have the capability to specify the target temperatures for locations where implanted sensors are placed as well as other locations in the target volume. Once a treatment has been completed, the user will be returned to the startup screen so that printing of the treatment information may be performed, and duplication of the treatment files may be accomplished.

The computational functions of the system are divided between two computers, the Treatment Control Computer and the Instrument Computer. The control computer's primary responsibility is to control the overall treatment functions and provide an intuitive user interface via a graphics monitor, keyboard, and mouse. The Instrument Computer is primarily responsible for communicating with other hardware devices such as the Cylindrical Array Applicator, the Video Sub-system, Cooling Sub-system, Thermometry Sub-system, and the Pause Switch. The system software diagram is shown in Figure 16.

The Treatment Control Computer is a standard architecture machine with no custom hardware interfacing requirements that connects to the Instrument Computer via an ethernet communications link and is also connected to a printer to allow hard copy of the treatment information. For treatment results analysis, demonstrations, and software development purposes the Treatment Control Computer can be operated without the Instrument Computer connected.

The Instrument Computer implements the user control and measurement interfaces to other hardware portions of the treatment instrument, is located in the patient table sub-system near the control and measurement points, and communicates with the Control Computer via a bi-directional communications link. For software design consistency and to avoid unnecessary costs, the Instrument Computer was implemented as PC-AT compatible computer (Intel 80486 CPU based) filled with interface cards.

IV.d.2.v. RF Power Subsystem (TMR Boards)

This subsystem resides on the 24 Transmit-Multiplex-Receive (TMR) boards and consists of 96 independent RF amplifiers driven by 96 separate oscillator sources. Each oscillator consists of a computer-controlled voltage controlled oscillator (VCO) operating over the frequency range 1 - 5 MHz. Each of the independent RF amplifiers incorporates its own voltage control/regulator circuit which provides independent computer control of amplitude (output power level) for each amplifier channel as described in section III.d.1 and figure 1. Each RF amplifier output is connected to a T/R MUX input circuit. A block diagram of the TMR board is shown in Figure 3. Also located on each TMR board is the receiver circuit used for pulse-echo and attenuation measurements.
IV.d.2.vi. Thermometry Subsystem

The thermometry utilized for invasive measurements in the breast is a multi-channel thermistor-based Profilometer system [2] (stand-alone module incorporated into therapy system) which provides a large number of sensor points within a single needle probe. The probes used to measure temperature are thermistors mounted on needles, molded into catheters, or other designs as desired. Stainless steel needles are planned for use with this system. These are 19 ga. needles, each contain 14 thermistor sensors. The length of the probes and the spacing of the temperature sensors can be tailored to the individual patient. This range of probe configurations permits selection of a probe appropriate for the particular site being monitored. The multi-channel temperature instrument monitors and records up to 6 multi-channel temperature probes. Each probe can measure temperature at up to 14 sites (thermistors), resulting in a total of $6 \times 14 = 84$ measurement sites.

The present instrumentation has a resolution down to 0.1 degree Celsius, and the temperatures from all channels are sampled once every 2 seconds. The thermometry sub-system
consists of a medically isolated driver card for each channel, a controller card, and an interface
card, which are illustrated in Figure 17. Each channel card contains excitation and signal
conditioning circuitry for the sensors. The controller card coordinates the different channel cards.
The interface card handles communication to and from the Instrument Computer. Analog-digital
conversion is handled by a commercially available board in the Instrument Computer.

Figure 17. Thermometry subsystem

IV.d.2.vii. Non-Invasive Monitoring Subsystem

As previously discussed, we have chosen to perform real-time measurements of ultrasound
attenuation, velocity and back-scatter in the breast tissue. This offers real-time assessment of the
breast position within the cylinder and of the three-dimensional power deposition, which can be
correlated with temperature.

(1) Contour Monitoring

Pulse-echo reflection data is collected using the cylindrical transducer array. The reflection
data is collected by the Instrument Computer's Receiver subsystem and sent to the Contour
Monitoring subsystem. The Contour Monitoring subsystem converts this information into image
data that outlines the contour of the breast and prepares it for display. It also maps 3D image
data into a 2D image space for the generation of 2D displays. This sub-system provides
information to the Dynamic Treatment Calibration Subsystem to locate the breast within the
treatment cylinder for detection of breast movement within extreme boundaries set in the
Configuration file, and for updating the treatment cells in which the contour (surface of the breast) resides. Figure 18 is a simplified depiction of the pulse-echo monitoring method.

Contour Monitoring is performed by selecting a single ultrasound transducer to transmit an ultrasound pulse into the treatment cavity and then receiving the same pulse while measuring the time it takes for the pulse to return. This measurement is called a "Pulse-Echo" measurement since it measures the time it takes for a pulse to return to the transducer. The sooner a pulse returns the closer the object is to the face of the transducer. The spatial resolution of this technique is about 2 mm. By pulsing all of the transducers sequentially one at a time a 3 dimensional contour map of the target tissue located in the applicator can be generated.

(2) Power Absorption/Attenuation Monitoring

The Power Absorption Distribution Subsystem calculates the power deposition within the tissue based on current temperature and power information and absorption models. Figure 19 is a simplified depiction of the "Through Transmission" power measurement.

During treatment, the power absorption throughout the target volume for each transducer pair is measured by the Instrument Computer, and sent to this subsystem. The Power Absorption Distribution subsystem converts this information into an array representing the computed absorption or SAR in (W/cm³) for each treatment cell (minimum unit treatment volume). This computed absorption array is then sent to the Thermal Dose Distribution subsystem for its next simulation model cycle.

The "Through Transmission" power is determined by selecting a single transducer to produce an ultrasound pulse while at the same time having the transducers that are located on the other side of the cylinder (through the tissue) receive the pulse and measure the change in magnitude of the pulse (pulse amplitude degradation) once it has been received. A correlation between the transmitted magnitude and the received magnitude can then be used to determine the amount of power that was absorbed in the tissue. This feature will not be utilized for direct control of treatment, but rather for obtaining information which may be useful as an aid to monitoring treatment.

IV.d.2.viii. Software System

The System Software Block Diagram (refer to Figure 16) shows the system control implementation approach. System control is divided between two computers, the Treatment Control Computer and the Instrument Computer. The Treatment Control Computer provides an operator control interface, measurement interpretation, feedback control, and data recording. The Instrument Computer provides direct hardware interfacing for collecting temperature measurements, collecting measured data from receivers, setting control output levels, and controlling the timing for multiplexing the transducer array.

(1) Operator Interface

The Treatment Control Computer performs several interrelated functions. The operator input and display subsystem provides control over the treatment and feedback to the user as the treatment progresses. User control over the treatment is a high interaction level; actual control
over the timing, power levels, and frequencies applied to the large numbers of individual transducer elements is complex and must be controlled rapidly. Therefore, an operator is not capable of controlling the individual transducer parameters directly.

Transmit/Receive

1. Threshold Technique
2. Correlation of digitized waveforms

Pulse-Echo
TOF = 33.4 microseconds (MIN)

Pulse-Echo
TOF = 167 microseconds (MAX)

Figure 18. Schematic illustration of contour monitoring.

The operator interface is one of the most important parts of the treatment system since it represents "the system" to the users. Therefore, the engineering design approach must be secondary to the user-oriented approach in this instance. Not only must the data interfaces be considered, but also the tools (keyboard, mouse, etc.) and the display organization and options. The operator interface will define the treatment control and reference data and display a variety of types of treatment progress and general display information.

The displays to be provided during treatment includes:
1. A breast contour
2. Display of the temperature probe locations
3. 2D cross section breast images, each with selected overlays of calculated isotherms, thermal dose, or temperature.
4. Hot spot alerting
5. An optional display of 2D cross sections by location
6. Continuous time and temperature monitoring displayed as a graph for each temperature probe
(2) Treatment Planning

The Treatment Planning Subsystem is responsible for obtaining information from the user necessary for proper treatment operation. Information required by this subsystem includes the number of treatment sensor probes, number of sensors per probe, spacing of the sensors on the probe, target temperature and temperature limits for individual sensors and/or sub-region locations in the treatment volume, patient name and/or number identifier, and therapy region (or regions) determination. The treatment plan subsystem maintains this information and provides it to other subsystems.

The Treatment Plan Subsystem will also provide a method for the user to select regions as small as an octant and select a temperature set-point for the entire octant at once. It further provides seeding of overall power to each ring. It also provides for selection of sub-regions within an octant which can be controlled independently. These sub-regions can be utilized to provide decreased power levels to areas such as scar tissue.

(3) Treatment Control

The Treatment Control Subsystem sets transducer output power based on information received from the operator assisted by the, Thermal Dose Distribution Subsystem, Treatment Plan Subsystem, Dynamic Treatment Calibration Subsystem, and Temperature Subsystem. Once output power and frequency setting have been determined, the Treatment Control Subsystem
sends those data to the RF Power Subsystem on the TMR board so that actual power changes can be made for the applicator transducers.

The Treatment Control Subsystem operates on treatment sub-regions (volumes) defined by the user. The actual volume of each treatment sub-region is determined by the treatment plan.

The Treatment Control Subsystem operates in a computer assisted manual mode, with the user making manual adjustments of the temperature set-points for each treatment cell volume during the treatment. The default control method will be to heat the breast to 43°C in all treatment volume cells.

IV.e. Monitoring procedure

A monitor from the DFCI will be appointed and a monitoring procedure will be established.

IV.f. Labeling

Labeling information including the preliminary operating manual are found in Appendix D and E.

IV.g. Informed consent

1. Procedures and time scheduling for obtaining informed consent:

   After a subject has been identified as a potential study participant, the subject will be informed by the investigating physician of the nature of the study and given an information package containing a complete explanation of the objectives and procedures of the study. The physician will discuss the study with the subject and clarify any questions that may exist. The subject will then be asked to sign the informed consent form, indicating his or her intentions.

2. Outline of documentation and information is provided in Appendix B.

3. The informed consent form itself contains the following items and will be given to the patient:
   a. An explanation of hyperthermia and how it has been used in cancer therapy in layman's terms.
   b. A detailed list of anticipated adverse effects, measures taken to minimize these effects and possible corrective therapy applied.
   c. A summary of the results of similar studies, detailing the reported response rates and adverse effects.

4. Informed consent statements

Informed consent statements are included in Appendix B.
IV.h. IRB information

The IRB at DFCI operates in full compliance with all HHS and FDA regulations covering the use of human subjects in research. We have a Multiple Project Assurance (#M 1034) approved by NIH's OPRR and an IRB (#01) which reviews all protocols used at DFCI.

IV.i. Additional records and reports

None.

V. Manufacturing methods, facilities, and control

1. The device was manufactured by Dornier Medical Systems, Inc., which is inspected by the FDA for compliance with Good Manufacturing Practice (GMP) regulation (43 FR 7/21/78, pp. 31508-31532 or CFR part 820). The device is a one-of-a-kind custom device built under contract to DFCI, is not intended for commercial production, and was not fabricated under strict GMP guidelines. Contact Dr. E.C. Burdette at Dornier Medical Systems, Inc., 206 N. Randolph, Suite 301, Champaign, Illinois 61820, (217) 355-6070 concerning fabrication of the BTS.

2. Non-destructive performance testing, including procedures, calibration, and final tests to be employed to determine that the device has not deteriorated between manufacture and the time of use are described below.

   The device itself is designed to perform "self checks" prior to and during operation. Diagnostics are run to insure proper computer operation. During therapy, the system monitors the tumor and normal tissue temperature distribution. Forward and reverse power on all applicator transducer elements are monitored during therapy. If the forward power level exceeds the level called for by the therapy control program, the system will shut down. Also, if the reverse power exceeds a preset percentage of the forward power for a given applicator element, that channel will automatically shut down. Output power monitoring is done both in hardware and software. A prominently displayed array of light emitting diodes indicates at all times if any power is applied to any of the transducer elements at any time. Any discrepancies will cause a separate circuit to produce a shutdown of the hardware.

3. The procedure for inspecting incoming device components and the methods, controls and other fabrication procedures used for the manufacturing, processing, packaging, and storage are in accordance with Dornier Medical Systems, Inc. procedures.

VI. Agreement to be signed by investigators.

Not applicable. The institute will assess the clinical and technical expertise of each individual investigator involved. Signed 1572 forms and CV's in appendix F.
VII. Name and address of IRB chairman

Arthur Skarin MD. (Scientific Chairman)
Richard D'Augusta R.Ph., M.P.A. (Administrative Chairman)
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115

VIII. Amount charged for the device.

The BTS is a custom device built to specifications determined by the DFCI. Its development was funded by USARMDC Contract DAMD 17-93-C3098.

IX. Other information.

None.

X. General References.


Appendix A

Clinical Protocol
PROTOCOL NUMBER: 95-006

APPROVED BY
DIVISION CHIEF/DFCI:

BIOSTATISTICAL REVIEW:

SCIENTIFIC REVIEW:

HUMAN PROTECTION COMMITTEE:

ORIGINAL DATE: 3/2/95 (Issue date of protocol reviewed by HPC.)
APPROVAL DATE: 4/24/95 (Date protocol met HPC conditions.)
ACTIVATION DATE: 6/22/95 (Open to patient entry.)

REVISION DATE

6/22/95

SECTION

Schema, table of Contents, Section 2.1, 3.12, 3.13, 3.10.2, 5.73, 5.73.4, 5.73.5, 9.0 and Appendix G.

HPC REVIEW DATE

8/3/95

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DANA-FARBER CANCER INSTITUTE
44 Binney Street, Boston, MA 02115
PROTOCOL ADMINISTRATION OFFICE
Tel. 617-632-3029
Fax 617-632-2686

CURRENT ISSUE: 6/22/95
GROUP #: None
SPONSOR: U.S. Army R&D
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PROTOCOL NUMBER*: 95-006
PROTOCOL NICKNAME: RT and HT for Breast Cancer
PROTOCOL NAME: Radiation and Thermal Therapy for Extensive Intraductal Carcinoma

PHASE OF STUDY: I

DRUGS:

DFCI STUDY CHAIRPERSON(S):
Bruce A. Bornstein, MD
Jay R. Harris, MD

OTHER INVESTIGATORS:
Jorgen L. Hansen, MSc
Abram Recht, MD
Kitt Shaffer, MD, PhD
Charles L. Shapiro, MD
Barbara L. Smith, MD, PhD
Goran K. Svensson, PhD

INSTITUTIONAL PARTICIPANTS:
DFCI INPATIENT
DFCI ADULT CLINIC
DFCI PEDIATRIC CLINIC
CHILDREN'S HOSPITAL
BIGHAM & WOMEN'S
BETH ISRAEL
DEACONESS HOSPITAL
HARVARD COMM. HEALTH
OTHER INSTITUTIONS:
Joint Center for Radiation Therapy

APPROVED FOR CCOP USE? 
RANDOMIZED? 

OTHER MODALITIES:
RADIATION THERAPY
CHEMOTHERAPY
SURGERY
BMT
QOL, SURVEYS, etc.
GENE THERAPY
OTHER: Hyperthermia

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SCHEMA

PHASE I

DEVICE EVALUATION STUDY

Radiation and Thermal Therapy for Extensive Intraductal Carcinoma
(in patients undergoing definitive radiation therapy for breast cancer)

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<th>Patients with:</th>
<th>Radiation Therapy</th>
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<td>6100 cGy / 6 weeks</td>
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<td>• re-excision with residual tumor</td>
<td>+</td>
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<tr>
<td>• positive or close (≤ 1 mm) margins</td>
<td>Hyperthermia</td>
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<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ (DCIS) of the breast</td>
<td>T = 40-43 °C X 45 min. x 2 Tx</td>
</tr>
<tr>
<td>• re-excision with residual tumor</td>
<td>(no target volume</td>
</tr>
<tr>
<td>• positive or close (≤ 1 mm) margins</td>
<td>temperature ≥ 43 °C)</td>
</tr>
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1.0 INTRODUCTION

The use of radiation therapy in combination with breast-conserving surgery has been established as a standard option for patients with early-stage breast cancer (1). The goal of this approach is to eradicate the cancer locally and to preserve the cosmetic appearance of the breast. This is achieved by resecting the tumor in the breast and using moderate doses of irradiation to destroy any remaining cancer cells in the breast. Randomized studies have demonstrated equivalent survival for patients treated with mastectomy and with breast conserving surgery and irradiation (2, 3).

1.1 Invasive Breast Cancer

Local recurrence of the cancer following breast-conserving treatment is seen in about 10 -15% of cases and, most commonly, these recurrences are treated by mastectomy (4). Studies from our institution, and elsewhere, have demonstrated that the likelihood of local recurrence is related to the presence and extent of the intraductal component of the cancer (5-9). Those cancers with an extensive intraductal component (EIC) have a much higher risk of local recurrence compared with those without an EIC. Boyages and colleagues at the Joint Center for Radiation Therapy (JCRT) found a recurrence rate of 26% (43/166) for patients with EIC-positive tumors compared to 7% (29/418) for EIC-negative tumors (p=0.0001) (9).

Schnitt reviewed 181 patients treated at the JCRT with conservative surgery and radiation therapy and whose final microscopic margins of resection were evaluable (10). No recurrences were observed in 18 patients with EIC-positive cancers with negative, close, or focally positive margins. However, among 12 EIC-positive patients with more than focally positive margins (cancer present at the margins in more than three low-power fields) 50% had a true recurrence or marginal miss. On the basis of these findings, the use of breast conserving treatment in patients with cancer containing an EIC and more than focally positive margins is not recommended. Most commonly, these patients are treated by mastectomy.

1.2 Non-Invasive Breast Cancer

Ductal carcinoma in situ, (intraductal carcinoma, DCIS) is a heterogeneous group of lesions whose common histologic feature is the proliferation of presumably malignant epithelial cells confined to the mammary ducts and lobules without demonstrable evidence of invasion through the basement membrane into the surrounding stroma. The treatment options for woman with DCIS include mastectomy, conservative surgery (CS) and radiation therapy (RT), or conservative surgery alone. Mastectomy for DCIS is associated with excellent disease-free and overall survival but, as with invasive cancers many women desire breast conservation. However, little information is available on the long-term results of breast-conserving treatment with either conservative surgery alone or conservative surgery combined with radiotherapy.
The NSABP B-17 trial is the only randomized study comparing CS with CS & RT that has reported results (59). With relatively short follow-up (mean, 43 months), the 5-year actuarial risk of local failure was 20.9% in 391 patients treated with CS alone, compared to 10.4% in 399 patients treated with CS & RT.

Figure 1 shows the results of treatment. The length of follow-up and the number of patients treated is limited, however these results suggest that there is a high risk of local recurrence over time. Overall, 50% of the recurrences were invasive. The results also suggest that RT reduces the rate of local recurrence. Possible prognostic factors (e.g., histology) have not been analyzed in this series yet. Similar findings have been found in single institution retrospective studies of either conservative surgery alone or conservative surgery and radiation therapy (11-14).

**Figure 1.**

Cumulative Incidence of Noninvasive and Invasive Ipsilateral Breast Cancers and of All Other First Events in Women Treated by Lumpectomy (○) or Lumpectomy and Radiation Therapy (●).

P values are for the comparisons of average annual incidence rates between treatment groups.

1.3 Why are breast cancers containing intraductal carcinoma less effectively managed by radiation therapy?

Breast conserving treatment is an important option for many women with breast cancer. Invasive breast cancers with an EIC or pure non-invasive intraductal breast cancers have a much higher risk of local recurrence as compared to breast cancers without these histologies. Prior experience has shown that breast cancers with an intraductal component are less effectively managed by radiation therapy (4-14).

The reason for the association between pure DCIS or an EIC-positive invasive breast cancer and recurrence are not well established. There is some evidence to suggest that these cancers may be more extensive in the breast than other cancers and that the doses of irradiation consistent with maintaining the cosmetic appearance is
often insufficient to destroy the numerous remaining cancer cells in these patients (5). It has also been noted that intraductal carcinoma is characterized by proliferation of cancer cells within breast ducts typically showing central necrosis. Lindley, et al., examined the histologic features predictive for an increased risk of early local recurrence in 272 patients after treatment with conservative surgery and radiation therapy with pathologic data available (8). In 213 EIC-negative patients 21 (10%) had local recurrence compared to 13 of 59 patients (22%) with EIC-positive cancers. Furthermore, when the EIC-positive group was examined for the presence of extensive necrosis (comedonecrosis), they found that the recurrence rate was 50% (9/18) in this subgroup compared to 10% (4/41) for the group without extensive necrosis. This necrosis is related to the absence of blood supply within the ducts and has been shown to correspond to hypoxic regions based on the calculation of oxygen diffusion (15). This is in agreement with evidence that even in microscopic tumors there can be hypoxic areas (pO2 < 12 mmHg) (16). Since hypoxia is known to increase radioresistance by as much as a factor of 3, it is possible that this may account, in part, for the poor results seen with irradiation in these patients (17, 18). Okunieff et al., recently reported that tumor oxygenation alone was sufficient to account for the slope of the observed dose response curve for human breast carcinoma (60). Moreover, the oxygen tension distribution is a critical modifier of radiation treatment response.

It is also known that heat is effective at killing cells in an hypoxic environment (18-21). In fact, the synergistic effect of heat and radiation on hypoxic tumor cells both in vivo and in vitro has been well demonstrated (19, 22, 23). Most studies find a greater interaction between these modalities when x-rays and heat are delivered as close together as possible, but potentiation is seen even for treatments given greater than an hour apart (23-25). Thus, patients with extensive amounts intraductal carcinoma may significantly benefit from a combined approach using thermal therapy and irradiation.

It is reasonable to anticipate that combined use of thermal therapy and radiation therapy may be more effective than radiation therapy alone (19, 22). Thus, it is of great clinical significance that this combined treatment approach extends breast conserving therapy to high risk breast cancer patients, offering the prospect of avoiding mastectomy for many patients.

1.4 Hyperthermia

Hyperthermia is a potent radiosensitizing agent. It is the use of temperatures above 37 °C (98.6 °F) to treat tumors. Temperatures are typically prescribed in the range of 40 °C to 43 °C (104-109 °F) when hyperthermia is combined with radiation or drugs. The investigation of hyperthermia in the laboratory is extensive. Hyperthermia has been shown in vitro to kill tumor cells (26) and markedly sensitize cells to the cytotoxicity of radiation (27) and chemotherapy (28). Cells are particularly sensitive to hyperthermia when they are at low pH or when they have insufficient nutrition. These are environmental conditions that reduce cell killing by radiation (19-21).
This provides the rationale for the potential therapeutic gain when hyperthermia is used alone or with radiation therapy (29). In the clinic, the results using hyperthermia alone have been disappointing. This has been the basis of a shift away from the use of hyperthermia as a sole modality of cancer therapy to hyperthermia being used in conjunction with radiation therapy or chemotherapy (30-33). The majority of early clinical studies of hyperthermia were not concerned with the feasibility of a particular technical approach, but rather efficacy and toxicity. Therefore, the capability of many devices to deliver heat uniformly to a specific target volume is unknown. In addition, most clinical studies of hyperthermia were done before the development of hyperthermia quality assurance guidelines (34-36). Not only were many of the techniques of heating inadequate, but also the sparse and artifact prone thermometry to measure temperature was inadequate. Few devices were designed and manufactured to optimize therapy to a specific tumor site, but rather were designed as machines that could treat everything. These devices were claimed to treat most tumor sites, but unfortunately they treated no tumor site well. In the field of radiation oncology, linear accelerators can treat most sites remarkably well, however, there are some sites that demand modification of the accelerator to afford therapy tailored to that site; e.g., the brain leading to the development of stereotactic radiotherapy and radiosurgery. The same is even more true of hyperthermia given the limited depths of heat penetration and the effect of biologic parameters, such as blood flow, on heating ability. Despite the technical limitations of hyperthermia some conclusions can be drawn.

1.41 Hyperthermia for Breast Cancer

A major clinical use of hyperthermia in patients with breast cancer is the treatment of chest wall recurrence following mastectomy. The long-term local control rate of recurrent chest wall lesions using radiation therapy alone is less than 50%. The combination of hyperthermia with radiation therapy, for infiltrating carcinomas, has resulted in complete response rates of 57-93% (37-46), which are superior to those seen in many series using radiotherapy alone (47-53). For example, in a study by the Radiation Therapy Oncology Group (RTOG) of twice-weekly hyperthermia and radiotherapy (given in conventional fractionation to 60-66 Gy), complete regression was seen in 85% of patients (n=54) with locally recurrent breast cancer (39). Among the small number of patients followed for 2 years, complete response was maintained in nearly all evaluable patients. Lindholm and associates (40) reported on 11 patients with multiple superficial recurrent breast cancers. The complete response rate for 17 lesions treated with radiation therapy and hyperthermia was 65% compared to only 35% for 17 matched lesions given radiation alone (p=0.0253). Other investigators have reported similar results (41-46).

In summary, for gross tumor nodules (infiltrating carcinomas) response rates of 70% to over 90% have been reported in patients treated with low-dose radiotherapy and hyperthermia, with many or most patients achieving maintained complete response and acceptable complication rates (37, 38, 40-46, 54-56).
More recently Kapp and colleagues (57) reported on the use of thermoradiotherapy for residual microscopic infiltrating breast cancer after local regional recurrence. They treated 262 fields in 89 patients and had a 68% three-year actuarial local-control rate. The number of acute and long term complications was small. For example, blisters developed after only 22 of 445 treatments (5%) and were usually self-limited. This is the first clinical report to suggest that hyperthermia may be given in the adjuvant setting of recurrent breast cancer.

1.5 Clinical Study

Our specific goal is to develop the thermal therapy technologies required to optimize the synergistic efficacy between heat and radiation for patients with infiltrating breast cancer containing an extensive intraductal component or for patients with extensive pure intraductal carcinoma. The data suggests that intraductal carcinoma is frequently necrotic or associated with necrosis and that this may be secondary to hypoxia (8, 15, 16, 60). The hypoxic environment of intraductal carcinoma may explain the relative radioresistance of tumors with extensive amounts of intraductal tumor (17, 18). Since heat is effective at killing cells in an hypoxic environment it is reasonable to anticipate that combined use of hyperthermia and radiation therapy may be more effective than radiation therapy alone (18-24).

Thermal therapy of the breast will be accomplished by a site specific multi-transducer ultrasound array applicator, developed under contract with the U.S. Army, USAMRDC Contract # DAMD 17-93-C-3098. A description of the applicator is given in the next section. The specific clinical study we propose is a Phase I - Device Evaluation Study to establish our ability to safely deliver heat to the breast using this new device (58). The purpose is to determine if we can control heat delivery and deliver heat uniformly.

Once we have established our ability to uniformly heat the breast can we then begin a Phase I/II clinical study to establish a safe and effective treatment protocol for combining thermal therapy and irradiation. We will test the hypothesis that patients with breast cancer containing an extensive intraductal component or with extensive pure intraductal carcinoma will have a reduced risk for local recurrence from a combined and non-disfiguring treatment approach using irradiation and thermal therapy. It will be of great clinical significance if this combined treatment approach extends breast conserving therapy to high risk breast cancer patients, offering the prospect of avoiding mastectomy for many patients.

1.6 Hardware: Treatment System

The device consists of the hardware components illustrated in Figure 2. A breast site-specific cylindrical array applicator of ultrasound transducers is used for thermal therapy induction and for multiple monitoring functions. The "heart" of the
hardware consists of the cylindrical array of transducers that deposits power into the breast tissue for therapy and monitors the dynamic course of the treatment.

The ultrasound transducers are geometrically arranged and operated to provide several monitoring functions. One important monitoring function is to determine the breast contour and the location of the breast within the treatment cylinder.

The system consists of an Instrument Computer (Figure 2) which provides all direct control and data interaction with the RF power subsystem, receiver subsystem, transmit/receive/multiplexing modules, thermistor thermometry subsystem, and cooling subsystem. The system electronics, instrument computer, and cylindrical transducer array/treatment cavity are integrated into a patient table assembly/subsystem, which provides a comfortable treatment support for the patient, accurate positioning of the breast within the treatment cavity, and convenient means for consolidating system components and functions.

Figure 3 is a schematic of the patient support system. The RF power subsystem generates the drive power for the transducers during therapy and is used for pulse-echo imaging of the breast contour and for ultrasound velocity measurements during a brief period every 4 seconds when the therapy is gated "off." The transmit/receive/multiplexing modules select which transducers are active for receiving or transmitting at any given moment during therapy.

The thermometry subsystem is used to provide high density (14 sensors per needle) invasive thermistor thermometry information within the breast regions of interest. This is a stand-alone module, which will be integrated into the overall system in the future.

The cooling subsystem consists of thermoelectric coolers attached to the cylindrical array shell and a temperature controller interfaced to the instrument computer. The control computer, including all operator interfaces, display and treatment recording functions, is located separately in the operator console.

1.7 Food and Drug Administration Investigational Device Exemption

Pending Institutional Review Board approval, this protocol will be included as a part of the FDA Investigational Device Exemption application for this new device. This study can not begin until after FDA approval is granted.

1.8 Future Studies

If the treatment device achieves tolerable hyperthermia in the breast target volume we plan to do a Phase I/II Study examining the long-term toxicity and efficacy of treatment. The findings of the current study may make necessary a change in the number of hyperthermia treatments or the duration of treatment required to achieve the clinically recommended therapeutic goal of T\textsubscript{90} at 10 minutes equivalent to 43 °C.
Figure 2. System hardware block diagram.

Figure 3. Schematic drawing of treatment table and cavity
2.0 OBJECTIVES

2.1 Evaluate the capability of the breast treatment device to deliver homogeneous heat therapy in a specified quadrant or half the breast.

2.2 Evaluate the acute and long-term toxicity and cosmetic outcome of thermal therapy combined with radiation therapy to treat early breast cancer.

3.0 PATIENT SELECTION

This protocol is open to all patients fulfilling the eligibility criteria below. However, the intent of this study is not to be used as a way to offer breast conservation to those women who would otherwise be treated with mastectomy. This protocol is only to be considered after the patient and her physicians have decided to go on with breast conservation as a treatment choice.

3.1 Histologic confirmation of breast cancer with all 3 criteria below:

3.11 Patients must have either:

A). Infiltrating ductal carcinoma with an extensive intraductal component (EIC+)

or

B). Ductal carcinoma in situ (DCIS) without invasion.

3.12 A re-excision of the biopsy cavity must show residual non-invasive tumor. (Note: residual invasive tumor in addition to residual non-invasive tumor is permitted.)

3.13 Margins of the re-excision must be positive or close (≤ 1 mm).

3.2 Breast imaging:

3.21 Preoperative film-screen mammography.

3.22 Postoperative mammograms may be valuable in assessing the extent of residual disease (if in question) for patients presenting with microcalcifications.

3.23 Postoperative MRI of the breast as a baseline, prior to treatment is suggested, but not mandatory.

3.3 Staging studies:

3.31 Chest x-ray.
3.32 Bone scan, only for patients with infiltrating ductal carcinoma.

3.4 EKG.

3.5 CBC with differential and platelet count. PTT and PT. (Bleeding time in patients with platelet counts <100,000.)

3.6 Age ≥18 years.

3.7 Karnofsky Performance Status ≥70 (capable of self care) [Appendix A].

3.8 Expected survival of at least 3 months.

3.9 Informed consent obtained.

3.10 Criteria for ineligibility:

3.10.1 Abnormal bleeding propensity that would make thermal probe placement excessively hazardous.

3.10.2 Previous treatment:

3.10.2.1 Previous radiotherapy to ipsilateral breast.

3.10.2.2 Chemotherapy in the previous 2 weeks.

3.10.2.3 Previous chemotherapy with a regime containing an anthracycline agent, such as doxorubicin.

3.10.3 Patients with severe insulin-dependent diabetes mellitus, and evidence of neuropathy or vasculopathy.

3.10.4 Patients with unstable cardiac status including:

3.10.4.1 Unstable angina pectoris on medication.

3.10.4.2 Patients with documented myocardial infarction within six months of protocol entry.

3.10.4.3 Congestive heart failure requiring medication.

3.10.4.4 Patients on anti-arrhythmic drugs.

3.10.4.5 Severe hypertension (diastolic BP > 100 on medication).

3.10.5 Severe cerebrovascular disease (multiple CVA or CVA within 6 months).
3.10.6 Pregnancy.

3.10.7 Inability to give informed consent.

4.0 PATIENT ENTRY

4.1 Confirm eligibility (Pathology checklist).

4.2 Contact Study Chair to enter a patient on study.

4.3 The Study Chair will contact the Quality Control Center (QCC), J810, (617) 632-3761, FAX (617) 632-2295 before the patient begins treatment with the following information:

- Your name and telephone number
- Protocol name and number
- Date treatment begins
- Patient name
- Date of birth
- Patient ID number
- Primary physician
- Primary treatment institution

5.0 TREATMENT PROGRAMS

This is a pilot study. Specifically it is a device evaluation study of a new ultrasound thermal therapy machine for the treatment of the breast. This is one of the few devices designed and built to specifically treat a single site with hyperthermia and possibly the only device made to treat the breast. The treatment programs objective is to integrate thermal therapy into a course of "standard" breast irradiation.

5.1 Timing and sequencing of treatment.

5.11 Radiation therapy will begin within 8 weeks of the patients' last breast surgery. If systemic chemotherapy is given prior to definitive radiation therapy then radiation therapy can begin more than 8 weeks after the patients' last breast surgery.

5.12 Thermal therapy will be given twice during the course of whole breast irradiation. Hyperthermia will be delivered one time per week during any two of the five weeks of external beam whole breast irradiation. Thermal therapy can not be given on the first or second day of radiation therapy, but can commence anytime after the second radiation treatment. The two treatments must be separated by a minimum of 72 hours.
5.13 On the day of thermal therapy radiation will follow hyperthermia by 30-60 minutes.

5.2 Radiation therapy:

5.21 Megavoltage linear accelerators with dose rates of between 200-400 cGy/min will be used.

5.22 The dose to the breast: 4500 cGy in 25 fractions (180 cGy/day), 5x/week.

5.23 Boost dose: 1600 cGy in 8 fractions, 5x/week; if electron beam therapy is used it is prescribed to the 80% isodose line.

5.24 Regional nodes (when treated): Supraclavicular +/- axillary nodes, dose: 4500 cGy in 25 fractions (180 cGy/day), 5x/week. An additional axillary boost if indicated is permitted. Internal mammary nodes when treated are included in the tangential fields.

