RADIATION THERAPY ONCOLOGY GROUP

RTOG 1014

A PHASE II STUDY OF REPEAT BREAST PRESERVING SURGERY AND 3D-CONFORMAL PARTIAL BREAST RE-IrrADIATION (PBRI) FOR LOCAL RECURRENCE OF BREAST CARCINOMA

Study Chairs

Principal Investigator/Radiation Oncology
Douglas W. Arthur, MD
Virginia Commonwealth University
MCV Campus, Massey Cancer Center
Department of Radiation Oncology
401 College St., Box 980058
Richmond, VA 23298-0058
804-828-7232/FAX 804-828-6042
darthur@mcvh-vcu.edu

Surgical Oncology
Henry M. Kuerer, MD, PhD
M. D. Anderson Cancer Center
Department of Surgical Oncology
1515 Holcombe Boulevard, Unit
Houston, TX 77030
713 745-5043/FAX 713-792-4689
hkuerer@mdanderson.org

Radiation Oncology
Bruce Haffty, MD
UMDNJ
Robert Wood Johnson Medical School
Cancer Institute of New Jersey
195 Little Albany St.
New Brunswick, NJ 09903-2681
732-235-5203/FAX 732-235-7493
hafftybg@umdnj.edu

Quality Assurance
Laurie Cuttino, MD
Virginia Commonwealth University
MCV Campus, Massey Cancer Ctr.
Department of Radiation Oncology
401 College St., Box 980058
Richmond, Virginia 23298-0058
804-287-4340
lcuttino@mcvh-vcu.edu

Translational Research
Wendy Woodward, MD, PhD
M.D. Anderson Cancer Center
1515 Holcombe Blvd, Box 1202
Houston, TX 77005
713-563-8481/FAX 713-563-6940
wwoodward@mdanderson.org

Physics
Dorin A. Todor, PhD
Virginia Commonwealth University
MCV Campus, Massey Cancer Center
Department of Radiation Oncology
401 College St., Box 980058
Richmond, VA 23298-0058
804-628-7415
dtodor@mcvh-vcu.edu

Senior Statistician
Kathryn Winter, MS
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-574-3108/FAX 215-928-0153
kwinter@acr-arrs.org

Activation Date: June 4, 2010
Version Date: May 21, 2010
Update Date: July 29, 2010

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
INDEX

Schema
Eligibility Checklist

1.0 Introduction
2.0 Objectives
3.0 Patient Selection
4.0 Pretreatment Evaluations/Management
5.0 Registration Procedures
6.0 Radiation Therapy
7.0 Drug Therapy
8.0 Surgery and Pathology
9.0 Other Therapy
10.0 Tissue/Specimen Submission
11.0 Patient Assessments
12.0 Data Collection
13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Study Parameters
Appendix IIA - CTCs/Serum/Blood/Tissue and Cosmesis Collection Time Points
Appendix III - Performance Status Scoring
Appendix IV - Staging System
Appendix V - Quality Assurance Contouring Guidelines
Appendix VI - Instructions for Submitting Cosmesis Photos
Appendix VII - Serum and Blood Processing Kit Instructions
Appendix VIII - Specimen Plug Kit Instructions
A Phase II study of Repeat Breast Preserving Surgery and 3D-Conformal Partial Breast Re-Irradiation (PBrI) for Local Recurrence of Breast Carcinoma

**Patient Population:** (See Section 3.0 for Eligibility)

- Histopathologic confirmation via lumpectomy of local in-breast ipsilateral recurrence
- Final breast surgery (lumpectomy and/or final re-excision) within 42 days prior to study entry;
- Initial lumpectomy followed by whole breast radiation >1 year prior to study entry;
- Bilateral breast mammogram and bilateral breast MRI within 120 days prior to study entry;
- Negative histologic margins of resection, no tumor on ink, following breast-preserving surgery of local recurrence.

**Required Sample Size:** 61
(Y) 1. Is there histopathologic confirmation of local in-breast ipsilateral recurrence?

(Y) 2. Did the patient have the initial lumpectomy followed by whole breast radiation > 1 year and final breast surgery within 42 days (lumpectomy and/or final re-excision) prior to study entry?

(Y) 3. Histology of the local in-breast recurrence invasive ductal, medullary, tubular, mucinous, lobular; or ductal carcinoma in situ?

(Y) 4. Is the recurrent tumor size ≤ 3cm in greatest dimension on pathologic specimen?

(Y) 5. Was a bilateral mammogram and bilateral breast MRI performed within 120 days of study entry?

(N) 6. Is there evidence of multicentric ipsilateral breast recurrence or regional recurrence (other than axilla) documented by diagnostic mammography, breast ultrasound (optional) and/or breast MRI?

(Y/N) 7. Were there suspicious regions identified on diagnostic mammography, breast ultrasound (optional) and/or breast MRI?

(Y) If yes, were they histologically proven negative?

(Y) 8. Was a history & physical exam performed within 120 days prior to study entry?

(Y) 9. Did the patient have a whole body PET/CT or all of the following; CT of the chest abdomen, pelvis and a bone scan within 120 days prior to study entry?

(Y) 10. Was an Estrogen/Progesterone analysis performed prior to study entry?

(Y) 11. Were there negative histologic margins of resection, no tumor on ink, following breast preserving surgery of the local recurrence?

(Y/N) 12. Is there evidence of axillary involvement?

(Y) If yes, are there ≤ 3 positive nodes without extracapsular extension documented after evaluation? (See section 8.1.15)

(Y) 13. Is the patient’s Zubrod Performance status 0-1?

(Y) 14. Is the patient’s age ≥ 18?

(Y) 15. Is the target lumpectomy cavity clearly defined and the target lumpectomy cavity/whole breast reference volume < 30% based on a postoperative, pretreatment CT scan?

(N) 16. Is there evidence of multicentric ipsilateral breast recurrence or regional recurrence (other than axilla) or simultaneous distant recurrence documented by physical exam or radiographic evaluation?

(N) 17. Is there any skin involvement?

(Continued on the next page)
(Y/N) 18. Is the patient of childbearing potential AND sexually active?
   (Y) If yes, is the patient willing and able to use a medically acceptable form of contraception while receiving protocol therapy?
   (Y) If yes, was a serum pregnancy test negative within 7 days of study entry?

(N) 19. Is the patient lactating?

(Y/N) 20. Has the patient had prior invasive malignancies, other than previous ipsilateral breast cancer and/or non-melanomatous skin cancers?
   (Y) If yes, has the patient been disease free for ≥ 3 years?

(N) 21. Has the patient had contralateral mastectomy, and/or Paget’s disease of the nipple?

(N) 22. Is the breast technically unsatisfactory for partial breast irradiation?

(Y) 23. Is the patient at least 2 weeks status post chemotherapy and recovered from non-hematologic side effects to less than or equal to grade 1?

(N) 24. Does the patient have collagenous diseases, specifically systemic lupus erythematosus, scleroderma, or dermatomyositis?

(N) 25. Does the patient have psychiatric or addictive disorders that would preclude obtaining informed consent?

(Y) 26. Has the patient signed a study-specific informed consent prior to study entry?

The following questions will be asked at Study Registration:

3D-CRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

1. Institutional person randomizing case.

(Y) 2. Has the Eligibility Checklist been completed?

(Y) 3. In the opinion of the investigator, is the patient eligible?

4. Date informed consent signed

5. Patient’s Initials (First Middle Last)

6. Verifying Physician

7. Patient ID

8. Date of Birth

9. Race

(Continued on the next page)
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>11.</td>
<td>Gender</td>
</tr>
<tr>
<td>12.</td>
<td>Country of Residence</td>
</tr>
<tr>
<td>13.</td>
<td>Zip Code (U.S. Residents)</td>
</tr>
<tr>
<td>14.</td>
<td>Method of Payment</td>
</tr>
<tr>
<td>15.</td>
<td>Any care at a VA or Military Hospital?</td>
</tr>
<tr>
<td>16.</td>
<td>Calendar Base Date</td>
</tr>
<tr>
<td>17.</td>
<td>Randomization date</td>
</tr>
<tr>
<td>18.</td>
<td>(Y/N) Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
</tr>
<tr>
<td>19.</td>
<td>(Y/N) Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?</td>
</tr>
<tr>
<td>20.</td>
<td>(Y/N) Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?</td>
</tr>
<tr>
<td>21.</td>
<td>(Y/N) Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).</td>
</tr>
<tr>
<td>22.</td>
<td>(Y/N) Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?</td>
</tr>
<tr>
<td>23.</td>
<td>(Y/N) Patient has consented to participate in the Cosmesis Study</td>
</tr>
<tr>
<td>24.</td>
<td>(Y/N) Patient has consented to take part in the Circulating Tumor Cell portion of the trial</td>
</tr>
</tbody>
</table>

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________     Date ___________________________
1.0 INTRODUCTION

Approximately 10% of patients treated with lumpectomy and radiation will have a subsequent in-breast local recurrence when followed long term. The current surgical standard of care is to perform mastectomy at the time of local recurrence. This is generally believed to be indicated because repetitive conservative surgery will result in an unacceptable cosmetic outcome and the risk of subsequent in breast local recurrence is too high given the inability to re-irradiate the breast. Neither of these indications for mastectomy has been evaluated in well-designed prospective studies.

Based on limited studies without definitive information regarding selection criteria to eliminate multicentric disease and the attainment of negative surgical margins, the rate of subsequent local in-breast secondary recurrence occurs in approximately 35% of patients treated with repetitive breast conserving surgery alone. This rate of local recurrence is similar to rates of local recurrence in the absence of radiation therapy in women treated with lumpectomy alone for primary breast cancer. Emerging radiation techniques involving three-dimensional– (3D-) conformal radiation have the potential ability to provide effective local control while limiting toxicity associated with additional whole-breast radiation. As an initial investigative step, this clinical trial is designed to evaluate the risk of treatment-related toxicity following repetitive breast preserving surgery followed by Partial Breast Re-irradiation (PBrI) in patients with in-breast failure following whole breast irradiation. It is our hypothesis that the use of 3D-conformal radiation treatment technique combined with a partial breast target will result in an acceptably low grade 3 toxicity, thus leading to a definitive trial regarding in-breast disease control.

Local Recurrence Rates Following Mastectomy for In-Breast Local Recurrence

Rates of subsequent chest-wall recurrence following mastectomy for in-breast local recurrence from several single institutional series demonstrate that a second local recurrence in the form of a chest-wall recurrence occurs in 2 to 31% of patients. This range of subsequent chest-wall recurrence is dependent on the length of follow-up and initial stage of the primary breast cancer. Thus, it is critical to note that mastectomy following in-breast local recurrence does not necessarily eliminate the risk of subsequent local secondary recurrences at the chest-wall.

Survival of Patients Treated with Mastectomy Following Local Recurrence

Death following a non-invasive breast recurrence is extremely rare, and generally results from the risk of distant metastases associated with the original diagnosis of invasive breast cancer. Patients with an isolated invasive local recurrence following breast-conserving surgery are at increased risk for distant metastases and death compared with patients without a local in-breast recurrence. The relative risk of breast cancer associated death is estimated to increase by a factor of 3.4 to 4.6 in patients who develop a local in-breast recurrence compared with patients who do not. The risk of death is highest when the local recurrence occurs in the first two years after treatment compared with greater than 2 years (breast cancer–specific survival at 5 years 68% vs 96%). This fact is likely related to the biology of disease rather than a cause of subsequent distant metastases, although this remains a controversial area of discussion. The overall survival of patients with in-breast local recurrences at 5 years ranges from 52% to 84%, with virtually all deaths occurring in patients with an invasive recurrence.