5.3 Thermal therapy:

5.31 Equipment: Hyperthermia will be delivered by the ultrasonic breast treatment system developed under contract from the U.S. Army Medical Research and Development Command. Treatment is delivered with the patient in the prone position and her treated breast submersed into water. The treatment cylinder contains of degassed water has a disposable liner that is discarded or sterilized after each treatment session.

5.32 The target volume is the quadrant of the breast that contains the biopsy cavity. If the biopsy cavity occupies two quadrants e.g., biopsy cavities located at 3, 6, 9, or 12 o'clock then the target volume is both quadrants (half the breast).

5.33 The treatment volume prescription temperature is 40 °C to 43 °C for 45 minutes.

5.34 Hyperthermia treatment duration is defined as starting 10 minutes after onset of power application or attainment of 40 °C in any part of the target volume, if the latter occurs in fewer than 10 minutes. After the starting time, treatment will continue for 45 minutes.
5.35 Ultrasound applicator transducer power will be increased until any one of the following occurs:

5.35.1 The recording of a target volume temperature > 43 °C for more than 1 continuous minute.

5.35.2 The maximum tolerated power level is reached.

5.36 Conditions dictating reduction of applied power and/or cessation of treatment:

5.36.1 Patient request.

5.36.2 Intractable pain or chest pain.

5.36.3 Monitored normal tissue temperature > 43 °C.

5.36.4 Pulse > 160.

5.36.5 Blood Pressure:

5.36.5.1 Systolic > 180 mmHg, diastolic > 100 mmHg.

5.36.5.2 Systolic < 90 mmHg, diastolic < 50 mmHg.

5.36.6 Altered mental status.

5.36.7 Systemic Temperature ≥ 40 °C.

5.4 Thermometry:

Target volume temperatures will be monitored continuously by interstitial and external temperature probes. Probes are placed interstitially using local anesthesia.

5.41 We will attempt to place two invasive thermometry probes, each containing 1 to 14 sensors, orthogonally with the target volume. Thermometry sensors will also be placed superficially on the surface of the breast.

5.42 Thermometry probe location:

5.42.1 The location of the regions for thermometry and the paths of insertion of the probes will be selected during therapy planning. RTOG guidelines (34-36) and methodology for estimating probe paths and location will be used compatible with patient safety.
5.42.2 Suggested specific locations to sample temperature include:

5.42.2.1 The biopsy cavity region, especially at the edges and center of the cavity. This is measured with the invasive probe.

5.42.2.2 At surgical scars, especially the biopsy cavity scar. This is typically measured with the non-invasive superficial skin sensors.

5.42.2.3 Measurements at the surface of the nipple.

5.42.2.4 Predicted "hot spots" within the breast, determined by treatment planning.

5.43 Thermometry probe insertion:

5.43.1 Diagnostic ultrasound will be attempted for probe placement in all patients (unless probes can be placed safely by clinical or by radiographic means and also be compatible with the requirements of treatment planning).

5.43.2 The thermometric probes will be inserted along the pre-selected tracks and inserted to the desired depth under diagnostic ultrasound guidance with patients in the prone treatment position.

5.43.3 After insertion, the location of the probes relative to the breast and target volume will be visualized with the ultrasound treatment unit.

5.43.4 A photograph will be taken to document the thermometry probe position prior to each treatment session.

5.44 A minimum of 28 invasive temperature points per treatment will be attempted.

5.45 Temperature sensors:

5.45.1 All temperatures will be measured by NIST traceable sensors.

5.45.2 Thermocouples or thermistors in 18-22 gauge needle probes with 1-14 sensors per needle will be used for static points [see Appendix B].
5.45.3 At the completion of the hyperthermia treatment session, the temperature sensing probes will be removed.

5.5 Other invasive sensors:

5.51 In selected cases, thermocouple/thermistor probes will be replaced by the Enhanced Thermal Diffusion Probe that, in addition to temperature, measures thermal conductivity, thermal diffusivity, and tissue blood flow [see Appendix B].

5.52 In selected cases, oxygen tension will be measured in the target volume, scar/biopsy cavity region both pre- and post-treatment.

5.6 Additional monitoring:

5.61 The P.I. or a physician designated by the P.I. will be in attendance during every treatment.

5.62 The treatment nurse will monitor vital signs continuously.

5.63 During treatment, the patient's pulse rate and EKG will be continually monitored. An automatic blood pressure device will obtain blood pressure every 5 minutes.

5.64 General anesthesia cannot be used, but light sedation (e.g. Ativan, Percocet, etc.) can be employed as well as previously prescribed analgesics. All patients, however, must be able to discern mild to moderate treatment-associated pain in order to avoid potentially severe thermal injury.

5.7 Adverse reactions and their management

5.71 Anticipated toxicities:

5.71.1 RADIATION THERAPY; related morbidity is discussed with the patient using a separate radiation therapy consent form. However, common immediate side effects include fatigue and skin redness and irritation in the treated breast. In patients that receive chemotherapy prior to treatment on this protocol, they may experience myelosupression.

5.71.2 THERMAL THERAPY; related morbidity includes acute pain in the treatment region secondary to treatment. Also associated with treatment are possible, burns, blisters, itching, or fever during the treatment session. If any of these are observed, it may be possible to change the heating pattern to eliminate the effect. Patients may feel
warm or sweat. After the hyperthermia session it is possible to develop pain, burns, or blisters that might persist. Patients may become uncomfortable from lying in the prone treatment position.

Late tissue changes, such as fibrosis, necrosis, ulceration, and vascular changes, in the treated breast could be seen. Some of these effects such as fibrosis could make follow-up examinations of the breast more difficult.

5.71.3 THERMOMETRY, related morbidity include pain during probe insertion, despite local anesthesia. As with any invasive procedure, there is a risk of bleeding or infection.

5.72 Toxicity management:

We expect most side effects associated with the use of thermal therapy and radiation therapy to be controllable. Thermal therapy related pain, warmth, and other acute effects are commonly eliminated by adjustment of the heating pattern or energy. Some burns and skin ulcers can be observed after superficial hyperthermia (heat) treatments to persist for more than 6 months in about 15% of patients who receive burns. These are usually treated with complete resolution of symptoms in the majority of cases by routine skin care management.

Unfortunately, possible late tissue changes are not reversible and if they develop may make follow-up examinations of the treated breast more difficult.

5.73 Criteria for Removal from Treatment:

5.73.1 Patient decision to withdraw from study.

5.73.2 Patient noncompliance with the requirements of the protocol.

5.73.3 A patient may be removed from this study if it is believed that the constraints of this protocol are detrimental to the patient's health or the ability to deliver planned radiation therapy to the breast.

5.73.4 Patients who are unable to tolerate therapy because of the side effects of hyperthermia delivery (pain, tachycardia, anxiety, etc.) will have treatment terminated. Intolerable side effects are defined as:
5.73.4.1 Any NCI Common Grade 3 or Grade 4 toxicity except for Blood Pressure changes and Second Degree Burns.

5.73.5 Patients who refuse a second session of breast hyperthermia.

5.73.6 Cessation of radiation therapy for any cause will result in the termination of hyperthermia treatments.

6.0 FEDERAL REPORTING REQUIREMENTS FOR ADVERSE REACTIONS

6.1 Unanticipated adverse device effects

6.11 The Protocol Chairman shall submit to the sponsor (U. S. Army Medical Research & Development Command) and to the reviewing IRB’s a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

6.12 The sponsor who conducts an evaluation of an unanticipated adverse device effect shall report the results of such evaluation to FDA and to all reviewing IRB’s and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.
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### 7.0 REQUIRED DATA

#### 7.1 Data to be collected:

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<tr>
<td>Survival</td>
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*† An ipsilateral mammogram of the treated breast will be done approximately 6 months after the patients pre-treatment mammogram. Then bilateral mammograms will be done 6 months later and repeated yearly after that.

* The first follow-up appointment will be one month after treatment. The patient will then return for follow-up every 3 months for 2 years and then every 6 months after that.

** MRI of the breast will be encouraged, but is not mandatory, prior to treatment, at the end of radiation therapy, at the first month follow-up, and then every 6 months.

#### 7.2 Data Collection:

<table>
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<tr>
<td>Thermal Therapy Evaluation</td>
<td>Within 2 weeks of treatment</td>
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<tr>
<td>Summary and Evaluation</td>
<td>Within 1 month of completion of therapy</td>
</tr>
<tr>
<td>Status Update</td>
<td>At each follow-up visit (see above)</td>
</tr>
</tbody>
</table>

### 8.0 MODALITY REVIEW

#### 8.1 Evaluation During Treatment Course:

While treatment is in progress, the following will be done at weekly intervals:
8.11 Patients will be examined at least once weekly and a treatment note will be done weekly with particular attention to acute reactions.

8.12 Patient discomfort [see Appendix C].

8.13 Acute systemic stress effects will be detailed and quantified as either non-treatment limiting or treatment limiting by the clinician.

8.14 An end of treatment evaluation and summary must be completed no later than 1 month after treatment.

8.2 Evaluation Post Treatment Course:

8.21 The time intervals to the development of late complications, first relapse, site(s) of relapse, disease-free survival and overall survival will be recorded.

8.22 The first follow-up appointment will be one month after treatment. The patient will then return for follow-up every 3 months for 2 years and then every 6 months after that.

8.23 History and physical examination will be performed at each follow-up. The investigator shall routinely observe and document the impact of the treatment on the patient's condition and provide an assessment in the following areas:

8.23.1 Late tissue changes, such as fibrosis, necrosis, ulceration, and vascular changes, in the treated breast.

8.23.2 Toxicity parameters will be recorded and evaluated according to the RTOG Late Morbidity Scoring Criteria [Appendix D] and the NCI Common Toxicity Criteria [Appendix E].

8.23.3 Breast cosmesis will be determined by physical examination. An attempt shall be made to quantify normal tissue changes/damage and tumor necrosis within the treated volume [Appendix F].

8.3 Thermal Dose Assessment:

In order to evaluate the capabilities and limitations of the breast treatment device to deliver homogeneous heat therapy in a breast we will assess a number of treatment parameters after each treatment. Several thermal
parameters will be calculated and recorded [Appendix G]. These parameters include:

\[
\begin{align*}
T_{\text{min}} &= \text{minimum temperature in the tumor area} \\
T_{\text{max}} &= \text{maximum temperature in the tumor area} \\
T_{\text{ave}} &= \text{average temperature in the tumor area} \\
T_{90} &= \text{the temperature index for which 90\% of all measured temperature points are above} \\
\% < 40.0 &= \text{percentage of measured temperature points below 40.0 }^\circ\text{C} \\
\% > 43.0 &= \text{percentage of measured temperature points above 43.0 }^\circ\text{C} \\
\% > 43.5 &= \text{percentage of measured temperature points above 43.5 }^\circ\text{C} \\
\% > 44.0 &= \text{percentage of measured temperature points above 44.0 }^\circ\text{C}
\end{align*}
\]

9.0  STATISTICAL CONSIDERATIONS

The primary objective of this pilot study is to evaluate the ability of the treatment device to deliver homogeneous heat therapy to the breast in patients with extensive intraductal breast cancer. A total of 15 patients, of whom 14 are expected to be fully evaluable, will be entered on study. Accrual is expected to require 18 months. The endpoint for the device evaluation is the proportion of patients for whom the treatment goal was achieved (as defined in Section 8.3 and Appendix G) without intolerable side effects (described in Section 5.73). Short- and long-term toxicities and cosmetic outcome will also be evaluated in each patient.

With 14 evaluable patients, the probability of failing to observe an adverse side effect that occurs in the population at a rate of 20% is 0.044. For rare toxicities occurring in the population at a rate of 10%, this probability is 0.23. Assuming 14 evaluable patients, the 95% confidence intervals for the proportion of patients who experience intolerable side effects are as follows:

<table>
<thead>
<tr>
<th>No. with Side Effect</th>
<th>Proportion with Side Effect</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00-0.23</td>
</tr>
<tr>
<td>1</td>
<td>0.071</td>
<td>0.0021-0.34</td>
</tr>
<tr>
<td>2</td>
<td>0.14</td>
<td>0.018-0.43</td>
</tr>
<tr>
<td>3</td>
<td>0.21</td>
<td>0.047-0.51</td>
</tr>
<tr>
<td>4</td>
<td>0.29</td>
<td>0.084-0.58</td>
</tr>
<tr>
<td>5</td>
<td>0.36</td>
<td>0.13-0.65</td>
</tr>
<tr>
<td>6</td>
<td>0.43</td>
<td>0.18-0.71</td>
</tr>
<tr>
<td>7</td>
<td>0.50</td>
<td>0.23-0.77</td>
</tr>
</tbody>
</table>

To ensure that only a limited number of patients experience potentially intolerable side effects, if "intolerable medical toxicity" (defined in Section 5.73.4.1), is observed in two patients or if five patients refuse a second session of breast hyperthermia, patient accrual will be suspended pending review of results and possible amendment of treatment procedures.
10.0 REFERENCES


APPENDIX A

KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX B

Description of Non-Commercial Temperature Probes

1. The Enhanced Thermal Diffusion Probe (ETDP):

The Enhanced Thermal Diffusion Probe (ETDP) system can accurately measure tissue temperature, thermal conductivity, thermal diffusivity and derive tissue blood flow. The ETDP measurement instrumentation permits the routine measurement of microcirculatory and physiologic tissue parameters via a single invasive probe. The probe is physically no different than the large diameter temperature measurement probe we use routinely in the hyperthermia clinic. It simply uses thermistors instead of thermocouples as the measurement elements. As is the case with all our temperature probes, the power supply is an isolated, medically certified unit that surpasses UL-544 regulations for isolation voltage and leakage current for medical and dental devices. In addition, the communication link between the host computer and the ETDP is optically isolated. Thus, there is no electrical connection between the ETDP and any of the other equipment in the hyperthermia center. (Please see the attached diagram at the end of this Appendix.) This probe is already approved for use in DFCI protocol 91-063.

2. The Oxygen Tension Probe:

The group providing us with the ETDP probe have added the additional ability to measure oxygen tension via a polarographic cathode that resides in a probe. This modified probe is available for use when treating patients with hyperthermia and is approved by the DFCI IRB for use in DFCI protocol 91-063. Of note, a similar probe is approved for a group of investigators at Brigham and Women's Hospital (BWH) by the BWH IRB for the measurement of oxygen tension.

General Electrical: The oxygen tension measurement is via a polarographic cathode residing in our 16 gauge or 18 gauge probe in conjunction with a conventional gel coated ECG electrode attached to roughened skin. There are no direct electrical connections between the instrument and host computer. In addition electrical isolation of the instrument from the wall ground is provided via use of an UL544 Medical Grade Power Supply. Further isolation of the oxygen tension measurement circuitry is provided via battery power of that portion of the circuit, and isolation of the resulting signal using an isolated amplifier. Finally, as done with our current probe and by the group using the similar probe at BWH we will have the isolation and safety features confirmed by the Biomedical Engineering Services at BWH.

Polarographic Oxygen Measurements: A -0.6 volt potential is applied to the polarographic cathode with respect to the anode, and the resulting induced current (0-10 nanoAmps) is measured and internally converted to oxygen tension by a predetermined calibration. The driving voltage used is on the order of magnitude of
galvanic stimulation routinely utilized in neurophysiologic testing and poses no added stress or discomfort to the patient. The American Association of Medical Instruments has set a current limit of 10 microAmps for use in implanted devices, and the techniques described here typically establish currents no greater than 10 nanoAmps (less than 0.1% of the safety limit). Passive safety circuitry limits current in the unlikely event of a complete probe and system failure to less than 6 microAmps.

3. Multi-Channel Temperature Probes:

The group providing us with the probe have now been able to manufacture a new multi-channel temperature instrument that is capable of driving one, two, or three multi-channel temperature probes. Each probe can measure temperature at up to 14 sites.

Accurate temperature measurement in both tumor and normal tissue is paramount to delivery of both safe and hopefully effective hyperthermia treatments. Each new multi-channel sensor probe provides only temperature data, however up to 14 sites could be monitored simultaneously per "invasive" placement. This is a major step up from our current commercially available multi-channel probes that can only measure data at a maximum of three sites. Increasing the number of temperature points monitored during treatment may allow us to deliver higher tumor temperatures and provide improved patient comfort.

The probes are either plastic or stainless steel needles, sized from 15 to 20 gauge and from 10 to 30 cm long, containing 10 to 14 thermistor temperature sensors. Each thermistor is individually tested for voltage isolation at an FDA-approved, GMP-certified fabrication facility. The probe instrumentation allows a temperature resolution down to 10-20 millidegrees Centigrade and temperature can be sampled (across all sites) at up to 10 times per second.

A range of probe configurations are provided and permits selection of a probe appropriate for the particular site being monitored. Since there is little change in the size of the probes from those presently in use, it should not add any additional patient discomfort.
General Electrical: There are no direct electrical connections between the patient and ground via the instrumentation. Within the measurement instrumentation, each probe is connected to an individual, electrically isolated probe driver card. The driver cards are powered by a UL-544 Medical Grade Power Supply and signals to and from the driver cards are passed through optical isolators and isolation amplifiers. This isolation ensures that there is no electrical connection between patient and ground. However, as a further safety precaution, hardware protection circuitry is provided to shut off power (within 65 microseconds) to a probe if an "out-of-range" signal is detected due to probe breakage or other mishap. Although the isolation circuitry described earlier ensures that there is no current path from the instrument to ground through the patient under such circumstances, this latter measure provides added assurance of patient safety.

We have shown that the instrument and probes have surpassed the 10 microAmp patient safety limit for leakage current, set by the American Association of Medical Instruments for implanted devices via experiments with a BioTek 170 Digital Safety Analyzer. Of course, as done with our other hyperthermia equipment and probes we will have the isolation and safety features confirmed by the Biomedical Engineering Services at BWH, before any patient use.

We would like to use the multi-channel instrument and all the accompanying temperature probes in appropriate patients. The additional information provided by these probes will add to our knowledge of the physiological changes in tumor and normal tissue during hyperthermia. The use of this thermometry system should not pose any additional risk or discomfort to our patients. Furthermore, the multi-channel temperature probe is of great value in the treatment of large deep tumors where many temperature points must continuously be monitored in order to provide both safe and effective treatment.
As in the case of all our temperature probes, the power supply is an isolated, medically certified unit that surpasses UL-544 regulations for isolation voltage and leakage current for medical and dental devices. In addition, the communication link between the host computer and the ETDP is optically isolated. Thus, there is no electrical connection between the ETDP and any of the other equipment in the hyperthermia center.
APPENDIX C

GRADING OF PATIENT DISCOMFORT

During Hyperthermia Session

Grade 1: Patient volunteers complaint of discomfort, which is tolerable, or can be relieved by counseling, medication, or positional changes, without reduction in applied power necessary to elevate tumor temperature.

Grade 2: Reduction in applied power is necessary, however, all scheduled sessions are completed, and minimum temperature elevation evaluability criteria are fulfilled.

Grade 3: One or more scheduled sessions are not completed or are canceled because of intolerable discomfort, however minimum temperature elevation evaluability criteria are fulfilled.

Grade 4: Intolerable discomfort prevents fulfillment of minimum temperature elevation evaluability criteria.

* Taken from RTOG Protocol 89-08. A phase I/II study to evaluate radiation therapy and hyperthermia for deep-seated tumors.
**APPENDIX D**

**RTOG Late Morbidity Scoring Criteria**

<table>
<thead>
<tr>
<th>ORGAN/TISSUE</th>
<th>GRADE 0</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
<th>GRADE 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Pigmentation change</td>
<td>Sloughing</td>
<td>Patchy atrophy</td>
<td>Marked atrophy</td>
<td>Ulceration</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>None</td>
<td>Sluggish turgor</td>
<td>Moderate telangiectasia/Fusiform hair loss</td>
<td>Severe Induration and loss of subcutaneous tissue</td>
<td>Necrosis</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>LARYNX</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>LUNG</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>HEART</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
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<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>None</td>
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<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
## APPENDIX E

### COMMON TOXICITY CRITERIA

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood/Bone Marrow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>≤ 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>PLT</td>
<td>≤ 75.0 - normal</td>
<td>50.0 - 74.9</td>
<td>25.0 - 49.9</td>
<td>&lt;25.0</td>
<td></td>
</tr>
<tr>
<td>Hgb</td>
<td>≤ 10.0 - normal</td>
<td>8.0 - 10.0</td>
<td>6.5 - 7.9</td>
<td>&lt;6.5</td>
<td></td>
</tr>
<tr>
<td>Granulocytes/Bands</td>
<td>≤ 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>≤ 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td><strong>Hemorrhage (clinical)</strong></td>
<td>none</td>
<td>mild, no transfusion</td>
<td>gross, 1-2 units transfusion per episode</td>
<td>gross, 3-4 units transfusion per episode</td>
<td>massive, &gt; 4 units transfusion per episode</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
<td>Life-Threatening</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>none</td>
<td>able to eat</td>
<td>reasonable intake</td>
<td>intake significantly decreased but can eat</td>
<td>no significant intake</td>
</tr>
<tr>
<td>Vomiting</td>
<td>none</td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>6-10 episodes in 24 hours</td>
<td>&gt;10 episodes in 24 hrs, or requiring parenteral support</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>none</td>
<td>increase of 2-3 stools/day over pre-Rx</td>
<td>increase of 4-6 stools/day, or nocturnal stools, or moderate cramping</td>
<td>increase of 7-9 stools/day, or incontinence, or severe cramping</td>
<td>increase of ≥10 stools/day or grossly bloody diarrhea, or need for parenteral support</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>none</td>
<td>painless ulcers, erythema, or mild soreness</td>
<td>painful erythema, edema, or ulcers, but can eat</td>
<td>painful erythema, edema, or ulcers, and cannot eat</td>
<td>requires parenteral or enteral support</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≤ 1.5 x N</td>
<td>1.5 - 3.0 x N</td>
<td>&gt;3.0 x N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminase (SGOT, SGPT)</td>
<td>≤ 2.5 x N</td>
<td>2.6 - 5.0 x N</td>
<td>5.1 - 20.0 x N</td>
<td>&gt;20.0 x N</td>
<td></td>
</tr>
<tr>
<td>Alk Phos or S'Nucleotidase</td>
<td>≤ 2.5 x N</td>
<td>2.6 - 5.0 x N</td>
<td>5.1 - 20.0 x N</td>
<td>&gt;20.0 x N</td>
<td></td>
</tr>
<tr>
<td>Liver-clinical no change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kidney, Bladder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>≤ 1.5 x N</td>
<td>1.5 - 3.0 x N</td>
<td>3.1 - 6.0 x N</td>
<td>&gt;6.0 x N</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>no change</td>
<td>1+ or &lt;0.3 g/l</td>
<td>2-3+ or 0.3 - 1.0 g/l</td>
<td>4+ or &gt;1.0 g/l or &gt;10 g/l</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hematuria</td>
<td>neg</td>
<td>micro only</td>
<td>gross, no clots</td>
<td>gross + clots</td>
<td>requires transfusion</td>
</tr>
<tr>
<td>Alopecia</td>
<td>no hair loss</td>
<td>mild hair loss</td>
<td>pronounced or total hair loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>none or no change</td>
<td>asymptomatic, with abnormality in PFT's</td>
<td>dyspnea at normal level of activity</td>
<td>dyspnea at rest</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dyspnea on significant exertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMMON TOXICITY CRITERIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>---------------------------</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>TOXICITY</strong></td>
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<td></td>
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</tr>
<tr>
<td><strong>GRADE</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac dyssrhythmias</strong></td>
<td>none</td>
<td>asymptomatic, transient, requiring no therapy</td>
<td>recurrent or persistent, no therapy required</td>
<td>requires treatment</td>
<td>requires monitoring; or hypotension, or ventricular tachyarrhythmias, or fibrillation</td>
</tr>
<tr>
<td><strong>Cardiac function</strong></td>
<td>none</td>
<td>asymptomatic, decline of resting ejection fraction by less than 20% of baseline value</td>
<td>asymptomatic, decline of resting ejection fraction by more than 20% of baseline value</td>
<td>mild CHF, responsive to therapy</td>
<td>severe or refractory CHF</td>
</tr>
<tr>
<td><strong>Cardiac ischemia</strong></td>
<td>none</td>
<td>non-specific T-wave flattening</td>
<td>asymptomatic, ST and T-wave changes suggesting ischemia</td>
<td>engine without evidence for infarction</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td><strong>Cardiac pericardial</strong></td>
<td>none</td>
<td>asymptomatic effusion, no intervention required</td>
<td>pericarditis (rub, chest pain, ECG changes)</td>
<td>symptomatic effusion; drainage required</td>
<td>tamponade; drainage urgently required</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>none</td>
<td>asymptomatic, transient increase by &gt;20 mm Hg (D) or to &gt;150/100 if previously WNL. No treatment required</td>
<td>recurrent or persistent increase by &gt;20 mm Hg (D) or to &gt;150/100 if previously WNL. No treatment required</td>
<td>requires therapy</td>
<td>hypertensive crisis</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>none</td>
<td>changes requiring no therapy (including transient orthostatic hypotension)</td>
<td>requires fluid replacement or other therapy but not hospitalization</td>
<td>requires therapy and hospitalization; resolves within 48 hrs of stopping the agent</td>
<td>requires therapy and hospitalization for &gt;48 hrs after stopping the agent</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-sensory</strong></td>
<td>none</td>
<td>mild paresthesia, or reflexes loss of deep tendon</td>
<td>mild or moderate objective sensory loss; moderate paresthesias</td>
<td>severe objective sensory loss or paresthesias that interfere with function</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-motor</strong></td>
<td>none</td>
<td>subjective weakness; no objective findings</td>
<td>mild objective weakness without significant impairment of function</td>
<td>objective weakness with impairment of function</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-cortical</strong></td>
<td>none</td>
<td>mild somnolence or agitation</td>
<td>moderate somnolence or agitation</td>
<td>severe somnolence, agitation, confusion, or hallucinations</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-cerebellar</strong></td>
<td>none</td>
<td>slight incoordination, dysdiadochokinesis</td>
<td>intention tremor, dysmetria, slurred speech, nystagmus</td>
<td>locomotor ataxia</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-mood</strong></td>
<td>none</td>
<td>mild anxiety or depression</td>
<td>moderate anxiety or depression</td>
<td>severe anxiety or depression</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-headache</strong></td>
<td>none</td>
<td>mild</td>
<td>moderate or severe but transient</td>
<td>unrelenting and severe</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-constipation</strong></td>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
<td></td>
</tr>
<tr>
<td><strong>Neuro-hearing</strong></td>
<td>none</td>
<td>asymptomatic hearing loss on audiometry only</td>
<td>tinnitus</td>
<td>hearing loss interfering with function but correctable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>deafness not correctable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

90
### Common Toxicity Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Toxicity</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Symptomatic subtotal blindness</td>
<td>Loss of vision</td>
</tr>
<tr>
<td>1</td>
<td>Generalized</td>
<td>Exfoliative</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic macular or vesicular eruption</td>
<td>Dermatitis or exfoliative</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic macular, ulcerating</td>
<td>Dermatitis</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

#### Neuro-vision
- None or no change
- Symptomatic subtotal or loss of vision

#### Skin
- None or no change
- Erythema that is asymptomatic or symptomatic, dermatitis or erythema

#### Allergy
- None or transient rash, drug fever < 38.0°C, 100.4°F
- Urticaria, drug fever 38.0°C - 40.0°C, mild bronchoospasm
- Serum sickness, bronchoospasm, require parenteral meds
- Anaphylaxis

#### Fever in absence of infection
- None or 37.1°C - 38.0°C, 98.7°C - 100.4°F
- 38.1°C - 40.0°C, 100.5°C - 104.0°F
- > 40.0°C, > 104.0°F for > 24 hrs or fever accompanied by hypotension

#### Local
- None, pain
- Pain and swelling, with inflammation or phlebitis
- Ulceration
- Plastic surgery indicated

#### Weight gain/loss
- < 5.0%
- 5.0% - 9.9%
- 10.0% - 19.9%
- ≥ 20.0%

#### Hematologic
- Hyperglycemia < 116 116 - 160 161 - 250 251 - 500 > 500 or ketoacidosis
- Hypoglycemia > 64 55 - 64 40 - 54 30 - 39 < 30
- Amylase WNL 1.5 x N - 2.0 x N 2.1 x N - 5.0 x N > 5.1 x N
- Hypercalcemia < 10.6 10.6 - 11.5 11.6 - 12.5 12.6 - 13.5 ≥ 13.5
- Hypocalcemia > 8.4 8.4 - 7.8 7.7 - 7.0 6.9 - 6.1 ≤ 6.0
- Hypomagnesemia > 1.4 1.4 - 1.2 1.1 - 0.9 0.8 - 0.6 ≤ 0.5

#### Coagulation
- Fibrinogen WNL 0.99 - 0.75 x N 0.74 - 0.50 x N 0.49 - 0.25 x N ≤ 0.24 x N
- Prothrombin time WNL 1.01 - 1.25 x N 1.26 - 1.50 x N 1.51 - 2.00 x N > 2.00 x N
- Partial thromboplastin time WNL 1.01 - 1.66 x N 1.67 - 2.33 x N 2.34 - 3.00 x N > 3.00 x N
**APPENDIX F**

Follow-up Visit Form

**FOLLOW-UP VISIT**

**J O I N T C E N T E R F O R R A D I A T I O N T H E R A P Y**

**DEFINITIVE BREAST CANCER TREATMENT**

<table>
<thead>
<tr>
<th>NAME</th>
<th>DATE</th>
<th>HOSP. NO.</th>
<th>THERAPY NO.</th>
</tr>
</thead>
</table>

**Systemic Treatment Since Prior Follow-Up Visit (type)**

If Recurrence Noted, Indicate Site:

a.) breast, compatible with primary  
b.) breast, separate from primary  
c.) axilla  
d.) supraclavicular area  
e.) opposite breast  
f.) other (state)

**NARRATIVE:**

**NORMAL TISSUE STATUS:**

<table>
<thead>
<tr>
<th>None</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
</table>

- Breast or chest wall tenderness
- Breast retraction
- Breast fibrosis
- Breast edema
- Matchline effect
- matchline effect at hockey stick
- Telangiectasia (indicate site)
- Hyperpigmentasia
- Arm edema
- Shoulder restriction
- Supraclavicular fibrosis
- Other

**Overall Cosmetic Result:**

Physician: Excellent Good Fair Poor  
Patient: Excellent Good Fair Poor

**STUDIES ORDERED:**

**NEXT VISIT:**

**COPIES SENT:**

<table>
<thead>
<tr>
<th>M.D.</th>
<th>RADIOETHERAPIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>8502-7/81</td>
<td>92</td>
</tr>
</tbody>
</table>
APPENDIX G

Equipment Evaluation Form
for
Breast Applicator

Last Name: ____________________________
First Name: ____________________________
Therapy #: ____________________________
Tr. Date: ____________________________
Tr. Number: ____________________________

Mark target area, surgical scar, and probe placement:

# Temperature sensors: Tumor: _____ Normal: _____ Skin: _____

Applicator power:

<table>
<thead>
<tr>
<th></th>
<th>LF</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># xducers</td>
<td>Max Pwr</td>
</tr>
<tr>
<td>Ring 1:</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Ring 2:</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Ring 3:</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Ring 4:</td>
<td>______</td>
<td>______</td>
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<tr>
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<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Ring 6:</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Ring 7:</td>
<td>______</td>
<td>______</td>
</tr>
<tr>
<td>Ring 8:</td>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

Treatment Descriptors:

<table>
<thead>
<tr>
<th></th>
<th>Tmin</th>
<th>Eq43min</th>
<th>Tave</th>
<th>T90</th>
<th>Tmax</th>
<th>% &lt; 40.0°C</th>
<th>% &gt; 43.0°C</th>
<th>% &gt; 43.5°C</th>
<th>% &gt; 44.0°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
<td>______</td>
</tr>
</tbody>
</table>

Was treatment goal achieved? Yes [ ] No [ ]

Successful treatment defines as '% < 40.0°C' ≤ 15% and '% > 43.5°C' ≤ 10% and '% > 44.0°C' ≤ 1%)

JLH 1/95

93
Appendix B

Informed Consent
RADIATION AND THERMAL THERAPY FOR EXTENSIVE INTRADUCTAL CARCINOMA OF THE BREAST

INTRODUCTION

Your physician has determined that you either have, invasive breast cancer that contains an extensive amount of intraductal carcinoma (non-invasive cancer), or that your have pure intraductal carcinoma without any associated invasion. Local recurrence of breast cancer following breast conserving treatment with lumpectomy and radiation therapy is seen in 10-15% of cases. However, breast cancers such as yours, with an extensive intraductal component may have a higher risk of local recurrence in the breast than cancers without an extensive intraductal component when treated with breast conservative therapy. For patients with an extensive intraductal component, the option of mastectomy may have a lower risk of breast recurrence, but many patients prefer breast conservation. The overall survival of patients treated with breast conservation is virtually identical to those treated with mastectomy.

Intraductal carcinoma may be more resistant to radiation therapy and this may account for the poor results seen with irradiation in these patients. Thermal therapy or hyperthermia refers to the use of temperatures 42°C (107.6°F) or higher to treat malignant tumors. Laboratory and clinical reports have demonstrated that heat kills
tumors, if tumors are heated to 43°C (109°F) for 30-60 minutes. Many studies suggest that the addition of heat may also improve upon the usual results of radiation therapy for many tumors, including recurrent invasive breast cancer, bladder cancer, and tumors of the head and neck region. Investigators have found an improvement in tumor response rates and a lengthened duration of response. This is the first study to attempt to treat non-invasive breast tumors.

You are being asked to participate in a research project to study the use of thermal therapy (heat treatments produced by sound waves) for the treatment of breast cancer with extensive intraductal carcinoma. We have developed the thermal therapy technologies required to make use of the positive interaction between heat and radiation. The specific clinical study we propose is a study to optimize and establish our ability to safely deliver heat to the breast using a new breast thermal therapy device. The purpose is to determine if we can control heat delivery.

**OBJECTIVE**

The purpose of this research study is to determine the safety and effectiveness of generating, and delivering, heat to the breast in combination with radiation therapy. We want to evaluate what side effects are associated with this treatment. Fifteen patients will be treated in this research study.
TREATMENT DESCRIPTION

Your radiation oncologist will schedule a radiation therapy treatment planning and an initial thermal therapy planning session. Both of these are conducted at the Dana Farber Cancer Institute even though the radiation therapy is carried out at another hospital. Photographs of the treatment site will be taken during the planning and at each of the thermal therapy sessions.