Outcome of Patients Treated with Conservative Surgery Alone after In-Breast Local Recurrence

There are very limited published studies on the outcome of patients treated with conservative surgery alone for an in-breast local recurrence. Potential obstacles in evaluating these single institutional studies with respect to efficacy have to do with the lack of information regarding margin status and use of breast imaging at the time of in-breast local recurrence. Many of the reported series do not report whether clear surgical margins were obtained at the time of local excision of the lesion and numerous patients were treated before modern day standard mammography and ultrasound were available to select appropriate patients. Not withstanding, Abner et al found a local recurrence rate of 31% at a median follow-up of 39 months and Voogd et al. reported a rate of 38% at a median follow-up of 52 months. It is also interesting to note the local recurrence rates associated with local excision versus mastectomy were not statistically significant (38% vs. 25%, P = 0.27), respectively in the Voogd series from the Netherlands. Kurtz et al. from Marseille, reported on the feasibility and outcome of breast conservative surgery after local recurrence in 50 patients. In this important study, the authors demonstrated that 5-year local control rates were highest in patients who had negative margins of resection compared with positive margins of resection (73% vs. 36%, respectively) and those with a local recurrence occurring after 5 years compared with shorter time intervals (92% vs. 49%, respectively). In another study from Sweden evaluating the local recurrence rate following local excision alone in 14 patients at a median follow-up of 13 years, the local recurrence rate was an alarming 50%. However, the authors did not include
information why these patients were specifically chosen to have local excision alone, if mammography and or ultrasound were utilized to select them as appropriate patients, and if negative margins of resection were obtained.

The largest series evaluating repetitive local resection for in-breast local recurrence was reported by investigators at the European Institute of Oncology in Milan, Italy. Although not a randomized study, at a median follow-up of 73 months after the second surgery, these investigators found that the overall survival at 5 years was 70% in the 134 patients who had a mastectomy for local recurrence compared with 85% following local excision of the recurrence. No difference was noted in disease-free survival between patients having a mastectomy versus local re-excision. A second local recurrence occurred in the breast in 19% of patients. In comparison, 4% of patients in the mastectomy group developed a chest-wall recurrence.

Investigators from Japan have recently reported their experience with repeat lumpectomy for patients with an ipsilateral breast tumor recurrence in 30 patients. Patients in this series did not receive additional radiation following the surgery. Nine of the 30 patients who underwent repeat lumpectomy developed second local relapse within 3 years after salvage operation. The 5-year overall survival rate at a median follow-up of 43 months after salvage surgery was 90.9% for 11 patients who received a mastectomy during the same time period compared to 90.0% for the lumpectomy group. The 5-year distant disease-free survival rate was 70.1% for the mastectomy group and 83.0% for the lumpectomy group.

Based on these few studies, survival does not appear to be adversely impacted following repetitive breast conserving surgery and local recurrence rates appear to be on average in the 35% range. This rate of local in-breast recurrence is similar to rates of local recurrence rates in patients initially treated with breast conserving surgery without the use post-operative operation. The question then becomes whether these rates of local recurrence can be lowered with partial breast re-irradiation in appropriately selected patients.

Prior Experience with Re-irradiation of Operative Bed Following Local In-Breast Recurrence

Investigators from France reported their experience with resection followed by brachytherapy in patients who either refused mastectomy or it was contraindicated in 15 patients with a local in-breast recurrence. Patients were not selected based on mammographic or ultrasound criteria and margins of resection were not reported in these patients. Following local resection of the invasive tumors that had a mean diameter of 2.4 cm, patients received interstitial brachytherapy with a total dose of 30 cGy (dose rate not mentioned). At a mean follow-up of 48 months, 4 patients had a second local recurrence (26%). Cosmesis in 8 reported patients was reported as minor or no sequelae in 5 and with major sequelae in 3 patients. One patient had skin necrosis that was successfully treated with local wound care and one patient had extensive erythema and mastectomy was performed (no tumor was evident on pathologic exam).

Deutsch recently reported his experience with repeat high-dose external beam irradiation for in-breast tumor recurrence after prior lumpectomy and whole breast irradiation in 39 patients treated since 1985 at the University of Pittsburgh Medical Center. There were 31 patients with recurrent invasive disease and 8 patients with DCIS. Eligibility and selection criteria with respect to size of the lesions and whether modern diagnostic mammography and or ultrasound were utilized to exclude multicentric disease were not stated in this report. Patients underwent re-segmental resection of the recurrence and 15% of patients remained with positive margins of resection. Patients were re-treated with external beam radiation to the operative bed with 50 Gy in 25 fractions at a medium of 63 months from their initial radiation treatment. At a median follow-up of 52 months, local in-breast recurrence was found in 20.5% of patients. Four of these patients (44.4%) also developed distant metastases. It is interesting to note that the occurrence of contralateral breast cancer in this cohort study was also 20.5%. The 5-year overall and disease-free survival rate was 77.9% and 68.5%, respectively. These survival rates are very similar to reported survival rates in women treated with mastectomy for local in-breast recurrence.

Although this was not a prospective study with strict criteria for reporting of toxicity and cosmesis, there were no reports of radiation-induced necrosis and the cosmesis was reported as excellent or good in 69% of patients. In 31% of patients, they were noted to have an obvious deformity and or a marked difference in size of the breast or excessive skin pigmentation. This study did not specifically report problems with wound healing.
There appears to be only two prospective published study on re-irradiation for local in-breast recurrence. In this study from Vienna University, nine patients were treated with partial breast irradiation with interstitial pulse dose rate brachytherapy with 40.2 to 50 Gy and eight patients were treated with repeat whole breast irradiation with 30 Gy combined with an additional pulse dose rate interstitial brachytherapy boost dose of 12.5 Gy to the operative bed in eight patients. Recurrences were diagnosed and then re-treated at a median follow-up of 50 months (range 11-208 months). At 5-years of follow-up, local recurrence occurred in 4 patients at a median of 8 months. All local recurrences occurred in the group of patients receiving combined whole-breast radiation with a boost with brachytherapy. One remarkable aspect of this study was that despite having previously having whole-breast irradiation, patients had side effects that were limited to grade one or two fibrosis, although long term follow-up greater than 5 years might alter these results. Cosmetic outcome as rated by a physician and the patient were excellent or good in one-third of the patients and moderate or acceptable in the remaining patients. Based on these limited single institutional reports, approximately 75% of women avoided mastectomy for their local recurrence without subsequent need for further local therapy.

The second is from Beth Israel Medical Center in New York City, NY. They conducted a phase I/II study to evaluate the role of a second conservative surgery and brachytherapy for patients presenting with a local recurrence/new primary following standard whole breast irradiation. Fifteen patients were treated post lumpectomy with low dose rate brachytherapy (first 6 – 30 Gy, last 9 – 45 Gy). Median follow-up at the time of reporting was 36 months. Of the group receiving 30 Gy, one patient was documented to have an in-breast failure for an overall in-breast control rate of 89%. No grade 3 or 4 fibrosis, telangiectasia, ulcer or necrosis was reported.

Three-Dimensional– (3D-) Conformal External-Beam Radiation Therapy
There is a growing literature evaluating the use of Partial Breast Irradiation (PBI) as the sole type of radiation therapy following breast-conserving surgery. As PBI by definition limits radiation to only a portion of the breast at risk for subsequent failure, use of PBI in patients previously treated with whole-breast radiation has the potential of limiting potential radiation induced toxicity. Several external beam partial breast techniques have been described. Formenti and colleagues have studied 3D-conformal partial breast irradiation using external-beam radiation therapy with the patient imaged and treated on a dedicated computed tomography scanner. The planning target volume used by these investigators was the tumor bed plus a 1- to 2-cm margin defined at post-lumpectomy computed tomography. Nine patients in this study received a total dose of 25 to 30 Gy in five fractions. At a median follow-up of 3 years, all patients had good to excellent cosmesis. The authors concluded that hypofractionated conformal breast irradiation is feasible and that further studies are warranted. The advantage of utilizing 3D-conformal external-beam radiation therapy is that it is less invasive than brachytherapy and most radiation facilities in the United States already have the tools required for this method of radiation delivery. Baglan et al. also recently reported on a novel 3D-conformal radiation therapy technique to treat the lumpectomy cavity plus a 1.5-cm margin in patients with early-stage breast cancer. Nine patients in this pilot study were treated with a prescribed dose of 34 Gy (5 patients) or 38.5 Gy (4 patients) delivered in 10 fractions over 5 consecutive days. The impact of breathing motion on clinical target volume was studied. The authors found that 98% to 100% of the clinical target volume was covered by the 95% isodose surface at the extremes of inhalation and exhalation when a 5-mm additional breathing margin was added in the planning target volume. They concluded that Accelerated Partial Breast Irradiation (APBI) using 3D-conformal radiation therapy is technically feasible with acute side effects being minimal and that additional studies are warranted to address long-term toxicity, cosmesis, and tumor control.

The updated experience from William Beaumont Hospital including 31 patients treated with 3D-conformal external beam APBI demonstrated no skin changes greater than grade 1 erythema were noted during treatment and at the initial 4-8 week follow-up visit, 61% of patients had grade 1 toxicity and 10% of patients had grade 2 toxicity. Cosmesis was rated as good or excellent in all patients with 15 patients being followed greater than 1 year. The clinical target volume (CTV) consisted of the lumpectomy cavity plus a 1cm to 1.5 cm margin. The CTV was limited to 5 mm from the skin surface and lung-chest wall interface. The mean and median coverage of the CTV by the 100% isodose line was 98%. The investigators concluded that 3D-APBI is technically feasible and acute toxicity is minimal. Furthermore, advantages of 3D conformal external beam APBI over other forms of PBI include its non-invasive approach and improved dose homogeneity within the planned target volumes, which may improve cosmetic results and reduce the risk of fat necrosis.
Current trial
The basis of this trial is formulated from observations of in-breast failure patterns, results from salvage treatment and experience with treatment techniques as described above. The trial is designed to properly evaluate the ability to safely deliver PBrI. Skin, breast, and chest wall toxicity endpoints will be evaluated at 1-year, 3-year, and 5-year intervals. These results will be compared to the reported toxicity outcome from the RTOG 0319 protocol documenting a combined grade 3 toxicity of only 4%. With the implementation of a rigorous quality assurance program, we hypothesize that the grade 3 toxicity with PBrI following whole breast irradiation will be acceptably comparable to partial breast irradiation as initial treatment. To reduce the risk of grade 3 tissue toxicity 3D-conformal external beam PBrI treatment technique will be universally utilized to maximize dose homogeneity and a hyperfractionated dose regimen will be employed. Total dose delivered to the partial breast target will be modeled after the head and neck re-treatment experience delivering 1.5 Gy bid X 30 treatments and a total of 45 Gy.30-32

Several secondary endpoints will be evaluated, including in-breast control rate, freedom from mastectomy rate, and overall survival. An additional second primary endpoint will be investigated in this trial. There is considerable interest in the correlation of circulating tumor cells to disease control outcomes and therefore a translation component has been incorporated into this trial.

1.1 Quantitation of Circulating Tumor Cells
Occult dissemination of tumor cells is the main cause of recurrent metastatic breast cancer in patients who have undergone resection of their primary tumor.33 While only approximately 5% of patients with breast cancer have clinically detectable metastases at the time of initial diagnosis, a further 30% to 40% of patients who appear clinically free of metastases harbor occult metastases.34,35 These are patients who either may not benefit from aggressive locoregional therapy, or who may only benefit if successful eradication of their micrometastatic disease can be achieved. We propose to measure pre and post-radiation occult circulating tumor cells (CTCs) in the blood of patients with an invasive local recurrence after breast conserving therapy enrolled on this trial to be treated with a re-irradiation repeat breast conserving therapy approach. Studies reviewed above highlight the high rates of local failure after surgery alone for in breast recurrence. We suggest that patients with residual microscopic disease after surgery may have detectable CTC counts that will decrease in patients with radiation sensitive disease, or remain stable in patients with radioresistant disease. Patients with occult distant disease may have detectable CTC counts that may rise after radiation since they remain untreated. Understanding the frequency and change in CTCs from this relatively small cohort will provide preliminary data to design a larger study testing CTCs to select patients for local therapies and potentially for radiosensitizer trials. This study will also demonstrate the feasibility of collecting fresh prospective samples for immediate analysis in this multi-institutional setting.