Thermal Therapy: At the Radiation Therapy Planning Department at the Dana Farber Cancer Institute you will receive two thermal therapy treatments. Each treatment will require at least two hours of preparation time prior to treatment. The heat treatment requires you to lay on your stomach on a soft flat table for approximately two hours. Therefore, on the day of thermal therapy you must plan for a total of approximately 5 hours from the time you arrive for therapy to the time you are ready to leave. The device used to generate heat produces ultrasonic sound waves to heat the breast. This device was developed under contract with the U.S. Army Medical Research & Development Command. This is a new heat treatment device. Your breast will fall through a cut-out (hole) in the table and rest in a tank of water for the heat treatment. The ultrasound energy waves enter the quadrant or half of the breast containing the original lump (tumor) region. The goal will be to reach 40 to 43 °C (104 to 109 °F) in the breast for 45 minutes. During heat treatments you will experience warmth and
occasionally mild discomfort. You will have an intravenous line inserted prior to treatment that may be used to give pain medications if needed. A technologist will be with you during treatment.

During the heat treatment, temperatures will be measured. Prior to each heat treatment at least two metal thermometer needle probes will be inserted into the breast. The thermometer probes help control the temperature in the breast and avoid burns. A Radiation Oncologist and Diagnostic Radiologist will place the small needle probes into the breast through numbed skin under sterile conditions using local anesthesia. The temperature measuring probes will be removed after each thermal therapy treatment. The total time for each treatment session will be at least three hours.

**Radiation Therapy:** In addition to the heat treatments, you will receive radiation therapy to your breast. Your radiation oncologist will decide what radiation dose you receive. On the basis of experience, we believe that the effectiveness of the radiation may be improved with heat. On days when both radiation and thermal therapy are given, radiation will follow thermal therapy by 30-60 minutes. Radiation will be given daily, five days a week, for 6 to 6 1/2 weeks.

After the treatment course is completed you will be asked to return at regular intervals for follow-up visits to evaluate the results of treatment and the potential long-term side effects. In order to assess your response to treatment certain diagnostic tests will be
done prior to beginning treatment and at intervals following treatment. This may include blood tests, mammography, breast ultrasound, breast magnetic resonance imaging (MRI), and other tests determined to be necessary by your physician. They will be explained to you at the time of your initial evaluation and at follow-up visits.

**POTENTIAL BENEFITS**

The potential benefits associated with the treatment include a possible reduced risk of tumor recurrence. Heat appears to increase the effectiveness of radiation therapy. However, no guarantee or assurance can be made regarding the results, if any, that may be obtained since research results cannot be foreseen. Your participation will contribute to the development of medical knowledge about the treatment of breast cancer and the use of this thermal therapy device.

If new information develops during the course of your treatment that may be related to the efficacy or risks of your treatment, you will be informed and options will be discussed.

**POTENTIAL SIDE EFFECTS**

Although hyperthermia has the potential to produce beneficial results, it may be of no benefit and may have injurious effects.
Thermometer probe placement: Despite local anesthesia to diminish pain during thermometer probe insertion, you may experience pain at the time of probe placement. When local anesthesia is given, you will experience a momentary stinging sensation. As with any invasive procedure, there is a risk of bleeding, infection, or perforation of normal structures in or near the region of treatment. There is the small risk of a permanent scar at the point where the thermometry probe enters the skin of the breast, but this risk should be small. There is a minor risk that tumor cells could track along the thermometry probe path in the breast, but this would be rare, and be included in the field receiving radiation therapy treatment.

Radiation Therapy: Your radiation oncologist will describe the possible side effects to you, and you will be asked to sign a separate consent form for the delivery of the radiation therapy. However, common immediate side effects include fatigue and skin redness and irritation in the treated breast. Thermal therapy may also make the normal tissues more sensitive to the toxic effects of radiation. Thus, all of the tissues that receive radiation therapy and heat are potentially more prone to radiation injury. Since this treatment is investigational, it is possible that unforeseen side effects could occur.

Thermal Therapy (heat treatment): Is associated with possible pain, burns, blisters, nausea, itching, or fever during the treatment session. If any of these is observed, it may be possible to change the heating pattern to eliminate them. You may also become
uncomfortable from lying on your stomach, in the treatment position. We will attempt to make you comfortable.

During treatment, your heart may beat faster and you will probably feel warm and begin to sweat. Your heart's electrical pulses and your blood pressure will be monitored during therapy. You may choose to stop receiving the study treatment at any time if any of the related side effects is intolerable. In addition if you experience dizziness, shortness of breath, or chest pain, you must notify your physician immediately, so that the treatment can be modified or stopped. We expect most side effects associated with the use of thermal therapy and radiation therapy to be controllable and reversible. We do, however, emphasize that we cannot rule out any unsuspected side effect. During this study, provisions and precautions will be taken to insure your safety throughout the course of treatment.

Should any of the above side effects appear, your physician(s) will take steps to reduce or eliminate these effects by whatever means are necessary, but there can be no assurance that such effects can be reduced or eliminated.

After the thermal therapy session it is possible to develop pain, burns, or blisters that might persist. In addition, infection or ulceration may occur. If persistent pain should develop, this may represent muscle or nerve injury. You will be evaluated by your
physician and further heat treatment sessions will be stopped until such problems have resolved.

Tissue changes, such as fibrosis (scar tissue), necrosis (dead tissue), and ulceration, in the treated breast could happen at any time following treatment and be permanent. Some of these effects such as fibrosis could make follow-up examinations of your breast by you or your physician more difficult. In addition, thermal therapy may make follow-up mammograms of the breast more difficult to interpret.

This is a new deep-heating device and with all investigational treatments, it is possible that unforeseen complications could occur.

ALTERNATIVE TREATMENTS

The alternative treatment is mastectomy with or without reconstruction of the breast. Reconstruction can be done at the time of the mastectomy or at a later time. Another alternative treatment would be conventional radiation therapy alone. Your physician has explained these procedures and both their advantages and their disadvantages to you.
CONTRAINDICATIONS

Thermal therapy is not to be given to patients whose sensitivity to heat sensation has been significantly decreased in the area to be treated by any means (previous treatment, anesthesia, diabetic nerve damage, etc.), patients with cardiac pacemakers, and patients having a known decrease in circulation in the area to be heated. General or regional anesthetic must not be given with thermal therapy and will not be used in your treatments. Pain-medication, sedatives, or tranquilizers may be used in your treatments as long as they do not significantly decrease your awareness of pain sensation in the treatment area.

FOR WOMEN OF CHILDBEARING POTENTIAL

Radiation therapy may have an adverse effect on an unborn child and should not be performed during pregnancy. You are advised NOT to become pregnant before or during this study. If you become pregnant, you would automatically be excluded from radiation therapy and this protocol study.

PARTICIPATION

Your participation is voluntary and you may refuse to participate and/or withdraw your consent and discontinue participation in the project at any time without penalty.
loss of benefits to which you are otherwise entitled, or penalty of prejudice in your future treatment.

Also, your physician can terminate your participation without your consent at any time in the event of physical injury or other condition that makes further treatment an unnecessary risk in the medical opinion of your physician.

CHARGES

You will not be charged for the hyperthermia treatment. However, you will be charged for the ultrasound examination of the breast that will occur at the time of thermometer probe placement. You will be charged in the usual fashion for radiation therapy, doctors visits, and any other portion of your care that is considered standard care. You are also responsible for payment of all charges for medical procedures to treat conditions resulting from adverse outcomes related to the study treatment.

CONTACT PERSONS

For more information concerning the research and research-related risks or injuries, you can contact Dr. Bruce Bornstein, the investigator in charge, at (617) 632-3591.
Appendix C

Publications
This paper describes the design of a novel ultrasonic therapy system dedicated to the breast cancer treatment and the theoretical investigation of the heating characteristics of the system. The applicator is a cylinder comprised of a stack of rings. Each ring has up to 48 transducers mounted on the inside of the ring and directed towards the centre. The transducers operate in one of two frequency bands (1.8–2.8 MHz and 4.3–4.8 MHz), arranged alternately in each ring. During treatment the patient is positioned in prone position, with the breast immersed in water and surrounded by this array. This design was modelled and optimized by 3-D simulations for a variety of treatment conditions. The simulated results demonstrate that the system has an excellent capability to achieve and maintain a temperature distribution (41–44°C) in a quadrant to a whole breast. Initial experiments using a single ring of transducers has been performed to verify the power deposition calculation.

**Key words:** Hyperthermia, breast treatment, ultrasound field, bio-heat transfer

1 Introduction

Clinical data show that combination of hyperthermia with radiation therapy or cytotoxic agents improve complete response rates for the treatment of many cancers (Kapp and Kapp 1993). A majority of these clinical studies pertain to hyperthermia treatment of superficial and small tumours (i.e. <4 cm in diameter). Considerable problems still remain when using external hyperthermia applicators for treatment of deep and large tumours. Ultrasound is capable of penetrating soft tissues to produce deep heating (Lele 1983, Fessenden et al. 1984, Hynynen et al. 1987, Hansen et al. 1994). To fully utilize its potential, however, tumour site specific applicators, that optimize heat delivery to the tumour, are needed. Only then can we expect improved efficacy and reduced complications of hyperthermia treatment.

Recent studies have shown that the use of conservative surgery and radiation in patients with an infiltrating breast cancer containing an extensive intraductal component (EIC) is associated with an increased risk of local failure (Boyages et al. 1990). Intraductal carcinoma is characterized by a proliferation of cancer cells within breast ducts typically showing central necrosis, which may correspond to hypoxic regions as indicated by a morphometric study (Mayr et al. 1991). It is known that hypoxia increases radioresistance by as much as a factor of 3 (Pelcic and Skarsgard 1984) and that heat is effective at killing cells in a hypoxic environment (Dewey et al. 1977). These patients, therefore, may benefit from a combined approach using hyperthermia and radiation therapy. Other potential patients who may benefit from the hyperthermia treatment include those with local recurrence after...
mastectomy, non-inflammatory stage III patients, and those with ipsilateral local recurrence after radiation therapy. A European phase III study randomized over 300 patients with recurrent or primary breast cancer to radiation alone or to radiation and superficial hyperthermia. The preliminary results (Vernon 1994) show an overall complete response rate of 60% for the combined treatments as compared to 40% for radiation alone.

Geometrically, the breast is a site particularly well suited for hyperthermia. This is due to its convex shape, the absence of large vessels and the relatively low perfusion. However, current applicators, using ultrasound or microwave, are still not able to deliver an optimized heating pattern for treatment of the intact breast. For these reasons, a dedicated applicator has been designed. The goals are as follows:

(I) The system should be able to produce hyperthermic temperatures in a treatment volume ranging from a quadrant to the whole breast, and to maintain a uniform temperature distribution to within ±2°C. The treatment objective for our application is to reach a minimum temperature of 41.5°C but not exceed 44°C in a treatment volume. It is critical to keep the temperature within this narrow range in order to minimize potential toxicity and yet maximize effectiveness of the treatment (Kapp et al. 1992, Oleson et al. 1993).

(II) The breast treatment system should have the operational flexibility to accommodate the uncertainties in tissue characteristics, such as ultrasound attenuation and perfusion rate, and the variability in the patient geometry.

(III) It should be easy to use the system in the clinic.

These requirements present a considerable technological challenge. To meet these goals the design has to rely on general physics considerations. We consider ultrasound to be most suitable for treatment of the breast tissue compared to other modalities. Reasons for the choice are that the penetration and the power deposition of ultrasound can be controlled by selecting appropriate frequencies, and air cavities and bone interfaces with soft tissue are minimal in the breast. The arrangement of the transducers has to be determined by the power deposition pattern that satisfies the thermal condition for uniform temperature elevation.

The purpose of the work described here is twofold. The first is to determine the basic configuration of the applicator based on a general physics and clinical consideration. The second purpose is to develop a theoretical model for ultrasound power deposition calculation and the three dimensional solution to the bioheat transfer equation. This model, approximating the system, offers insights to the physical process. Based on the model and the available data of the tissue characteristics, the ultrasound frequency bands are optimized. An initial experiment using a single transducer ring was performed to verify the ultrasound power deposition. This experiment also serves as a test for the electronics design.

2. Methods
2.1. Basic design

It is desirable to achieve a uniform hyperthermic temperature region covering the tumour volume with sharp temperature gradients at the edge towards the normal tissue. Several investigators (Ocheltree and Frizzell 1987, Roemer 1991) have theoretically studied the power deposition pattern required to achieve such temperature distribution.
It was found that in the absence of large blood vessels, the ideal temperature distribution can be achieved by depositing power properly in the boundary and the interior of the treatment region. The power deposited in the boundary compensates for the conduction losses to the surrounding volume, and the power deposited interiorly in the treatment region overcomes the effect of blood perfusion.

An important lesson can be drawn from these studies for the design of the breast applicator. When the whole breast needs to be treated, the boundary consists of the breast surface and the chest wall. In order to elevate the temperature uniformly in the breast, independent adjustment of the power deposition in the interior of the breast and the two boundaries is necessary. We found that this capability cannot be obtained by the current ultrasound devices, in which only one frequency is applied in a treatment. It was determined that transducers with two different frequencies surrounding the breast should be used simultaneously. The low frequency is more penetrating and deposits power deeper into the breast tissue, thus compensating for the energy removed by blood flow in the interior of the breast. The high frequency, with a higher attenuation rate, deposits most of the power near the breast surface and compensates for heat loss to the outside of the breast. The chest wall boundary, on the other hand, can be addressed by using both high and low frequencies. An optimized power deposition, therefore, can be obtained by appropriate combinations of these two frequencies.

In some clinical situations, only a quadrant of the breast needs to be treated. The pie shaped treatment region is bounded by a quadrant of the breast surface, a quadrant of the chest wall base, and two planes inside the breast, for which the same principle can be used. The breast surface quadrant is insonated using high frequency ultrasound, and the boundaries deep into the tissue are insonated using low frequency ultrasound.

To implement this approach, a cylindrical applicator was designed which consists of a stack of eight rings with an inner diameter of 25 cm (Figure 1). There are 48 transducers (PZT-8) in each of the upper four rings, and this number decreases to 24 in the rest rings toward the apex of the breast. The size of the transducers is 1.5 x 1.5 cm. The gap between two adjacent rings is 0.24 cm. This small size permits a better spatial control of power deposition. Low frequency and high frequency transducers are arranged alternately in each ring. Inherent to the design of this device, the transducers with overlapping fields are driven non-coherently to avoid phase effect.

The patient lies in a prone position with her breast submerged, through a hole in treatment table, into the water filled applicator. The water bath, in which the temperature is controllable from 30 to 40°C, serves the purpose of skin sparing and provides an excellent coupling for ultrasound propagation.

Due to the considerable uncertainties in various tissue parameters (in particular the attenuation and perfusion rate), the use of relatively broad frequency-band transducers is a necessity. This is especially true for the low frequency transducers. The electronics is designed to be able to control the frequency, power and duty cycle in wide ranges for each transducer individually. This feature gives the system a great deal of flexibility to adapt to various treatment scenarios.

2.2. Simulation

Due to the complexity of the acoustic wave propagation and the bio-heat transfer process, it is desirable to have a comprehensive numerical model to verify the
Figure 1. The dual frequency, cylindrical transducer array mounted on a hyperthermia treatment table. Circulating water in the array is maintained at a constant, adjustable temperature (30–40°C).

Figure 2. The geometric model for the breast used in the simulation. The surface is assumed to be a paraboloid. H is the height, D is the diameter at the base, h is the depth beneath the chest wall (where the temperature is assumed constant at 37°C).

general concept and to guide the detailed design. The modeling efforts consist of three parts: the geometric model of the breast, the acoustic-field model, and the bio-heat transfer model. The geometric model is shown in Figure 2, where a paraboloidal surface with a height H and a diameter D on the base are assumed. Clinically relevant breast sizes, when submerged in water, were estimated from direct measurements as well as CT scans on patients positioned prone with the breast hanging freely in air. The parameter h shown in Figure 2 is a depth into the chest wall, where the temperature is assumed to be maintained at 37°C. The
Table 1. Parameters used in the model. Parameters D, H, h are indicated in Figure 2. The most-likely tissue parameters are based on the published values. A large breast size is used as the most-likely value.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Most-likely value</th>
<th>Range studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenuation in breast</td>
<td>0.086 ( (f^{1.5} \text{np cm}^{-1}) ) ( (\text{Foster et al. 1979}) )</td>
<td>0.052–0.12</td>
</tr>
<tr>
<td>Attenuation in water</td>
<td>0.0002 ( (f^2 \text{np cm}^{-1}) ) ( (\text{Kaye 1973}) )</td>
<td></td>
</tr>
<tr>
<td>Conductivity in breast</td>
<td>0.5 ( (W \text{m}^{-1} \text{K}^{-1}) ) ( (\text{Bowman 1981}) )</td>
<td>0.3–0.8</td>
</tr>
<tr>
<td>Heat Capacity for unit volume</td>
<td>3000 ( (J \text{Kg}^{-1} \text{K}^{-1}) )</td>
<td>3000–3500</td>
</tr>
<tr>
<td>Perfusion rate constant in breast</td>
<td>0.52 (at 37°C) ( (W \text{m}^{-1} \text{K}^{-1}) )</td>
<td>0.52–1.7</td>
</tr>
<tr>
<td></td>
<td>1.7 (at 44°C) ( (W \text{m}^{-1} \text{K}^{-1}) )</td>
<td>1.7–3.4</td>
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<tr>
<td></td>
<td>( (\text{kg m}^{-3} \text{s}^{-1}) )</td>
<td></td>
</tr>
<tr>
<td>( T_{\text{water}} )</td>
<td>37°C</td>
<td>30–40°C</td>
</tr>
<tr>
<td>D</td>
<td>15.3 (cm)</td>
<td>10.2, 15.3</td>
</tr>
<tr>
<td>H</td>
<td>7.8 (cm)</td>
<td>5.2, 7.8</td>
</tr>
<tr>
<td>h</td>
<td>7.5 mm</td>
<td>0–12</td>
</tr>
</tbody>
</table>

most-likely values of these and other parameters, as well as the range being studied, are listed in Table 1.

An efficient and accurate numerical method for acoustic field calculation in a homogeneous medium generated by a rectangular plane source has been reported (Ocheltree and Frizzell 1989). In this method, the plane source is divided into small rectangular elements, surrounded by a rigid baffle. The method sums the contributions to the pressure at a point from all elements. This method can be extended to a two-layer medium, such as water-tissue or tissue-tissue, if the density (\( \rho \)) and the speed of sound (\( c \)) in the two layers are close so that the reflection and refraction at the interface of the two materials can be ignored (Lu et al. 1995). In the case of water and breast tissue, the density and speed are 1000 Kgm\(^{-3}\) and 1519 m sec\(^{-1}\) at 35°C (Kaye and Laby 1973) for the former, 1020 ± 40 Kgm\(^{-3}\) (Duck 1990) and 1553 ± 35 m sec\(^{-1}\) (Scherzinger et al. 1989) for the latter. Therefore, the effect at the interface can be neglected. For a uniformly excited rectangular plane source, the sound pressure amplitude \( P_0 \) at a point inside the breast can then be calculated by:

\[
P_0 = \frac{j \rho c \Delta A}{\lambda} \sum_{n=1}^{N} \left[ \frac{u}{R} \cdot e^{-(\alpha_w r_w + \alpha_b r_b + jkr_w + jkr_b)} \right] \times \text{sinc} \left( \frac{kx'_n \Delta h}{2(r_w + r_b)} \right) \cdot \text{sinc} \left( \frac{ky'_n \Delta w}{2(r_w + r_b)} \right)
\]

where \( \rho \) is the density, \( c \) is the phase velocity of the sound waves, \( u \) is the velocity amplitude of the plane source, \( \lambda \) is the wavelength, \( k \) is the wave number, \( \Delta A = \Delta h \cdot \Delta w \) is the element size, \( x'_n \) and \( y'_n \) are the coordinates of the field point with respect to the centre of the element \( n \), \( \alpha_w \) and \( \alpha_b \) are the attenuation coefficient in water and breast, \( r_w \) and \( r_b \) are the propagation distances within water and breast.
The size of $\Delta w$ and $\Delta h$ must be small enough to satisfy the conditions for the applicable far-field approximations. The distance between the transducer and the breast is approximately 5 cm in the applicator, which leads to a condition that the element size should be 1 mm or less (Lu et al. 1995). In this calculation a size of 1 mm is used.

The power deposition (PD), i.e. the power absorbed per unit volume in the breast, can be calculated from the acoustical pressure amplitude $P_0$ at a point:

$$PD = \frac{\alpha_b P_0^3}{\rho c},$$

where the attenuation coefficient $\alpha_b$ is used, assuming that the majority of the attenuated power is absorbed locally.

The PD value is calculated at the centre of each voxel in the breast. A voxel size of $2 \times 2 \times 2$ mm$^3$ is used for the smaller breast size, and $3 \times 3 \times 3$ mm$^3$ for the larger breast size (Table I). To reduce the number of calculations, only the voxels within 2 cm of the plane passing through the centres of the transducers in the ring are calculated. Beyond this region the PD value is negligible. Since these calculations are very CPU intensive, they are performed only once for each configuration. Power deposition patterns from each transducer are normalized to 1 W applied acoustic power and stored in a data base. In the thermal calculation, these data can be retrieved and the actual absorption pattern from each transducer can be determined once the total deposited power by the transducer is assigned. The total PD at a field point is the arithmetic sum of the contributions by all the transducers. This simple arithmetic relation is possible due to the fact that there is no phase coherence or interference between the transducers as discussed in the previous section.

The standard bio-heat transfer equation (Pennes 1948) is used for the thermal model. Usefulness and limitations of this model have been discussed by several authors (Chen 1980, Eberhart et al. 1980, Bowman 1982, Roemer 1988). A main concern of this model is the methodology for handling the effect of the blood flow. In contrast to the thermal conduction process, the effect of blood flow is neither well understood nor mathematically rigorously characterized. Given the complexity and variability of the blood flow patterns, it is understandable that a simple linear perfusion term in the model is a gross simplification of reality. On the other hand, this equation is still the practically operational formula, and has been successfully applied in many cases (Cravalho et al. 1980, Dickinson 1984, Roemer et al. 1984, Strohbehn and Roemer 1984). Particularly, in the absence of large vessels and when perfusion is not the dominating factor, this formula predicts well the temperature elevation produced by acoustic or electromagnetic fields. For convenience, this bio-heat transfer equation is written as follows (NCRP 1992):

$$\frac{\partial T}{\partial t} = \left(\frac{K}{c_v}\right) \nabla^2 T - \left(\frac{T - T_0}{\tau}\right) + \frac{q_v}{c_v},$$

and

$$\tau = \rho_b c_v \left(\omega_{st} c_{ib}\right)^{-1},$$

where $T$ is the temperature, $t$ is the time, $K$ is the thermal conductivity, $T_0$ is body temperature ($37^\circ$C), $c_v$ and $c_{ib}$ are the heat capacity per unit volume of tissue and blood, respectively, $\tau$ is the perfusion time constant, $\omega_{st}$ is the perfusion rate constant, and $q_v$ is the heat production rate per unit volume. In the case of ultrasound heating $q_v$ is the value of PD calculated Formula (2). The heat production due to metabolism is relatively small, and therefore ignored.
The finite difference method is used in the 3-D numerical treatment of the partial differential equation (Ames 1977, Press et al. 1985). This method provides a great deal of flexibility in dealing with different geometries, boundary and initial conditions. Once these conditions are clearly defined and the PD in each voxel is given, the temperature evolution for a whole treatment session, i.e. the temperature distribution in each voxel as a function of time, can be calculated. The voxels in this calculation are the same as those defined for the PD calculation. The choice of their size is a compromise between an acceptable accuracy and a reasonable CPU time required. A time step of 3 s is used, which satisfies the requirement of the stability criterion (Ames 1977). In this approach the PD values, boundary conditions and tissue parameters, all can be assigned as functions of time and position. Therefore, a realistic hyperthermia treatment can be simulated.

The breast tissue parameters listed in Table 1 are based on published data wherever available. To date very little perfusion data for breast are available. A recent report based on seven hyperthermia treatments by use of a modified thermal clearance technique (Waterman and Kramer 1994) indicates that blood flow can be in a range from $<0.3 \text{ kg m}^{-3} \text{s}^{-1}$ in the first treatment to $1.3 \text{ kg m}^{-3} \text{s}^{-1}$ in the later treatment. These data are consistent with the fact that there are no large blood vessels in breast, and that the breast tissue has a high content of adipose tissue, which would tend to reduce the perfusion rate. The perfusion in breast is, therefore, likely similar to or less than that of resting skeletal muscle. The perfusion rate constant for anterior thigh and forearm have been measured as $0.48 \text{ kg m}^{-3} \text{s}^{-1}$ and $0.59 \text{ kg m}^{-3} \text{s}^{-1}$, respectively (Sekins and Emery 1982). Thus, the perfusion rate constant for breast is assumed to be about $0.52 \text{ kg m}^{-3} \text{s}^{-1}$, but could be as high as $1.7 \text{ kg m}^{-3} \text{s}^{-1}$. It was further assumed that when the temperature is elevated to $44^\circ C$, the perfusion rate may linearly increase by a factor of two. Even at this higher value, the perfusion rate is still relatively low compared to other organs. Consequently, the standard bio-heat transfer equation can be used and reliable results can be expected.

The initial temperature inside the breast is assumed to be $37^\circ C$ uniformly. Near the surface, the actual initial temperature may be lower than this value. However, this initial uncertainty causes no concern, since it has little effect on the temperature distribution after several minutes of heating. Water temperature is adjustable between 30 and $40^\circ C$. It is assumed that the voxels in the superficial breast adjacent to water are kept at this temperature. When the water is well circulated, this is a practical and very reasonable approximation. For the boundary condition below the chest wall, which is outside the ultrasound field, it is assumed that the temperature is maintained at $37^\circ C$ at a depth $h$.

The simulation is performed with the parameter values listed in Table 1. In all simulated cases the acoustic power from each transducer is adjusted manually by the operator according to the temperature feedback until the resulting temperature elevation is satisfied. The two frequencies were optimized by the simulation. The low frequency was determined to be 2 MHz in the first two rings and 2.5 MHz elsewhere. The high frequency was determined to be $\sim 4.5 \text{ MHz}$. The results obtained using these frequencies are presented in § 3.

2.3. Experiment

Experiments have been conducted using a single ring of transducers. The main purpose of the experiment was to verify the power deposition calculations. Another
purpose is to verify that the transducers are driven non-coherently with the designed electronics.

This transducer ring has 48 transducers operated alternately at low (2.0 MHz) and high (4.5 MHz) frequency. The electronic system used to drive the test ring has six amplifiers, each having its own oscillator (Figure 3A). The output of one amplifier is connected to eight transducers through a multiplexer. Consequently, the transducer ring is divided into eight groups, each consisting of six transducers.

In this experiment, each transducer group is powered for a duration of 55 m sec in a sequential manner. Consequently, one complete cycle is $8 \times 55 \text{ m sec} = 440 \text{ m sec}$, which is less than the time constant relevant to thermal processes (such as $\tau$). The insonation can therefore be treated as if the transducers are turned on continuously with a temporally averaged power.

The ultrasonic tissue-mimicking phantom consists of water-based pharmaceutical gels containing uniform distributions of graphite powder and alcohol (Madsen et al. 1978). The phantom, which has a diameter of 13 cm at the base and a height of 8 cm, is immersed in water and surrounded by the transducer ring. The base is covered by a 2 mm rubber sheet. The plane in the middle of the ring is 1.35 cm below the base.

Multisensor thermocouples, inserted into 20 gauge needles, were used for temperature measurement. These probes (Dickinson 1985, Hynynen and Edwards 1989) have a fast response time ($0.1 \text{ s}$) and minimal acoustic artifact. Three probes were inserted in the plane as shown in Figure 3 (B). The water temperature and room temperature were 24°C during the experiment.

As the first step of the experiment, the PDs, normalized to the total output power of all the amplifiers operating at the same frequency, are determined at each sensor point. It is calculated from the initial rate of the temperature change from a stable state, which can be derived from Formula (3) by ignoring the conductivity and perfusion term and written as:

$$ q_0 = \frac{q_0}{N} = \frac{c v}{\Delta t} / N, $$

where $q_0$ is denoted as the normalized PD at each sensor point, $N$ is the total output power by the amplifiers (2.5 W for 2 MHz transducers and 10 W for 4.5 MHz transducers in this experiment), $\Delta T$ is the temperature elevation at the sensor point in a small time interval $\Delta t$, which is between 1–11 s after the power is turned on. The measured temperature within the first second is ignored, so that the artifacts can be eliminated. Normalized PDs are determined separately for the low and high frequencies.

In the second step, the output powers to the high and low frequency transducers were adjusted manually until a uniform and pseudo-steady temperature distribution was reached in the plane ($\sim 6\text{C}$ above the baseline) and maintained. The total output power by the amplifiers to achieve the temperature distribution was found to be 1.9 W for the 2.0 MHz transducers and 15 W for the 4.5 MHz transducers.

These same experimental conditions were simulated by the methods discussed previously. The experimental results are compared to the simulations in §3 and discussed in §4.

3. Results

3.1. Simulation results

The most-likely values of ultrasound and tissue characteristics used in the simulation are listed in Table 1. They are closest to those found in the literature for
Figure 3. (A) The schematic diagram of the electronics used in the single ring experiment. Six RF generators, each consists of a voltage controlled oscillator (VCO) and an amplifiers, are connected to one of the octant of the 48 transducers for a duration of 55 m sec. The eight octants are powered alternately by the six generators. As a result, the ultrasound beams from different transducers are always out of phase. It also shows that the system can operate in transmit or receive mode. All these operations are under the control of a PC; (B) cross section coincident with the centres of transducers in the single ring experiment. The lines represent the positions of the probes. The dots represent the positions of the sensors.
Figure 4. PD distribution applied in the simulation. The most-likely parameter values in Table 1 are used: (A) sagittal section passing through the centre of the breast; (B) coronal section 25.5 mm from the chest wall, corresponding to the second transducer ring; (C) sagittal section passing through the centre of the breast due to the low frequency transducers; (D) sagittal section passing through the centre of the breast due to the high frequency transducers.
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Figure 4. Continued.

the appropriate frequency and tissue type. Simulations were performed over a range of ultrasound and tissue parameters, representing extreme tissue types, breast sizes, attenuation and perfusion conditions. We therefore can examine the ability of the treatment system to control the temperature distribution over a large range of conditions.

To simulate a typical treatment, the power level may be changed during the session. This is an important feature of the approach in this study. For simplicity in the presentation, however, we only show simulations in which the powers are constant. Figure 4 shows the steady PD distribution for the most-likely case. The total deposited power is about 42 W. Figure 4A is the sagital view passing through the centre of the breast. In this plot, five rings with higher PD can be seen, corresponding to the five transducer rings. Figure 4B is the coronal view at 25.5 mm from the chest wall coincident with the centre of the second transducer ring. For understanding the operating principles of the device, Figure 4C and D illustrate the power deposition patterns due to each frequency component. The contributions from each transducer is
Figure 5. Simulated temperature distribution 40 min after the steady PD shown in Figure 4 is applied. Maximum temperature is 44.0°C: (A) sagital section passing through the centre of the breast; (B) coronal section at 25.5 mm from the chest wall, corresponding to the second transducer ring. The corresponding temperature distributions after 40 min are also listed in Table 2. The corresponding temperature distributions after 40 min are shown in Figure 5A and B.

Figure 6 plots the temperature evolutions in the line passing through the centre of the sagital sections and in the horizontal diameter in the coronal plane. The
Table 2. The power deposition by each transducer required to maintain the steady state temperature distribution. Three cases are shown. ‘M.L. Value’ means the most-likely parameter values listed in Table 1. The power distribution for this case is also shown in Figure 5. ‘$T_{\text{water}} = 30^\circ \text{C}$’ indicates the circulating water temperature is changed to 30°C. ‘High Perfusion’ indicates the perfusion time constant is changed from 600 s at 37°C to 300 s at 44°C. All other parameters remain as the most-likely values.

<table>
<thead>
<tr>
<th>Ring</th>
<th>Frequency (MHz)</th>
<th>Number of transducers</th>
<th>Power deposition (W)/transducer</th>
<th>M.L. values</th>
<th>$T_{\text{water}} = 30^\circ \text{C}$</th>
<th>High perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>24</td>
<td>0.42</td>
<td>0.41</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>24</td>
<td>0.28</td>
<td>0.38</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>24</td>
<td>0.15</td>
<td>0.15</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>24</td>
<td>0.26</td>
<td>0.45</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>24</td>
<td>0.16</td>
<td>0.15</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>24</td>
<td>0.20</td>
<td>0.3</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>24</td>
<td>0.04</td>
<td>0.04</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>24</td>
<td>0.18</td>
<td>0.33</td>
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</tr>
<tr>
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<td>12</td>
<td>0.04</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>12</td>
<td>0.04</td>
<td>0.10</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>41.5</td>
<td>54.8</td>
<td>58.8</td>
<td></td>
</tr>
</tbody>
</table>

Figure 6. Simulated temperature distribution 10, 20, 40 min after the corresponding PD shown in Figure 6 is applied and the distribution 3 min after the power is off: (A) the distribution in a perpendicular line passing through the centre of the sagittal section; (B) the distribution in a perpendicular line passing through the centre of the coronal section.
temperature distributions 10, 20 and 40 min after the power is on, and the distribution 3 min after the power is off are plotted. Note that after 20 min, the temperature distribution is approaching steady state and becomes quite uniform. Also note that the distribution after power off becomes smooth.

The simulation parameters were changed to examine the effects of boundary conditions and perfusion rate on the computed temperature distribution. For a better understanding of the effects of these changes, only one parameter is varied at a time, and all other parameters remain as the most-likely values. In Table 2, the power contributions by each transducer for two more simulations are shown. In one case, the surrounding water temperature is kept at 30°C. In another case, the perfusion rate is increased. It is assumed that the perfusion rate is 1.7 kg m$^{-3}$ s$^{-1}$ at 37°C, and

Figure 7. Sagittal section passing through the centre of the breast for simulated temperature distribution 40 min after steady PD described in Table 2 is applied (A) water temperature is changed to 30°C. Other parameters remain as the most-likely values in Table 1; (B) a high perfusion rate is used (600 s at 37°C and 300 s at 44°C). Other parameters remain as the most-likely values in Table 1.
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One particular clinical concern, that has been raised for recurrent breast cancer treatment, is for scar tissue resulting from lumpectomy or other surgical interventions. Scar tissue has poor blood supply and very low perfusion rate and, therefore, tends to be overheated. Such overheating can create undesirable treatment toxicity and one goal of this design is to have adequate temperature control to avoid such toxicities. To study this problem, different sizes of biopsy cavities determined by CT scans were examined. These cases included a biopsy cavity of the size of \(12 \times 60 \times 80 \text{ mm}^3\) which was added to the theoretical model. It was assumed that the biopsy volume had no perfusion and that the attenuation range and other parameters remain the same. Obviously, hot spots will occur in this region unless the heating pattern is changed accordingly. This hot region is shown in Figure 8A where the lumpectomy volume exists by the same power level as in Figure 4 is applied, and the maximum temperature reaches 45.3°C. To prevent this overheating of the scar and lumpectomy volume, the breast treatment applicator must have enough control capacity to reduce the power deposition locally in the biopsy scar cavity. This is shown in Figure 8B where a satisfactory temperature distribution is achieved when corrected PD is applied, and the maximum temperature is 44.0°C.

To treat a quadrant of the breast, the boundaries inside the breast need to be sufficiently heated, in addition to the quadrant of the surface and the base. Figure 9 demonstrates the PD pattern from the breast applicator needed to satisfy that requirement. The corresponding steady state temperature distribution is shown in Figure 10.

3.2. Experimental results

The measured pseudo-steady state temperature distribution is plotted in Figure 11. To determine the corresponding power deposition in each sensor point, the normalized PD \(q_0\), deduced by Equation (4), is multiplied by the total steady power output (i.e. 1.9 W for 2.0 MHz and 15 W for 4.5 MHz). This was performed separately for high and low frequencies, and their results were added together. This gives the measured constant power deposition which is shown in Figure 12.

The power deposition was simulated by the acoustic model. The total absorbed powers for the low and high frequencies in the simulation were adjusted such that the calculated PD values in the sensor points match reasonably well with the measurement as shown in Figure 12. Based upon this calculated PD, the pseudo-steady state temperature distribution in the whole phantom is calculated. The result 20 min after the steady power was 'turned on' in the simulation is shown. The computed temperature distribution in the sensor positions is superimposed into the experimental data in Figure 11.

The total absorbed power used in the simulation is 0.84 and 7.9 W for the low and high frequency transducers, respectively. These values are lower than the measured total output powers of the amplifiers (1.9 and 15 W for low and high frequency respectively). This difference is expected due to the losses in the cables and transducers.
4. Discussion

In this paper we have reported the general design and the simulation models for the ultrasound applicator for intact breast treatment. The simulations demonstrated that a combination of low and high frequencies is capable of delivering appropriate power deposition to the boundaries and interior of the breast as shown in Figures 4–10. This capability is enhanced by the small transducer size and the separate power control for each transducer. As a result, the heat losses due to conduction and perfusion can be properly compensated, and a uniform temperature distribution can be achieved and maintained.

The different roles of the high and low frequency transducers for maintaining uniform temperature can be clearly seen by comparing the data in Table 2, where the power deposition per transducer with low and high frequencies are listed for three cases. When the circulating water temperature is changed from 37 to 30°C, the power of the high frequency source has to be increased by more than 30% to compensate the increased heat losses to the water. Meanwhile, the low frequency power remains the same, because the perfusion rate did not change. On the other hand, when the perfusion rate is high but the water temperature remains at 37°C, the power at the low frequency has to be increased significantly to overcome the higher perfusion, while only a slight power change is needed at high frequency.

It has been demonstrated that a target area from a quadrant to a whole breast can be treated satisfactorily. The application of the treatment system, however, is not limited to these examples. By combining Figures 5 and 7A, it is clear that a smaller target volume in the centre can be heated by using low water temperature and/or reduced high frequency power. Meanwhile, the technique for heating a quadrant may be used for a smaller arc. By combining the centre area and one or more arcs, treatment of non-symmetric tumours is also possible. Furthermore, in this paper results only for a large size breast are shown. Better results were found for a smaller breast, because a more uniform power deposition can be obtained for a smaller size breast, where the conduction effect becomes more pronounced.

Since individual transducer rings are stacked together, the power deposited to a given plane is delivered predominantly from the ring that defines the plane. As a result, in the first order of approximation the temperature in a plane can be adjusted by the corresponding ring of transducers. The lack of significant interaction between adjacent rings simplifies the power control.

The simulation is a useful tool for the design of a hyperthermia system of this complexity. However, the results are based on certain assumptions and may be of limited predictive value for individual patients due to uncertainties in the breast tissue characteristics. To better understand the magnitude of these uncertainties the tissue and ultrasound parameters have been varied over a large range of values covering both assumed extremes and published data (Table 1). The purpose of studying the effect of parameter uncertainties on the system performance is to demonstrate that the power frequency control of the breast applicator has enough range to accommodate different clinical situations and individual breast tissue variations.

Figure 8. Sagittal section of simulated temperature distribution 40 min after power is 'on'. It is assumed that there is no perfusion in a volume indicated by the dash lines \((12 \times 60 \times 80 \text{mm}^3)\). (A) The steady PD, shown in Figure 4, is applied. The maximum temperature is 45.3°C; (B) after corrected PD is applied, the maximum temperature is 44.0°C.
Figure 9. Steady PD distribution to treat a quadrant of the breast. The most-likely parameter values in the Table 1 are used: (A) sagittal section passing through the centre of the breast; (B) coronal section at 25.5 mm from the chest wall, corresponding to the second transducer ring.

The transducer frequencies are determined by the simulation in order to achieve the heating pattern discussed in §2.1. for the assumed tissue attenuation rate. Measurements of the acoustic attenuation coefficient for breast tissue show variations of ±40% (Foster and Hunt 1979, Edmonds et al. 1991), which can only be
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Figure 10. Temperature distribution 40 min after the steady PD, shown in Figure 9, is applied: (A) sagital section passing through the centre of the breast; (B) coronal section at 25.5 mm from the chest wall, corresponding to the second transducer ring.

compensated by changing the frequency. For a higher attenuation, a lower frequency should be used, and vise versa. Therefore, a broadband transducer is needed, especially for the low frequency. The bandwidth of the transducers is about 30% at -3 dB of maximum. The voltage controlled oscillators (VCO) in the system can operate between 1 MHz and 5 MHz, and the desired frequency band can be selected.
by computer control. With these features, the system will be able to compensate for the uncertainties.

The effect of blood perfusion is a difficult parameter to simulate. Only limited data are available and it varies significantly with tissue heterogeneity and changing temperature. Recently reported blood flow data, measured at the same point in a human breast adenocarcinoma during hyperthermia over four weeks of hyperthermia, indicate that the flow rate may change significantly even in the same measurement point (Waterman and Kramer 1994). The uncertainties in the breast tissue perfusion, therefore, remains a main concern. Due to these uncertainties, we simulated the breast applicator over a wide range of temperature dependent perfusion rates. In the case of high perfusion rate (Figure 7(B)), it is noticed that the 42°C line is well up into the region being 'treated'. This is due to the fact that the transducers are focused at the centre. A relatively hot spot is found in the centre and a cooler area is between the centre and surface. To correct the problem, the applicator may be translated a few centimeters away from the centre of the breast, and a circular movement made around it. The inhomogeneity of the perfusion in the breast is another clinical concern. The biopsy example shown in Figure 8 demonstrated that the small transducer size and the individual power control made a compensation...
possible, given that the nature of the inhomogeneity is known.

The simulation used in this work is dynamic. The tissue parameters can be changed over time and the power deposited by each transducer can be adjusted based upon the feedback of the temperature distribution. When the time to reach steady state temperature is considerable (i.e. 10 min or more) or when other factors such as perfusion are known to vary as a function of temperature and time, the dynamic simulation allows one to study realistic temperature variations. Important parameters highly associated with the outcome of the treatment, such as the $EQ MIN T_x$ 43 (Oleson et al. 1993), can be estimated.

The single ring experiment was mainly used to verify the power deposition calculation method. Several factors contributed to the uncertainties in the experiment. First, the sensor positions are not known exactly due to bending of the needle probes. The uncertainty is estimated to be $\leq 1$ cm at the tip of the probes. The second source of uncertainty is from non-uniformity in the transducer efficiency. The average efficiencies (RF to ultrasound field) for the transducers are determined to be $70 \pm 3\%$ for low frequency and $58 \pm 10\%$ for high frequency transducers. Furthermore, inhomogeneities can occur in the phantom material due to evaporation of water and alcohol. In the simulations, however, it was assumed that all transducers
were identical and the phantom was homogeneous. Given these uncertainties, the agreement between the experimental data and the simulations (Figure 12) is fair. A reasonable uniform temperature distribution (within approximately 2°C) was indeed reached in the experiment and it matches the simulation results well (Figure 11). The function of the low frequency in the experiment is only to compensate the heat lost to the neighbouring tissue volume. As a result, the power needed at low frequency was small (0.84 W), compared with that at high frequency (7-9 W). Therefore, this is a useful check for the two-frequency concept discussed in § 2.1.

One important assumption in the design and simulation is that there is no phase interference between different beams. This is achieved by an electronics design that prevents any two beams from being in-phase, while keeping the number of oscillators and amplifiers moderate. The single ring experiment with associated electronics proved that the electronics design is appropriate in this respect. No unexpected hot spots were observed. For the multi-ring applicator the circuits for any two neighbouring rings are independent, which guarantees the validity of the assumption.

The choice of grid size in the simulation has been carefully studied. We used 2 mm for a small size model and 3 mm for a large size model. The total number of voxels used is $53 \times 53 \times 30$ in both cases. The PD calculation is more CPU intensive than the thermal computation. When the breast is assumed to be symmetric, the CPU time needed for PD calculation is greatly reduced. It takes about 20 min for five transducer rings on a dedicated work station HP 9000/735. For thermal calculation, it takes about 5 min to simulate a complete treatment session (~50 min). Using a smaller grid size has proven not to be beneficial, because reducing the grid size by a factor of two requires CPU time increase by a factor of $2^4$ in the thermal calculation and $2^3$ in the PD calculation, while the difference in the resulting temperature distribution is insignificant.

The use of the minimally temperature invasive sensors, currently being developed (Szajda et al. 1994), will be more tolerable to patients due to its small size (22 gauge). Still, the number of probes will be limited to, perhaps, three in a patient. Therefore, the arrangement of these probes needs to be optimized. To facilitate treatment planning and control, knowledge of the breast profile is essential. This may be obtained on-line by employing pulse-echo signals using the same transducers. Two operating modes (transmit and receive) have been built into the system electronics for this purpose. It may also be possible to use the methods and algorithms being developed for on-line control in the treatment (Hartov et al. 1993, VanBaren and Ebbini 1995). All of these require further study.

5. Conclusions
A therapeutic ultrasound system dedicated to breast cancer treatment has been developed. It consists of an array of dual frequency, multilayer transducer rings and associated electronics, coupled with thermometry and closed-loop control. Its performance has been modelled and optimized using a comprehensive 3-D simulation, which offers insights in the physical process and the design criteria. The simulations demonstrate the system's capability to deliver a power deposition to achieve uniform hyperthermia (41.5-44°C) under various perfusion and boundary conditions. The two frequency bands and the small size transducers provide a flexibility for treating target volumes with different sizes and shapes. With these
Design of an ultrasonic therapy system for breast cancer treatment

features the designed system is able to meet clinical needs in breast cancer treatment.

6. Acknowledgement

This work is supported by the US Army Medical Research and Development Command, under contract #DAMD 17-93-C-3098. The views, opinions and/or findings contained in this paper are those of the authors and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation. The authors would like to thank H. F. Bowman, W. H. Newman of MIT, R. X. Huang of Woods Hole Oceanographic Institution, and P. Neubauer, P. Barthe, M. H. Slayton of Dornier-AI for many helpful discussions, and Jamie Pellegati for his technical support.

References


Design of an ultrasonic therapy system for breast cancer treatment


EXPERIMENTAL VERIFICATION OF A CYLINDRICAL MULTI-TRANSDUCER ULTRASOUND BREAST HYPERTERMIA TREATMENT SYSTEM.


Joint Center for Radiation Therapy, Department of Radiation Oncology, Harvard Medical School, Boston, MA, USA, and *Dornier Medical Systems Inc. Champaign, IL, USA

1. Introduction
The use of limited surgery and radiation therapy for early stage breast cancer achieves breast conservation with excellent results and relatively low rates of local tumor recurrence. However, a subgroup of patients with Ductal Carcinoma in Situ (DCIS) has shown increased rates of local recurrence when treated with breast conservation. DCIS generally has a large number of hypoxic cells which has proven to respond well to hyperthermia. In addition, the female breast is very well suited to treatment with ultrasound hyperthermia due to the lack of air cavities or bony structures within the breast. For these reasons we decided to develop an ultrasound hyperthermia Breast Therapy System (BTS) dedicated to treatment of the female breast.

2. Material & Methods
A schematic drawing of the BTS is shown in figure 1. The patient is placed prone on a padded treatment couch, with the breast to be treated, extended through an opening in the tabletop. A cylindrical transducer array applicator is mounted on a three-dimensional translation table underneath the table opening. The applicator is filled with degassed water, brought up under, and centered around the breast. A six probe, 84 sensors thermistor based thermometry system is used to monitor the temperature distribution during therapy. The system is computer controlled and displays temperatures and thermal dose, as a function of time, in three dimensions. The breast contour is monitored and displayed in real time throughout the treatment to ensure accurate geometric alignment of the applicator.

To achieve accurate and flexible control of the power deposition in the breast tissue, the applicator consists of 384 ultrasound transducers, each 15 x 15 mm, mounted on the inner surface of a 25 cm diameter cylinder. Alternate transducers are optimized at a low frequency of 2.5 MHz and a high frequency of 4.0 - 4.5 MHz. The low frequency transducers are depositing energy at depth in the breast, and the high frequency transducers deposit energy superficially and thereby compensate for thermal conduction to the ultrasound coupling medium. The system is designed to heat individual quadrants or the whole breast to a uniform temperature between 40 and 42 °C. The BTS is further discussed by E.C. Burdette et. al. in “Real-Time Computer Controlled Ultrasound Therapy and Monitoring System for Breast Cancer Treatment”.

The system has been developed and is being extensively tested on non-perfused tissue mimicking breast phantoms. Several phantoms have been manufactured using the plastic ‘skin’ of ultrasound guided biopsy breast phantoms manufactured by RMI (Middleton, WI) as a mold. The mold was filled with a liquid solution of 83% distilled degassed water, 3% agar, 8% n-Propanol, and 6% graphite powder (all by weight). The mold was set to solidify and 3 temperature probes, each
containing 14 temperature sensors, were inserted in the phantom. The phantom was positioned in the transducer array, and the cylinder was filled with degassed coupling water (see figure 2).

The phantom was insonated for short duration's of 20-30 seconds, each time heating individual sectors or the whole breast phantom. The initial temperature rise (compensated for thermal artifacts) was evaluated, and the ultrasound power deposition patterns along the temperature probes were deduced from the expression \( \text{SAR} = \frac{\Delta T}{\Delta t} / c \), where \( \text{SAR} \) = specific absorption rate, \( \Delta T/\Delta t \) = the temperature rise per unit time, and the specific heat of the phantom material \( c = 3.26 \, \text{J/g} \, ^\circ\text{C} \). As a first approximation thermal conduction was ignored due to low thermal gradients during the initiation of the experiments.

3. Results

Predicting the temperature field in a blood perfused breast from the measurements in a non-perfused phantom is very complex. For this reason we decided to investigate the power deposition patterns in the phantom. Computer models indicates that, to produce a uniform temperature distribution, initially a uniform SAR distribution is required. However, after therapeutic temperatures have been reached, the power delivered to the core of the breast has to be decreased to prevent overheating. Therefore, the measurements were performed in 3 steps: 1) the low frequency transducers were engaged to quantify the power deposition at the core; 2) the high frequency transducers were engaged to quantify the power deposition at the surface; 3) both low and high frequency transducers were engaged and adjusted to create a variable power deposition profile over the extend of the breast phantom. All measurements were repeated for all sectors and the whole breast.

Figure 3 shows the SAR profiles at the base of the breast, where the breast diameter is 12 cm and figure 4 the profiles close to the apex of the breast, where the diameter is 6.5 cm. Computer modeling of the BTS by Lu et al. indicated, that after reaching temperature equilibrium, a power ratio of 8 high frequency units to 1 low frequency unit is required to produce a uniform temperature field. Figure 5 shows the measured SAR profiles at the base of the breast as well as the computer model for this power ratio. The agreement between theoretical calculations and experimental results is excellent.

Figure 1. Schematic drawing of the Breast Therapy System. The transducer array is mounted on a 3 dimensional adjustable table allowing fine positioning of the array after the patient is placed in treatment position.

Figure 2. Schematic drawing of the BTS applicator showing the transducer array in 8 rings, the breast phantom placed in the array, and the location of the temperature probes in the phantom.
Figure 3. SAR profile through the center and close to the base of the breast where the diameter is 12 cm. The solid line indicates the SAR profile for the high frequency transducers at 8% of full power, and the broken line the SAR profile for the low frequency transducers at 8% of full power.

Figure 4. SAR profile through the center and close to the apex of the breast where the diameter is 6.5 cm. The solid line indicates the SAR profile for the high frequency transducers, and the broken line the SAR profile for the low frequency transducers.

Figure 5. SAR profiles through the breast phantom close to the base. The solid line shows the results of a theoretical calculation using a computer model of the BTS. In this calculation the power of the high frequency transducers were 8 times the power of the low frequency transducers. The symbols show the phantom measurements as shown in figure 3 using the same power ratios as the computer model.

4. Conclusion
We have demonstrated, that the BTS can deposit uniform ultrasound power throughout the core of a female breast, and that the BTS can deliver power to the surface of the breast to compensate for thermal conduction to the ultrasound coupling medium without overheating the core of the breast. We feel confident, that the BTS will be able to raise the breast target volume temperature to 40-42 °C with relative uniformity, and maintain this temperature.

Supported in part by US Army Research and Material Command contract # DAMD-93-C-3098.

REAL-TIME COMPUTER CONTROLLED ULTRASOUND THERAPY AND MONITORING SYSTEM FOR BREAST CANCER TREATMENT


Dornier Medical Systems, Inc. Champaign, IL, USA and Joint Center for Radiation Therapy, Department of Radiation Oncology, Harvard Medical School, Boston, MA, USA*

Introduction
Conservative breast therapy for early stage infiltrating breast cancer consists of lumpectomy and radiation therapy. However, patients with extensive intraductal component (EIC) of tumor or patients with Ductal Carcinoma In Situ (DCIS) have shown increased rates of local recurrence when treated with conservative therapy. EIC+ patients currently face mastectomy as the recommended treatment course. DCIS and EIC+ have a large fraction of hypoxic cells which have been shown to be vulnerable to heat and therefore, patients with intraductal disease may benefit from thermal therapy to the whole breast or to a quadrant of the breast.

System Description
An ultrasound Breast Therapy System (BTS) has been designed for the treatment of the intact breast. The system incorporates both therapeutic and imaging capabilities utilizing a cylindrical array applicator which surrounds the breast with the patient in a prone position. The cylindrical transducer array consists of eight “rings” of transducers surrounding the breast. The transducers are operated in a time-multiplexed mode to provide both therapy and monitoring functions in real time. Each ring has 48 transducers operating in alternating low (2-2.5 MHz) and in high (4.5-5 MHz) frequency bands.

The patient will lay on the top of the system with the breast descending through a hole in the table. Needle probes are inserted under local anesthesia. These probes contain thermistors for temperature measurements and ultrasonic receiver chips to help locate the probes. Thermistors are also taped to the breast surface. The cylindrical array applicator, filled with water, is then brought up under the breast and positioned with the aid of a motor to raise and lower the cylinder, x and y vernier controls and a rotational vernier control. A small video camera mounted at the bottom of the cylinder is used to monitor the position.
Ultrasound hyperthermia

The system controls the water bath temperature as patient information and a treatment plan are entered. After this step, the system begins to acquire data from the temperature probes and from ultrasonic measurements in order to form a temperature map of the breast. Once an initial map is produced, therapy can begin. The operator initiates therapy and the system begins to apply therapy heating power while continuing to maintain a temperature map, thermal dose map, and ultrasonic power levels map. All necessary information is logged while therapy is in progress. At the end of the therapy period, the system continues to monitor conditions while the breast returns to normal temperature levels.

3. Data Acquisition
The major task of the system is to provide ultrasonic power to the entire breast or to a portion of the breast in order to produce a desired temperature profile. The temperature range and affected areas must, therefore, be controlled very closely. In order to accomplish this, it is necessary to have good information about the target. Breast location, probe positions, and temperature and thermal dosimetry are monitored throughout treatment.

A contour of the breast is determined by echo-location where each transducer is used to transmit and then receive its own transmission. The time-of-flight gives us the breast outline and detects any motion of the breast.

The system checks the temperature probes' location by using ultrasonic time-of-flight from a ring transducer through the receiving transducers in each probe. Multiple measurements are made for each sensor so that its position may be triangulated. Since the probes are embedded in the breast, the calculation of the distance becomes complex due to the different ultrasonic velocities through the water and breast.

The temperature within the breast is known due to direct measurement by as many as 5 probes each having 14 sensors. The temperature at other points in the breast must be calculated by interpolation with a thermal model. Thermistor temperature acquisition techniques are used to monitor the temperature of the water bath and of the interior and exterior of the breast.

The system is also equipped to provide imaging of the breast as well through tomographic reconstruction of measured ultrasound attenuation. This will allow the operator to position the patient based on internal as well as external alignment points giving more precise control of the treatment.

Control Algorithms
The control of the water bath temperature is accomplished by a proportional-integral-derivative (PID) control loop algorithm. The breast therapy control algorithm, however, is significantly more complicated. There are 384 effectors (the ultrasonic transducers) plus the water bath. There are also two frequency bands of transducers. High frequency transducers have a greater effect on temperatures close to the surface of the breast and the low frequency transducers effect temperatures nearer the center. The algorithm controls the temperature of an active therapy section of the breast (1, 2, 3, 4 or 8 octants) and any specified "exclusion region" corresponding potentially to scar tissue. PID techniques in conjunction with a "thermal wall" heuristic is the first order control. The exclusion region conforms to the shape of a small grouping of transducers.
Safety and Fault-Detection

It is very important not to expose tissue to too high a temperature or to too large a thermal dose. Three techniques are used in combination to ensure these safety requirements. First, watchdog timers are used to indicate to the other compute elements that no fault has occurred. These timers are used inside of the multitasking compute elements to indicate that each task is functioning properly. Secondly, the mechanism of a "system mode" is introduced as a safety interlock. The "system mode" provides a check on the system's operation by only allowing operations to occur within the proper system modes. In this manner, rogue commands for action by an out of control task will not be acted upon as will cause the system to treat this rogue command as a fault. Lastly, a coding style that double checks its own operation and the operation of other software modules is used.

Computer System

The computing system consists of a Pentium PC and an 80486 PC both running the iRMX real-time operating system and 26 specialized boards containing 80166 microcontrollers running their application with simple loop schedulers. The Pentium PC runs Microsoft DOS as a task under iRMX which is used to run Microsoft Windows and the specialized system interaction application. This application gives operators a window into the system and allows data entry and control over system operations. The iRMX networking facilities are used to provide a virtual circuit connection between the machines and to delineate application level packets. A proprietary high-speed serial bus is used to allow communications between the 80486 PC and the 80166 microcontrollers. A master-slave protocol is used in accordance with the synchronous nature of the application -- waiting for commands to the microcontrollers to be fulfilled before it can move on.

System Hardware

The system is modular in design, with 24 circuit cards each supporting 16 individual transducers. A microcontroller on each card controls the functions, including transmit-receive switches, transmitter-amplifiers and receiver. The system uses a built-in frequency measuring capability to fine tune what control voltage needs to be used for each transducer. Each card communicates with the host instrument computer system via high-speed links. The instrument computer oversees the function of all cards plus three specialized cards in the system: one with receivers for transponder crystals located within temperature probes and two for precision phase quadrature measurements. These signals are routed to the other boards through a buffer board designed for flat group delay. The Pulse card uses its counter-timer capabilities to produce the duty-cycle modulated signal that controls a thermoelectric heater/cooler for the water bath temperature control. Finally, the card can be used to generate an arbitrary phase signal for calibration purposes. The above components, including the instrument computer, power supplies, and water circulation and heating/cooling system are located within a patient treatment table pedestal which supports the patient table.

Acknowledgment

This work is supported by the U.S. Army Medical Research and Materiale Command, under contract DAMD17--93-C-3098. Views, opinions and/or findings contained in this paper are those of the authors and should not be construed as an official Dept. of the Army position, policy or decision unless so designated by other documentation.
The ultrasound Breast Therapy System is labeled with the following information:

Currently the stand of the BTS is labeled with a 'Caution’ label limiting the use of the device to laboratory animal and testing experiments only.
When an IDE for the BTS device has been awarded, the ‘Caution’ label will be replaced with a label limiting the use of the device to ‘Investigational’ use only.
The applicator can be positioned exactly around the breast to be treated by a number of controls. These controls are labeled "Speed", "Rotation", "B+F", "L+R", and "Up/Down". In addition, a camera is placed in the applicator to visually verify the position of the breast. A brightens control for illumination of the breast is labeled "Intensity".
An indicator box with a number of light emitting diodes. These diodes light up whenever any of the 24 power boards are emitting power. The diodes are marked “Hi” for high frequency boards and “Lo” for low frequency boards.

The same box contains an indicator for the temperature control of the degassed coupling water labeled “Red-Heater” and “Green-Cooler”, and a switch labeled “Pause”. The pause switch, when depressed, will remove all power from all power boards bypassing of all computers and software.
Appendix E

Operators Manual
ULTRASOUND BREAST THERAPY SYSTEM (BTS) MANUAL

Version 1.0
15 November 1996
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I. INTENDED APPLICATION OF THE BREAST THERAPY SYSTEM

Breast cancer patients with extensive intraductal component (EIC) of tumor currently face mastectomy as the best treatment course available. EIC is characterized by proliferation of cancer cells within the ducts. Mastectomy of the entire breast is currently indicated due to the high recurrence rate in this type of cancer compared to cancer without an EIC. These cancer cells have been shown to be vulnerable to heat and therefore patients with intraductal disease may benefit from thermal therapy. Another case of interest is treatment of locally advanced breast disease using heat therapy either for non-resectable lesions or to reduce lesion volume prior to surgery.

An ultrasound system has been designed for the treatment of the intact breast. It is dedicated to optimizing the synergistic effect between thermal therapy and radiation in the treatment of early stage breast disease in patients with intraductal disease. The system incorporates both therapeutic and imaging capabilities utilizing a cylindrical array applicator which surrounds the breast with the patient in a prone position. The cylindrical transducer array consists of eight rings of transducers surrounding the breast. The transducers are operated in a time-multiplexed mode to provide both therapy and monitoring functions in real time.

The rings each have 48 transducers in two different frequency bands with each odd numbered transducer operating in the low frequency band and each even numbered transducer operating in the high frequency band.

In operation, a patient will lay on the top of the system with the diseased breast descending through a hole in the platform. Probes, in the form of long needles, are inserted under local anesthesia. These probes contain thermistors for temperature measurements. Thermistors are also taped to the breast surface. The cylindrical array applicator, filled with water, is then brought up under the breast and positioned with the aid of a motor to raise and lower the cylinder, x and y vernier controls and a rotational vernier control. A small video camera mounted at the bottom of the cylinder is used to monitor the position of the breast relative to the center of the treatment cylinder.
II. BREAST THERAPY SYSTEM DESCRIPTION

The ultrasound Breast Therapy System (BTS) consists of the hardware components illustrated in Figure 1. A breast site-specific cylindrical array applicator of ultrasound transducers is used for thermal therapy induction and for multiple monitoring functions. The "heart" of the hardware consists of the cylindrical array of transducers which both deposit power into the breast tissue for therapy and monitor the dynamic course of the treatment. The ultrasound array is described in more detail below. The ultrasound transducers are geometrically arranged and operated to provide both therapy and monitoring functions. The monitoring functions are comprised of: diagnostic pulse-echo monitoring to determine breast contour and location within the treatment cylinder and through-transmission monitoring of power during therapy for determination of absorbed power distribution (SAR) in the breast tissue being monitored. The hardware capability for future addition of the measurement of "time-of-flight" throughout regions of the target breast tissue referenced to a limited number of invasive temperature measurements for non-invasive mapping of temperatures throughout the treatment volume is also included in the BTS.

The system consists of an Instrument Computer which provides all direct control and data interaction with the Transmit-Multiplex-Receive (TMR) Subsystem, including receiver circuits, transmit/receive/multiplexing modules, Thermistor Thermometry Subsystem, and Cooling Subsystem. The system electronics, Instrument Computer, and Cylindrical Transducer Array/Treatment Cavity are integrated into a Patient Table Assembly/Subsystem, which provides a comfortable treatment support for the patient, accurate positioning of the breast within the treatment cavity, and a convenient means for consolidating system components and functions.

A. Ultrasound Breast Applicator

The Transducer Array Subsystem is illustrated graphically in Figure 2. A photo of the cylindrical array is shown in Figure 3. The array consists of eight (8) individual rings which are stacked with water-tight seals between rings. Each ring has 48 transducers. Based on analyses performed, it is not necessary to fill all available ring locations with transducers, in order to achieve adequate therapy, but populating all positions is important to noninvasive monitoring. Each transducer is square having dimensions of 15mm x 15mm. Spacing between transducers along the vertical dimension of the cylinder is 2.4mm and a bottom clearance of 1cm is added. Therefore, 8 rings accommodates breast lengths of 14cm or less, suspended in water in the prone position. Table 1 states the number of rings, transducers per ring, and the frequencies of the transducers in each ring. Table 2 indicates expected ring activation for examples of large and small breasts.
Figure 2. Transducer array configuration arranged in rings of cylinder.
Figure 3
Photo - Cylindrical Array
Table 1. Numbers and distribution of transducers per ring.

<table>
<thead>
<tr>
<th>CYLINDRICAL ARRAY APPLICATOR DESIGN</th>
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<tbody>
<tr>
<td>Total Cylinder I.D. = 25 cm</td>
</tr>
<tr>
<td>Transducer Dimensions: 15 mm x 15 mm</td>
</tr>
<tr>
<td>Rings of Transducers: 8 (numbered from top down)</td>
</tr>
<tr>
<td>Each 1/8 ring vertical section driven by RF Amplifiers whose outputs are multiplexed to step around ring</td>
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</table>

<table>
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<tr>
<th>Ring No.</th>
<th>FQ 1 (MHz)/No. XDCRS</th>
<th>FQ 2 (MHz)/No. XDCRS</th>
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<td>1</td>
<td>4.5/24</td>
<td>2.0/24</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>4.5/24</td>
<td>2.0/24</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>4.5/24</td>
<td>2.0/24</td>
<td>48</td>
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<td>4.5/24</td>
<td>2.0/24</td>
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</tr>
<tr>
<td>5</td>
<td>4.5/24</td>
<td>2.5/24</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>4.5/24</td>
<td>2.5/24</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>4.5/24</td>
<td>2.5/24</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>4.5/24</td>
<td>2.5/24</td>
<td>48</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>384</strong></td>
</tr>
</tbody>
</table>

Table 2. The table illustrates how many rings and transducer elements in a ring that will be activated when treating a large breast and a small breast respectively.

<table>
<thead>
<tr>
<th>CYLINDRICAL ARRAY APPLICATOR DESIGN</th>
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<tbody>
<tr>
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<tr>
<td>Each 1/8 ring vertical section driven by RF amplifiers whose outputs are multiplexed to &quot;step around&quot; ring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ring No.</th>
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<th>Breast Size (cm)</th>
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<td></td>
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<td>1</td>
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</tr>
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<td>2</td>
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<td>8</td>
<td>48</td>
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The transducers used in the cylindrical array subsystem were fabricated with the crystal (2.0, 2.5, or 4.5 MHz) mounted in a machined transducer housing, sealed with a watertight seal and faced with a matching layer. Each transducer has been individually performance-tested to determine its operating acoustic efficiency, center frequency and bandwidth. Tables containing the efficiency and frequency bandwidth data for each transducer in the cylindrical array are presented in Appendix C of this manual.

Each transducer in each ring of the cylinder is “mapped” into both the cylindrical array and to the TMR board. A diagram of the T/R MUX applicator transducer interconnections map is provided in Appendix D.

A close up view of the cylindrical array of transducers is shown in Figure 4.

B. Patient Table Subsystem

The patient table subsystem is shown in the two perspective photos in Figures 5 and 6 (indicating front side and rear views, respectively). A close up of the shroud covering the cylindrical array is shown in Figure 7. The patient table is designed to maximize utilization of symmetry of the breast by positioning the patient in a prone position with the breast suspended through an opening in the table top. Its specifications are described in Table 3. The table top consists of sheet steel with a tubular steel outer frame fabricated to provide for insertion of a 1.5” foam padding insert. The foam is sealed and the entire table top covered with a naugahyde covering which is stretched tight and snapped into place, and is easily removed for cleaning. The foam insert (and naugahyde) taper near the hole through which the breast is suspended in order to ensure that the entire breast can be extended beneath the table top for treatment if indicated.

The central column, or “pedestal”, beneath the table houses all of the system electronics, power supplies, and cylindrical array of transducers. The Instrument Computer is also located within the pedestal behind a side cover panel. Drawings of the internal layout are shown in Figures 8 and 9. Note the positions of the key electronic system components. The 25 TMR subsystems and microcontrollers are located in the two card cage racks above the fan trays. The transducer coaxial cable connections are routed from the rear of the card cages to panel connectors on a subpanel behind the dress panel at the front of the system (just behind the cylindrical array).
Figure 4

Photo - Cylindrical array
Close up

Shroud

Transducer Array

Patient Table Opening for Breast
Figure 5
Front View of BTS Patient Table

Figure 6
Back View of BTS Patient Table
Figure 7
Photo - Shroud covering cylindrical array
<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT TABLE SYSTEM SPECIFICATIONS</strong></td>
</tr>
</tbody>
</table>

| Table Top Overall Length: | 78" |
| Table Top Height (to floor): | 37" |
| X-Y Table: Positioning | ± 2.5" X-Y Vernier Drive  
± 6" Vertical Motion Motor Drive  
180° Rotation Capability - Motor Drive |
| Structural Materials: | Stainless steel |
| Paint: | Non-toxic textured (Color chip supplied by Dornier) |
| Construction Restrictions: | No sharp edges |
| Aesthetics: | Per design drawings |
| Load Capacity: | 300 lbs. |
| Table Top Hole Size: | 10" diameter |
| Table Top Cover: | Naugahyde cover (with snaps or velcro) over 1 1/4" foam pad |
| Other Requirements: | Make sure areas that could get patient fluids on them can be easily cleaned. There should be no areas where spilled fluids could be trapped. |
View of support column.
Figure 9

Drawing of internal layout of the key electronic system components inside the table central column
C. System Control Design

When power is turned on to the system, the treatment software initializes automatically so that no interaction is required by the user to start the software. All available options are displayed to the user in a graphical format. Options that will be available at the startup screen include access to the treatment planning software, file handling utilities, diagnostic mode selections, treatment record printing, and treatment initiation. The user makes requests of the system via the computer keyboard, computer mouse, or a mechanical pause switch during all phases of the treatment. A hardware Pause switch is provided that guarantees no power output will occur in case of emergency.