It has been speculated that mammary stem cells represent the cellular origins of cancer, because they exist quiescently over long periods and could accumulate multiple mutations over the lifetime, ultimately giving rise to tumors when stimulated to proliferate. It was recently reported that highly tumorigenic cells possessing properties consistent with those of stem/progenitor cells can be isolated from human breast cancers based on their CD44+CD24- marker expression.36 These cancer stem cells may be detectable in the peripheral blood and bone marrow and could account for ultimate development frank of metastatic disease. Indeed, in a study of bone marrow from patients with early stage primary breast cancer, Balic et al report the presence of CD44+CD24- cells in all 50 cytokeratin positive samples with a median prevalence of 66%37, suggesting that disseminated or circulating tumor cells may be surrogate stem cell biomarkers. In patients with metastatic breast cancer, the presence of more than 5 of these cells in 7.5 mL of peripheral blood predicts for overall survival.38 These cells are detected by the presence of the epithelial cell marker CD326 (aka ESA or Ep-CAM), can be found in up to 30% of patients without known metastatic disease appreciated on standard staging studies even after systemic chemotherapy39-41 and may predict for response to treatment.42 Importantly, these cells exist as single cells, eliminating the technical difficulties in translating stem cell marker studies from flow cytometry studies after tissue digestion to in situ tissue markers, an otherwise formidable challenge. Incorporation of CTC collection and evaluation into clinical trials is feasible based on standardized FDA approved detection methods, and may well be the ideal way to incorporate stem cell hypotheses into clinical trials given the available information today. Although multiple
alternative approaches including Adnagen and magnetic bead separation are under investigation and in use in the translational lab where the CTC analysis for this study will be performed, the recent NIH conference on CTCs maintained that these approaches are still investigational at this time. Incorporation of appropriately tested new CTC technology will be undertaken if appropriate depending on the timing of the study opening and sample collection. All samples will be analyzed using the same technology once the study begins, however, to maintain consistency within the study. If the technology advances sufficiently to perform multiple analyses for the same endpoint these analyses will also be incorporated, again, however, ensuring that all samples are processed and analyzed using the same approach.

Detection of CTCs by the CellSearch™ system
Advances in technology have facilitated the detection of even very small numbers of CTCs in the peripheral blood of cancer patients. The principle of these methods is based on the expression of epithelial cell adhesion molecule-1 (EpCAM), a 40-kDa glycoprotein, on most epithelial carcinomas. Moreover, recent studies indicate that this molecule has a major morphoregulatory function, relevant not only to epithelial tissue development but also to carcinogenesis and tumor progression.43,44

There are many published reports on the detection of epithelial cells in peripheral blood; however, these methods lacked the standardization necessary for direct comparison between methods. Recently, the U.S. Food and Drug Administration approved an assay for the detection of circulating tumor cells in peripheral blood using a semi-automated system, the CellSearch™ system, developed by Immunicom Corporation (Huntington Valley, PA) and licensed to Veridex LLC (Warren, NJ) for commercial distribution. This assay requires a small sample of peripheral blood to react with ferrofluids coated with antibodies to EpCAM that can be concentrated by a magnet. Thereafter, the enriched EpCAM-positive cells are allowed to react with the nucleic acid dye 4',6-diamidino-2-phenylindole (DAPI) and monoclonal antibodies specific for leukocytes (anti-CD45 antibodies conjugated with allophycocyanin) and epithelial cells (phycoerythrin-conjugated antibodies to cytokeratin 8, 18, and 19) and analyzed by the CellSpotter™ Analyzer (Veridex). The CellSpotter Analyzer is a semi-automated fluorescence-based microscopy system that enables computer-generated reconstruction of cellular images. The CellSpotter interrogates each cell image to determine if it meets the very stringent requirements of an algorithm to be classified as a CTC. The algorithm insures that a CTC expresses EpCAM and not leukocyte lineage-specific antigens (represented by CD45), exhibits cytoplasmic expression of cytokeratin (CK), and contains a nucleus that binds DAPI. Absence of any of these characteristics disqualifies a cell image as a CTC. In the process of identifying CTC, the procedure identifies cell objects that possess some, but not all, of the required characteristics to be a CTC and are labeled as “unclassified” objects.45 The stringent criteria of CellSearch for identifying a CTC are laudable; however, the merits of the assay continue to be debated as it minimizes the scientific or clinical significance of unclassified objects.

Although CellSearch is a very reproducible and reliable method for the identification and enumeration of CTCs in the peripheral blood of patients with breast cancer, its clinical utility has been limited by its high cost. The semi-automated assay is also somewhat labor-intensive. In addition, the need to permeabilize the cell membrane of a viable cell to introduce DAPI and anti-cytokeratin antibodies to label intracellular structures further deters the possibility of interrogating viable cells for their growth potential, colony formation, and genomics among others. To address these issues, the CellProfile™ kit was introduced that permits the retrieval of EpCAM-positive cells prior to cell permeabilization and interrogation for genomic or proteomic profiles of the CTCs.

### 2. OBJECTIVES

#### 2.1 Primary
To evaluate skin, breast, and chest wall adverse events occurring within 1 year from the completion of reirradiation.

#### 2.2 Secondary
2.2.1 To evaluate adverse events occurring after 1 year from the completion of re-irradiation and at any time.
2.2.2 To evaluate in-breast control rate.
2.2.3 To evaluate freedom from mastectomy rate.
2.2.4 To evaluate the rate of circulating tumor cells in this patient population and document eradication of CTCs by locoregional therapy.
2.2.5 Translational objective will correlate eradication or presence of CTCs with in-breast recurrence and distant metastasis-free survival.
2.2.6 To evaluate cosmesis as judged by the patient and independent evaluation.
2.2.7 To evaluate distant metastasis-free survival, mastectomy-free survival and overall survival.

3.0 PATIENT SELECTION
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED
3.1 Conditions for Patient Eligibility
3.1.1 Histopathologic confirmation via lumpectomy of local in-breast ipsilateral recurrence and final breast surgery (lumpectomy and/or final re-excision) within 42 days prior to study entry. Patients must have had an initial lumpectomy followed by whole breast radiation >1 year prior to study entry.
3.1.2 Histology of the local in-breast recurrence consistent with invasive ductal, medullary, tubular, mucinous, lobular; or ductal carcinoma in situ
3.1.3 Bilateral breast mammogram and bilateral breast MRI within 120 days prior to study entry
3.1.4 Recurrent tumor size ≤3 cm in greatest dimension on pathologic specimen
3.1.5 Negative histologic margins of resection, no tumor on ink, following breast-preserving surgery of local recurrence (Re-excision is permitted to achieve negative margins)
3.1.6 Estrogen/progesterone analysis performed prior to study entry
3.1.7 Axilla negative or ≤3 positive lymph nodes without extracapsular extension documented after evaluation – as described in section 8.1.15
3.1.8 Whole body PET-CT or all of the following: CT of the chest, abdomen, pelvis and bone scan within 120 days prior to study entry
3.1.9 For females of childbearing potential, negative serum pregnancy test ≤7 days prior to study entry
3.1.10 History and physical exam performed within 120 days prior to study entry
3.1.11 Zubrod Performance status 0-1
3.1.12 Age ≥18 years of age
3.1.13 The target lumpectomy cavity must be clearly defined and the target lumpectomy cavity/whole breast reference volume must be <30% based on a postoperative, pretreatment CT scan
3.1.14 Patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility
3.2.1 Pregnancy or women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception
3.2.2 Women who are breast feeding
3.2.3 Evidence of multicentric ipsilateral breast recurrence or regional recurrence (other than axilla) documented by diagnostic mammography, breast ultrasound (optional), and/or breast MRI. Suspicious regions must be histologically proven negative to be eligible
3.2.4 Evidence of simultaneous distant recurrence documented by physical exam or radiographic evaluation
3.2.5 Clinical or radiographic evidence of metastatic disease
3.2.6 Patients with skin involvement
3.2.7 Prior malignancy other than previous ipsilateral breast cancer and/or non-melanoma skin cancer unless disease free for a minimum of 3 years
3.2.8 Contralateral mastectomy
3.2.9 >3 positive axillary lymph nodes and/or metastatic axillary disease with extracapsular extension documented after evaluation – as described in section 8.1.15
3.2.10 Patients with Paget’s disease of the nipple
3.2.11 Patients with a breast technically unsatisfactory for partial breast irradiation.
3.2.12 Chemotherapy administered <2 weeks prior to study entry and failing to recover from non-hematologic side effects ≤ grade 1
3.2.13 Patients with collagenous diseases, specifically systemic lupus erythematosus, scleroderma, or dermatomyositis
3.2.14 Patients with psychiatric or addictive disorders that would preclude obtaining informed consent

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
4.1 Required Evaluations/Management
   See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.
   4.1.1 Breast CT for treatment planning
   4.1.2 For patients who have consented to participate in the cosmesis portion of the protocol, forms and photographs for the cosmesis endpoint must be submitted (See Sections 11.0 and 12.0)
   4.1.3 Her2Neu analysis

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements for 3D-CRT Treatment Approach (7/29/10)
   (Note: Intensity Modulated RT (IMRT) Is Not Allowed)
   5.1.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.
   5.1.2 All participating institutions must submit a facility questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) to the RTOG for review prior to entering any cases. INSTITUTIONS THAT HAVE BEEN PREVIOUSLY CREDENTIALED AND HAVE ENROLLED PATIENTS ON PRIOR RTOG or joint RTOG/cooperative group partial breast irradiation protocols (for example RTOG 0413/NSABP B39), will be eligible to participate without having to proceed through the credentialing process. Institutions not previously credentialed for 3D-CRT on prior partial breast irradiation trials, will additionally perform a “Dry-Run” QA test. Upon review and successful completion, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Credentialing specifics are also available at the RPC website: http://rpc.mdanderson.org/rpc/

   If the institution plans on using electrons on this study the institution must demonstrate digital data submission capabilities with this modality by submitting planned electron data to the ITC.

   5.1.3 For those institutions not previously credentialed for a RTOG partial breast protocol the treatment plan for the first patient to be treated on this protocol will undergo a Rapid Review that will be performed PRIOR TO DELIVERING ANY PROTOCOL TREATMENT. After complete data submission to ITC, the Rapid Review process will be facilitated by the RTOG and one of the radiation oncology investigators (Dr Douglas Arthur, Dr Bruce Haffty or Dr. Laurie Cuttin0) and suggestions regarding protocol compliance will be forwarded to the participating institution. All aspects of the treatment delivery must be compliant before approval and treatment. Subsequent cases and all cases submitted by institutions previously credentialed for a RTOG partial breast protocol will undergo a timely review process with feedback of protocol guideline compliance to the institution

5.2 Regulatory Pre-Registration Requirements (7/29/10)
5.2.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group or a CTSU CICRS site. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 0436 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For non-lead group institutions an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

In addition to the requirements noted above, U.S. and Canadian institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206 prior to registration of the institution’s first case:
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number renewal as appropriate

5.2.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.2.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS
5.2.3.1 For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.2.3.2 For institutions that have an approved LOI for this protocol:
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.3 OPEN Registration (7/29/10)
Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (RTOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:
- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
• To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.  
• To perform registrations on protocols for which you are a member of the RTOG, you must have an equivalent 'Registrar' role on the RTOG roster. Role assignments are handled through the Groups in which you are a member  
• To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.  
• NOTE: If you are enrolling as a non-RTOG site: Prior to beginning the enrollment, call the RTOG Randomization desk at 215-574-3191 or 215-574-3192 to obtain an RTOG, non-Lead Group, site-specific institution number.  

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.  

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.  

5.3.1 In the event that the OPEN system is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual’s e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment, confirmation of registration, and patient-specific calendar) will occur.  