Prior to beginning a treatment, the user is required to complete a treatment plan. The treatment planning software is in graphical form to simplify data entry, such as target volume locations, the number and location of temperature sensors, target temperatures for each sensor, scar tissue locations, and patient information. Custom treatment plans can be configured for each patient prior to the actual treatment. These can be stored in the system and recalled at the time of treatment.

The BTS can perform the treatment in both computer assisted and manual modes. At any time during treatment, the system operator will be capable of interrupting the computer and/or provide advice to the computer concerning the treatment. The operator selects different target tissue regions on the computer screen and set a target temperature value for each region. The computer system will then determine which ultrasound transducer’s output power needs to be adjusted to accommodate the operator’s request. Alternatively, the operator can directly control the power levels to different groups of transducers (1 to 4 groups) comprising any selected number or to an entire region of the applicator.

Treatment progress and status information is available via a graphical user interface that provides treatment information such as temperature distribution, power absorption distribution, thermal dose distribution, target contour information, and treatment time information. The operator is not required to determine power levels for the individual transducers since temperature distribution information is continually available on a graphics screen. The operator has the capability to make suggestions about the target temperatures for locations where implanted sensors are placed as well as other locations in the target volume. Further, the operator may manually select and adjust the power on any active transducers (e.g. reduce power deposition directly over a scar). Selection of active transducers, control of receive and transmit mode and gated on-off periods are under control of the Instrument Computer.

Once a treatment has been completed, the operator returns to the startup screen so that printing of the treatment information may be performed, and duplication of the treatment files may be accomplished.
D. TMR Subsystem

The TMR (Transmit-Multiplex-Receive) subsystem is the “heart” of the system’s electronics. It resides on a custom 10in. x 16in. four layer circuit board, with sockets for two daughter boards - a microcontroller board (MCB) and a digital signal processor (DSP). The TMR subsystem includes the RF power generators and VCO’s, transmit-receive (T/R) circuits, receiver circuits, transducer multiplexer circuits, an on-board microcontroller daughter card and provision for addition of a DSP. The breast therapy system contains 25 TMR subsystem boards, 24 being for system therapy and noninvasive interrogation operation and one for temperature probe location. Each TMR subsystem contains four independent RF generators with separate VCO’s, receiver circuits, T/R switches, and multiplexers for driving 16 transducers. All functions on the TMR are controlled via the MCB daughter board microcontroller (a custom-designed six-layer surface-mount board). The microcontroller interfaces to the system’s Instrument Computer. A block diagram and controller signals map of the TMR subsystem is shown in Figures 10 and 11, respectively. This comprehensive design, including T/R switches and receivers plus DSP provisions, provides the capability for the addition of non-invasive measurements including tomographic reconstruction of interrogated ring “slices”.
Figure 10  TMR Subsystem Block Diagram
Figure 11
TMRCARD
EMBEDDED CONTROLLER
SIGNSALS

EXISTING
CONFIGURATION

<table>
<thead>
<tr>
<th>EXISTING CONFIGURATION</th>
</tr>
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<tbody>
<tr>
<td>DO -&gt; XMIT 0 ENABLE</td>
</tr>
<tr>
<td>DO -&gt; XMIT 1 ENABLE</td>
</tr>
<tr>
<td>DO -&gt; XMIT 2 ENABLE</td>
</tr>
<tr>
<td>DO -&gt; XMIT 3 ENABLE</td>
</tr>
<tr>
<td>DO -&gt; XMIT START</td>
</tr>
<tr>
<td>DI -&gt; XMIT STOP</td>
</tr>
<tr>
<td>DO -&gt; XMIT MODE 0</td>
</tr>
<tr>
<td>DO -&gt; XMIT MODE 1</td>
</tr>
<tr>
<td>DO -&gt; T/R CHANNEL 0</td>
</tr>
<tr>
<td>DO -&gt; T/R CHANNEL 1</td>
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<tr>
<td>DO -&gt; T/R CHANNEL 2</td>
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<tr>
<td>DO -&gt; T/R CHANNEL 3</td>
</tr>
<tr>
<td>DO -&gt; RCV 0 ENABLE</td>
</tr>
<tr>
<td>DO -&gt; RCV 1 ENABLE</td>
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<td>DO -&gt; RCV 2 ENABLE</td>
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<tr>
<td>DO -&gt; RCV 3 ENABLE</td>
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<tr>
<td>AI -&gt; POWER CHANNEL 0</td>
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<tr>
<td>AI -&gt; POWER CHANNEL 1</td>
</tr>
<tr>
<td>AI -&gt; POWER CHANNEL 2</td>
</tr>
<tr>
<td>AI -&gt; POWER CHANNEL 3</td>
</tr>
<tr>
<td>DI -&gt; SELF TEST</td>
</tr>
</tbody>
</table>

EMBEDDED CONTROLLER BLOCK

D/A - VREF BLOCK

VCO
- XMIT EN0: DO
- XMIT EN1: DO
- XMIT EN2: DO
- XMIT EN3: DO

RF GEN
- RF PWR0: AO
- RF PWR1: AO
- RF PWR2: AO
- RF PWR3: AO
- PWR CH0: AI
- PWR CH1: AI
- PWR CH2: AI
- PWR CH3: AI

T/R MUX
- XMIT EN0: DO
- XMIT EN1: DO
- XMIT EN2: DO
- XMIT EN3: DO
- RCV EN0: DO
- RCV EN1: DO
- RCV EN2: DO
- RCV EN3: DO
- T/R CH0: DO
- T/R CH1: DO
- T/R CH2: DO
- T/R CH3: DO
- T/R CH4: DO

RCVR FE
- RCV GAIN 0A&0B: AO
- RCV GAIN 1A: AO
- RCV GAIN 1B: AO
- HYB EN0: DO
- HYB EN1: DO

PLL
- PLL EN: DO
Each section of the TMR subsystem is described in detail as follows.

D.1. RF Section

The RF Power Section consists of 96 independent RF amplifiers driven by 96 separate oscillator sources. Each oscillator consists of a computer-controlled VCO operating over the frequency range of 1 - 5 MHz and is used to drive one RF amplifier. Each oscillator is preset to operate at one of the three operating frequencies (2.0, 2.5, 4.5 MHz). The individual VCOs' frequency may be controlled by the microcontrollers under direction of the Instrument Computer. Each of the 96 independent RF amplifiers incorporates its own voltage control/regulator circuit which provides independent computer control of amplitude (output power level) for each amplifier channel. A block diagram of the RF Amplifier Subsystem is shown in Figure 12. Each RF amplifier output is connected to a T/R MUX input circuit.

D.2. Receiver Section

The Receiver Section consists of 25 independent receiver with 24 dedicated to noninvasive monitoring and one for temperature probe location. Inputs can be received from any of the 384 transducers in the array, dependent upon multiplexer selection. Each of 24 receiver circuits receives inputs from up to 16 transducers and multiplexes those transducer signals to two receiver hybrids per card. There are 24 identical circuits comprising the Receiver Section plus two cards with sampling, phase comparator, and PLL circuits. Specifications for the receiver hybrids are listed in Table 4. Each hybrid consists of an analog multiplexer and a 15 dB low noise amplifier as illustrated in Figure 13. The hybrid output is processed through two high gain VGA stages as shown in Figure 12. Receiver outputs are digitized and sent to the Instrument Computer for processing. The complete Receiver Section block diagram is illustrated in Figures 14 and 15.

D.3. T/R Mux Section

The Transmit-Receive Multiplexer blocks connect each of the transducers in the array to the RF amplifiers and the receivers. The fundamental block has 6 ports, 4 of these are for individual transducers, 1 is for transmit RF, and 1 is for receive. The design consists of 6 single pole RF diode switches all connected to one common pole. Certain switch combinations are not desired such as transmitting at high power levels into the receiver so control logic prevents this and other undesired combinations. Performance of the design was evaluated at 4.5 MHz and is slightly better at 2.5 and 2.0 MHz. Transmit loss was around 0.1 dB, receiver loss was 1.0 dB, transmit receive isolation was 58 dB, and cross channel isolation was 35 dB. Each TMR card has 4 of the basic T/R Mux blocks, the system has 24 fully used TMR cards so 96 of the T/R
Figure 12 RF Amplifier Subsystem
Figure 13. Receiver Hybrid
Figure 15. RF Receiver Amplitude and Coarse TOF Measurement.
Mux circuits allow for 96 RF amps to drive 384 transducers. 96 receiver ports are further multiplexed down to 24 separate receivers, one per board.

D.4. Microcontroller Section

A separate surface-mount microcontroller daughter card is mounted onto (and plugged into) the TMR subsystem board. The schematic of the microcontroller daughter card is shown in Figure 16. The processor contains on-board memory and 64 Bytes of SRAM. Each microcontroller board also contains 16 digital control lines and 8 each A/D and D/A lines. The requirements of this therapy system were unique enough that it would have been very difficult to implement an "off the shelf" controller board. Also, physical space constraints in this system are severe. As a result, we designed and layed out our own circuit card a 6-layer surface mount 3"x 5" package. The microcontroller card layout is shown in Figure 17. Much of the receiver peak-detect and A/D functionality reside in the microcontroller, whose programmable functions can be optimized.

D.5. VCO/PLL Input Section

The TMR subsystem board contains a section which permits injection of a phase-locked oscillator source into the RF generator/amplifier circuits on a selected channel basis. The PLL input is buffered through phase-matched buffer arrays to maintain equal phases to all amplifier inputs. This permits use of the same generator/amplifiers for both therapy and pulsed signal interrogation. During the therapy mode, the VCO on each generator section drives the RF amplifier. The VCO frequency is computer-controlled by the microcontroller under direction of the Instrument Computer. Since each RF generator/amplifier section of the TMR subsystem has its own VCO, the outputs of each amplifier are incoherent. This permits avoidance of any undesired phase addition or cancellation in the emitted ultrasound energy used for thermal therapy. During the interrogation mode of system operation, the pulse signal must be phase-locked to a single source in order to permit accurate measurement of pulse-echo and through-transmission times. This in turn permits accurate representation of the breast contour on the operator's treatment screen. This section of the TMR subsystem functions to switch the generators/amplifiers between these two modes and to provide buffered, phase-matched signals to the drivers. It is shown on the upper right corner of the TMR layout in Figure 18.
Figure 17
MicroController Board
Layout Diagram
D.6. DSP Add-On Provision

This section of the TMR subsystem represents one of the important “looking ahead” features which has been incorporated into the BTS. The TMR circuit board contains sockets for plug-in addition of a digital signal processor (DSP) to be developed at a future date (Figure 18). DSPs are widely used today in many applications and in this case, will provide the only reliable method to obtain “clean” received signals for the through-transmission data to be used for both noninvasive temperature monitoring and real-time breast image reconstruction within the treatment system. This work is beyond the scope of the present contract. It is a very important provision, however, and is the only method whereby these capabilities may be readily retrofitted to the overall system without complete rework of the TMR subsystem at considerable cost and time consumption.

E. Non-Invasive Monitoring Subsystem

The noninvasive monitoring subsystem resides on the TMR subsystem circuit cards and on three separate circuit cards contained within the system enclosure.

The receiver section of the TMR subsystem, in conjunction with the T/R Mux circuits and VCO/PLL control circuits comprise the heart of the noninvasive monitoring subsystem. This portion of the system changes the functional state of the transducers from therapy to target interrogation and receives both reflected and transmitted signals from and through the breast, respectively. Functional descriptions of each of these TMR subsystem sections are given previously in Section D. of this manual.

One of the three additional circuit cards contains the phase-locked oscillators for each of the three transducer interrogation-mode operating frequencies (2.0, 2.5, 4.5 Mhz), filters for eliminating noise from the high-resolution time measurement signals, and the time-of-flight (TOF) measurement circuitry. A microcontroller also resides on this card for the purpose of communicating with the Instrument Computer which directs the TOF measurements. The other two cards contain large phase-matched buffer arrays for distributing the phase-locked oscillator outputs to each of the 96 RF generator/amplifier channels.
F. Thermometry Subsystem

Minimally invasive thermometry is performed by a multichannel thermistor thermometry system (Profilometer) developed by Drs. Bowman and Newman at the Massachusetts Institute of Technology (Bowman, et al., 1991; Hansen, et al., 1994).

The multi-channel temperature measurement instrument accommodates up to 6 multi-channel temperature probes. Each probe can measure temperature at up to 14 sites providing a total of 84 channels of information. The present instrumentation has resolution down to 10-17 millidegrees C, and temperature can be sampled at variable rates dependent on the data acquisition system being used and the amount of data averaging and signal processing. Each of the 84 channels can be sampled at 20 Hz which provides 10,080 samples of temperature data per second. Multi-site temperature data are collected and stored by the Instrument Computer. Data signal conditioning is performed by the Instrument Computer and the data then passed to the Control Computer for interaction with the control algorithm and display for the operator.

The instrument consists of two card types; the isolation cards and a digital control card. The isolation card is a medically isolated driver card external to the Instrument Computer which provides isolation for each channel and also provides multiplexing of the analog and digital signals. The digital control card provides function selection including card selection, channel selection, gain selection for a Programmable Gain Amplifier, and resetting of an Over Current Protection Latch. The controller card also handles communication to and from the Instrument Computer. Analog-digital conversion is presently handled by a commercially available system in the Instrument Computer, and all instrument control, data display, and data storage is handled by the computer.

Within the measurement instrumentation, each probe is connected to an individual, electrically isolated probe driver card. The driver cards are powered by a UL-544 approved power supply certified for medical use, and signals to and from the driver cards are passed through optical isolators and isolation amplifiers. This isolation ensures that there is no electrical connection between the patient and ground via the instrumentation.

The instrument also contains common circuitry - the controller and interface cards - for coordinating the activities of the several driver cards and for communicating with the Instrument Computer. This common circuitry is powered from a separate power supply, so that the probe driver cards are electrically isolated from the common circuitry, from the AC line, from the host computer, and from the other probes.

The probes used to measure temperature can be mounted on needles, molded into catheters, or other designs as desired. Stainless steel needle probes are planned for use with this system. These are 19 ga. needles, from 6" to 12" long, and contain 14
thermistor sensors. This range of probe configurations permits selection of a probe appropriate for the particular size breast being monitored.

The sensors used to measure temperature are thermistors. There is no electrical connection from the probe to the patient in normal operation. However, as a further safety precaution, hardware protection circuitry is provided to shut off power to a probe if an out-of-range signal is detected due to probe breakage or other mishap. Should such a condition occur, probe excitation will be shut off within 65ms. Although the isolation circuitry ensures that there is no current path from the instrument to ground through the patient under such conditions, this additional measure of redundancy provides added assurance of patient safety.

A unique feature of this system is that various temperature displays are available in real-time on the Control Computer screen during treatment. The display modes are as follows:

- **Temperature-Time Display Mode**: This mode presents a graph of all sensors on a common time axis. For the breast system, use of 3 probes simultaneously is anticipated for most treatment cases, which is easily seen on the display.

- **Spatial Temperature Distribution Mode**: This mode is displayed on the operator treatment control screen directly on the breast contour/slice map and shows spatially where each of the sensors is located within the breast profile and the temperature of each sensor.

- **Thermal Dose Spatial Distribution Mode**: This mode is displayed on the operator treatment control screen directly on the breast contour/slice maps and shows spatially the thermal dose distribution within the breast. Thermal dose is displayed as the instantaneous value of accumulated thermal dose, expressed as equivalent minutes at 43 deg. C.

A block diagram of the thermometry subsystem used in the breast therapy system is shown in Figure 19.

The profilometer system and displays are fully developed and approved by the IRB at the Dana Farber Cancer Institute. A profilometer system (operating as a stand-alone device) is currently in clinical use for other thermal therapy systems at the JCRT.
G. Cooling/Heating and Water Circulating Subsystem

This subsystem consists of a 110 watt thermoelectric cooler/heater, water circulating system, and a temperature controller interfaced to the Instrument Computer.

The thermoelectric cooler/heater is attached to a thermal plate which includes a machined serpentine groove and cover plate for placing the tubing which carries the circulating water. Using this approach makes it possible to maintain sterility of the water which comes in contact with the patient and avoid circulating the water directly through the cooler body itself. The cooler maintains the water at a preset temperature which is under operator control via the Control and Instrument Computers. The interface communicates bi-directionally with the Instrument Computer. The temperature controller controls the setpoint temperature based upon information feedback from the thermometry monitor module and the setpoint temperature selected by the operator. A PID control algorithm is incorporated in the software. The setpoint temperature range is 25°C to 42°C.
H. Computer Subsystems

The computational functions of the system will be divided between two computers, the Control Computer and the Instrument Computer. The control computer's primary responsibility is to control the overall treatment functions and provide an intuitive user interface via a graphics monitor, keyboard, and mouse. The Instrument Computer is primarily responsible for communicating with other hardware devices such as the Cylindrical Array Applicator, the Video system, Cooling System, Thermometry system, and the Pause switch.

H.1. Control Computer

A photo of the Control Computer workstation is shown in Figure 20.

The Control Computer is a standard architecture machine with no custom hardware interfacing requirements that connects to the Instrument Computer via a communications link and is also connected to a printer to allow hardcopy of the treatment information. For treatment results analysis, demo, and software development purposes the Control Computer is able to be operated without the Instrument Computer connected.

The bi-directional communications link has been implemented via a parallel port using off-the-shelf hardware. The communications software design employed is independent of the communications link technology, except for the low-level driver implementation.

Control Computer Specifications:

Processor:
- Pentium, 66 MHz
- PC/AT, MS-DOS, Windows, iRMX Compatibility
- 32 MB RAM
- 520 MB hard disk
- 3.5" 1.44 MB floppy drive
- Printer Port
- Bi-directional Communications link to Instrument Computer (Ether Express Network)

Graphics and operator entry subsystem:
- 1280 x 1024 x 256 resolution
- 21" monitor size
- PCI bus with graphics accelerator
- Standard 101-key keyboard

Microsoft Windows supported mouse
Figure 20

View of Control Computer Operator Workstation
Inputs to Control Computer:
- Keyboard
- Mouse
- Ether Express Network from Instrument Computer.

Outputs from Control Computer:
- Display Screen
- Parallel Port to Printer
- Ether Express Network to Instrument Computer.

H.2. Instrument Computer

The Instrument Computer implements the custom control and measurement interfaces to other hardware portions of the treatment instrument, is located within the system enclosure beneath the patient table and near the control and measurement points, and communicates with the Control Computer via a bi-directional communications link. For software design consistency and to avoid unnecessary costs, the Instrument Computer is implemented as a PC-AT compatible computer filled with interface cards.

- The bi-directional communications link was implemented via a parallel port using off-the-shelf hardware. The communications software design is based on iRMX and is independent of the communications link technology, except for the low-level driver implementation.

Instrument Computer Specifications:
Processor:
- 80486 DX2/66, upgradable to Pentium
- PC/AT, MS-DOS, iRMX Compatibility
- 16 MB RAM
- 250 MB hard disk [deleted from final system]
- 3.5" 1.44 MB floppy drive [deleted from final system]
- Ether Express Network link to Treatment Control Computer

Custom designed transducer array interface hardware

TTI Temperature Profilometer System:
- Low profile card cage
- 14 Channels per board
- 6 boards
- Isolation card
- Digital control card

Coolant system interface hardware
Video system interface hardware

**Inputs to Instrument Computer**
- Safety Controls --- Emergency Shutdown, Pause control.
- T/R Switch Status
- Demultiplexer Status
- Receiver data
- Invasive Thermometry Sensors
- Coolant Temperature
- Ether Express Network from Control Computer

**Outputs from Instrument Computer**
- Safety Shutdown
- Image Pulser
- RF Power On/Off, Gated CW burst
- RF Frequency Sweep On/Off
- T/R Switch Control
- Demultiplexer Switch Control
- Cooling System Control
- Ether Express Network to Control Computer

**I. Video Subsystem**

The breast ultrasound therapy system also incorporates a charge-coupled-device (CCD) solid-state video system for visual imaging of the breast within the treatment cylinder. This video subsystem was not anticipated in the original system design; however, several physicians within our group and our outside scientific reviewers suggested that real-time video imaging of the breast would provide useful information concerning the breast's position within the treatment cylinder and would confirm the breast contour outline provided by the noninvasive interrogation pulse-echo ultrasound. The video image from the CCD device is coupled through a video digitizer to the Instrument Computer and transferred to the Control Computer. The resultant image is displayed within a "window" on the operator treatment control screen.

**J. Safety Subsystem**

This subsystem automatically tests for any system ground faults and monitors leakage currents. It also directly monitors RF output power from the generator/amplifier subsystems independently of any computer-based monitoring of output power. It provides for system shutdown in the event of RF power malfunction, such that a "power on" failure mode is not possible. Also, a system level emergency shutdown switch is provided.
III. SYSTEM SOFTWARE

A. System Software Overview

The System Software Block Diagram shows the system control implementation approach. System control is divided between two computers, the Control Computer and the Instrument Computer. The Control Computer provides an operator control interface, measurement interpretation, feedback control, and data recording. The Instrument Computer provides direct hardware interfacing for collecting temperature measurements, collecting measured data from receivers, setting control output levels, and controlling the timing for multiplexing the transducer array.

B. Operating System

The Control Computer and the Instrument Computer are each configured with a 32-bit real-time multitasking operating system (Intel's iRMX for Windows). The software for each computer is written as a collection of well-isolated tasks, with intertask communications implemented via a consistent mailbox communication approach, with each task having its own separate GDT entries for its code, data, and stack segments (except that multiple iterations of a task, if any, use a shared code segment), and with minimal use of shared memory between tasks. All tasks are written as iRMX native tasks, except in the Control Computer where the operator interface is written as a Microsoft Windows application. Any task using mutual exclusion mechanisms rigidly adheres to an access order regimen to prevent deadlock situations from occurring.

C. Interprocess Communication

A standard intertask communications message structure is used for most intertask communication messages. This structure contains message type, response mailbox, destination, and standard auxiliary information fields. For passing large messages, an auxiliary information field will be used to pass a pointer to a memory segment containing the passed information. To avoid conflicts, in most circumstances this segment will not be accessed again by the sending task until it is returned by the receiving task. Preallocated communications buffer queues are used where possible rather than dynamic memory allocation and deallocation to exercise explicit control over message queuing performance and to avoid memory fragmentation.

D. Initialization
The initialization task has the responsibility to start up all the other primary application tasks in the system. Each iRMX task is separately bound, and loaded by the initialization task with the iRMX application loader. This approach encourages good design practices such as maintaining task isolation, automatically provides independent data segments for each task, and minimizes compile, build, and bind cycle time.

Each task has a synchronous initialization phase, and may also have asynchronous initialization. During synchronous initialization, each task establishes communications mailboxes and message queues, perform any other synchronous initialization required, send the token for its main command mailbox to the initialization task, and wait for an initialization message from the initialization task. After synchronous initialization is complete, the task may also do other initializations asynchronously.

E. Control Computer

The Control Computer performs several interrelated functions. The operator input and display subsystem provides user control over the treatment and feedback to the user as the treatment progresses. User control over the treatment is at a high interaction level; actual control over the timing, power levels, and frequencies applied to scores of individual transducer elements is too complex and must be controlled too fast for an operator to control individual transducer parameters directly.

E.1. Operator Subsystem

The operator interface is one of the most important parts of the treatment system since it represents "the system" to the users. Therefore, the engineering design approach must be secondary to the user-oriented approach in this instance. Not only must the data interfaces be considered, but also the tools (keyboard, mouse, etc.) and the display organization and options. These are each discussed in the paragraphs below.

The operator interface will be used to define the treatment control and reference data and to display a variety of types of treatment progress and general display information.

Treatment Definition and Control Data
Treatment definition and control data will be suggested to the operator through the presentation of a configuration file, or files, and by requests to the operator to:

1) accept the configuration file in its entirety
2) specify new data for particular fields of the file
3) specify data not included in a configuration file.

Treatment Associated Data
Treatment associated data is measured by the system from sources external to the therapy system and therefore must be provided to it. Such data includes:

1) the number of temperature probes
2) the locations of the probes
3) the number and spacing of sensors on each probe
4) the spatial locations of the temperature sensors
5) the size and location of scar tissue
6) the patient's name and any identification being used

Definition of these data and the procedures for providing it to the operator interface are defined on their respective screens.

E.2. Display Subsystem

The displays to be provided during treatment include:

1) a breast contour (every 3 to 5 seconds),
2) periodic imaging of the temperature probe(s),
3) 2D cross section breast images, each with overlays of temperature data,
4) Hot spot alerting,
5) An optional display of 2D cross sections by location,
6) continuous time and temperature monitoring displayed as a graph for each cross section.

Where temperature is to be indicated by color shading scale shown below will be used. The actual temperature values that map to these colors and the colors used will be defined and configurable via the Configuration Subsystem.

- White - over temperature (above 44.5 °C)
- Red - upper temperature threshold (44.0 °C)
- Orange - 43.0 °C
- Yellow - 42.0 °C
- Green - 41.0 °C
- Blue - below lower temperature threshold (40.5 °C)
- Gray - shading

All display software are designed with the resolution-independent features available in Windows, so that the treatment software will be able to run satisfactorily on machines with lower resolution for remote treatment replay purposes, with the acknowledgment that display detail will be lost.

E.3. Configuration Subsystem

System configuration information will be read from a file into a configuration information structure, then passed to each task as part of the synchronous initialization
message. The configuration information will be defined as a constant structure and may be compiled into a binary file prior to system startup.

The system configuration information structure definition will be contained in a common file, "SYSCONFG.HC", and included by all referencing files.

The configuration subsystem reads all configurable parameters from the storage media (hard disk) and returns the appropriate data to the module that requests the information. The types of configurable parameters that this subsystem is responsible for obtaining are power calibration table or tables and system behavioral preferences.

E.4. Messaging Subsystem

The messaging subsystem handles all messages that are to be displayed to the user. This subsystem uses the Display Subsystem to display pre and post treatment messages, error messages during the treatment, and informational messages that are provided for the user. This subsystem accepts messages from any of the other subsystems and displays them in the appropriate fashion. For example, if an error occurs during a treatment, this subsystem will display an error message in a pop-up window and inform the Treatment Control Subsystem to pause the treatment. If the message is an informational message, the message will be displayed in a message bar located on the display screen. All messages received are also transmitted to the Treatment Records Subsystem.

E.5. Treatment Records Subsystem

The function of this subsystem is the collection, organization, control, and distribution of data between subsystems, tasks, and modules, and to store all relevant treatment data for post-treatment recall and analysis. In addition, the Treatment Records Subsystem provides treatment information to the user in paper form. A printout of key treatment parameters including temperature vs. time for all of the sensors will be provided upon request.

Information that the Treatment Records Subsystem is responsible for storing and retrieving includes the system configuration, all temperature measurement results, patient information, cooling system information, treatment cell information, automated control decisions, and user keypresses and mouse events during each treatment session. This task will also allow the data to be retrieved in an off-line simulation mode, for post-mortem analysis of the treatment session, operator training, system demonstration, and software development support. Other utilities and function will also be provided to assist in hardware testing, system calibration, and printing treatment data.
E.6. Treatment Plan Subsystem

The Treatment Plan Subsystem is responsible for obtaining information from the user that is necessary for proper treatment operation. Information that this subsystem will require includes the number of treatment sensor probes, number of sensors per probe, spacing of the sensors on the probe, target temperature and temperature limits for individual sensors and/or subregion locations in the treatment volume, patient name and/or number identifier, and possibly suggestions about the method of heating. The treatment plan subsystem maintains this information and provides it to the other subsystems.

The Treatment Plan Subsystem will also provide a method for the user to select regions as small as an octant and select a temperature setpoint for the entire octant at once.

E.7. Treatment Control Subsystem

The Treatment Control Subsystem makes transducer output power and frequency decisions based on information received from the Power Absorption Distribution Subsystem, Thermal Dose Distribution Subsystem, Treatment Plan Subsystem, Dynamic Treatment Calibration Subsystem, and the Temperature Subsystem. Once output power and frequency settings have been determined the Treatment Control Subsystem sends those data to the RF Power Subsystem via the PC Interface Module so that actual power changes can be made for the Transducer Array.

The Treatment Control Subsystem operates on predefined Treatment Cell Volumes. The actual volume of each treatment cell may be determined by the configuration file. The Treatment Cell center points, volume corners, and transducers that affect a treatment cell are stored in a Treatment Cell Information File (TCIF.DAT). If the volume defined in the configuration file for a treatment cell does not match the volume used to calculate the current treatment cell information file, the Treatment Control Subsystem will generate a new treatment cell information file.

The Treatment Control Subsystem will operate in automatic mode, yet it will be capable of allowing the user to make manual adjustments of the temperature setpoints for each treatment cell volume during the treatment. The default control method will be to heat the entire breast to 43 °C in all treatment volume cells.

To achieve the desired temperatures for the target volume the Control Subsystem may begin the treatment by selecting the Low Frequency Setting (2.0 - 2.5 MHz) until the center treatment cells have reached their target temperatures and then switching to the High Frequency Setting (4.5 MHz) to maintain these temperatures.

Treatment Cell Volume
A Treatment Cell Volume is a volume located inside the Cylindrical Transducer array. All treatment cell volumes are the same volume (or as close to the same as possible while still cumulatively encompassing the entire volume inside the Cylindrical Transducer array). The actual value for this volume is stored in the configuration file (default = $1 \text{ cm}^3$). A data file containing the treatment cell center point location, volume corner points locations, and the transducers that affect each cell is accessed prior to the treatment as the Control Subsystem sets up the Treatment Cell list. The Treatment Records Subsystem will check the Treatment Cell information file to ensure that the configuration file volume selection matches the volume used to generate the treatment cell information file. If it does not match, then the Treatment Records Subsystem will call on the Control Subsystem to generate a new file prior to starting the treatment.

This subsystem calculates the center point location for each volume, the corner points for each volume, and then determines which ultrasound transducers affect this volume. Although the volume for each cell will be equal, the actual shape of each volume will not be exactly the same. Figure 20 shows a simplified view of how the center points of each volume cell is determined for a single ring of transducers (48 in this case).
Center Points of Treatment Cells
(Defined by line intersections)

Center Cell

Figure 12. Treatment Cell Centerpoints

Treatment Cell Volume Centers

Each treatment cell volume's centerpoint is located on a line from the center of the face of a transducer to the centerpoint of the cylindrical array. The central treatment cell volume is actually a cylinder with a radius selected such that the volume will match the volume contained in the configuration file. The remainder of the treatment cells for a given transducer ring are in the shape of a rhombus (see Figure 22). Once the central treatment cell radius has been determined, the radius (distance from array center) for the center point of the rest of the treatment cell volumes is calculated and the centers determined. If a volume is selected such that all cells cannot be the same size, the treatment cells located closest to the transducer face will be of different
volume so that the entire cylinder volume is represented by an individual treatment cell volume (These cells could be ignored since they will never contain target tissue).

Treatment Cell Volume Corner Points

Once the center points for each treatment cell are computed, the eight corner points for the Treatment Cell Volume are calculated. Each treatment cell volume is defined by 6 planes (except for the center cells). For a given treatment cell, the top and bottom plane are horizontal planes that are centered between the ring of transducers above and below the ring that the current transducer resides (see Figures 21 and 22). The left and right planes are vertical planes that extend from between the left and right neighbors of the transducer to the center point of the Cylindrical array applicator. The front and back planes are normal to a vector originating from the center point of the cylindrical array to the center point of the transducer. The distance of the front plane is half way between the current volume center and the center of the volume closer to the origin, and the back plane is halfway to the volume center further from the origin. Once all six planes have been determined, 8 volume corner points are calculated by finding the intersection of 3 planes.

![MultiView of treatment Cell.](image)

A Treatment Cell

Figure 22. Treatment Cell Volume

Transducers Affecting a Particular Volume Cell

A center and 8 corner points define each volume cell. After all cell points have been calculated each of the points defining a cell are checked to see if they fall within either the Near Zone or Far Zone regions of each Transducer in the array; if so they are said to be touching a cell. The control subsystem creates a list for each volume cell of all transducers that "touch" a volume. In addition to whether or not a transducer "touches" the volume, information about whether the ultrasound field that touches the
volume is in the Near Zone or the Far Zone region is also maintained. A "strength capability value" is also given for each transducer. For example, if a given transducer touches both a corner and the center points it will be given a higher strength capability value than a transducer that only touches a corner point. The strength value will be used by the Control Subsystem during the treatment to determine what the output power configuration should be to perform the desired treatment.

**Treatment Cell Structure Definition**

The structure definition below describes the types of information that will be maintained for each treatment cell volume.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>point</td>
<td>Center Location of center of cell</td>
</tr>
<tr>
<td>point</td>
<td>Corners[8] Location of 8 corners</td>
</tr>
<tr>
<td>float</td>
<td>Volume Volume of this cell</td>
</tr>
<tr>
<td>float</td>
<td>AbsorbedPower Current absorbed power</td>
</tr>
<tr>
<td>float</td>
<td>ThermalDose Current thermal dose</td>
</tr>
<tr>
<td>float</td>
<td>Temperature Current cell temperature</td>
</tr>
<tr>
<td>float</td>
<td>SetPoint Temperature setpoint</td>
</tr>
<tr>
<td>float</td>
<td>TempLimit Temperature limit</td>
</tr>
<tr>
<td>short</td>
<td>Type Scar, NormalTissue, ContourTissue, NoTissue</td>
</tr>
<tr>
<td>sensor</td>
<td>*sensors List of sensors in treatment cell</td>
</tr>
<tr>
<td>xducers</td>
<td>*xducers List of transducers touching cell</td>
</tr>
</tbody>
</table>

**E.8. Contour Monitoring Subsystem**

Pulse-echo reflection data is collected using the cylindrical transducer array. The reflection data is collected by the Instrument Computer's Receiver Subsystem and sent to the Contour Monitoring subsystem. The Contour Monitoring Subsystem will convert this information into 3D image data that outlines the contour of the breast and prepare it for display. It will also map 3D image data into a 2D image space for the generation of 2D displays. This subsystem will also provide information to the Dynamic Treatment Calibration Subsystem to locate the breast within the treatment cylinder for detection of breast movement within extremes (boundaries) set in the Configuration file, and for updating the treatment cells in which the contour (surface of the breast) resides. Figure 23 is a simplified depiction of the pulse-echo monitoring method.