6.0 RADIATION THERAPY  
Note: Intensity Modulated RT (IMRT) Is Not Allowed  

A rapid review of first enrolled case from each site (unless previously participating on RTOG or RTOG/cooperative group PBI protocols), will be conducted prior to RT treatment (see Section 6.8)  

Protocol treatment must begin within 21 days after treatment planning CT but no more than 9 weeks after last breast surgery (lumpectomy or final re-excision).  

6.1 Dose Specifications  
3D-CRT PBrI will begin within 21 days after treatment planning CT but no more than 9 weeks after last breast surgery (lumpectomy or final re-excision). The treatment unit isocenter will be positioned at the approximate center of the PTV as defined in section 6.3. A total of 45 Gy will be prescribed to this point. Two fractions per day, each of 1.5 Gy, separated by at least six hours, given in fifteen consecutive working days will sum to 30 fractions and 45 Gy.  

6.2 Technical Factors  
6.2.1 Megavoltage equipment is required with effective photon energies of ≥ 6mv.  
6.2.2 3D-CRT capabilities are required as defined and confirmed by the ITC. See appendix V for 3D-CRT QA guidelines.  

6.3 Localization, Simulation, and Immobilization  
A treatment planning CT scan with the patient, depending on the treatment position used, in a supine or prone position will be required. The CT should start at or above the mandible and extend several cm below the inframammary fold (including the entire lung). A CT scan thickness of ≤ 0.5 cm should be employed. Cases will only be acceptable if the following structures are contoured (see appendix V): excision cavity, clinical target volume (CTV) and planning target volume (PTV), the planning target for evaluation (PTV_EVAL), skin, ipsilateral and contralateral whole breast reference volume, thyroid, ipsilateral and contralateral lung, and heart. The chin, shoulders and contralateral breast should be included in the scan. The target structures and
normal tissue structures must be outlined on all CT slices. The extent of normal tissue contouring is necessary with 3D-CRT to guide beam arrangement and normal tissue avoidance.

6.4 Treatment Planning/Target Volumes

6.4.1 The participating institution may choose whatever beam arrangement, number of beams they desire as long as the necessary dose volume constraints (see Section 6.7) can be met. Typically, a 3-, 4-, or 5-field non-coplanar beam arrangement utilizing high-energy photons can be used. There are no restrictions on 3D-CRT beam arrangement assuming the dose volume histogram criteria for both target and normal tissue volumes are preserved. Guidance on field design can be found in the published literature, examples are listed below:


6.4.2 Field arrangements are at the discretion of the physician and will be determined by 3D-treatment planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV_EVAL and critical normal tissues. **Dose calculations with tissue inhomogeneity correction must be used.** Therefore, photon field combinations (with or without electrons), and field within a field treatment approaches are accepted assuming successful dosimetric planning occurs on a treatment planning platform approved by the ITC. Treatment can be delivered with the patient in a supine or prone position. Although field within a field technique to improve dosimetric coverage can be utilized; the use of dynamic multi-leaf collimator (MLC) to facilitate the delivery of intensity-modulated distributions derived from constraints-based computer optimization (i.e. inverse planning) is excluded.

6.4.3 The excision cavity will be outlined based either on clear visualization on CT or, if placed, with the help of surgical clips. The clinical target volume (CTV) will be defined by uniformly expanding the excision cavity volume by 15mm (see APPENDIX V - 3D-CRT QA GUIDELINES). However, the CTV will be limited to 5mm from the skin surface and by the posterior breast tissue extent (chest wall structures and pectoralis muscles are not to be included). The planning target volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment setup and motion of the breast with breathing. The PTV will be defined as a minimum of 10mm around the CTV (superior, inferior, medial and lateral dimension) to account for anticipated breathing motion and set-up uncertainty. The PTV is saved and is used to generate the beam aperture, (with an additional margin to take penumbra into account). Since a substantial part of the PTV often extends outside the limits of breast tissue an additional contour, PTV for Evaluation (PTV_EVAL), is generated and used for DVH constraints and analysis. To create the PTV_EVAL contour the PTV is copied and labeled as PTV_EVAL and then edited: This PTV_EVAL is limited to exclude the part outside the ipsilateral breast and the first 5mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excludes (if applicable) the PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung). This PTV_EVAL CANNOT be used for beam aperture generation.

6.5 Critical Structures

6.5.1 Uninvolved Normal Breast

Ideally, <60% of the whole breast reference volume should receive ≥50% of the prescribed dose and <35 % of the whole breast reference volume should receive the prescribed dose. For these calculations, the whole breast reference volume is defined as per Appendix V.

6.5.2 Contralateral Breast

The contralateral breast reference volume, contoured using the same methods described for the ipsilateral breast reference volume, should receive < 3% of the prescribed dose to any point.
6.5.3 Ipsilateral Lung
< 15% of the lung can receive 30% of the prescribed dose.

6.5.4 Contralateral Lung
< 15% of the lung can receive 5% of the prescribed dose.

6.5.5 Heart (right-sided lesions)
< 5% of the heart should receive 5% of the prescribed dose.

6.5.6 Heart (left-sided lesions)
The volume of the heart receiving 5% of the prescribed dose (V5) should be less than the 40%.

6.5.7 Thyroid
Maximum point dose of 3% of the prescribed dose.

6.6 Documentation Requirements

6.6.1 Before First Treatment
Portal films or images of each beam and an orthogonal pair (AP and lateral) must be obtained prior to initiation of treatment.

6.6.2 Subsequent Images or Films
Subsequent orthogonal pair (AP and lateral) films or images must be obtained prior to fraction number 5. Additional images or films may be obtained at the investigator's discretion.

All films or images are to be maintained at the local facility. Do not submit to ITC unless requested. (Please refer to Section 12.2 for data submission)

6.7 Compliance Criteria

6.7.1 The protocol PIs will compare submitted DVHs for the PTV for evaluation, designated critical structures, and unspecified tissues.

6.7.2 Each treatment plan shall be scored as:
- **Per Protocol**: >90% of the prescription isodose surface covers >90% of the PTV_EVAL. All specified critical normal tissue DVH limits have been met. Maximum dose does not exceed 110% of the prescription dose. Treatment delivered within 15 consecutive work days.
- **Variation Acceptable**: All specified PTV-EVAL dosimetric coverage goals and critical normal tissue DVH limits fall within 5% of the guidelines. Maximum dose is 110%-120% of the prescription dose. Treatment delivered within 17 consecutive work days.
- **Deviation Unacceptable**: If the PTV-EVAL dosimetric coverage goals or any of the critical normal tissue DVH limits exceed 5% of the guidelines. Maximum dose exceeds 120% of the prescription dose. Treatment delivered over greater than 17 consecutive work days.

6.8 RT Quality Assurance Reviews
A Radiation Oncology Chairs, Dr. Douglas Arthur, Dr. Bruce Haffty, or Dr. Laurie Cuttino, will perform RT Quality Assurance Rapid Reviews on the first case from each site after ITC has received complete data and before the start of treatment unless previously participating on RTOG or RTOG/cooperative group PBI protocols. The subsequent cases submitted to ITC will be reviewed in a timely fashion with feedback of protocol guideline compliance to the participating institution on an ongoing basis (RT may begin and accrual continue before review feedback on these timely reviews). All RT reviews must be completed prior to reporting the treatment results.

6.9 Radiation Therapy Adverse Events

6.9.1 Acute
Fatigue is the anticipated systemic reaction to radiation treatment. Skin erythema, desquamation, breast edema, breast tenderness and myositis are potential local reactions.

6.9.2 Late
Late effects possibly could include radiation pneumonitis, rib fractures, and for left-sided lesions, cardiac complications.

6.10 Adverse Events (AEs) And Serious Adverse Events (SAEs) Reporting Requirements

6.10.1 Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.
**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

**Definition of an SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

**Note:** All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

**AdEERS REPORTING REQUIREMENTS**

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

**In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (see section 12.1).** In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:
- Phase II & III Studies: All unexpected potentially related SAEs
- Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>3 Unexpected</th>
<th>3 Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>Unrelated Unlikely</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible Probable</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>3 Unexpected</th>
<th>3 Expected</th>
<th>4 &amp; 5 Unexpected</th>
<th>4 &amp; 5 Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td>Unrelated Unlikely</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible Probable</td>
<td>10 Calendar Days</td>
<td>Not required</td>
<td>Not required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

RTOG REPORTING REQUIREMENTS
AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via AdEERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

7.0 DRUG THERAPY
Not applicable to this study

8.0 SURGERY AND PATHOLOGY
Although the lumpectomy surgical procedure occurs prior to study enrollment, surgical guidelines are detailed below to assure eligibility criteria met and optimal outcome achieved.

8.1.1 These guidelines have evolved from the NSABP experience and implementation will result in improved cosmesis. These guidelines are suggestions and are not mandatory for patient entry or protocol compliance.

8.1.2 Lesions located in the upper half of the breast. It is recommended that circumferential curvilinear incisions be performed directly over the tumor site.

8.1.3 Lesions in the lower half of the breast. Radial incisions tend to provide superior cosmesis.

8.1.4 Radial incisions in the upper half of the breast are to be avoided. Such incisions tend to result in unacceptable cosmesis. Similarly, circumferential curvilinear or transverse incisions in the lower half of the breast may result in cosmetic deformity.

8.1.5 The initial biopsy should be performed per-cutaneously under image guidance if possible. If a surgical excision is needed for the initial biopsy it should be performed as a lumpectomy; i.e., precautions should be taken to ensure that the margins of the resected tissue are grossly free of tumor thus avoiding a re-excision of breast tissue if biopsy is positive for cancer and the final margins are histologically negative. Surgical clips to delineate surgical cavity are optional. For the purpose of this protocol, surgical margins are unacceptable if there is invasive or noninvasive tumor present at the inked margin of resection, and acceptable if there is no tumor extending to the inked margin. If the margin is positive, a re-excision achieving a negative margin is required for continued eligibility. In some cases, a second reexcision may be required to achieve negative surgical margins.

8.1.6 Regardless of the type of incision, extensive undermining of the skin should be avoided. The dissection of thin skin flaps adjacent to the incision may result in unsatisfactory cosmesis. Unless the tumor is very superficial, excision of a skin ellipse is not recommended because it degrades cosmetic outcome and skin recurrences are rare. This is also true for the reexcision.
8.1.7 Drainage of the breast wound, either with Penrose drains or suction catheters, is not recommended. Careful approximation of the skin incision is essential. It is recommended that subcuticular closure be utilized in most cases.

8.1.8 In all cases, the surgeon should mark specimens with removable sutures at the superior (12 o’clock) and lateral positions of the resected breast tissue, short for superior and long for lateral allowing delineation and assessment of the surgical margins by the pathologist.

8.1.9 Surgical clips are allowed but not required. If used should be placed by the surgeon at the time of lumpectomy to define the excision cavity. Ideally, clips are placed marking the superficial, deep, right, left, superior, and inferior dimensions of the tylectomy or reexcision cavity. This procedure may add additional information for target delineation beyond the information obtained with the treatment planning CT.

8.1.10 Pathology review at the participating institution and review by a pathologist at the participating institution of any specimen obtained from referring surgeons from outside institutions will be considered sufficient for the purposes of this study. However, all blocks should be preserved, in case at some future date, central review is necessary as a quality control measure.

8.1.11 Measurement of the anteroposterior (ap), transverse, and superior-inferior (si) dimensions of the resected breast specimen should be obtained and recorded.

8.1.12 The pathologist should find the dominant mass in the resection specimen and measure the tumor in three dimensions.

8.1.13 Estrogen receptor, Progesterone receptor and Her2/neu analysis should be performed as per institutional standards.

8.1.14 Multiple blocks of the primary tumor and of breast tissue from the inked margins should be taken, to confirm 6 negative histologic margins: 1) anterior; 2) posterior, 3) medial, 4) lateral, 5) superior, 6) inferior.

8.1.15 Axillary management
8.1.15.1 If the in-breast recurrence is DCIS, a sentinel lymph node (SLN) evaluation is not required. If performed:
   • Patients with a negative SLN biopsy are eligible for enrollment
   • Patients with a positive SLN biopsy or the SLN is not identified require an ALN dissection. Patient is eligible if 0-3 positive axillary lymph nodes without extra capsular extension is documented.
8.1.15.2 If the in-breast recurrence is invasive disease and:
   • No prior axillary dissection or sentinel lymph node procedure (SLN) only:
     o Patient is required to undergo axillary evaluation with either a sentinel lymph node procedure (SLN) or axillary lymph node (ALN) dissection.
     o If the SLN is not identified or if the SLN is positive for metastatic disease then an ALN dissection is required.
     o Patient is eligible for enrollment if encounter 0-3 positive lymph nodes without extracapsular extension.
   • Prior ALN dissection: negative clinical exam: patient is eligible for enrollment.
     o It is recommended but not required that the patient undergo Ultrasound evaluation of the axilla and the lymph node draining regions of the breast. Any suspicious areas are to be biopsied and if positive followed with an ALN dissection.
     o Patient is eligible for enrollment if biopsies are negative or 0-3 axillary lymph nodes without extracapsular extension are encountered.
   • Prior ALN dissection: positive clinical exam: biopsy required
     o If biopsy is negative, patient is eligible for enrollment.
     o If biopsy is positive an ALN dissection is required.
     o Patient is eligible for enrollment if biopsies are negative or 0-3 axillary lymph nodes without extracapsular extension encountered.

9.0 OTHER THERAPY
9.1 Permitted Therapies
9.1.1 Tamoxifen
9.1.2 Aromatase inhibitor

9.2 Non-permitted Therapies
9.2.1 The use of chemotherapeutic agents, including Herceptin, during radiation therapy is not allowed; if chemotherapy regimens are given first, a minimum of 2 weeks from the last cycle must lapse before the start of radiation therapy; if planned after radiation, then chemotherapy must start no earlier than 30 days after the completion of radiation.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the tissue/specimen submission portion of the protocol. If the patient consents to participate in this component of the study, the site is required to submit the patient’s specimens as specified below.

Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, circulating tumor cells (CTCs) will be submitted to Dr. Wendy Woodward for translational purposes (strongly recommended) and serum and whole blood will be submitted to the RTOG Biospecimen Resource for banking purposes (strongly recommended).

In addition, primary tumor paraffin blocks from the patient’s original breast cancer will be obtained from the institution’s Pathology Department (or requested if done at an outside hospital) as well as biopsy of recurrent lesion if this has been done previously as part of routine care (strongly recommended).

10.2 Circulating Tumor Cells (CTCs) for Translational Research and Serum/Whole Blood for Banking (strongly recommended) (7/29/10)

For patients who have consented to participate in the circulating tumor cells (CTCs) and tissue/blood components of the study (See Appendix I).

Collection Kits and PrePaid Mailing Labels may be requested from the Biospecimen Resource at RTOG@ucsf.edu.

The presence of circulating cells in the blood positive for epithelial marker CD326, negative for committed lineage markers will be quantified, and serum and whole blood will be archived.

CTCs have been identified in the bone marrow of approximately 20% of patients with primary breast cancer, and in the blood of ≥ 30% of patients with metastatic breast cancer. We anticipate that patients with recurrent disease may have rates closer to that of patients with metastatic disease, and use 25% as a conservative estimate given the lower power of detection from blood compared to bone marrow. We propose to take blood prior to radiation and within 3 weeks after the last radiation treatment prior to receiving chemotherapy. Use of any additional systemic therapy will be recorded. We anticipate that approximately 12 patients will have detectable CTCs in the blood prior to surgery. We hypothesize that (primary endpoint) locoregional treatment, surgery or radiation can decrease or eradicate CTCs in some patients, and that (secondary endpoint) the absence or eradication of CTCs will predict for increased distant metastasis free survival. These data will be used to design a larger study using CTCs as a biomarker to predict response to locoregional treatment.
The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 Blood Samples: CTC, Whole Blood, and Serum Analysis

At protocol-specified times, consenting patients will have 7.5 ml of whole blood drawn by phlebotomy or through a central venous access device into a "CellSave" tube as per 10.2.3 to collect and quantify CTCs as well as 7.5 ml into a red top tube and spun down for serum and 7.5 mL into an EDTA tube for whole blood banking (DNA extraction). (See Appendix VII for kit instructions).

10.2.2 Blood samples for CTC analysis will be clearly labeled with patient study number, type of sample and date collected. ****Blood will be drawn in CellSave blood collection tubes containing EDTA and a stabilizer (Immunicon Corporation), will be shipped to UTMDACC and processed within 72 hours. When possible schedule this blood draw early in the week so the sample can be received and processed in the same week****.

The CTC Assay (CellSave tube) will be sent for analysis to UTMDACC. [NOTE: serum tube and whole blood tube are sent to the RTOG Biospecimen Resource per 10.2.5].

Wendy Woodward
c/o Summer Jackson
Breast Medical Oncology
1155 Pressler St.
Unit 1354 ACB5.2320
Houston, TX 77030
713-792-9137 (office); 713-606-1030 (pager); sjackson@mdanderson.org

10.2.3 CTC Analysis: Systems and Materials Required

CellSave® Preservative Tubes (Shipped to participating institutions by the RTOG at time trial is opened)
Stabilizes CTC for up to 72 hours at room temperature
- Improves assay reproducibility
- Allows shipment of samples from remote sites for analysis

CTC are fragile and tend to disintegrate in just a few hours when collected in standard evacuated blood collection tubes. This disintegration can adversely affect the reproducibility and reliability of CTC analysis and does not allow overnight shipment of samples for testing.

CellTracks® AutoPrep System (To be performed at UTMDACC)
The first system to fully automate and standardize both the selection and staining of CTC for analysis, the CellTracks® AutoPrep® System features easy-to-use software assay protocols that allow batch processing of samples with complete walk-away operation. Sensors check for sample and reagent parameters at multiple points during analysis to ensure quality results. Fully automated sample preparation device for CTC capture and staining. Up to 8 samples can be processed in a single batch. Hands-on time and off-line processing are minimal. Enables standardized pre-analytical preparation of CTCs with complete process control.

CellTracks® Analyzer (To be performed at UTMDACC)
A specially configured fluorescent analyzer that relocates the original position of CTCs and after Fluorescent In-Situ Hybridization captures the fluorescent images of the probes and presents them in gallery format for final classification.

CellTracks® Analyzer II (To be performed at UTMDACC)
A specially configured fluorescent analyzer that semi-automates circulating tumor cell (CTC) analysis. Simple on-screen commands provide user-friendly interface. Analysis of each cartridge is complete in approximately 10 minutes. Candidate images of CTCs are presented in gallery format for final classification as CTCs by the user. Image galleries are recorded for long-term archiving.

10.2.4 Serum and Whole Blood Analysis

Participating patients at all sites will have up to 7.5 ml of blood collected for serum in a red top tube and up to 7.5 ml of whole blood in an EDTA tube to be archived at the RTOG Biospecimen Resource in a coded fashion labeled with study and case number and date of draw only. An
additional serum will be drawn and sent at the time of first follow-up. See Appendix II for
detailed schedule of blood collection and Appendix VII for serum and blood kit and shipping
details.

The following materials must be provided to the RTOG Biospecimen Resource: A Specimen
Transmittal Form documenting the date of collection of the serum; the RTOG protocol number,
the patient's case number, and method of storage, for example, stored at -80°C, must be
included.

10.2.5 Submission Address
Submit materials for Serum Banking and Translational Research [Not including CTC collection
in CellSave tube] as follows:

Courier Address (FedEx, DHL, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.2.6 Serum and Whole Blood Storage Conditions
Store at –80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
• Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to
  one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).
  OR:
  • Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out
    Monday-Wednesday only; Canada: Monday-Tuesday).
  OR:
  • Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only;
    Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

10.3 Tissue Banking (strongly recommended)
For patients who have consented to participate in the tissue/blood components of the study (See
Appendix I).

Primary tumor paraffin blocks from the patient’s original breast cancer will be obtained from the
institution’s Pathology Department (or requested if done at an outside hospital) as well as biopsy
of recurrent lesion if this has been done previously as part of routine care.

The following must be provided in order for the case to be evaluable for the Biospecimen
Resource:

10.3.1 One H&E stained slide
10.3.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tumor tissue,
punched from the tissue block containing the tumor with a punch tool and submitted in a plastic
tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and
instructions can be obtained free of charge from the Biospecimen Resource. (See Appendix
VIII for plug kit instructions and shipping details.) Block or core must be clearly labeled with the
pathology identification number that corresponds to the Pathology Report.

10.3.3 A Pathology Report documenting that the submitted block or core contains tumor. The report
must include the RTOG protocol number and patient’s case number. The patient's name and/or
other identifying information should be removed from the report. The surgical pathology
numbers and information must NOT be removed from the report.

10.3.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG
Biospecimen Resource; if for translational research, this should be stated on the form. The form
must include the RTOG protocol number and patient’s case number.

10.3.5 Submission Address
Submit materials for Tissue Banking as follows:
**10.4 Specimen Collection Summary**

<table>
<thead>
<tr>
<th>Specimen Details</th>
<th>Assay (done at baseline and within 3 weeks after the last radiation treatment and before chemotherapy begins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site(s)</td>
<td>ALL</td>
</tr>
<tr>
<td>Tube Size</td>
<td>10 cc</td>
</tr>
<tr>
<td>Tube Type</td>
<td>Cell Save/EDTA</td>
</tr>
<tr>
<td>Blood Amt per Tube</td>
<td>7.5 ml</td>
</tr>
<tr>
<td>Number of Tubes</td>
<td>1</td>
</tr>
<tr>
<td>Total Blood Amt</td>
<td>7.5 ml</td>
</tr>
</tbody>
</table>

**Processing and Shipping**

- Blood to be sent in tube on day of collection by overnight express mail at room temperature to Dr Woodward at UT MDACC
- Spin down blood to separate serum, and aliquot into 4-8 1ml cryovials. Store frozen until ready to ship. Ship on 10 lbs dry ice by overnight courier to the RTOG Biospecimen Resource

**Tumor Blocks and Whole Blood for Banking (strongly recommended)**

<table>
<thead>
<tr>
<th>Specimens taken from patient:</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor</td>
<td>Pre-treatment form patient’s original breast cancer</td>
<td>H&amp;E stained slide</td>
<td>Slide shipped ambient to RTOG Biospecimen Resource</td>
</tr>
<tr>
<td></td>
<td>From biopsy of recurrent lesion if done previously as part of routine care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a 2 mm punch tool</td>
<td>Pre-treatment form patient’s original breast cancer</td>
<td>Paraffin-embedded tissue block or 2 mm punch from block.</td>
<td>Block or punch shipped ambient to RTOG Biospecimen Resource</td>
</tr>
<tr>
<td></td>
<td>From biopsy of recurrent lesion if done previously as part of routine care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 ml of anticoagulated whole blood in purple/lavender EDTA tube for DNA</td>
<td>Pre-treatment</td>
<td>Frozen whole blood samples containing a minimum of 0.5 ml per aliquot in 1 ml cryovials</td>
<td>Whole blood sent frozen to RTOG Biospecimen Resource on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>
10.5 Reimbursement
RTOG will reimburse institutions per case for the protocol-specified materials submitted to the Biospecimen Resource at the University of California San Francisco. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.6 Confidentiality/Storage
(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.6.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.6.2 Specimens for banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS
11.1 Study Parameters
See Appendix II for a summary of assessments and time frames. Details and exceptions to Appendix II appear below.

11.1.1 Mammograms
A mammogram of the ipsilateral breast is required at 6 months after the start of radiation therapy. The next bilateral mammogram should be timed to be no more than 12 months after the pre-study mammogram. Subsequent mammograms must be performed at least every 12 months.

11.2 Response Criteria—Treatment Failure
11.2.1 The definition of treatment failure is histologic evidence of recurrent carcinoma, either invasive or non-invasive (except LCIS) in the ipsilateral breast.