Contour Monitoring is performed by selecting a single ultrasound transducer to transmit an ultrasound pulse into the treatment cavity and then receiving the same pulse while measuring the time it takes for the pulse to return. This measurement is called a "Pulse-Echo" measurement since it measures the time it takes for a pulse to return to the transducer. The sooner a pulse returns the closer the object is to the face of the transducer. By pulsing all of the transducers one at a time a 3 dimensional contour map of the target tissue located in the applicator can be generated.
Transmit/Receive

Time-of-Flight may be determined via:
1) Threshold Technique
2) Correlation of digitized waveforms (echoes)

Figure 23. Contour Monitoring
E.9. Dynamic Treatment Calibration Subsystem

The Dynamic treatment calibration subsystem's primary responsibility is the detection of movement of the sensors, or the contour information. Once movement has been detected, this subsystem sends updated spatial target coordinate information to the subsystems that will be required to update their respective information tables.

Subsystems requiring the updated spatial information concerning target position include the Power Absorption Distribution Subsystem, the Temperature Subsystem, the Thermal Dose Distribution Subsystem, the Treatment Control Subsystem and the Safety Subsystem.

Whenever the breast moves within the treatment cylinder, new contour information is generated by the Contour Monitoring Subsystem based on pulse-echo measurements which are made every 4 seconds. This new breast contour information is passed to the Dynamic Treatment Calibration Subsystem to update the breast/target 3-dimensional spatial position within the treatment cylinder volume, relative to the transducers. This information is utilized by each of the subsystems requiring the updated spatial information. The Safety Subsystem compares the new breast/target spatial location against the maximum movement threshold specified in the Configuration file in order to determine whether or not to pause treatment.

Whenever sensors move the Sensor Locator Subsystem updates its sensor location table and warns the Dynamic Treatment Calibration Subsystem. This subsystem then sends the new sensor location information to the Temperature Subsystem and/or the Safety Subsystem. If a sensor that is to be used for the treatment is not located in tissue, the Safety Subsystem must be warned so that the treatment may be paused and the sensor deselected for control purposes.

E.10. Power Absorption Distribution Subsystem

The Power Absorption Distribution Subsystem calculates the power deposition within the tissue based on current temperature and power information and absorption models. Figure 24 is a simplified depiction of the "Through-Transmission" power measurement.

During treatment, the actual absorption throughout the target volume for each transducer pair is measured by the Instrument Computer, and sent to this subsystem. The Power Absorption Distribution Subsystem converts this information into an array representing the computed absorption or SAR (in W/cm³) for each treatment cell (minimum unit treatment volume). This computed absorption array is then sent to the Thermal Dose Distribution subsystem for its next simulation model cycle.

The "Through-Transmission" power is calculated by selecting a single transducer to produce an ultrasound pulse while at the same time having the transducers that are located on the other side of the cylinder (through the tissue) receive the pulse and
measure the change in magnitude of the pulse (Pulse Amplitude Degradation) once it has been received. A correlation between the transmitted magnitude and the received magnitude can then be used to determine the amount of power that was absorbed in the tissue.

![Diagram of power monitoring](image)

Figure 24. Power Monitoring

E.11. Temperature Subsystem (Not included in present system software)

The Temperature Subsystem collects temperature values for all temperature sensors and "Time-of-Flight" temperature measurements from the Instrument Computer. These temperatures are then provided to the rest of the system upon request. In addition, this subsystem calculates the temperature distribution for all spatial volume cells based on the sensor, Time-of-Flight/Pulse Amplitude Degradation measurements. Invasive temperature sensor measurements and Time-of-Flight/Pulse Amplitude Degradation measurements occupying the same volume cells are set equal to the invasive sensor measured temperature and all derived temperatures in neighboring volume cells are calibrated according to the nearest invasive sensor measurement. Time-of-Flight/Pulse Amplitude Degradation measurements are depicted in Figure 25.

Actual temperature at a few points within the target volume will be directly measured with an invasive thermometry system, using two needles each carrying fourteen temperature sensors. These measurements will be collected by the
Instrument Computer, and sent to the Temperature Subsystem. The Temperature Subsystem will convert the measured temperature information into an array representing measured temperature per treatment cell, also using the needle position information provided to it by the Sensor Locator Subsystem. The measured and calculated temperature per treatment cell will be sent to the Thermal Dose Distribution and Treatment Control Subsystems.

Temperature monitoring using ultrasound transducers is accomplished by selecting a single transducer to transmit a pulse while at the same time either one or a small set of transducers on the opposite side of the Cylindrical Array measure both the Time-of-Flight and Pulse Amplitude Degradation of the pulse that was transmitted. A correlation between the Time-of-Flight and Pulse Amplitude Degradation can then be made to the actual temperature of the treatment cells.

![Through-Transmission TOF Measurement](image)

Requires nanosecond resolution for millimeter to centimeter spatial characterization of phase velocity (Temperature)

Figure 25. Temperature Monitoring

**E.12. Thermal Dose Distribution Subsystem (not included in present system software)**

The Thermal Dose Distribution Subsystem is responsible for calculating the thermal dose distribution in the tissue. This calculation is done based on the temperature for each cell over time. This information is generated by the Temperature Subsystem and consists of current measured temperature, calculated temperatures, and derived temperatures from Time of Flight/Pulse Amplitude Degradation measurements, all with 3-dimensional spatial correlation within the cylinder volume.

The Thermal Dose Distribution task will calculate cumulative thermal dose for each spatial treatment cell and update that information continually during treatment. For each treatment interval, the Thermal Dose Distribution subsystem will compute the temperature dose distribution within the breast from the measurements provided by the
Power Absorption subsystem and then compare the simulation modeling results with the direct invasive temperature measurements and temperature volume-cell measurements derived from Time-of-Flight/Pulse-Amplitude-Degradation measurements in order to correct the model. The Thermal Dose Distribution subsystem will distribute modeling parameters and results to the Treatment Control Subsystem and the Display Subsystem.

E.13. Hardware Calibration Subsystem

The Hardware Calibration Subsystem provides a method for calibrating the ultrasound output for each channel. The input control voltage for each channel is determined for a given ultrasound field intensity. This subsystem is executed prior to shipment of the system and may be executed again on a regular basis or when a ultrasound transducer is replaced or a portion of the circuit that feeds the transducer is changed. During the calibration procedure, a calibration table is generated. Once calibration is completed, the table is written to a file to be used for the next treatment.

E.14. Safety Subsystem

The Safety Subsystem checks safety relevant system hardware prior to and during the therapy session. It ensures that all safety relevant hazards are accounted for and recognized by the software.

Prior to beginning the therapy session the Safety Subsystem will test the Pause Button, Water level error latch, A/D and D/A converters, Heartbeat Error Latch, and the Power Inhibit Latch. During the therapy, this subsystem will monitor the Pause button, Water Level Signal, Water Level Latch, periodically test the A/D and D/A converters, Power Inhibit latch, and confirm that the Instrument computer is generating a Heartbeat signal appropriately. The Instrument Computer will generate a heartbeat at the same time as the Control Computer so that each computer will be watching the other.

This subsystem will also monitor and compare the breast/target positioning error threshold in the configuration file with the actual breast/target location determined by the Contour Monitoring Subsystem. The "zero reference" position will be the central axis of the treatment cylinder.

If an error condition is detected, this subsystem will be responsible for inhibiting the power supply, and/or inhibiting the Ultrasound output power.

E.15. Sensor Locator Subsystem

The Transducer array will be used to determine the positions of the thermometry needles. The Sensor Locator Subsystem is responsible for determining the sensor location of all sensors.
The location of each sensor is determined as follows. Each thermometry needle is a 19-gauge needle with 14 sensors. Spacing of the sensor is retrieved from the Treatment Plan Subsystem. Each needle contains two ultrasound transducer transponders which are utilized to locate the position of the implanted needle exactly within the breast and within the treatment cylinder. The known sensor spacing information is then used to determine the spatial location of each sensor within the total treatment cylinder volume and within the breast. Within these volumes, each sensor is "assigned" by the Temperature Subsystem to a spatial volume cell.

The location of each sensor is also supplied to the Dynamic Treatment Calibration Subsystem so that movement in the sensor locations can also be recognized by the rest of the system.

E.16. PC Interface Subsystem

The PC Interface module initiates and maintains communications with the Instrument computer. This subsystem is capable of operating in three modes. The three modes of operation are Treatment mode, Test mode, and replay mode and are discussed below.

Treatment Mode

In the Treatment Mode, this subsystem communicates with the Instrument Computer to send and receive information about the hardware. The information received by this subsystem includes current measured forward and reflected power for each ultrasound transducer, Through-Transmission", and "Pulse-Echo" measurements for each ultrasound transducer, Current Cooling System Temperature and setpoint, actual temperature measurements as measured by the thermisters, a Heartbeat signal, Video System information, and periodic safety testing information.

Simulation Mode

When operating in the Simulation Mode, this subsystem requests information from the Treatment Records Subsystem such that all requests from the other subsystems will be handled as if a Instrument Computer was present. This mode is provided primarily for testing and debug sessions when the Instrument Computer is not present.

F. Instrument Computer Functions

The Treatment Instrument Computer will receive measurement requests and control output requests via the communication link, act upon the requests as needed, and send replies to the Control Computer containing the measurement results or acknowledging the control operation. Measurement and control parameters needed are detailed below.
F.1. RF Power Subsystem Software

The RF Power Subsystem consists of 96 independent transmitters each driving a 4-way T/R Multiplexer which switches the RF output to the appropriate transducer.

The Instrument Computer will control the switching on/off of each of the VCO sources, the RF output power of each of the amplifier channels, the on-off status of each amplifier channel, the T/R MUX status of each channel relative to the 4 transducers which it may possibly drive, and the selection of which receivers are active at any given instant.

F.2. Receiver Subsystem Software

The Receiver Subsystem consists of 24 independent receiver modules which are interconnected to the T/R MUX devices as shown in Figure 14. The status of each is detected by the Instrument Computer and provided to the Contour Monitoring Subsystem and the Temperature Subsystem.

F.3. Cooling/Heating Control Software Subsystem

This subsystem is responsible for maintaining the proper coolant fluid temperature prior to and during the therapy session. This subsystem sets the cooling system temperature setpoint according to the Configuration file and continuously checks the measured cooling temperature to ensure that the cooling system has not malfunctioned. In the event that the measured temperature value is not within the tolerance (also set in the configuration file) set this subsystem will report the error to the Safety Subsystem. This subsystem is also responsible for turning on/off the cooling system as requested by the Control Subsystem.

F.4. Thermometry Interface Software Subsystem

The Thermometry Interface Subsystem communicates with the thermistor thermometry subsystem in the appropriate manner to receive all temperature information. The temperature information is requested from the Thermometry Subsystem every 4 seconds and is then sent to the Temperature Subsystem in the Control Computer.
F.5. Safety Software Subsystem

The Safety Subsystem checks safety relevant system hardware prior to and during the therapy session. It ensures that all safety relevant hazards are accounted for and recognized by the software.

Prior to beginning the therapy session the Safety Subsystem will test the Pause Button, Water level error latch, A/D and D/A converters, Heartbeat Error Latch, and the Power Inhibit Latch. During the therapy, this subsystem will monitor the Pause button, Water Level Signal, Water Level Latch, periodical test the A/D and D/A converters, Power Inhibit latch, and confirm that the Instrument computer is generating a Heartbeat signal appropriately. The Instrument Computer will generate a heartbeat at the same time as the Control Computer so that each computer is watching the other.

This subsystem will also monitor and compare the breast/target positions within the treatment cylinder volume to the position error threshold specification in the Configuration file and pause the treatment if out of range. If an error condition is detected, this subsystem is responsible for inhibiting the power supply, and/or inhibiting the Ultrasound output power.
Appendix A

Schematics
Appendix B

Measured Angular Beam Profile Data for 2.0 Mhz and 4.5 Mhz Transducers
0.5 MHz Beam Pattern for Square Transducer, Case 1

4.5 MHz, Case 1
Appendix C

Efficiency Data for each Transducer in the Cylindrical Array
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<th>Transducer#</th>
<th>Col</th>
<th>#</th>
<th>Rng</th>
<th>Freq in MHz</th>
<th>Measured Acoustic Watts at D/A V = 2.37</th>
<th>Measured Acoustic Watts at D/A V = 5.00</th>
<th>Calculated D/A Voltage at 0.5 Watts</th>
<th>Calculated D/A Voltage at 4.5 Watts</th>
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<tbody>
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<td>4-230A</td>
<td>C</td>
<td>2</td>
<td>R</td>
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<td>2.64</td>
<td>11.75</td>
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**Total No. Tested** 144

**Frequencies**

- AVE: 4.55 MHz
- MIN: 4.33 MHz
- MAX: 4.82 MHz

**Measured Acoustic Watts**

- AVE: 1.51 Watts
- MIN: 1.08 Watts
- MAX: 2.88 Watts

**Calculated Acoustic Watts**

- AVE: 6.72 Watts
- MIN: 4.81 Watts
- MAX: 12.82 Watts

**Calculated D/A Voltage**

- AVE: 1.38 Watts
- MIN: 0.99 Watts
- MAX: 1.61 Watts

**Calculated D/A Voltage**

- AVE: 4.14 Watts
- MIN: 2.96 Watts
- MAX: 4.84 Watts
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Transducer#  Frequency, in MH  Most Efficient  Power, Watts Ultrasound  DC Watts  Efficiency, %  Transducer Efficiency, %
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Min Value 4.33 1.16 3.98 26.83 45.34
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12 pairs of transducers with identical serial numbers.

*2 - defective (wedge) surface: note #4-170 & #4-168 transducer.

4 - with one serial number written on top of a different serial number: Ex:
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**% Efficiency, RF to Ultrasound**

Efficiency from DC to RF is 60% as measured with Bird meter at 2 to 3 watts ultrasound.
DC to RF efficiency increases to around 75% at 10 watts ultrasound power.
DC to RF efficiency increases to around 90% at 20 watts ultrasound power.
Appendix D

T/R MUX Applicator Transducer Interconnections Map
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Appendix F

FDA Forms 1572 and CV's
STATEMENT OF INVESTIGATOR

1. NAME AND ADDRESS OF INVESTIGATOR.
   Bruce A. Bornstein, M.D.
   Joint Center for Radiation therapy
   Dana-Farber Cancer Institute Division
   330 Brookline Avenue
   Boston MA 02215

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
   - CURRICULUM VITAE
   - OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.
   Clinical Laboratory
   Dana-Farber Cancer Institute
   44 Binney Street, D521
   Boston MA 02115

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).
   Institutional Review Board
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.
   Protocol name: Radiation and Thermal therapy for Extensive Intraductal carcinoma.
   Protocol number: 95-006
FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

2. Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR

Bruce A. Barnste

11. DATE

11-14-96

Public reporting burden for this collection of information is estimated to average 84 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

Please DO NOT RETURN this application to either of these addresses.
Curriculum Vitae

Name: Bruce Alan Bornstein

Address: 11 Edgewater Drive
         Dover, MA 02030

Date of Birth: February 8, 1957

Place of Birth: Boston, MA

Education:
1979 S.B. Massachusetts Institute of Technology, Cambridge, MA
        (Biomedical/Mechanical Engineering)
1983 M.D. Tufts University School of Medicine, Boston, MA

Postdoctoral Training:

Internship and Residency:
1983-84 Intern in Medicine, Mount Auburn Hospital,
        Harvard Medical School, Cambridge, MA
1984-88 Resident in Radiation Therapy, Joint Center for Radiation
        Therapy, Harvard Medical School, Boston, MA

Research Fellowships:
1977-79 Research Assistant, Laboratory for Medical Technology,
        Massachusetts Institute of Technology, Cambridge, MA
1986-87 Research Fellow in Radiation Therapy, Joint Center for
        Radiation Therapy, Harvard Medical School, Boston, MA
1987-88 Research Fellow, Department of Cancer Biology, Harvard
        School of Public Health, Boston, MA

Licensure and Certification:
1984 Diplomate of the National Board of Medical Examiners
1984 Massachusetts License Registration
1988 American Board of Radiology (Therapeutic Radiology),
        Certificate

Academic Appointments:
1984-88 Clinical Fellow in Radiation Therapy, Joint Center for
        Radiation Therapy, Department of Radiation Therapy,
        Harvard Medical School
1988-95 Instructor, Joint Center for Radiation Therapy, Department of
        Radiation Therapy, Harvard Medical School
1993- Deputy Division Chief, Dana-Farber Cancer Institute Division, Joint Center for Radiation Therapy, Harvard Medical School
1993- Director of Clinical Hyperthermia, Joint Center for Radiation Therapy and Dana-Farber Cancer Institute, Harvard Medical School
1995- Assistant Professor, Joint Center for Radiation Therapy, Department of Radiation Therapy, Harvard Medical School

Other Professional Positions:

1979-80 Mechanical Engineer, Lion Precision Corporation, Newton, MA

Awards and Honors:

1978 Tau Beta Pi - National Engineers Honor Society
1978 Pi Tau Sigma - Mechanical Engineers Honor Society
1978 Awarded by MIT Mechanical Engineering Department for Best Tensile Test Specimen produced by a Student

Major Committee Assignments:

1988-93 Scientific Review Board and Committee for Protection of Human Subjects (IRB), voting member, New England Deaconess Hospital, Boston, MA
1996- Executive Committee; Clinical Operations Committee; Education Committee; Information Systems Sub-committee; Women's Cancer Program, Dana-Farber Partners Cancer Care, Boston, MA

Memberships, Offices and Professional Societies:

1980- American Medical Association (AMA)
1980- Massachusetts Medical Society
1985- American Society for Therapeutic Radiology and Oncology (ASTRO)
1985- American College of Radiology (ACR)
1988- Radiation Research Society
1988- North American Hyperthermia Society (NAHS)
1988- New England Society of Radiation Oncology (NESRO)
1989- President, MIT Class of 1979
1990- American Society of Clinical Oncology (ASCO)
1994- American College of Radiation Oncology (ACRO)
1995- Elected Office, Councilor in Medicine of the NAHS
Major Research Interests:


Research Funding Information:

Past:
1987-88 National Research Service Award-Radiation Training Grant Fellowship, NCI CA 09078-12, P.I. John B. Little, M.D.

Current:

Teaching Experience:

Harvard Medical School
1985-87 Lecturer, Radiation Therapy Resident Seminar Series, Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA.
1993 Faculty Speaker and Panel Member, Modern Surgical Oncology for the General Surgeon, Department of Continuing Education, Harvard Medical School, Cambridge, MA. "Breast cancer: Radiation techniques." (5/22/93)
Faculty Speaker and Panel Member, Critical Issues in Breast Cancer Management, Department of Continuing Education, Harvard Medical School, Boston, MA. "Ductal Carcinoma In Situ: How should it be treated." (12/10/93)

1994- Faculty Speaker, Hyperthermia: Biology, Technology, and Cancer Therapy (subject HST532J), Health Sciences and Technology Program, Harvard Medical School & Massachusetts Institute of Technology, Cambridge, MA. (2/8/94 and 2/23/95)

Invited Presentations

1985- Lecturer, Radiation Therapy Technology Program, Allied Health Sciences Department, Massachusetts College of Pharmacy. (1985-present)

1988 Visiting Lecturer, Academic Conference, Breast Evaluation Center, Dana-Farber Cancer Institute, Boston, MA. "The role of radiation therapy and hyperthermia in the management of chest wall recurrence." (12/7/88)

1989 Visiting Lecturer, Breast Cancer Tumor Conference, Beth Israel Hospital, Boston, MA. "Role of radiation therapy and hyperthermia in breast cancer." (1/89)

1991 Invited Speaker, Rehabilitation Services Conference, New England Deaconess Hospital, Boston, MA. "The management of lytic lesions in the lower extremities." (3/21/91)

Invited Lecturer, Fifteenth Annual Meeting of the American Society of Radiologic Technologists, Washington D.C. "Hyperthermia may help to improve local tumor control." (11/6/91)


Visiting Lecturer, Academic Conference, Breast Evaluation Center, Dana-Farber Cancer Institute, Boston, MA. "Hyperthermia and the potential roles in the treatment of breast cancer." (8/19/92)

Surgical Grand Rounds, Cambridge Hospital, Cambridge, MA. "Hyperthermia: An additional modality of cancer treatment." (10/29/92)

Invited Speaker, American Association of Physicists in Medicine (New England Chapter), Worcester, MA. "Hyperthermia: An additional modality of cancer treatment." (12/9/92)
1993 Invited Speaker/Participant, Working Group on the Pulmonary Complications Associated with Breast Cancer Therapy, National Heart, Lung, and Blood Institute, Rockville, MD. "Pulmonary complications related to radiotherapy for breast cancer." (9/20/93)

Oncology Grand Rounds, Tufts-New England Medical Center, Boston, MA. "Current Trends in the Clinical Application of Hyperthermia." (12/17/93)

1994 Invited Speaker and Panel Member, Oncologic Issues of the 90's: "Daily Dilemmas in Cancer Care," Twenty-sixth Annual Southeastern Wisconsin Cancer Conference, American Cancer Society, Milwaukee, WI. "Breast Cancer: Ductal Carcinoma In Situ." (4/9/94)

Invited Speaker, Second Annual Oncology Conference of the Spohn Health System and Texas Medical Association, Corpus Christi, TX. "DCIS of the Breast: Natural history, early detection, and radiotherapeutic management." (4/23/94)

Invited Speaker, Eleventh Annual New England Radiation Therapist Student Day, Joint Center for Radiation Therapy, Boston, MA. "Hyperthermia." (6/1/94)

1995 Invited Speaker, Medical Grand Rounds, Lowell General Hospital, Lowell, MA. "New developments in hyperthermia and its current role in cancer management." (12/6/95)


Invited Speaker, Urologic Oncology Conference, Dana-Farber Cancer Institute, Boston, MA. "Prostate cancer: The possible role of hyperthermia." (5/23/96)

Invited Speaker, Breast Cancer Conference, Women's Cancer Program, Dana-Farber Cancer Institute, Boston, MA. "Long-term cardiac effects of left-sided breast irradiation." (11/6/96)

Leadership Roles:
1993-1996 Coordinator of Monthly Lecture Series, Breast Cancer: Critical issues of local treatment, Breast Evaluation Center, Dana-Farber Cancer Institute, Boston, MA. Role: select speakers and chair meeting. (7/93-8/96)
1996-

Coordinator of Monthly Lecture Series, Breast Cancer: Critical issues of local treatment using radiation therapy, Breast Cancer Conference, Women's Cancer Program, Dana-Farber Partners Cancer Care, Dana-Farber Cancer Institute, Boston, MA. Role: select speakers and chair meeting. (9/96-present)


REVIEWS AND CHAPTERS


Bornstein BA, Svensson GK: Real-time computer controlled ultrasound therapy 
and monitoring system for breast cancer treatment. In Franconi C, Arcangeli G, 
Congress. p391-393. Rome, Italy, Tor Vergata, 1996.

10. Bornstein BA, Harris JR, Hetelekidis S, Hiramatsu H, Recht A: Joint Center for 
Radiation Therapy Experience. In Silverstein MJ, Lagios MD, Poller DN, Recht A 
ed: Ductal Carcinoma in situ: A Diagnostic and Therapeutic Dilemma. 
Baltimore, Williams & Wilkins, [In press].
ABSTRACTS


1. NAME AND ADDRESS OF INVESTIGATOR.
   Jay R. Harris, M.D.
   Joint Center for Radiation therapy
   Beth Israel Deaconess Medical Center Division
   330 Brookline Avenue
   Boston MA 02215

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
   - CURRICULUM VITAE
   - OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.
   Clinical Laboratory
   Dana-Farber Cancer Institute
   44 Binney Street, D521
   Boston MA 02115

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).
   Institutional Review Board
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.
   Protocol name: Radiation and Thermal therapy for Extensive Intraductal carcinoma.
   Protocol number: 95-006
ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION.

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed of their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572

STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

2. Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

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11. DATE

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Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0014)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.
CURRICULUM VITAE

Name: Jay Robert Harris
Address: 12 Byfield Road
Newton, MA 02168
Date of Birth: June 29, 1944
Place of Birth: Weehawken, New Jersey

Education:
1965 B.A., Cornell University, Ithaca, New York
1969 M.A. (Statistics), Stanford University, Stanford, California
1970 M.D., Stanford University, Stanford, California

Postdoctoral Training:
Internship and Residencies:
1970-1971 Medical Intern, St. Louis Jewish Hospital, St.
Louis, MO
1971-1973 Captain, M.D., U.S. Army
1973-1977 Resident in Radiation Therapy, Department of
Radiation Therapy, Joint Center for Radiation
Therapy, Harvard Medical School, Boston, MA

Licensure and Certification:
1971 Massachusetts License Number 37185
1976 Certified by American Board of Radiology in
Therapeutic Radiology

Academic Appointments:
1977-1979 Instructor in Radiation Therapy, Department of
Radiation Therapy, Harvard Medical School, Boston, MA
1979-1982 Assistant Professor in Radiation Therapy,
Department of Radiation Therapy, Harvard Medical
School, Boston, MA
1982-1991 Associate Professor in Radiation Therapy,
Department of Radiation Therapy, Harvard Medical
School, Boston, MA
1991- Professor of Radiation Oncology, Department of
Radiation Oncology, Harvard Medical School,
Boston, MA.

November 20, 1996
Clinical Appointments:

1977- Staff Radiation Therapist, Joint Center for Radiation Therapy, Department of Radiation Therapy, Harvard Medical School, Boston, MA
1981- Clinical Director, Joint Center for Radiation Therapy, Department of Radiation Therapy, Harvard Medical School
1983- Division Chief, Beth Israel Hospital Division, Joint Center for Radiation Therapy, Department of Radiation Therapy, Harvard Medical School
1983-1985 Acting Head, Joint Center for Radiation Therapy, Department of Radiation Therapy, Harvard Medical School
1985- Clinical and Educational Director, Joint Center for Radiation Therapy

Major Committee Assignments:

National and Regional:

1984-1985 National Council on Radiation Protection and Measurements, Scientific Committee
1986- American Cancer Society Breast Cancer Task Force
1987-1995 American Board of Radiology Written and Oral Examination Committee
1991-1993 Scientific Program Chairman, American Society for Therapeutic Radiology and Oncology
1991-1993 President's Panel Special Commission on Breast Cancer
1993-1994 President-Elect, American Society for Therapeutic Radiology and Oncology
1994-1995 President, American Society for Therapeutic Radiology and Oncology
1995-1996 Chairman of the Board, ASTRO
1995- Trustee, American Board of Radiology

Beth Israel Hospital:

1983- Medical Executive Committee
1988- Education Committee
1987- Radiation Safety Committee

Joint Center for Radiation Therapy:

1985- Chairman, Quality Assurance Committee
1985- Vice-Chairman, Credentialing Committee
1988- Radiation Safety Committee
1987- Vice President, JCRT Foundation

Harvard Medical School
1992-1994 Promotions and Reappointment Committee
1995- Subcommittee of Professors

November 20, 1996
Editorial Boards:

1985-1988 Journal of Clinical Oncology
1987- Breast Diseases
1990- Radiotherapy & Oncology
1991- Associate Editor, Cancer
1993- Int J Rad Onc Biol Phys
1993- Breast Cancer Research and Treatment
1993- Journal of Surgical Oncology
1995- Editor, Int J Rad Onc Biol Phys

Ad Hoc Reviewer:

New England Journal of Medicine

Memberships, Offices and Committee Assignments in Professional Societies

1976- American Society for Therapeutic Radiology and Oncology Program committee, 1989
1978- American College of Radiology
1979- Radiation Research Society
1980- American Society of Clinical Oncology Membership Committee, 1985
1983- New England Cancer Society
1985- Massachusetts Medical Society
1985- Massachusetts Radiologic Society
1985- American Medical Association
1985- American Society for the Advancement of Science

Research Interest:

1. The utilization of radiation therapy in the management of breast cancer

2. The causes of breast cancer recurrence following conservative surgery and radiation therapy for early breast cancer

Honors:

1991 Gold Medal, Gilbert Fletcher Society

Faculty Supervision:

Geoffrey Beadle, M.D., Fellow in Radiation Therapy, 1982-1983
John Boyages, M.D., Fellow in Radiation Therapy, 1987-1988
Anthony Abner, M.D., Fellow in Radiation Therapy, 1989-1990
Frank Vicini, M.D., Fellow in Radiation Therapy, 1989-1990
Irene Gage, M.D., Fellow in Radiation Therapy, 1993-1994

November 20, 1996
BIBLIOGRAPHY:

Original Reports


November 20, 1996


Reviews and Chapters


November 20, 1996


16. Harris JR, Hellman S: The treatment philosophy, technique, and results of primary radiation for early breast cancer at the Joint Center for Radiation Therapy. Presented at the 26th Annual Clinical Conference on Cancer, the University of Texas, M.D. Anderson Hospital and Tumor Institute at Houston, November 3-6, 1982.


November 20, 1996


Books


1. NAME AND ADDRESS OF INVESTIGATOR
   Jorgen L. Hansen, M.Sc.
   Joint Center for Radiation therapy
   330 Brookline Avenue
   Boston MA 02215

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE
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   ☐ OTHER STATEMENT OF QUALIFICATIONS

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   44 Binney St
   Boston MA 02115

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10. SIGNATURE OF INVESTIGATOR

[Signature]

11. DATE

[Date] 11/14/96

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200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:
Office of Management and Budget
Paperwork Reduction Project (0910-0014)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.
NAME: Jørgen Lindberg Hansen
ADDRESS: 32 Beverly Road, Wellesley, MA 02181-1154
DATE OF BIRTH: April 14, 1947
PLACE OF BIRTH: Vissenbjerg, Denmark
CITIZENSHIP: Denmark, US Permanent Resident

EDUCATION:
1969 Diploma Danish Airforce (Electronics Engineering)
1980 B.S. University of Copenhagen, Denmark, (Physics)
1982 M.S. University of Wisconsin, Madison, (Medical Physics)

Additional Courses:
1969 Maintenance and repair of analog computers and radar’s for missile control, El Paso, TX.
1975 Maintenance and repair of Varian Linear Accelerators, Palo Alto, CA.
1977 Maintenance and repair of Philips Linear Accelerators, Crawley, United Kingdom.
1984 Maintenance and Repair of GE Dose Planning System (RTPLAN), London, United Kingdom.
1984 Electron Dose Planning, Umeaa, Sweden
1984 Dose Optimization, U. of Wisconsin, Madison
1986 Physics and Technology of Hyperthermia, Urbino, Italy
1987 Physical Aspects of Hyperthermia, Durham NC.

LICENSURE AND CERTIFICATION:
1989 American Board of Radiology Certificate (Therapeutic Radiological Physics)

ACADEMIC APPOINTMENTS:
1985-1989 Visiting lecturer, Harvard Medical School, Boston, MA.
1989-1991 Lecturer, Harvard Medical School, Boston, MA.
1991- Instructor, Harvard Medical School, Boston, MA.
1989- Adjunct Assistant Professor, Mass. College of Pharmacy, MA.

HOSPITAL POSITIONS
1983-1985 Medical Physicist, Radiophysics Laboratory, Vejle Hospital, Denmark
1985- Medical Physicist, JCRT Harvard Medical School, Boston, MA
OTHER POSITIONS:
1964-1974 Electronics Engineer, Danish Airforce
1974-1975 Electronics Engineer, Radiation Division, Varian Europe, Denmark.
1975-1980 Electronics Engineer, Radiophysics Dept., University Hospital of Copenhagen, Herlev, Denmark

AWARDS AND HONORS:

MEMBERSHIPS, OFFICES AND COMMITTEE ASSIGNMENTS IN PROFESSIONAL SOCIETIES:
1986- Institute of Electrical and Electronics Engineers.
1987- North American Hyperthermia Group. (Associate)
1990- Association for Computing Machinery
1991- Chairman of AAPM's committee for QA of Ultrasound Hyperthermia.

RESEARCH INTERESTS:
- Treatment planning of hyperthermia.
- Electromagnetic and ultrasound hyperthermia.
- Invasive and non-invasive thermometry.

TEACHING EXPERIENCE:
1981 TA in health physics for graduate students, UW Madison.
1982 TA in diagnostics radiation. Physics for graduate students, UW, Madison.
1987 - Physics and operation of MW and US hyperthermia equipment for therapists, medical residents, and post doctoral fellows.
1988 - Medical radiation physics for radiation therapists and residents.

INVITED TALKS:
May 1996 Data acquisition and statistical problems in hyperthermia.
Department of Biostatistics, School of Public Health, Harvard Medical School.
May 1996 Advances in hyperthermia at JCRT, Harvard Medical School.
Annual meeting of New England chapter of AAPM, Sturbridge, MA.
ORIGINAL REPORTS:


PUBLISHED ABSTRACTS:


1. NAME AND ADDRESS OF INVESTIGATOR.
   Abram Recht, M.D.
   Joint Center for Radiation therapy
   Beth Israel Deaconess Medical Center Division
   330 Brookline Avenue
   Boston MA 02215

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
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3. Attach protocol outline as described in Section 8.