11.2.2 Clinical evidence of carcinoma by physical examination and/or mammograms and/or MRI will not be construed as evidence of treatment failure without biopsy proof but will be considered as suspicious for recurrence. Ipsilateral breast recurrences will be considered local (infield) if they occur within the prescription isodose volume; they will be considered peripheral if they occur between the prescription isodose volume and a volume 2 cm outside of the prescription isodose volume. Ipsilateral recurrences will be considered non-contiguous or extra field if they are beyond the peripheral volume described above.

11.2.3 Ipsilateral axillary, infraclavicular, internal mammary, or supraclavicular recurrences or distant metastases will not be considered a treatment failure unless accompanied by ipsilateral breast recurrence.

11.3 Cosmetic Evaluation
For patients who have consented to participate in the cosmesis component of the study (see Appendix I)

11.3.1 Cosmetic results will be evaluated in several ways. First, the Breast Cancer Treatment Outcome Scale (BCTOS) will be used to assess cosmetic results using patient self-reports. This brief self-report instrument has high reliability and validity, and it has been used in a variety of previous studies on recovery from breast cancer treatment. The first patient-rated cosmetic evaluation will occur at baseline (prior to the start of radiation but after surgery). The BCTOS will also be used to assess cosmesis at 1-year and 3-year follow-up (see Appendix IIa).

11.3.2 Second, at baseline (prior to the start of radiation but after surgery), a cosmetic evaluation will be made by the radiation oncologist (or surgeon), using criteria established in previous RTOG
trials. Ratings of cosmetic outcome will then be made by the radiation oncologist (or surgeon) at 1-year and 3-year follow-up (see Appendix IIa), in order to be able to compare physician-generated versus patient-generated ratings and to characterize the evolution of cosmetic outcome from multiple perspectives.

11.3.3 Finally, digital images (photographs) will be taken of the treated and untreated breasts, again using RTOG-established protocol. For practical reasons, these digital images will only be taken at three points in time, at baseline (prior to the start of radiation but after surgery) and at the 1-year and 3-year (final) assessment points. Two digital images will be taken at each of these assessment points. One will be a close up of the treated breast alone, in order to provide detailed information regarding the treatment effects. The second digital image will be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands symmetrically placed on her hips, taking care to exclude her face and framing and focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry.

These photographs will then be uploaded as j-peg files @ https://silver1.phila.acr.org/clinical_rtog/pgsitetools.html. (See Appendix VI)

These digital images will later be evaluated for cosmetic results by a panel of physicians using diagnostic criteria established in previous RTOG trials (e.g., degree of scarring, extent of pock marks and/or dimpling, degree of symmetry between the breasts, extent of changes to the skin). We think it is of interest and important to obtain multiple measures of cosmetic outcome, in order to assess the degree of correspondence between physician-generated and patient-generated outcomes. Prior research, taken together with data generated from previous NSABP trials, suggests that physician-generated ratings often underestimate the degree of dissatisfaction experienced and problems perceived by the patient. Our plan is to use the patient's self-report as our primary cosmetic endpoint.

11.4 Criteria for Discontinuation of Protocol Treatment
11.4.1 Progression of disease
11.4.2 A delay in protocol treatment, as specified in Section 6.0.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.
### 12.0 DATA COLLECTION

Data should be submitted to:  
**RTOG Headquarters***  
1818 Market Street, Suite 1600  
Philadelphia, PA  19103

*If a data form is available for web entry, it must be submitted electronically.*

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

### 12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Slides/Blocks (P2)</td>
<td>See Section 10</td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td>Within 2 weeks of registration and at recurrence of primary tumor</td>
</tr>
<tr>
<td>Surgical Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Cosmesis Questionnaires</td>
<td>Prior to start of radiation <em>but after surgery</em>, and at 1 and 3 years from the start of radiation</td>
</tr>
<tr>
<td>▪ Radiation Oncologist/Surgeon Evaluation Form (QP)</td>
<td></td>
</tr>
<tr>
<td>▪ Patient Evaluation Form (BQ)</td>
<td></td>
</tr>
<tr>
<td>Cosmesis Photos</td>
<td></td>
</tr>
<tr>
<td>Photograph Submission Notification Form (T7)</td>
<td></td>
</tr>
<tr>
<td>RT Summary Form (T1)</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>[copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>RT Treatment Record (T5)</td>
<td>At 6 weeks from the start of radiation; every 3 months from the start of radiation for the first year; every 4 months for years 2 and 3, every 6 months for the next 2 years and yearly thereafter. Also at progression/relapse and at death</td>
</tr>
<tr>
<td>[copy to HQ and ITC]</td>
<td></td>
</tr>
</tbody>
</table>
## 12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD)</td>
<td></td>
</tr>
<tr>
<td>†Digital Data Submission – Treatment Plan</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>Digital data submission includes the following:</td>
<td>(* unless “Rapid review”; see section 6.8)</td>
</tr>
<tr>
<td>• CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>• Digital beam geometry for initial beam sets</td>
<td></td>
</tr>
<tr>
<td>• Doses for initial treated beams</td>
<td></td>
</tr>
<tr>
<td>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan</td>
<td></td>
</tr>
<tr>
<td>Digital Data Submission Information Form (DDSI) –</td>
<td></td>
</tr>
<tr>
<td>Submitted online (Form located on ATC web site,</td>
<td></td>
</tr>
<tr>
<td><a href="http://atc.wustl.edu/forms/ddsi/ddsi.html">http://atc.wustl.edu/forms/ddsi/ddsi.html</a></td>
<td></td>
</tr>
<tr>
<td>Hard copy isodose distributions for total dose plan †</td>
<td>(T6)</td>
</tr>
<tr>
<td>NOTE: Sites must notify ITC via e-mail (<a href="mailto:itc@wustl.edu">itc@wustl.edu</a>) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.</td>
<td></td>
</tr>
<tr>
<td>Final Dosimetry Information</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Modified digital patient data as required through consultation with Image-Guided Therapy QA Center</td>
<td></td>
</tr>
</tbody>
</table>

†Available on the ATC web site, http://atc.wustl.edu/  
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

### 12.2.1 Digital Data Submission to ITC

Digital data submission may be accomplished using media or the Internet.  
**For network submission:** The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to: itc@wustl.edu  
**For media submission:** Please contact the ITC about acceptable media types and formats.  
**Hardcopies** accompanying digital data should be sent by mail or Federal Express and should be addressed to:  

Image-Guided Therapy Center (ITC)  
ATTN: Roxana Haynes  
4511 Forest Park, Suite 200  
St. Louis, MO 63108  
314-747-5415  
FAX 314-747-5423
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
Grade 3+ treatment-related skin, fibrosis, and breast pain adverse events occurring within 1 year from the completion of reirradiation.

13.1.2 Secondary Endpoints

13.1.2.1 In-breast recurrence (failure per definitions in Section 11.2)
13.1.2.2 Freedom from mastectomy (failure: mastectomy of the treated breast)
13.1.2.3 Rate of circulating tumor cells (CTCs) pre- and post-treatment
13.1.2.4 All treatment-related adverse events for the following time periods:
   13.1.2.4.1 After 1 year from completion of re-irradiation
   13.1.2.4.2 Overall
13.1.2.5 Cosmesis (evaluated at 1 and 3 years)
13.1.2.6 Distant metastases-free survival (failure: appearance of distant metastasis confirmed radiographically and/or pathologically or death due to any cause)
13.1.2.7 Mastectomy-free survival (failure: mastectomy of the treated breast or death due to any cause)
13.1.2.8 Overall survival (failure: death due to any cause)

13.2 Study Design

13.2.1 Sample Size Derivation
The primary objective of this study is to evaluate the rate of grade 3+ treatment-related skin, fibrosis, and breast pain adverse events occurring within 1 year from the completion of reirradiation. Based on a rate of 4% for these adverse events from first line PBI treatment in RTOG 0319, the investigators have determined that a rate of 13% or more for these adverse events with re-irradiation would be unacceptable. A sample size of 55 evaluable patients (eligible and started protocol treatment) will provide the following: 86% power to conclude that the treatment has an unacceptable rate of the specified adverse events, if the true adverse event rate is at least 13% and 93% probability to not conclude that the treatment has an unacceptable rate of the specified adverse events, if the true adverse event rate is 4%. Adjusting this figure by 10% to allow for patients determined to be ineligible, that do not start protocol treatment, or lack of data, a total sample size of 61 patients will be required for this study.

13.2.1.2 Power for Secondary Endpoints
For the secondary endpoint of in-breast recurrence, assuming a 3-year rate of 25% using a chi-squared test, a sample size of 55 patients will ensure at least 90% probability of detecting a reduction in the 3-year ipsilateral in-breast recurrence rate from 25% to 9%, with a significance level of 0.05 (1-sided).

13.2.2 Patient Accrual
It is projected that there will be a period of approximately 6 months with very slow accrual at the beginning of this study to allow for both institutional IRB approval and 3D approval by the RTOG QA center. Following this initial period, it is projected that the study will accrue 4 patients/month and that accrual will be completed in approximately 23 months. If the average monthly accrual is less than 2 cases per month 12 months after it the study is opened, the study will be re-evaluated with respect to feasibility.

13.2.3 Fatal Treatment Morbidity
If a fatal adverse event occurs (1) during or within 30 days of protocol treatment completion, regardless of relationship to protocol treatment, or (2) at any time and is related to protocol treatment, the event will be reported to the study chairs and the RTOG Breast/GYN Committee Chair for Breast Cancer Trials for review. At this time it will be determined if accrual to the trial must be suspended pending this review for patient safety. The data manager will, after requesting additional supporting documentation if necessary, have all documents scanned and transmitted electronically to the study chairs and the head of the RTOG Data Safety Monitoring Board (DSMB) for their review. This will take place within 2 weeks of each reported adverse event if at all possible.

13.3 Analysis Plan

13.3.1 Interim Reports
Interim reports will be prepared every 6 months until the primary endpoint has been accepted for presentation or publication. In general, these reports include:

- the patient accrual rate with projected completion date
- institutional accrual
- exclusion rates and reasons
- pretreatment characteristics
- compliance rates of treatment delivery with respect to the protocol prescription
- the frequency and severity of adverse events

13.3.2 CDUS Reports
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.3.3 Data Safety Monitoring Board (DSMB) Review
To monitor the safety of this study, it will be officially reviewed by the RTOG DSMB twice a year in conjunction with the RTOG semi-annual meeting and on an "as needed" basis in between meetings.

13.3.4 Analysis for Reporting Treatment Results
13.3.4.1 Initial Results
The analysis for reporting the initial primary endpoint results of treatment will be undertaken when each patient has been potentially followed for a minimum of 1 year from the completion of reirradiation. Only patients who meet the eligibility requirements of this protocol and start protocol treatment will be included. If 5 or more, out of 55 evaluable, patients experience the treatment-related adverse events specified in Section 13.2.1.1, then the treatment-related adverse event rate will be considered unacceptable and the treatment will not be considered further; otherwise the treatment-related adverse event rate will be considered to be acceptable and the treatment will be considered for further study.

13.3.4.2 Efficacy and Additional Adverse Events Analyses
Efficacy, cosmesis, and additional adverse event endpoints, as listed in Section 13.1.2, will be analyzed 3 years after completion of accrual.

13.3.4.3 Analysis Components
The usual components of the above mentioned analyses are:

- tabulation of all cases entered and reasons for any patients excluded from the analysis
- institutional accrual
- patient accrual rate
- distribution of important pretreatment characteristics
- observed results with respect to the appropriate endpoints

13.3.4.4 Estimation of Secondary Endpoints Related to Efficacy
In-breast recurrence and freedom from mastectomy will be estimated using the cumulative incidence method.47 Distant metastases–free survival, mastectomy-free survival, and overall survival rates will be estimated using the Kaplan-Meier method.48

13.4 Inclusion of Women and Minorities
In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered differences in prognosis by race and ethnicity. If the distributions allow, an exploratory statistical analysis will be performed to examine the possible differences between the among the race and ethnicity categories.
## Gender and Minority Accrual Estimates

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>8</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>53</td>
<td>NA</td>
<td>53</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>61</td>
<td>NA</td>
<td>61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Black or African American</td>
<td>6</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>53</td>
<td>NA</td>
<td>53</td>
</tr>
<tr>
<td>More than one race</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>61</td>
<td>NA</td>
<td>61</td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX I

Informed Consent Template for Cancer Treatment Trials
(English Language)

RTOG 1014

A Phase II study of Repeat Breast Preserving Surgery and 3D-Conformal Partial Breast Re-Irradiation (PBri) for Local Recurrence of Breast Carcinoma

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

You are being asked to take part in this study because another cancer has been found in your breast that was previously treated with surgery and radiation.

Why is this study being done?

When a second cancer is discovered in a breast previously treated with radiation to the whole breast following lumpectomy, the standard treatment is a mastectomy. Very few studies have been done to find out if breast conservation therapy (repeat lumpectomy and re-irradiation to part of the breast) can be applied as an alternative to mastectomy.

The purpose of this study is to evaluate the side effects of partial breast re-irradiation given after a lumpectomy. The lumpectomy will remove the breast cancer and a limited amount of surrounding normal breast tissue. Following the surgery, you will receive three dimensional conformal radiation therapy (3D-CRT) to treat only the area in the breast where the lumpectomy was performed. 3D-CRT tries to lower the amount of radiation that normal tissues receive, while still delivering the desired amount of radiation to your cancer and to areas that your study doctor thinks may have cancer cells.

How many people will take part in the study?

About 61 people will take part in this study.

What will happen if I take part in this research study?

If you take part in this study, you will have the following treatment: You will first have a lumpectomy. You may have more surgery if the lumpectomy does not remove all of the cancer. Within 9 weeks after your last breast surgery, you will receive radiation therapy to the area of the lumpectomy 2 times per day for 15 consecutive working days. The radiation will be given 6 hours apart on each of the 15 days.

Chemotherapy and/or hormonal therapy may be necessary depending on the size and extent of your tumor and other risk factors. Your participation in this study will not influence whether or not you receive such additional treatment.

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.
• History and physical exam
• Mammograms
• PET/CT or all of the following: CT scan of the chest, abdomen and pelvis and bone scan
• Blood tests (pregnancy test if applicable)
• Lumpectomy
• Repeat surgery if the lumpectomy does not remove all of the cancer
• Surgery on nodes (Axillary) if indicated by your physician

You will also need have the following exam. It is not part of standard cancer care in this setting, but it will help us to better understand whether there are additional areas of cancer in the breast that we need to address.
• Breast MRI

During the study …
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures.

• Blood tests if indicated by your study doctor
• Bone scan or X-rays if indicated by your study doctor

During follow-up:
When you are finished receiving all treatment, you will have the following tests and procedures:

At 6 weeks from the start of radiation therapy:
• History and physical exam
• Breast assessment exam
• Evaluation of any side effects from treatment you may be having

Every 3 months from the start of radiation therapy for 1 year, then every 4 months for 2 years, then every 6 months for 2 years, then yearly:
• History and physical exam
• Breast assessment exam
• Evaluation of any side effects from treatment you may be having
• Blood tests, CT scans, and X-rays if indicated by your study doctor

In addition, you will receive a mammogram at 6 months from the start of radiation therapy, no more than 1 year from your pre-study mammogram, then yearly.

How long will I be in the study?
The radiation therapy will take approximately 3 weeks to complete. Follow-up visits will be scheduled at 6 weeks from the start of radiation therapy, every 3 months from the start of radiation therapy for the first year, then every 4 months for 2 years, then every 6 months for 2 years, then yearly.

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

It is important to tell the study doctor if you are thinking about stopping so that he/she can evaluate any risks from the treatment. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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

What side effects or risks can I expect from being in the study?
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don’t know all the side effects that may happen. Side effects may be mild or
very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

**Risks Associated with Radiation Therapy to the Breast**

**Very likely:**
- Reddening or tanning of the skin
- Fatigue and weakness
- Chest muscle tightness/discomfort
- Swelling of breast

**Less likely, but serious:**
- Peeling of the skin in the treatment area
- Pain at the site of treatment

**Unlikely, but serious**
- Cough
- Pericarditis (irritation of the sac surrounding the heart)
- Myocarditis (inflammation of the heart muscle)
- Rib fractures
- Scar tissue formation and cosmetic change (bad cosmetic result)
- Pulmonary fibrosis

The study treatment may have a higher risk than mastectomy of your cancer returning and the need to have a mastectomy

The study treatment may have an overall effect not as good as the standard treatment of your second cancer (mastectomy)

**Reproductive risks:** This study may be harmful to a nursing infant or an unborn child. You should not nurse your baby while on this study. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. You should not become pregnant while on this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while you are on this study, you must tell your study doctor immediately. Ask about counseling and more information about preventing pregnancy.

**Are there benefits to taking part in the study?**
Taking part in this study may or may not make your health better. While researchers hope that with this treatment you can avoid mastectomy and control the cancer, there is no proof of this yet. We do know that the information from this study will help researchers learn more about the application of breast conservation therapy as an alternative to mastectomy. The information gained from this clinical trial could help future cancer patients.

**What other choices do I have if I do not take part in this study?**
You may choose not to participate in this study. Other treatments that could be considered for your condition may include the following: (1) mastectomy, (2) taking part in another study, (3) no treatment. Treatments could be given either alone or in combination with each other. Your study doctor can tell you more about your condition and the possible benefits of the different available treatments. Another option may be to get the treatment plan described in this study at this center and other centers even if you do not take part in the study.

Talk to your study doctor about your choices before you decide if you will take part in this study.
Will my medical information be kept private?
Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, including the photographs of your breast, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- Your Institutional Review Board (IRB), a group of people who review the research study to protect your rights;
- The Radiation Therapy Oncology Group (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?
You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at __________________ [telephone number].

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

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Monitoring Board (DMB) will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.
In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about the study?**

*(This section must be completed)*

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

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

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

**You can say “yes” or “no” to the following studies. Below, please mark your choice for each study.**

**Cosmesis Study**

We want to know your opinion about the cosmetic outcome following the re-treatment of your breast. This study will allow us to gather information from you and your study doctors about how your breast looks after treatment and how satisfied you are with the appearance of your breast after your surgery and repeat radiation therapy.

You will be asked to complete a questionnaire that will take about 15-20 minutes to fill out at 3 study visits: once between surgery and radiation therapy, once 12 months from the start of radiation therapy, and once 36 months from the start of radiation therapy.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this cosmesis study, your study doctor will also fill out questionnaires that ask for a medical opinion of the appearance of your breasts after completion of your therapy. Also, photographs of your breast will be taken once between surgery and radiation therapy, once 12 months from the start of radiation therapy, and once 36 months from the start of radiation therapy. The photographs will only include your breasts. Your face will not be in the photos and your name and other personal information will not be given out. These photos will be checked only by the doctors in charge of this study. The study doctors’ opinions about the appearance of your breast after study therapy will be compared to your opinion.

This information will help doctors better understand how patients feel during treatments and what effects the radiation therapy is having. In the future, this information may help patients and doctors as they decide which radiation therapy to use to treat breast cancer.

You may change your mind about completing the questionnaires or having the photos taken of your breast at any time. It will not affect your taking part in the main study.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

*Please circle your answer.*

*I choose to take part in the Cosmesis Study. I agree to fill out the three Cosmesis Questionnaires.*

YES NO
Circulating Tumor Cells (CTCs)

CTCs have been identified in the bone marrow and blood of patients found to have breast cancer. We anticipate that 25% of patients like yourself, with new disease in the breast after previous treatment, may have CTCs present in the blood. This study is investigating whether or not these CTCs are present and how the treatment we are delivering affects them. This information will help us understand more about cancer treatment outcome.

If you decide to participate in this additional study you will be asked to give a sample of blood at the following times: (1) before the radiation is started, and (2) within 3 weeks after completing radiation.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Circulating Tumor Cell Study. I agree to give blood samples at the requested time intervals.

YES     NO

Use of Tissue and Blood for Research: Consent Form

About Using Tissue and Blood for Research

You have had two lumpectomies in the treatment of your breast cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over from both lumpectomies for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site:

http://www.rtog.org/tissue%20for%20research_patient.pdf

In addition, we would like to collect and keep for future research about 3 tablespoons of the blood taken at the following times: (1) before radiation is started, and (2) within 3 weeks after completing radiation. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue and blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

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

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue and blood that remain will no longer be used for research. Remaining tissue will be returned to the institution that submitted it, and remaining blood will be destroyed.

In the future, people who do research may need to know more about your health. While the [doctor/institution] may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.
Benefits
The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

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

Making Your Choice

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

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

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

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   - Tissue ☐ Yes ☐ No
   - Blood ☐ Yes ☐ No

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

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/
   - For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
   - For NCI's general information about cancer, go to http://cancer.gov/cancertopics/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ______________________________

Date ________________________________
# APPENDIX II
## STUDY PARAMETER TABLE

<table>
<thead>
<tr>
<th>Required Studies</th>
<th>Pre-Treatment</th>
<th>During Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W/i 120 days prior to study entry</td>
<td>w/i 42 days prior to study entry</td>
<td>6 weeks, q 3 month for 1 yr, q 4mo for 2 yrs, q 6 months for 2yrs and then yearly from the start of radiation</td>
</tr>
<tr>
<td></td>
<td>Prior to study entry</td>
<td>Weekly during radiation</td>
<td>Annually during follow-up</td>
</tr>
<tr>
<td>Final breast surgery (lumpectomy and/or final re-excision)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and physical exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Breast assessment/exam</td>
<td>X (post-op)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Zubrod performance status</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Estrogen and Progesterone analysis and HER2</td>
<td>X*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td>≤ 7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT of chest, abdomen and pelvis, Bone scan</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Body PET/CT(Optional)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Ultrasound (Optional)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral mammogram</td>
<td>X</td>
<td></td>
<td>X*</td>
</tr>
<tr>
<td>Bilateral breast MRI</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See Sections 4.1 and 11.1 for exceptions and details*
APPENDIX IIA

Tissue/Serum/Whole Blood and Circulating Tumor Cell Blood Collection Time Points (for consenting patients)

<table>
<thead>
<tr>
<th></th>
<th>Prior to Start of Radiation Therapy</th>
<th>Within 3 Weeks of Completing Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating Tumor Cells</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tissue</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Whole Blood</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Cosmesis Collection Time Points (for consenting patients)

<table>
<thead>
<tr>
<th>Cosmesis Collection: (Questionnaires &amp; Digital Images)</th>
<th>Prior to start of RT (but after surgery)</th>
<th>At 1 year from the start of Radiation Therapy</th>
<th>At 3 years from the start of Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD/Patient reported Cosmesis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Digital Images of Breast</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
APPENDIX III

ZUBROD PERFORMANCE SCALE

0  Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1  Restricted in physically strenuous activity but ambulatory and able to carry work if a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3  Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4  Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5  Death (Karnofsky 0).
APPENDIX IV
AJCC STAGING SYSTEM

BREAST

Primary Tumor (T)
The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

T0 No evidence of primary tumor.
Tis Carcinoma in situ
Tis (DCIS) Ductal carcinoma in situ
Tis (LCIS) Lobular carcinoma in situ
Tis (Paget’s) Paget’s disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget’s disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget’s disease should still be noted

T1 Tumor ≤20 mm in greatest dimension
T1a Tumor >1 mm but ≤5 mm in greatest dimension
T1b Tumor >5 mm but ≤10 mm in greatest dimension
T1c Tumor >10 mm but ≤20 mm in greatest dimension
T2 Tumor >20 mm but ≤50 mm in greatest dimension
T3 Tumor >50 mm in greatest dimension
T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Note: Invasion of the dermis alone does not qualify as T4

T4a Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d’orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c Both T4a and T4b
T4d Inflammatory carcinoma (see “Rules for Classification”)

Note: Inflammatory carcinoma is restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.