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and to:
Office of Management and Budget
Paperwork Reduction Project (0910-0014)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

FORM FDA 1572 (12/92)
GENERAL

Date of Birth: June 13, 1952

Place of Birth: Pittsburgh, PA USA

Current Position: Associate Professor
Joint Center for Radiation Therapy
Department of Radiation Oncology
Harvard Medical School, Boston, MA

Work: Department of Radiation Oncology
Beth Israel Deaconess Medical Center
East Campus, Finard Building B25
330 Brookline Avenue
Boston, MA 02215

Phone: (617) 667-2345
FAX: (617) 667-4681
e-mail: arecht@bih.harvard.edu (text only)

Home: 15 Thatcher Street, Apt. 6
Brookline, MA 02146
EDUCATION, TRAINING, LICENSURE AND CERTIFICATION

Education:

1974  B.A.  Yale University, New Haven, CT
1974-75 Yale Law School, New Haven, CT
1975-76 Yale University, New Haven, CT
1980  M.D.  Johns Hopkins Medical School, Baltimore, MD

Postdoctoral Training:

Internship and Residencies:

1980-81 Intern in Medicine, New England Deaconess Hospital, Boston, MA
1981-84 Clinical Fellow, Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA

Licensure and Certification:

1981 Certification of the National Board of Medical Examiners
1982 Permanent Registration, Board of Registration in Medicine, Commonwealth of Massachusetts
1984 Certification of the American Board of Radiology, Therapeutic Radiology
1985 Permanent License, Medical Board of California
Abram Recht - Professional/Administrative Activities

ACADEMIC AND HOSPITAL APPOINTMENTS

Academic Appointments:

Harvard Medical School (Boston)
1984-86 Clinical Instructor of Radiation Therapy
1986-1992 Assistant Professor of Radiation Therapy
1992- Associate Professor of Radiation Oncology

Hospital Appointments:

Beth Israel Deaconess Medical Center (Boston) — successor to Beth Israel Hospital and New England Deaconess Hospital as of October 1, 1996
1996- Senior Radiation Oncologist

Beth Israel Hospital (Boston)
1984-1985 Assistant Radiation Therapist
1985-1995 Radiation Therapist
1995-1996 Senior Radiation Oncologist

Dana-Farber Cancer Institute (Boston)
1984-1985 Consulting Staff, Radiation Therapy
1985-1986 Clinical Associate with Active Staff Privileges
1986-1990 Assistant Physician with Active Staff Privileges
1990- Physician with Active Staff Privileges

New England Deaconess Hospital (Boston)
1984-1996 Courtesy Affiliate Staff, Radiation Therapy

Brigham and Women's Hospital (Boston)
1985- Associate in Radiation Therapy

Children's Hospital Medical Center (Boston)
1985- Courtesy Staff, Radiation Therapy

Faulkner Hospital (Boston)
1985- Courtesy Staff, Radiology

Mount Auburn Hospital (Cambridge MA)
1994- Active Staff, Radiation Oncology
PROFESSIONAL AND ADMINISTRATIVE POSITIONS AND ACTIVITIES

Memberships in Professional Societies:

1980- American Association for the Advancement of Science
1984- Massachusetts Medical Society
1984- Norfolk County (MA) Medical Society
1984- American Society for Therapeutic Radiology and Oncology
1985- American Society for Clinical Oncology
1985- American College of Radiology
1985- Massachusetts Radiological Society
1985- New England Society for Radiation Oncology
1987- European Society for Therapeutic Radiology and Oncology
       (corresponding member)
1990- American Society for Breast Disease
1991- American Medical Writers Association
1994- European Society of Mastology

Professional Society Committees and Positions:

American Society of Clinical Oncology
1995- Member, Health Services Research Committee
1996- Member, Subcommittee on Guideline Methodology, Health Services
       Research Committee

Workshop, Study-Group, and Review Committee Memberships and Positions:

Joint Center for Radiation Therapy
1994- Radiation Modifiers Working Group

Longwood Medical Area (Boston) Gynecologic Oncology Group
1987-90 Member

American College of Radiology
1988- Breast Committee, Patterns of Care Study (development of consensus
       on best current management)
1994- Reviewer of the breast cancer portion of the Radiation Oncology
       Practice Accreditation Program
1995-96 Task Force on Appropriateness Criteria, Expert Panel on Radiation
       Oncology, Breast Work Group (creation of practice guidelines)

Massachusetts Breast Cancer Research Program
10/95 Research Review Committee (review of grant applications)

National Cancer Institute
2/96 Site review committee, renewal application for National Surgical
       Adjuvant Breast and Bowel Project

Departmental Positions and Responsibilities:

Joint Center for Radiation Therapy (JCRT) (Boston)
1984- Deputy coordinator for breast tumors
Abram Recht - Professional/Administrative Activities

1985- Coordinator for gastrointestinal tumors
1988- Director of JCRT Resident Seminar program
1990- Deputy Section Chief, Beth Israel Hospital division
1991- Editor, The Joint Center for Radiation Therapy Handbook
(dpartmental policy manual)
1994- Member, Clinical Investigations Committee
1995- Member, Dose-Standardization Subcommittee, Quality Improvement Committee
1995- Chair, Scientific Review and Audit Subcommittee, Clinical Investigations Committee
1996- Deputy Section Chief, Beth Israel Deaconess Medical Center

Hospital Positions and Responsibilities:

Beth Israel Hospital (prior to October 1, 1996), then Beth Israel Deaconess Medical Center (Boston)

1990- Member, Radiation Safety Committee
1992- Member, Graduate Medical Education Committee
1994- Member, Medical Executive Committee, Cancer Subcommittee

Authorship of Departmental Treatment Policies:

1. Recht A, Harris JR
Primary Radiation Therapy for Early Breast Cancer: Treatment Policy
Joint Center for Radiation Therapy, September 1985; revised edition, July 1986

2. Recht A, Rose MA, Harris JR
Ductal Carcinoma in Situ: Treatment Policy
Joint Center for Radiation Therapy, April 1988

3. Recht A, Pierce SM, Harris JR
Breast - DCIS, Stages I, II
in: Recht A, Buck B, eds
The Joint Center for Radiation Therapy Handbook, April 1994

4. Recht A
Esophageal Cancer
in: Recht A, Buck B, eds
The Joint Center for Radiation Therapy Handbook, April 1994

5. Recht A
Upper Abdominal Cancers
in: Recht A, Buck B, eds
The Joint Center for Radiation Therapy Handbook, April 1994

Editorial Work and Positions:

Ad Hoc Review of Manuscripts
1985- International Journal of Radiation Oncology, Biology, & Physics
1986- Journal of Clinical Oncology
1989- American Journal of Clinical Oncology
1991- European Journal of Cancer
Abram Recht - Professional/Administrative Activities

1991- Radiotherapy and Oncology
1992- Cancer
1992- Plastic and Reconstructive Surgery
1994- Breast Cancer Research and Treatment

Editorial Boards
1995- Journal of Clinical Oncology

Journal/Book Editor
1990-92 Guest Editor, Seminars in Radiation Oncology, issue on "Conservative Management of Early Breast Cancer", April 1992
1995-96 Silverstein M, Lagios MD, Poller DN, Recht A, editors Ductal Carcinoma In Situ of the Breast Williams and Wilkins, Baltimore (associate editor)

Other Administrative Posts and Committees:
5/89-6/90 Member, Host Committee, preparation for the Sixth International Congress on Breast Diseases, Boston MA, June 1990
6/91- Member, Breast Cancer Advisory Group, Risk Management Foundation of the Harvard Medical Institutions
CLINICAL AND RESEARCH ACTIVITIES

Clinical Responsibilities and Positions:

7/84- Radiation Oncologist, Beth Israel Hospital/ Beth Israel Deaconess Medical Center (as of October 1, 1996)

7/84-3/96 Staff Physician, Breast Evaluation Center, Dana-Farber Cancer Institute

12/95- Radiation Oncologist, Gastrointestinal Cancer Clinic, Dana-Farber Cancer Institute/Brigham and Women's Hospital

5/96- Radiation Oncologist, Multidisciplinary BreastCare Clinic, Beth Israel Hospital/ Beth Israel Deaconess Medical Center (as of October 1, 1996)

Participant/Discussant in Hospital Clinics and Conferences:

7/84-5/88 Surgical Tumor Conference, Beth Israel Hospital (monthly meetings)

7/84- Breast Evaluation Center, Dana-Farber Cancer Institute/ Partners Breast Cancer Conference (as of July 1, 1996) (weekly and special monthly)

7/85- Gynecologic Tumor Board, Beth Israel Hospital/ Beth Israel Deaconess Medical Center (as of October 1, 1996) (weekly)

3/87- Breast Tumor Conference, Beth Israel Hospital/ Beth Israel Deaconess Medical Center (as of October 1, 1996) (biweekly)

6/87- Medical-Surgical Gastrointestinal Conference, Beth Israel Hospital (quarterly sessions devoted to GI malignancies)

4/91-4/92 Biliary/Pancreatic Disease Center Conference, Beth Israel Hospital (weekly)

9/91-3/94 Beth Israel (then Longwood) Head and Neck Cancer Clinic, conference and patient clinic (monthly to weekly)

12/95- Gastrointestinal Cancer Clinic, Dana-Farber Cancer Institute-Brigham and Women's Hospital (weekly and special monthly)

Cooperative Research Group Activities:

Cancer and Acute Leukemia Group B (CALGB)
1986- Affiliated investigator
1986-89 Radiotherapy representative from DFCI
1986-88 Participant, Quality Assurance Committee in Radiotherapy (QARC)
1986-88 Radiotherapy Committee representative on the Transplantation Planning Core Committee

European Organization for Research on Treatment of Cancer
11/88 Invited participant, EORTC In Situ Breast Cancer Workshop, Castle Marquette, Heemskerk, the Netherlands
Abram Recht - Professional/Administrative Activities

9/91 Invited participant and chief rapporteur, EORTC DCIS Consensus Meeting, Leuven, Belgium

2/94 Invited participant and chief rapporteur, EORTC DCIS Consensus Meeting, Venice, Italy

Gastrointestinal Cancer Consortium (GCC)
1986-88 Representative from JCRT/Harvard for radiotherapy
1987-88 Executive Committee, Harvard group

Gastrointestinal Tumor Study Group (GITSG)
1985 Radiotherapy representative from Dana-Farber Cancer Institute (DFCI)/JCRT

German Breast Study Group
1996- Data Monitoring Committee, GBSG Trial V

Harvard Cooperative Oncology Group (HCOG)
1992- Member, Breast Committee

National Surgical Adjuvant Breast and Bowel Program (NSABP)
1987- Affiliated investigator

Radiation Therapy Oncology Group
1995- Member, Breast Committee

Listed Investigator on Formal Protocols:

Beth Israel Hospital
92-02-17-1929 Concurrent adjuvant chemoradiotherapy for early breast cancer (principal investigator); activated 3/92 (also open at Brigham & Women's Hospital as #91-3981-1, and DFCI as 92-106); closed 11/94

Dana-Farber Cancer Institute (and affiliated hospitals)
85-136 Wide excision and axillary dissection as definitive local treatment for patients with T1N- breast cancer; activated 5/86, closed 7/92

87-072 A phase I trial of radiotherapy and chemotherapy for treatment of non-metastatic carcinoma of the esophagus (co-chairman); activated 11/87, closed 6/88 (replaced by DFCI 87-073)

87-073 A phase I trial of SR 2508 radiosensitizer combined with radiotherapy and chemotherapy for treatment of non-metastatic carcinoma of the esophagus (co-chairman); activated 5/88, closed 12/92

87-126 A phase I protocol of combined modality therapy utilizing whole abdominal radiotherapy with concurrent cisplatin in patients with predominantly abdominal metastatic disease; activated 2/88; closed

92-128 Chemoradiotherapy in high risk breast cancer patients (co-chairman); activated 11/93; closed 3/95
94-012  A Phase II trial of surgical staging and multimodality therapy for resectable esophageal carcinoma (principal investigator); activated 3/94 (also open at BWH since 2/94 as protocol # 94-6345-1); closed 2/96

Gastrointestinal Cancer Consortium

87-01  Colon cancer - surgical adjuvant treatment, high-risk, local recurrence: a randomized comparison of surgery (control arm) vs. surgery plus postoperative irradiation and 5-FU; group activation 3/87, closed 6/88 (as DFCI 87-023, activated 5/87, closed 6/88)

Cancer and Acute Leukemia Group B

8783  Cyclophosphamide, BCNU, etoposide, and autologous marrow transplantation for resistant Hodgkin's disease (radiotherapy chair); activated 12/87; resigned as co-chair, 10/88

National Surgical Adjuvant Breast and Bowel Project

B-17  A clinical trial to evaluate natural history and treatment of patients with non-invasive intraductal adenocarcinoma; group activation 8/85 (as DFCI 88-026, activated 5/88) (DFCI co-chair); closed 12/90
HONORS AND AWARDS, GRANTS, AND MISCELLANEOUS

Honors and Awards:

1973   Phi Beta Kappa, Yale University
1974   Departmental Honors, Archeology, Yale University
1974   B.A., Summa Cum Laude, Yale University
1990   Martin B. Levene Teaching Award, Joint Center for Radiation Therapy
       (chosen by the residents)

Grants:

1989   Travel Grant, American Society for Therapeutic Radiology and
       Oncology, for travel to visit a European radiotherapy department and
       annual meeting of the ESTRO

Visiting Professorships:

12/92   McGill University Dept of Oncology/Réseau interhospitalier de
        Cancérologie, Université de Montréal Montréal, Québec, Canada
11/95   Department of Radiation Oncology, University of Virginia School of
        Medicine, Charlottesville VA
3/96    Department of Radiation Oncology, M.D. Anderson Cancer Center,
        Houston TX
10/96   Department of Radiation Oncology, Yale University School of
        Medicine, New Haven CT

Miscellaneous:

4/89    Listed among the 184 leading breast cancer specialists in the US in a
        poll of academic physicians conducted by Good Housekeeping
        Magazine
        Smith, eds, Aiken SC: Woodward/White
10/92   Listed among the 419 leading adult cancer specialists (51 breast cancer
        specialists) in the US in a poll of academic physicians conducted by
        Good Housekeeping Magazine
        and GW Smith, eds, Aiken SC: Woodward/White
1993-   Professional Advisory Committee, the Wellness Community, Newton
        MA
TEACHING EXPERIENCE: MEDICAL STUDENTS/RESIDENTS

Awards and Honors:

6/90  Martin B. Levene Teaching Award, Joint Center for Radiation Therapy (chosen by the residents)

Departmental Teaching/Supervision, Medical Students/Residents:

7/84-  Lectures, one-to-one daily clinical supervision and teaching of residents and medical students, and participation in daily morning teaching conferences and weekly resident seminars, Joint Center for Radiation Therapy, Dept. of Radiation Oncology, Harvard Medical School

7/88-  Director of JCRT Resident Seminar program

Departmental Teaching/Supervision, Other Health Professionals:

7/84-  Lectures to radiation therapy technology students, breast cancer and gastrointestinal cancers, at Joint Center for Radiation Therapy

Teaching, Medical Students/Residents in Other Departments:

1/85  Radiotherapy in the treatment of gynecologic malignancies; Lecture, GYN residents, Beth Israel Hospital

2/86  Radiotherapy in the treatment of gynecologic malignancies; Lecture, GYN residents, Beth Israel Hospital

3/89  Radiotherapy in the treatment of colorectal cancer; Lecture, "Professor's Rounds" for Medical Oncology Fellows, Beth Israel Hospital

12/93  Controversies in Breast-Conservation Therapy; Fellow's Lecture Series, Dana-Farber Cancer Institute

12/94  Ajduvant therapy for colon and rectal cancer; Basic Science Curriculum, Dept of Surgery, Beth Israel Hospital
Abram Recht - Educational Activities

TEACHING EXPERIENCE: POSTGRADUATE
(Invited Lecturer, Panel/Symposium Participant)

US National Societies:

11/86  Breast cancer - primary irradiation; Refresher Course, 28th Annual Meeting, American Society for Therapeutic Radiology and Oncology, Los Angeles CA (instructor, with JR Harris)

10/87  Breast cancer - primary irradiation; Refresher Course, 29th Annual Meeting, American Society for Therapeutic Radiology and Oncology, Boston MA (instructor, with JR Harris)

10/88  Breast cancer - primary irradiation; Refresher Course, 30th Annual Meeting, American Society for Therapeutic Radiology and Oncology, New Orleans LA (instructor, with JR Harris and MA Rose)

10/88  Controversial Issues in the Treatment of Breast Cancer; Panel, 30th Annual Meeting, American Society for Therapeutic Radiology and Oncology, New Orleans LA

4/89  Role of radiotherapy in cancer of the rectum and colon; Lecture, 17th Annual Spring Meeting, American College of Surgeons, Boston MA

11/92  Cancer of the Breast - Controversies in Treatment; Refresher Course, 33rd Annual Meeting, American Society for Therapeutic Radiology and Oncology, San Diego CA (instructor, with Susan Pierce)

11/92  Breast Cancer - Oral Presentation of Proffered Papers; 33rd Annual Meeting, American Society for Therapeutic Radiology and Oncology, San Diego CA (session co-moderator)

11/92  Panel - The Integration of Conservative Surgery and Radiation and Adjuvant Chemotherapy for Early Stage Breast Cancer; 33rd Annual Meeting, American Society for Therapeutic Radiology and Oncology, San Diego CA (panel member)

11/93  Cancer of the Breast - Controversies in Treatment; Refresher Course, 34th Annual Meeting, American Society for Therapeutic Radiology and Oncology, New Orleans LA (instructor)

5/94  Integration of radiation and chemotherapy for patients with early-stage breast cancer; Educational Symposium, 30th Annual Meeting, American Society of Clinical Oncology, Dallas TX (speaker)

10/94  Cancer of the Breast - Controversies in Treatment; Refresher Course, 35th Annual Meeting, American Society for Therapeutic Radiology and Oncology, San Francisco CA (instructor)

10/94  Breast Cancer - Oral Presentation of Proffered Papers; 35th Annual Meeting, American Society for Therapeutic Radiology and Oncology, San Francisco CA (session co-moderator)
Abram Recht - Educational Activities

5/95 The role of radiation therapy in organ preservation: implications of treating patients with organ-preserving surgery without radiation therapy; Educational Symposium, 31st Annual Meeting, American Society of Clinical Oncology, Los Angeles CA (speaker)

10/95 Cancer of the Breast - Primary Irradiation; Refresher Course, 36th Annual Meeting, American Society for Therapeutic Radiology and Oncology, Miami Beach FL (instructor)

10/95 Categorical Course on Breast Cancer, 36th Annual Meeting, American Society for Therapeutic Radiology and Oncology, Miami FL (panel member)

10/95 Does adjuvant radiation therapy improve survival?; International Symposium on Breast Cancer, Annual Meeting, American College of Surgeons, New Orleans LA

10/96 Breast Cancer - Oral Presentation of Proferred Papers; 37th Annual Meeting, American Society for Therapeutic Radiology and Oncology, Los Angeles CA (session co-moderator)

International Societies:

11/88 Radiotherapy of ductal carcinoma in situ; EORTC In Situ Breast Cancer Workshop, Castle Marquette, Heemskerk, the Netherlands (invited participant and speaker)

6/90 The role of the radiation therapist in early breast cancer; Sixth International Congress on Breast Diseases, International Society of Senology, Boston (symposium panelist)

6/90 Treatment of noninvasive ductal carcinoma; Sixth International Congress on Breast Diseases, International Society of Senology, Boston (symposium panelist)

9/91 Radiotherapy of ductal carcinoma in situ; EORTC DCIS Consensus Meeting, Leuven, Belgium (invited participant, speaker, and chief rapporteur)

2/94 Ductal carcinoma in situ; EORTC DCIS Consensus Meeting, Venice, Italy (invited participant and chief rapporteur)

9/94 Breast Conserving Therapy - Oral Presentation of Proferred Papers; 6th EORTC Breast Cancer Working Conference, Amsterdam, the Netherlands (session chair)

9/96 Ductal carcinoma in situ; 7th EORTC Breast Cancer Working Conference, Bordeaux, France (rapporteur)

Harvard-Affiliated Hospitals/Harvard Medical School:

2/85 Adjuvant radiotherapy for sarcomas; Medical Oncology Conference, Beth Israel Hospital

6/87 Radiotherapy in the treatment of GI malignancies; Medical-Surgical Gastrointestinal Conference, Beth Israel Hospital
Abram Recht - Educational Activities

8/87 Adjuvant radiotherapy in colorectal cancer - new protocols; Surgical Grand Rounds, Beth Israel Hospital

2/88 Treatment options and policies for noninvasive ductal carcinoma; Breast Evaluation Center Academic Conference, Dana-Farber Cancer Institute

6/89 New modalities in the treatment of esophageal cancer; Medical-Surgical Gastrointestinal Conference, Beth Israel Hospital

9/89 Treatment of the axilla: a radiotherapist's view (panel); Breast Evaluation Center Academic Conference, Dana-Farber Cancer Institute

5/90 Chemotherapy-radiotherapy interactions in the treatment of early stage breast cancer; Breast Evaluation Center Academic Conference, Dana-Farber Cancer Institute

9/90 The role of radiation therapy in the treatment of upper gastrointestinal cancers; Surgical Grand Rounds, Beth Israel Hospital

3/91 Post-mastectomy radiotherapy in the era of adjuvant systemic treatment; Breast Evaluation Center Academic Conference, Dana-Farber Cancer Institute

3/91 Radiation Oncology; Breast Cancer: State of the Art - Nursing Conference Program, Beth Israel Hospital

4/91 Update of the JCRT experience in the treatment of early-stage breast cancer; Breast Cancer Conference, Harvard Community Health Plan

10/91 New protocol of concurrent chemotherapy-radiotherapy for patients with early-stage breast cancer; Breast Evaluation Center Academic Conference, Dana-Farber Cancer Institute

4/92 Post-mastectomy radiotherapy for early-stage breast cancer; Breast Evaluation Center Morning Conference, Dana-Farber Cancer Institute

5/92 Radiation exposure and the development of breast cancer; Breast Evaluation Center Morning Conference, Dana-Farber Cancer Institute

10/92 Concurrent chemotherapy and radiotherapy protocol for patients with early stage breast cancer; Protocol Review Conference, Division of Medical Oncology, Beth Israel Hospital

10/92 Combining chemotherapy and radiotherapy in the treatment of patients with early stage breast cancer; Combined Hematology/Oncology Grand Rounds, Beth Israel/Brigham & Women's/New England Deaconess Hospitals

7/93 Integration of chemotherapy and radiotherapy in the treatment of patients with early stage breast cancer; Breast Evaluation Center Morning Conference, Dana-Farber Cancer Institute

12/93 What is the best way to combine irradiation and chemotherapy after conservative surgery?; Controversies in Breast Cancer, Joint Center for Radiation Therapy/Harvard Medical School
Abram Recht - Educational Activities

4/94 Controversies in the use of radiation therapy for cancer of the esophagus; Multimodality Therapy of Chest Malignancies, Harvard Medical School

11/94 The axilla; Breast Evaluation Center Morning Conference, Dana Farber Cancer Institute (with Susan Troyan)

1/95 Implications of treating patients with early stage breast cancer with conservative surgery without radiation therapy; Beth Israel/Brigham & Women's/New England Deaconess Hospital Hematology/Oncology Grand Rounds

9/95 Local control and survival; Beth Israel Hospital Multidisciplinary Breast Conference

1/95 Adjuvant therapy for rectal cancer; Surgical Grand Rounds, Beth Israel Hospital

2/96 Breast cancer: local control and survival; Combined Hematology/Oncology Grand Rounds, Beth Israel/Brigham & Women's/New England Deaconess Hospitals

4/96 Sequencing of multi-modality treatment; A Comprehensive Approach to the Management of Breast Cancer 1996 (lecture series), Cancer Center, Massachusetts General Hospital

7/96 Sequencing chemotherapy and radiotherapy in the treatment of patients with early-stage breast cancer; Breast Evaluation Center Morning Conference, Dana Farber Cancer Institute

10/96 Radiation therapy as adjuvant treatment for patients with rectal cancer; Lecture Series, Dana Farber Cancer Institute/Brigham & Women's Hospital Gastrointestinal Cancer Clinic

Other American Institutions and Organizations:

8/84 Current concepts in the treatment of breast carcinoma; Conference on the Treatment of Breast Cancer, Don and Sybil Harrington Cancer Center, Amarillo TX

11/84 Conservative treatment of breast carcinoma; Third Annual Lecture in Memory of Dr. John W. Spellman, Dept. of Surgery, St. Elizabeth's Hospital, Boston MA (panel and speaker)

4/85 Breast carcinoma treatment; Visiting Professor Program, Akron City Hospital, Akron OH

8/85 Controversies in carcinoma of the breast; Conference, University of South Florida, held at Orlando FL

9/86 Conservation therapy in early breast cancer - the role of radiation therapy; Cancer Symposium, Central Arkansas Radiation Therapy Institute, Little Rock AK

4/87 Conservative management of early breast cancer; Advances in Radiation Oncology, Central New York Academy of Medicine, New Hartford NY

5/87 Radiation therapy in breast cancer; Current Update in the Treatment of Breast Carcinoma, St. John Hospital, Detroit MI

300
Abram Recht - Educational Activities


10/87  Radiation therapy following initial diagnosis of breast malignancy; Initial Diagnosis and Treatment of Breast Malignancies, American Cancer Society/St. Mary's Hospital, Milwaukee WI

1/88  Breast cancer - the radiation therapist's approach; and, The Role of radiation in the therapy of colorectal cancer; Eleventh Annual Winter Symposium - Cancer for the Primary Care Physician, St. Mary's Hospital, Grand Junction CO

2/88  Radiotherapeutic management of early breast cancer; Early Diagnosis of Breast Cancer: the Physician's Role (Diagnosis, Medicolegal Issues and Treatment), American Cancer Society, Pinellas County Unit, Tampa FL

3/88  Controversies in primary breast cancer; Monthly Meeting, Clinical Oncology Association of Georgia, Atlanta GA

4/88  Treatment of ductal carcinoma in situ; Internal Medicine Ground Rounds, Harper Hospital, Detroit MI

4/88  Controversies in the treatment of early-stage invasive breast cancer; Oncology Grand Rounds, Harper Hospital, Detroit MI

5/88  Conservative surgery and radiation therapy for early breast cancer; Breast Cancer Update, American Cancer Society of Indiana, Lake County Unit/Indiana University School of Medicine, Northwest Center, Merrillville IN

10/88  Controversies in the management of early stage breast carcinoma; San Diego County Radiological Society, Radiation Therapy Section, San Diego CA

11/88  Symposium - Preinvasive breast cancer (speaker and panel member); 99th Meeting, New England Cancer Society, Boston MA

3/89  Conservative surgery and radiation therapy in the treatment of early breast cancer; Third Annual Columbus Cancer Conference, Riverside Methodist Hospital, Columbus OH

4/89  Conservative surgery and radiation therapy for early-stage breast cancer; and, Controversies in the treatment of breast cancer; Seminar on Breast Cancer, American Cancer Society, Sarasota Unit, Sarasota FL

7/89  Conservative surgery and radiation therapy for early breast cancer; Breast Cancer: Diagnosis and Treatment Modalities, University of Kentucky Medical Center/St. Claire Medical Center, Morehead KY

9/89  Adjuvant radiotherapy in node-negative breast cancer; Perspectives in the Management of Early Breast Cancer, Macomb Hospital Center, Warren MI

11/89  Conservative surgery and radiation therapy for early stage breast cancer; Breast Cancer 1990, Cancer Care Associates, Rexford NY
2/90  Breast cancer: electron boost vs. implant; The Role of High Energy Electrons in the Treatment of Cancer, 25th Annual San Francisco Cancer Symposium, St. Mary's Hospital and Medical Center, San Francisco CA

9/90  Controversies in the treatment of early breast cancer; The Diagnosis and Management of Early Breast Cancer, Seventh Annual Update in Surgical Pathology, Washington Hospital Center, Washington DC

4/91  Conservative surgery and radiation therapy for early-stage breast cancer; Medical Grand Rounds, St. Elizabeth's Hospital, Boston MA

9/91  Integration of conservative surgery, radiation therapy, and chemotherapy in the treatment of patients with early-stage breast cancer; and, Panel on DCIS; Current Trends in Breast Cancer, Pennsylvania Oncologic Society, Gettysburg PA

11/91  Management of early breast cancer: conservative surgery and radiation therapy; Management of Breast Cancer: Present Strategies - Future Trends, First Annual Cancer Symposium, Crozer Regional Cancer Center, Upland PA

1/92  Radiotherapy and conservative surgery in invasive breast cancer; Why do we fail in conservation treatment of breast cancer?; and, In situ cancer - considerations for therapy; Diagnosis and Treatment of Early Breast Cancer, Dept. of Radiology, University of Alabama at Birmingham, held in Naples FL

3/92  Treatment of in situ breast cancer; and Radiotherapy/chemotherapy integration in breast conservation therapy; Organ Conservation in Curative Cancer Treatment, 27th Annual San Francisco Cancer Symposium, St. Francis Memorial Hospital, San Francisco CA

9/92  The role of radiotherapy in the management of DCIS; and The role of radiotherapy in the treatment of early stage invasive breast cancer; Early Breast Cancer Diagnosis & Treatment: the State-of-the-Art Team Approach, Orlando FL

10/92  Treatment of ductal carcinoma in situ; Annual Meeting, Piedmont Oncology Association, Hilton Head SC

10/92  Integration of chemotherapy and radiotherapy in the treatment of early-stage breast cancer; New York Roentgen Society, Oncology Section, New York NY

1/93  Extensive intraductal component (EIC) and other risk factors for failure of conservation treatment of breast cancer; and, What the diagnostic radiologist should know about conservation treatment of breast cancer; 3rd Annual Mammography Course, Dept. of Radiology, University of Alabama at Birmingham, held at Naples FL

2/93  Conservative therapy in radiation oncology for early stage breast cancer; and Controversies and difficult questions in radiation oncology; New Trends in Breast Cancer, Georgia Division, American Cancer Society, Atlanta GA

6/93  Controversies in the management of early stage breast cancer; Oncology Conference, Goddard Memorial Hospital, Stoughton MA
Abram Recht - Educational Activities

9/93 Integration of chemotherapy and radiotherapy; National Symposium on Concurrent Modalities of Cancer Treatment, South-Eastern Michigan Division, American Cancer Society and Michigan Institute of Radiation Oncology, Dearborn MI

9/93 Radiation therapy for breast cancer; 13th Annual Breast Imaging Conference, Medical College of Wisconsin, Palm Springs CA

11/93 Treatment options for ductal carcinoma in situ; Conference, Center for Breast Care, St. Elizabeth's Hospital, Boston MA

4/94 Controversies in breast-conservation therapy; McIntyre Symposium on Breast Cancer, Veterans Memorial Medical Center, Meriden CT

5/94 Controversies in breast conservation management; 24th Annual Course, Current Concepts in Radiation Therapy, Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis MN

5/94 Management of DCIS; Breast Cancer Symposium, St. Francis Hospital and Medical Center, Hartford CT

6/94 Controversies in breast-conservation therapy; Department of Radiation Oncology, Tufts-New England Medical Center, Boston MA

6/94 Controversies in management of early breast cancers; Diagnosis and Management of Early Breast Cancer, South Nassau Communities Hospital, Oceanside NY

8/94 Radiation therapy for in situ and Stages I/II disease: patient selection and results; and, Radiation strategies and outcome data for advanced local-regional disease; Comprehensive Management of Breast Cancer and Breast Reconstruction, Brown University School of Medicine, Goat Island RI

10/94 Breast; ChemoRadiation 1994, The Cancer Center at Saint Agnes and Kaweah Delta Cancer Care Center/University of California, San Francisco, at Yosemite National Park CA

11/94 Role of radiation therapy for in situ carcinoma; Role of radiation therapy for early invasive carcinoma; and, Integration of chemotherapy and radiotherapy; Multidisciplinary Conference on Diagnosis and Treatment of Early Stage Breast Cancer, Mammography Education Inc, at Maui HI

3/95 The role of radiation therapy in the treatment of early breast cancer; Medical Grand Rounds, St. Elizabeth's Hospital, Boston MA

4/95 Conservative surgery and radiation therapy; Controversies in Breast Cancer, Sacred Heart Hospital and University of Pennsylvania Cancer Center, Allentown PA

5/95 Conservative surgery without radiation therapy for early stage breast cancer: the importance of local control; 25th Annual Course, Current Concepts in Radiation Therapy, Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis MN

6/95 Radiation therapy in the management of breast cancer; American Cancer Society Annual Symposium, Glens Falls Hospital/American Cancer Society Warren-Essex
South Division/Adirondack Education Consortium for Health Organizations, Glens Falls NY

7/95 Debate: Women who undergo breast-preserving therapy for Stage I and II breast cancer greater than 1 cm (ER/PR negative) should receive systemic chemotherapy prior to radiotherapy; Annual Meeting, Southern Association for Oncology, West Palm Beach FL

9/95 Ductal carcinoma in situ; Tumor Board Series, St. Annes's Hospital, Fall River MA

9/95 Early breast cancer: the role of radiotherapy; Perspectives in Breast Cancer, Indiana University Cancer Center, at Phoenix AZ

11/95 Patient selection and integration of chemotherapy and radiation therapy for patients with early-stage invasive breast cancer; Visiting Professors Lecture Series, Department of Radiation Oncology, University of Virginia Health Sciences Center, Charlottesville VA

11/95 Controversies in early-stage breast cancer; Annual Meeting, Mid-Atlantic Society of Radiation Oncology, Annapolis MD

4/96 Local control and survival in breast cancer; Grand Rounds, Hematology/Oncology Division, Department of Veterans Affairs Hospital, Boston MA

5/96 Patient selection for treatment with breast-conserving surgery and radiation therapy; 26th Annual Course, Current Concepts in Radiation Therapy, Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis MN

9/96 Radiation therapy for breast conservation; Approaches to the Management of Breast Cancer, Memorial Medical Center, Savannah GA

10/96 Integration of chemotherapy and radiotherapy in the treatment of patients with early-stage breast cancer; Grand Rounds, Yale Cancer Center, New Haven CT

Other Institutions and Organizations Outside the US:


9/88 Loco-regional therapy of breast cancer; Early Cancer: Detection and Management - 25th Clinical Conference, Ontario Cancer Treatment and Research Foundation, Thunder Bay, Ontario, Canada

11/88 Conservative surgery and radiotherapy for early stage breast cancer: update of the JCRT experience; Lecture, Netherlands Cancer Institute, Amsterdam

8/89 Conservative management of breast cancer: the JCRT experience; Lecture, Royal Marsden Hospital, Sutton, Surrey, UK
Abram Recht - Educational Activities

12/92  Selection factors for integration of conservative surgery and radiotherapy; Management of ductal carcinoma in situ; Integration of breast-conserving surgery, radiotherapy, and chemotherapy for patients with early-stage breast carcinoma; Treatment of regional lymph nodes - the controversy; Visiting Professor, Department of Oncology, McGill University School of Medicine, Montréal PQ, Canada

5/93  The role of radiation therapy in conservative breast cancer therapy; and Radiotherapy for ductal carcinoma in situ; Fourth International Symposium on Current Aspects of the Treatment of Gynecological and Breast Cancers, Universitäts-Frauenklinik, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Federal Republic of Germany

10/93  The use of margin assessment and histology in the selection of patients for breast conservation therapy; A Symposium on Breast Diseases (Second Annual Symposium), Ottawa Regional Cancer Center, Ottawa ON, Canada

Abram Recht - Educational Activities

PUBLISHED SYLLABI/MATERIALS FOR CORRESPONDENCE COURSES

ONCOLIT 1988  Summary of Literature: Conservative Surgery and Radiation Therapy for Early-Stage Breast Cancer (with JR Harris); published under the auspices of the American Society for Therapeutic Radiology and Oncology

ONCOLIT 1989  Summary of Literature: Conservative Surgery and Radiation Therapy for Early-Stage Breast Cancer (with JR Harris); published under the auspices of the American Society for Therapeutic Radiology and Oncology

PUBLIC EDUCATION/INFORMATION ACTIVITIES

5/85-6/88  Adviser, Cancer Information Service, Division of Cancer Control, Dana-Farber Cancer Institute, Boston, regarding weekly newspaper column of cancer information (Boston Sunday Globe)

5/86  Interview on newscast, WBZ-TV, Ch. 4, Boston, concerning breast cancer detection and mammography (with Dr. Lucy Hahn, Dept. of Radiology, Beth Israel Hospital)

4/87  Appearance on radio talk-show, WIBX-AM, and news interview, WUTR-TV, Ch. 20, Utica NY, concerning breast cancer treatment

11/92  Interview for the Hometown Radio Interview Program, sponsored by the American Society for Therapeutic Radiology and Oncology

10/94  Interview for the Hometown Radio Interview Program, sponsored by the American Society for Therapeutic Radiology and Oncology
ABRAM RECHT, M.D.

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   When is more better?

8. Recht A
   Commentary on Chaudhuri et al, Distribution of estrogen receptor in ductal carcinoma in situ of the breast, Surgery 113: 134-137, 1993

9. Recht A
   Breast Diseases: A Year Book Quarterly 4(4): 58, 1993

10. Recht A, van Dongen JA, Peterse JL
    Ductal carcinoma in situ (conference news)
    Lancet 343: 969, 1994

11. Recht A
12. Recht A, Harris JR
Commentary on DiPacia et al, Ipsilateral breast tumor recurrence following conservative surgery and definitive radiation therapy
Oncology (Huntington) 8(12): 71-75, 1994

Third meeting of the DCIS Working Party of the EORTC (Fondazione Cini, Isola S. Giorgio, Venezia, 28 February 1994) — conference report
Eur J Cancer 30A: 1895-1900, 1994

14. Recht A
Influence of the surgery-radiotherapy interval on the risk of local failure in patients treated with conservative surgery and radiation therapy for early-stage invasive breast cancer
Breast Disease: A Year Book Quarterly 6(3): 249-250, 1995

15. Recht A
The return (?) of postmastectomy radiotherapy

16. Recht A
Commentary on Pierce and Lichter, Defining the role of post-mastectomy radiotherapy: the new evidence
Oncology (Huntington) 10(7): 1006, 1996
LETTERS TO THE EDITOR, CORRECTIONS, AND MISCELLANEOUS

1. Loeffler J, Recht A, Harris JR
Letter to the editor

2. Minsky BD, Recht A
Prognostic factors for colon cancer (reply to correspondence)
J Clin Oncol 6: 1066-1067, 1988

3. Klein RL, Recht A, Swain SM, Marchant DJ
Tumor Board: Treating "aggressive" early breast cancer
Oncology Times 12(11): 5-6, Nov 1990

4. Recht A, Harris JR
Response to letter to the editor by Pezner et al

5. Recht A
Radiotherapy and ductal carcinoma-in-situ of breast (letter)
Lancet 340: 312, 1992

6. Recht A, Coleman CN, Harris JR, Come SE, Gelman RS
Response to letter to the editor by McCormick et al
J Clin Oncol 11: 192-193, 1992

7. Recht A
Response to letter to the editor by Mansfield

8. Recht A
Radiotherapy and management of the axilla in early breast cancer (letter)
Br J Surg 82: 421-422, 1995

9. Recht A
High-dose chemotherapy for metastatic breast cancer (letter)

10. Recht A
Effects of radiotherapy and surgery in early breast cancer (letter)

11. Recht A, Come SE, Harris JR
Sequencing of chemotherapy and radiotherapy in breast cancer: response to letter to the editor by Dr. James J. Stark (letter)
ARTICLES AND ABSTRACTS SUBMITTED FOR PUBLICATION

   The use of radiotherapy in the conservative management of Paget's disease of the breast
   Int J Radiat Oncol Biol Phys, submitted for publication 10/96
1. NAME AND ADDRESS OF INVESTIGATOR:
   Kitt Shaffer, M.D., Ph.D.
   Department of Radiology
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
   ☑ CURRICULUM VITAE   ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED:
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY:
   Clinical Laboratory
   Dana-Farber Cancer Institute
   44 Binney Street, D521
   Boston MA 02115

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES):
   Institutional Review Board
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S):

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR:
   Protocol name: Radiation and Thermal therapy for Extensive Intraductal carcinoma.
   Protocol number: 95-006
CURRICULUM VITAE

DATE PREPARED: 5/28/96

NAME: Kitt Shaffer, M.D., Ph.D.

ADDRESS: 14C Bellis Circle
          Cambridge, Massachusetts 02140

PLACE OF BIRTH: Kansas City, Missouri, U.S.A.

EDUCATION:

1976  B.A. Kansas State University
      Manhattan, Kansas

1983  M.D. Tufts University School of Medicine, Boston, Massachusetts

1983  Ph.D. University of Kansas (Anatomy)
      Kansas City, Kansas

POST DOCTORAL TRAINING:

1983-84 Medical/surgical internship Newton-Wellesley Hospital
        Newton Lower Falls, Massachusetts

1984-88 Radiology residency New England Medical Center
        Boston, Massachusetts

1988-89 Clinical fellowship Brigham and Women's Hospital,
        Boston, Massachusetts
LICENSURE AND CERTIFICATION:

1979 National Board of Medical Examiners, Part 1
1983 National Board of Medical Examiners, Part 2
1984 National Board of Medical Examiners, Part 3
1985 Massachusetts medical license
1987 American Board of Radiology

ACADEMIC APPOINTMENTS:

1976-77 Graduate Division of Biology
    Teaching Kansas State University,
    Assistant Manhattan, Kansas
1979-81 Graduate Department of Anatomy
    Teaching University of Kansas Medical
    Assistant School, Kansas City, Kansas
1989- Instructor Harvard Medical School
    in Radiology Boston, Massachusetts

HOSPITAL APPOINTMENTS:

1989-91 Clinical Staff member, Division of Thoracic
    Radiology, Brigham and Women's Hospital, Boston,
    Massachusetts
1991-92 Acting Co-Director, Division of Thoracic Radiology,
    Brigham and Women's Hospital, Boston,
    Massachusetts
1992-93 Clinical Director of Radiology, Dana-Farber Cancer
    Institute, Boston, Massachusetts

AWARDS AND HONORS:

1981 first place in Graduate Student Research
    Central States Electron Microscopy Society
1982 Alpha Omega Alpha medical honor society
    Tufts University School of Medicine
1988 Warren Widrich Award for Radiology
    Boston Veteran's Administration Hospital
1992-95 Editor's Recognition Award for Excellence in
    Reviewing-Radiology

334
MAJOR COMMITTEE ASSIGNMENTS:

1989 Radiology residency selection committee-BWH
1990 CT clinical research committee-BWH
1990 Radiology forms committee-BWH
1990 Radiology quality improvement committee-BWH
1991 Education committee-BWH

MEMBERSHIPS IN PROFESSIONAL SOCIETIES:

1980-1983 Tissue Culture Association
1981-1983 Electron Microscopy Society of America
1983-1988 National Association of Residents and Interns
1977- American Medical Association
1977- American Medical Women's Association
1980- Amer. Assoc. for the Advancement of Science
1981- Sigma Xi
1982- Massachusetts Medical Society
1983- Radiological Society of North America
1991- Reviewer for Radiology
1983- New England Roentgen Ray Society
1983- American Association of Women Radiologists
1990- American College of Radiology

MAJOR RESEARCH INTERESTS:

1. Imaging and diagnosis of mediastinal masses with special attention to anatomic considerations, subdivisions of mediastinal compartments, and use of CT and MR in the mediastinum.

2. Teaching methods for radiology and radiological anatomy at the resident and medical student level, with emphasis on computer-assisted instruction and one-on-one discussion.


4. Imaging and treatment of advanced lung carcinoma using a
combined chemotherapeutic-surgical approach, with emphasis on application of MR in staging and follow-up.

5. Imaging of lung transplants and complications thereof.

6. Imaging of lymphoma and breast carcinoma using radiography, CT and nuclear medicine.

No research grant support.

PRINCIPAL CLINICAL RESPONSIBILITIES:

1988- Staff Radiologist
   Division of Thoracic Radiology
   Brigham and Women's Hospital
   Boston, Massachusetts

1991- Clinical Director of Radiology
   Dana-Farber Cancer Institute
   Boston, Massachusetts

MAJOR ADMINISTRATIVE RESPONSIBILITIES:

1991-92 Acting Co-Director, Division of Thoracic Radiology
   Brigham and Women's Hospital
   Boston, Massachusetts

1992- Clinical Director of Radiology
   Dana-Farber Cancer Institute
   Boston, Massachusetts

1996- Director of Medical Student Education
   Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts

TEACHING EXPERIENCE:

1979-1980 Laboratory instructor, first-year medical gross anatomy
   University of Kansas Medical School
   15 students, 20 hours/week

1980-1981 Laboratory instructor, first-year medical
histology
University of Kansas Medical School
30 students, 10 hours/week
1980-1981 Lecturer, first-year medical anatomy
University of Kansas Medical School
150 students, 1 hour/2 weeks
1984-1988 Lecturer, first-year medical radiographic anatomy
Tufts University School of Medicine
30 students, 2 hours/month
1984-1988 Lecturer, fourth-year medical radiology
Tufts University School of Medicine
10 students, 4 hours/month
1985-1988 Lecturer, second-year medical physiology
Tufts University School of Medicine
30 students, 4 hours/semester
1988-pres Lecturer, Radiology noon conference
Brigham and Women's Hospital
15 residents, 1 hour/2 months
1988-pres Lecturer, Radiology noon conference
New England Medical Center
15 residents, 1 hour/month
1988-pres Lecturer, third-year medical Radiology
Brigham and Women's Hospital
10 students, 3 hours/month
1988-1992 morning teaching rounds, Thoracic Radiology
Brigham and Women's Hospital
2 residents and fellow, 6 hours/month
1989-1992 Lecturer, second-year medical Pathology
Harvard Medical School
25 students, 2 hours/semester
1990-pres Lecturer, Radiology afternoon conference
Boston Veteran's Administration Hospital
10 residents, 1 hour/2 months
1993-pres Lecturer, noon conference, BU Radiology
Boston City Hospital
10 residents, 1 hour/2 months
1994-pres Lecturer, noon conference, Lahey Clinic
Lahey Clinic, Department of Radiology
10 residents, 1 hour/2 months
BIBLIOGRAPHY:

Original Reports-


10. Stark P, Jacobson F, Shaffer K. Standard imaging in silicosis


Proceedings of Meetings:


STATEMENT OF INVESTIGATOR

1. NAME AND ADDRESS OF INVESTIGATOR.
   Charles L. Shapiro, M.D.
   Breast Evaluation Center
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
   ☑ CURRICULUM VITAS
   ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.
   Clinical Laboratory
   Dana-Farber Cancer Institute
   44 Binney Street, D521
   Boston MA 02115

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).
   Institutional Review Board
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.
   Protocol name: Radiation and Thermal therapy for Extensive Intraductal carcinoma.
   Protocol number: 95-006
8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION.

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.66.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572

STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

2. Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR

11. DATE

Public reporting burden for this collection of information is estimated to average 84 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

Please DO NOT RETURN this application to either of these addresses.

FORM FDA 1572 (12/92) PAGE 2 OF 2
CURRICULUM VITÆ

Name: Charles Louis Shapiro

Address: 4 Fairbanks Road, Lexington, MA 02173

Place of Birth: Brooklyn, New York

Education:

1979 B.S. State University of New York, Binghamton, NY
1984 M.D. State University of New York, Buffalo, NY

Postdoctoral Training:

Internship and Residency:

1984-1985 Intern in Medicine, Temple University Hospital, Philadelphia, PA
1985-1986 Junior Assistant Resident, Internal Medicine, Temple University Hospital
1986-1987 Senior Assistant Resident, Internal Medicine, Temple University Hospital

Fellowships:

1988-1991 Clinical Fellow in Medicine, Harvard Medical School
1988-1991 Fellow in Medical Oncology, Dana-Farber Cancer Institute
1988-1991 Clinical Fellow in Medicine, Brigham and Women's Hospital

Licensure and Certification:

1984 Pennsylvania License Registration
1987 American Board of Internal Medicine Certificate
1988 Massachusetts License Registration
1991 American Board of Internal Medicine, Medical Oncology Certificate

Academic Appointments:

1991-1996 Instructor in Medicine, Harvard Medical School
1996- Assistant Professor of Medicine, Harvard Medical School
Hospital Appointments:

1991-1992 Clinical Associate, Dana-Farber Cancer Institute
1991-1996 Instructor in Medicine, Dana-Farber Cancer Institute
1991- Associate Physician, Brigham and Women's Hospital
1991-1994 Staff Physician, New England Deaconess Hospital

Awards and Honors:

1979 B.S. with Outstanding Academic Achievement
1984 Alpha Omega Alpha
1984 John Watson Award for Scholarship in Medicine
1984 Baccilli Award for Academic Excellence
1991 Honorary Member of the Sociedad Venezolana de Mastologia

Major Committee Assignments:

1993- Medical Records Committee, Dana-Farber Cancer Institute
1996- Drug Use Evaluation Committee, Dana-Farber Cancer Institute
1996- Scientific Review Committee, Dana-Farber Cancer Institute
1996- Pharmacy and Therapeutics Committee, Dana-Farber Cancer Institute

Research Interests:

1. Treatment-related toxicities of cancer therapy
2. Phase I/II clinical evaluations of new drugs and new drug combinations
3. Evaluation and management of bone metastasis

Research Funding Information:

Past: 1991-1994 American Cancer Society PI Clinical Oncology Career Development Award

1992-1994 NIH/P01 Co-PI Optimization of hyperthermia: biologic and physical studies


Principal Clinical and Hospital Service Responsibilities:

Dana-Farber Cancer Institute:

1989-1994 Coordinator, Breast Evaluation Center Academic Conferences
1996- Associate Director, Breast Program, Dana-Farber Cancer Institute

Self Report of Teaching:

Local Contributions

Harvard Medical School

1993-1995 Dana-Farber Cancer Institute
Cancer Medicine Course
Lecturer - "Renal Cell Carcinoma"
500 CME students and postdocf/end fellows
20 hours of preparation for handout/lecture, and 30 minute lecture every other year

1994-1996 Brigham and Womens Hospital and Dana-Farber Cancer Institute
Urologic Oncology Course
Lecturer - "Immunotherapy"
200 CME students and postdocf/end fellows
20 hours of preparation for handout/lecture, and 45 minute lecture every other year

1994-1996 Deaconess Hospital
Modern Surgical Oncology for the General Surgeon
Lecturer - "How does venous access help the chemotherapist?"
Lecturer - "Selection of Adjuvant Chemotherapy by Use of Prognostic Indicators"
150 CME students and postdocf/end fellows
20 hours of preparation for handouts/lecture and 45 minute lecture every other year

1996- Dana-Farber Cancer Institute
Attending
3 interns, 1 resident, and 2 oncology fellows
2 months/year
1994- Emerson Hospital, Concord MA  
Tumor Board  
Discussant  
15 CME students  
3 hours of preparation/month  

Regional, National, and International Contributions  

Invited Presentations:  

1993  National Cancer Institute Symposia on Breast Cancer in Young Women  
Invited speaker; “Late effects of adjuvant therapy”  
1995  University of Louisville Oncology Minisymposia  
Invited speaker; “Late effects of adjuvant therapy”  
1995  Chemotherapy Foundation Symposium XII  
Invited speaker; “Liposomal Adriamycin for Breast Cancer”
BIBLIOGRAPHY

Original Reports:


Proceedings of Meetings:


Reviews and Educationally Relevant Publications:


Books and Monographs:

Abstracts:


1. NAME AND ADDRESS OF INVESTIGATOR.
   Barbera L. Smith, M.D., Ph.D.
   Comprehensive Breast Health Center
   Massachusetts General Hospital
   Emerson Place
   Boston MA 02114

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE
   DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
   ☑ CURRICULUM VITAL ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL
   BE CONDUCTED.
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.
   Clinical Laboratory
   Dana-Farber Cancer Institute
   44 Binney Street, D521
   Boston MA 02115

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).
   Institutional Review Board
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE
   CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.
   Protocol name: Radiation and Thermal therapy for Extensive Intraductal carcinoma.
   Protocol number: 95-006
CURRICULUM VITAE

Name: Barbara L. Smith, M.D., Ph.D.

Address: Massachusetts General Hospital
Comprehensive Breast Health Center
Zero Emerson Place, Suite 112, Boston, MA 02114

Date of Birth: May 14, 1955

Place of Birth: Longbeach, California

Education:

1977 S.B. Massachusetts Institute of Technology
1983 Ph.D. Harvard Graduate School of Arts and Sciences
1983 M.D. Harvard/MIT Division of Health Sciences and Technology,
Harvard Medical School

Postdoctoral Training:

Internship and Residencies:

1983 - 1984 Intern in General Surgery, Brigham and Women's Hospital, Boston, MA
1984 - 1988 Resident in General Surgery, Brigham and Women's Hospital, Boston, MA
1988 - 1989 Chief Resident in Surgery, Brigham and Women's Hospital, Boston, MA

Licensure and Certification:

1988 Massachusetts License Registration
1990 Board Certified, American Board of Surgery

Academic Appointments:

1978 - 1980 Teaching Assistant, Harvard Medical School
1983 - 1989 Clinical Fellow in Surgery, Harvard Medical School
1989 - 1994 Instructor in Surgery, Harvard Medical School
1994 - Assistant Professor, Harvard Medical School

Hospital Appointments:

1988 - 1992 Associate Surgeon, Brigham and Women's Hospital, Boston, MA
1989 - 1990 Staff Surgeon, West Roxbury Veteran's Administration Medical Center,
West Roxbury, MA
1989 - 1992  Associate Surgeon, Dana Farber Cancer Institute, Boston, MA
1992 - Director, Comprehensive Breast Health Center, Massachusetts General Hospital, Boston, MA
1995 - Director Massachusetts General Hospital/Brigham and Women's Hospital
1996 - Partner's Comprehensive Breast Health Center, Boston, MA
1996 - Associate Visiting Surgeon, Massachusetts General Hospital, Boston, MA

Awards and Honors:
1973  Highest female score in state, New York State Regents' Scholarship Exam
1977  Phi Beta Kappa, MIT
1977  MIT Alumnae Association Award to an Outstanding Senior
1984, 1988  Medical Student Teaching Award, Brigham and Women's Hospital

Major Committee Assignments

National and Regional
1994  NIH Study Section, Pathology B, ad hoc member

Brigham and Women's Hospital

1990 - 1992 Associate Director Surgical Residency Program
1991 - 1992 Member Executive Committee, Brigham Surgical Group

Massachusetts General Hospital

1993  Chairman, Breast Center Task Force
1993 - 1994  Chairman, Oncology Subcommittee, Task Force on the Future of Clinical Research
1993 -  Member, Women's Health Committee
1993 -  Member, Cancer Affairs Committee
1994 -  Member, Information Systems Committee, MGH Cancer Center

Membership, Offices and Committee Assignments in Professional Societies:

1983 - American Medical Association
1988 - Massachusetts Medical Society
1991 - New England Cancer Society
1991 - Association for Academic Surgery
  1993 - Program Committee
  1994 - Chairman, Membership Committee
1991 - Breast Cancer Advisory Group, Harvard Risk Management Foundation,
Chairman, Surgical Subcommittee
1991 - Cancer and Leukemia Group B
   1992 - Fellow, American College of Surgeons
   1993 - Surgical Principal Investigator, Massachusetts General Hospital
   1993 - Member, Breast Surgery Committee
   1993 - Massachusetts Chapter American Cancer Society, Breast Cancer Task Force
   1993-1994 Medical Vice President, Board of Directors, Central Boston Unit, American Cancer Society
   1993 - Massachusetts Chapter, American College of Surgeons
   1994 - Society of Surgical Oncology

Editorial Boards

1993 - Advisory Board, Harvard Women's Health Watch

Major Research Interests:

1. Investigation of early molecular level changes in early breast cancer, with particular attention to oncogenes and suppressor genes.
2. Investigation of molecular level changes in high risk or premalignant breast tissues including breast tissue of women with lobular carcinoma in situ or a family history of breast cancer.
3. In vitro culture of breast epithelial cells.

Research Funding Information:

Past: 1978 - 1983 NIH/Medical Scientist Training Program Grant
      1987 - 1988 American Cancer Society Regular Clinical Fellowship
      1988 - 1992 American Cancer Society Career Development Award Cellular and Molecular Changes in Breast Cancer

Current: 1993 - 1995 NIH/RO1 CA61226-01 PI Detection of markers of malignancy in breast specimens

Principal Clinical and Hospital Responsibilities:

1989 - 1992 Member, Division of Surgical Oncology, Brigham and Women's Hospital, Boston, MA

1989 - 1992 Attending Surgeon, Breast Evaluation Clinic, Dana Farber Cancer Institute, Boston, MA
Barbara L. Smith, M.D., Ph. D.

1992 - Assistant Visiting Surgeon, Massachusetts General Hospital, Boston, MA
1992 - Director, Comprehensive Breast Health Center, Massachusetts General Hospital, Boston, MA
1992 - Member, Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA
1995 - Director MGH-BWH Partners Comprehensive Breast Health Center

Local Contributions

Harvard Medical School

1978 - 1980  Microbiology, lecturer and teaching assistant microbiology course first year medical students

Brigham and Women's Hospital

1990 - 1992  Introduction to Clinical Medicine, surgery instructor, post graduate course, two-three second year Harvard Medical students for six 3.5 hour sessions per year


Massachusetts General Hospital

1992 -  Surgery, Attending, Massachusetts General Hospital - teaching residents and medical students on the ward service and breast surgery techniques in the operating room

1993, 1995  Introduction to Clinical Medicine, surgery instructor

1993  Primary Care of Women, lecturer, post graduate course, "Evaluation of Breast Problems" 7/93

1993  Management Decisions for the General Surgeon, lecturer, post graduate course in "Surgical Treatment of Breast Cancer: Mastectomy vs Less" 9/93

1993  Advances in Cancer Management for the Surgeon, lecturer, post graduate course, "Management of High Risk Patients" 11/93

1993  Surgical Grand Rounds - "Management of Locally Advanced Breast Cancer"
Barbara L. Smith, M.D., Ph.D.

1994  Primary Care of Women, lecturer, post graduate course in "Evaluation of Breast Problems"  7/94

1994  Plastic Surgery Grand Rounds - "Management of High Risk Patients"


1994  Advances in Cancer Management for the Surgeon, lecturer, post graduate course in "Identification and Management of Patients at High Risk for Breast Cancer"  11/94


1994  Obstetrics and Gynaecology Grand Rounds, "High Risk Patients - New Developments", Massachusetts General Hospital, Boston, MA

1994  Lecturer Nurse Practitioner Program MGH Institute of Health Professions "Management of Breast Disease"

Regional, National, and International Contributions

Invited Presentations

1991 -  Pathology Grand Rounds, "Breast Cancer Update for Pathologists and Surgeons", Baystate Medical Center, Springfield, MA

1993  1993 Update in Obstetrics and Gynecology, lecturer, post graduate course, in "Early Detection of Breast Cancer", Brigham and Women's Hospital, Boston, MA  3/93

1993  Invited speaker; "Update on Surgical Management of Breast Cancer", Middlesex Medical Society, Burlington, MA  4/93

1993  Surgical Grand Rounds,"Axillary Dissection", Salem Hospital, Salem, MA  4/93


1993  Invited speaker, The University of New Mexico,"Treatment of Breast Cancer: Mastectomy vs Less" and "Sterotactic Core Needle Biopsy", Albuquerque, NM  7/93

1993 Lecturer, Mount Auburn Hospital, Seminar on Breast Health, "Current Treatment Options for Breast Cancer", Newton, MA 9/93


1993 Invited speaker, Beijing/Chinese Medical Association, "Epidemiology and Therapy of Breast Malignancy", Beijing, China 10/93

1993 Grand Rounds - Lawrence Memorial Hospital "Breast Cancer: A Selective Review", Medford, MA 12/93


1994 1994 Update in Obstetrics and Gynecology, lecturer, post graduate course, "Early Detection of Breast Cancer", Brigham and Women's Hospital, Boston, MA 3/94

1994 Invited speaker and course co-director, University of Arkansas Medical Sciences, Advances in the Diagnosis and Treatment of Breast Cancer, "Axillary Dissection", Little Rock, AK 4/94

1994 Invited speaker, Symposium on Breast Diseases, "Management of Ductal Carcinoma in Situ", Middlesex Hospital, Middleton, CT 4/94


1994
Invited speaker, "Current Management of Breast Cancer", Alumnae Seminar XV,
Women's Health: "What We Need - What We Get", sponsored by the alumnas of
Barnard, Bryn Mawr, Mount Holyoke, Radcliffe, Smith, Vassar and Wellesley,
New Canaan, CT 10/94

1994
Surgical Grand Rounds, "Molecular Markers and Prognostic Factors in Breast
Cancer", Beth Israel Hospital, Boston, MA 10/94

1995
Surgical Grand Rounds, "Breast Cancer Risk Identification and Management of
High Risk Patients", The Cambridge Hospital, Cambridge, MA 1/95

1995
Harvard-MIT Division of Health Sciences and Technology - Program Speaker -
Dinner Seminar - "Evolution of Treatment for Breast Cancer", Cambridge, MA,
2/95

1995
37th American Cancer Society Science Writers Seminar, Moderator, Breast
Cancer Sessions, New Orleans, LA 3/95

1995
1995 Update in Obstetrics and Gynecology, lecturer, post graduate course, in
"Early Detection of Breast Cancer", Brigham and Women's Hospital, Boston, MA
3/95

1995
Invited speaker, John O. Vetta, M.D. Memorial Lectureship, "Risk Factors in
Breast Carcinoma, Lenox Hill Hospital, New York, NY 4/95

1995
Invited speaker and course co-director, Advances in the Diagnosis and Treatment
of Breast Cancer, post graduate course in "Practice Guidelines in Managing
Breast Disease", Philadelphia, PA 4/95

1995
Invited speaker, American College of Surgeons, 81st Annual Clinical Congress,
"Management of High Risk Patients - Clinical and Medicolegal Issues", Boston,
MA 5/95

1995
Invited speaker, "Breast Cancer Risk: What is New", Concord Hospital, Concord,
NH 6/95

1996
Invited speaker, "Benign and High Risk Breast Disease," Brigham and Women's
Hospital, Boston, MA 2/96

1996
Invited speaker, "Early Detection of Breast Cancer," Post-graduate course,
Brigham and Women's Hospital, Boston, MA 3/96

1996
Invited speaker, "Recent Advances in Breast Cancer," MGH Plastic Surgery
Grand Rounds 4/96

1996 Invited Speaker, Journal Club, MGH Breast Rounds 5/96

1996 Invited Speaker, "Cancer of the Breast," Harvard Medical School Post-graduate Course in General Surgery, Blake Auditorium, MGH 9/96


1996 Invited speaker, Institute for International Research workshop on how to "Develop a Breast Cancer Disease Management" program, Ritten House Hotel, Philadelphia, PA 11/96


1997 Invited speaker, BWH ICM Course, "Breast Examination," Duncan Reid Conference Room, BWH 3/97

Bibliography

Original Reports:


Reviews:


11. Smith BL, Schnitt SJ, Harris JR. A Prognostic Index for Ductal Carcinoma In Situ of the Breast, CANCER, June 1, 1996; Vol. 77, No. 11, pp.2189-2192.


Abstracts:


STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)
(See instructions on reverse side.)

1. NAME AND ADDRESS OF INVESTIGATOR.
Goran K. Svensson, Ph.D.
Joint Center for Radiation therapy
330 Brookline Avenue
Boston MA 02215

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:
   ☑ CURRICULUM VITAE    ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.
   Clinical Laboratory
   Dana-Farber Cancer Institute
   44 Binney Street, D521
   Boston MA 02115

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).
   Institutional Review Board
   Dana-Farber Cancer Institute
   44 Binney St
   Boston MA 02115

6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.
   Protocol name: Radiation and Thermal therapy for Extensive Intraductal carcinoma.
   Protocol number: 95-006
ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION.

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572

STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

2. Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR

[Signature]

11. DATE

[Date]
NAME: Göran K. Svensson

ADDRESS: 77 Brush Hill Road, Sherborn, MA 01770

PLACE OF BIRTH: Göteborg, Sweden

CITIZENSHIP: U.S.

EDUCATION:
1960 M.Sc. (Fil. kand.), University of Lund, Sweden
1963 M.Sc. (Fil. kand.), University of Lund, Sweden
1967 Ph.D. (Fil. lic.), University of Lund, Sweden

CERTIFICATION:
1984 American Board of Radiology, certified in Therapeutic Radiological Physics.

ACADEMIC APPOINTMENTS:
1962-1967 Research Engineer, University of Lund, Sweden
1967-1971 Health Physicist-Staff Member, Stanford University (SLAC), Stanford, CA
1971-1977 Assistant Professor in Radiation Therapy, Harvard Medical School, Boston, MA
1973-1984 Lecturer in Medical Radiological Physics, Harvard School of Public Health, Boston, MA
1979-1984 Associate Professor of Radiation Therapy, Harvard-MIT Division of Health Sciences and Technology, Boston, MA
1977- Associate Professor of Radiation Therapy, Harvard Medical School, Boston, MA

HOSPITAL APPOINTMENTS:
1971-1983 Head of Clinical Physics Section, Joint Center for Radiation Therapy, Boston, MA
1983-1986 Head of Engineering Section, Joint Center for Radiation Therapy, Boston, MA
1986-1987 Acting Director, Division of Physics and Engineering, Joint Center for Radiation Therapy, Boston, MA
1987- Director of Physics Division, Joint Center for Radiation Therapy, Boston, MA.
MAJOR COMMITTEE ASSIGNMENTS:

International.


National and Regional.

1978-1984 Planning committees and site visits for the Patterns of Care Study. (NCI).
1987, 1990 Site visit the Radiological Physics Program, Houston Texas (NCI).
1993 Site visit chairman for PO1 program. National Cancer Institute (NCI).

University and Hospital.


MEMBERSHIPS, OFFICES, AND COMMITTEE ASSIGNMENTS IN PROFESSIONAL SOCIETIES:

1968-1984 Member Health Physics Society
1968- Member American Association of Physicists in Medicine (AAPM)
1979-1982 Radiation Therapy Committee of the AAPM
1985-1987 Radiation Therapy Committee of the AAPM
1980- Member American Society of Therapeutic Radiology and Oncology (ASTRO)
1984- Member American College of Radiology (ACR)
1984- Commission on Radiation Therapy of the ACR:
a)Committee on Quality Assessment
b)Committee on Radiation Therapy Physics

MAJOR RESEARCH INTERESTS:

1. Hyperthermia
2. Improved radiation treatment techniques
3. Quality Assurance
RESEARCH FUNDING INFORMATION:

Past:

1979 - 1982 NIH/NCI 5 PO1 CA17588 PI: M.B. Levene.

1983 DFCI Biomedical Research Grant. PI: GK Svensson.
Evaluation of the clinical use of a CT/Simulator. (see paper 24)

Training program in the Physics of Radiation Therapy.

Current:

Optimization of hyperthermia.


PRINCIPAL HOSPITAL SERVICE RESPONSIBILITIES:

1987- Member of the JCRT senior management team. Clinical and academic short and long range planning for JCRT and its member hospitals.

MAJOR ADMINISTRATIVE RESPONSIBILITIES:

1986- Director of the Physics Division.

SELF REPORT OF TEACHING:

1. Local Contributions

a. Advising responsibilities.

1977 Ph.D. Thesis advisor for one student, HSPH.
1979 Ph.D. Thesis advisor for one student, HSPH.
1980 Ph.D. Thesis advisor for one student, HSPH.
1987-1994 Preceptor for one postdoctoral fellow per year. JCRT.
1990 Ph.D. Thesis advisor for one student, MIT-Nuclear Engineering.
1994 Ph.D. Thesis advisor for two students, MIT-HST Program.
b. Leadership roles.
1972- Lectures and tutoring (annually) of radiation therapy residents, HMS.
1974-1984 Lecture-series for graduate students (annual), HSPH.
1976 Organized a series of seminars for the Department of Radiation Therapy, HMS.
1987- Program Director for postdoctoral training program.
1992- Organize weekly Radiological Physics Seminars and Research Seminars.
1992- Organize weekly lecture for JCRT postdoctoral fellows.

2. Regional, National and International Contributions.

a. Invited presentations.

b. Professional leadership role related to teaching.
1981 Member of NCI funded Committee on Radiation Oncology Studies. Participated in writing Criteria for Radiation Oncology in Multidisciplinary Cancer Management. The 1981 "Blue Book"
1986 Hosted three day meeting on Quality Assurance in Radiation Oncology for the International Commission on Radiological Units and Measurements. Boston, MA
1990 Wrote the Physics Model QA program for the American College of Radiology; Committee on Quality Assurance in Radiation Oncology.
BIBLIOGRAPHY

ORIGINAL REPORTS:


PROCEEDINGS OF MEETINGS.


REVIEWS AND EDUCATIONALLY RELEVANT PUBLICATIONS.


BOOKS AND MONOGRAPHS.


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MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports. Request the limited distribution statement for reports on the enclosed list be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for Information Management
Reports to be changed to "Approved for public release; distribution unlimited"

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