Regional Lymph Nodes (N) Clinical
NX Regional lymph nodes cannot be assessed (e.g., previously removed)
N0 No regional lymph node metastases
N1 Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of
clinically evident level I, II axillary lymph node metastases

<table>
<thead>
<tr>
<th>N3</th>
<th>Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>N3a</td>
<td>Metastases in ipsilateral infraclavicular lymph node(s)</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)</td>
</tr>
<tr>
<td>N3c</td>
<td>Metastases in ipsilateral supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

*Note: Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

**Regional Lymph Nodes Pathologic (pN)**

<table>
<thead>
<tr>
<th>pNX</th>
<th>Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis identified histologically</td>
</tr>
<tr>
<td>Note:</td>
<td>Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.</td>
</tr>
<tr>
<td>pN0(i-)</td>
<td>No regional lymph node metastases histologically, negative IHC</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&amp;E or IHC including ITC)</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastases histologically, negative molecular findings (RT-PCR)</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC</td>
</tr>
<tr>
<td>pN1</td>
<td>Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***</td>
</tr>
<tr>
<td>pN1mi</td>
<td>Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN1a</td>
<td>Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2.0 mm</td>
</tr>
<tr>
<td>pN1b</td>
<td>Metastases in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***</td>
</tr>
<tr>
<td>pN1c</td>
<td>Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastases in 4-9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases</td>
</tr>
<tr>
<td>pN2a</td>
<td>Metastases in 4-9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN2b</td>
<td>Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>pN3a</td>
<td>Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes</td>
</tr>
<tr>
<td>pN3b</td>
<td>Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***</td>
</tr>
</tbody>
</table>
**pN3c** Metastases in ipsilateral supraclavicular lymph nodes

**Notes:**
*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

**RT-PCR:** reverse transcriptase/polymerase chain reaction

***“Not clinically detected” is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

****“Clinically detected” is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>M0</th>
<th>No clinical or radiographic evidence of distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>cM0(i+)</td>
<td>No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm</td>
</tr>
</tbody>
</table>

### Anatomic Stage/Prognostic Groups

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T0</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1mi</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0</td>
<td>N1**</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1**</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Notes:**
*T1 includes T1mi.

**T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

Post neoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0
APPENDIX V
Quality Assurance Guidelines

The current version of the Quality Assurance Guidelines must be obtained from the ITC web site: http://itc.wustl.edu

The Quality Assurance Guidelines contain the following informational and directive items:

1. Background information to assist participants in meeting protocol specified radiation therapy treatment planning and delivery requirements.
2. Credentialing requirements to be completed for eligibility to enroll patients in the protocol.
   a. Facility Questionnaire assistance. Note that the Facility Questionnaire form is available only from the ITC web site identified above. Download this form in close time proximity to when it will be completed because it may be updated depending on protocol developments and modifications.
   b. Dry Run test requirements.
3. Patient digital data submission requirements including standard names for target volumes and organs at risk.
4. Evaluation criteria and scoring system applied to submitted radiation therapy patient data.
   a. Scoring system for critical structures and tumor/target volumes.
   b. Scoring system for port and isocenter localization films.
   c. Scoring system for dose delivery analysis.
   d. Methods of obtaining scores assigned.
APPENDIX V (CONT’D)
CONTOURING GUIDELINES

1.0 TARGET CONTOURING

Target definitions are outlined in the protocol and are listed here with figure depictions.

**CTV** – 1.5 cm beyond excision cavity. Volume expansion limited to exclude pectoralis muscles, chest wall, and the first 5 mm beneath the skin (See Figure 2).

**PTV** – 1.0 cm beyond CTV (See Figure 3).

**PTV_EVAL** – the PTV excluding pectoralis muscles, chest wall and the first 5 mm beneath the skin (See Figure 4).

2.0 NORMAL STRUCTURE CONTOURING

Contouring accurately and consistently is essential for the case evaluation and data comparison in this protocol. The following target structures will be contoured in all cases: excision cavity, clinical target volume (CTV) and planning target volume (PTV), the planning target for evaluation (PTV_EVAL). The following normal tissue structures will be contoured in all cases: skin, ipsilateral and contralateral breast, thyroid, ipsilateral and contralateral lung, and heart. The chin, shoulders and contralateral breast should be included in the scan. The target structures and normal tissue structures must be outlined on all CT slices.

2.1 Thyroid

The thyroid is easily visible on a non-contrast CT due to its preferential absorption of Iodine, rendering it “brighter” or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape, and often do not converge anteriorly at mid-line. All “bright” thyroid tissue should be contoured.

2.2 Heart

The heart should be contoured beginning just below the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart’s 4 chambers are present. All the mediastinal tissue below this level should be contoured, including the great vessels (ascending and descending aorta, inferior vena cava). The heart should be contoured on every contiguous slice thereafter to its inferior-most extent near the diaphragm. If one can identify the esophagus, this structure should be excluded. One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

2.3 WHOLE BREAST REFERENCE VOLUME CONTOURING

Delineation of breast tissue extent remains difficult and free-handed CT interpretation by each individual investigator will yield significant variability despite the introduction of the RTOG breast atlas. For the purposes of this protocol and for consistency with previous partial breast treatment protocols, the whole breast reference volume will continue to be used to represent the whole breast volume and will be defined as all tissue volume, excluding lung, within the boundaries of standard whole breast tangential fields (See Figures 1 and 2). The whole breast reference volume should also exclude any non-breast structure deep to the lung-rib interface such as heart, pre-cardiac fat, and liver. This is meant to be only an approximation of the actual breast tissue volume, and it is recognized that the chest wall and some degree of adjacent soft tissue will be included. However, with this definition it is anticipated that this volume will be reproducible and consistent from case to case and that the process can be automated within the 3D planning system for time conservation. The methodology of contouring, free-handed or automated, is at the discretion of the individual investigator assuming the contour represents the defined volume. To facilitate, the patient should be positioned in standard whole breast external beam treatment position. It is recommended that external marker wires be placed to
indicate the clinical expectations of the external beam tangential field borders as a guide. The CT should be obtained from the mandible to the base of the lungs with a slice thickness of \( \leq 5 \) mm.

2.3.1 Free-handed contouring

Although it requires additional time, free-handed contouring can be easily completed if an auto-contouring method is not available within the 3D planning system. Within a 3D treatment planning system, standard virtual whole breast medial and lateral tangential fields should be designed and used to guide free-handed contouring. The superior, inferior, medial and lateral borders are defined by the borders of the simulated whole breast tangential beams. The skin will be the anterior/superficial boundary while the base of the simulated tangential fields and the lung/chest wall interface will delineate the posterior boundary of the breast tissue volume, thereby, including chest wall and excluding the lung (See Figures 1 and 2). The contours will be entered on all CT slices within the boundaries of the simulated tangential fields.

2.3.2 Automated contouring

Each 3D planning system has available different contouring functions and the specific methods may vary from system to system. Institutions are encouraged to investigate the capabilities of their planning system in regards to these contouring functions. Within the Pinnacle 3D planning system, auto-contouring the whole breast reference volume, as defined above, is easily accomplished and can be completed in several ways. Outlined below is an example of one of these methods:

The Pinnacle 3D planning system has within its contouring functions a Region of Interest (ROI) expansion/contraction tool, found under Options within the contouring window, which allows a selected contour to be altered/limited automatically by selected ROIs already entered in the patient's plan. At the start of each case, the skin and lung contours will be entered with automated functions and the virtual standard whole breast tangent fields designed. By way of the ROI expansion/contraction tool, the planning system will start with the skin contour and alter it by limiting this contour to within the boundaries of the tangential fields and lung/chest wall interface, thus creating a new contour that represents the whole breast volume as defined above. Since this ROI expansion/contraction tool only uses entered contours, ROI's representing the borders of the tangential fields must first be entered. To represent the superior and inferior field borders, a simple box contour that encompasses the entire body on each CT slice superior and inferior to the tangential field borders, are entered under a new ROI (i.e., field borders). This can be accomplished by entering manually on each appropriate CT slice or expediting by utilizing the interpolation tools (See Figure 3). Added to the newly created ROI, named here field borders, is a contour that is placed along the posterior field border, extending the contour beyond the CT slice and viewing window (See Figure 3). This contour can be entered manually on each appropriate CT slice or, to save time, the interpolation tool can be used to automate. Once field boundary contouring is complete, each CT slice will have either a simple encompassing box contour (if superior or inferior to the tangential fields) or a posterior field boundary contour (if within the tangential field borders). At this time, the ROI expansion/contraction window is brought up. Designate the skin as the source ROI and designate the lung and field borders limiting ROI's. Highlight "contract" as the function and designate the destination of the newly created ROI (simply create a new ROI which will then be listed in the destination list). Click on Proceed with Contraction to complete the process.

3.0 3D-CRT BEAM ARRANGEMENT

There are no restrictions on 3D-CRT beam arrangement assuming the Dose Volume Histogram criteria for both target and normal tissue volumes are preserved. Guidance on field design can be found in the published literature, examples are listed below


Figure 1. Whole breast reference volume contour – lumpectomy cavity
Figure 2. Excision cavity and expansion to CTV
Figure 3. Excision cavity – CTV and expansion to PTV
Figure 4. Excision cavity – CTV – PTV expansion to PTV_EVAL

- Planning Target Volume for evaluation (PTV_EVAL)
  - excludes chest wall/pectoralis muscles
  - extends to within 5mm of skin

Excludes pectoralis muscles and chest wall

5mm inside skin
APPENDIX VI

INSTRUCTIONS FOR SUBMITTING COSMESIS PHOTOS

To submit cosmesis photos:

- Make sure photos are available in a JPEG format on the computer that you are using. Identify the photos as follows:
  - Baseline photos: Single_B for Treated Breast view  Both_B for Both breasts view
  - 1-year photos: Single_1 for Treated Breast view  Both_1 for Both Breasts view
  - 3-year photos: Single_3 for Treated breast view  Both_3 for Both Breasts view
- Go to the RTOG website [http://www.rtog.org/](http://www.rtog.org/)
- Click on site tools link at the top of the page
- Click on RTOG 1014
- Log in using the ID and Password that was supplied on the e-mail that you received confirming registration
- Complete the required fields and upload the photos
- Please be sure to upload one photo of the treated breast and one photo showing both breast as instructed in Section 11.3.3 of the protocol
RTOG 1014 BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, CTC, and whole blood collection kit (CTC kit components may be shipped separately)

This kit includes:

- Two 10 ml Red Top Tubes for Serum
- One 10 ml Purple Top EDTA Tube for Whole Blood
- Two CellSave tube for CTC analysis
- Twelve 1.2 ml cryovials
- Biohazard bags (2)
- Absorbent shipping material (2)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Kit Instructions

Serum (if requested): (Red Top Tube)

- Using four-eight 1.2 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot 0.5 ml serum into each of 4-8 cryovials labeled with RTOG study and case numbers, collection date/time, timepoint collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at –70 to –80°C Celsius.
5. Store serum at –70 to –80°C Celsius until ready to ship.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

Anti-coagulated Blood for DNA (if requested): (Purple Top EDTA Tube #2)

- Using up to four 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “blood”

Process:
1. Mix Blood in EDTA (purple top) tube for at least 5 minutes at room temperature.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until aliquotting is performed.
3. Aliquot 0.5 ml serum into each of 4-8 cryovials labeled with RTOG study and case numbers, collection date/time, timepoint collected, and clearly mark specimen as “blood”.
4. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C Celsius.
5. Store blood samples frozen (-70 to -80°C Celsius) until ready to ship.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**
APPENDIX VII (CONT’D)

Storage Conditions

Store Frozen biospecimens at -80°C (-70°C to -90°C) until ready to ship on dry ice.
If a -80°C Freezer is not available:
- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).
- OR:
  - Samples can be stored in sufficient dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).
- OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Mon.-Wed. only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing for Serum and Whole Blood:

- Ship specimens overnight Monday-Wednesday to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted. We recommend that Canadian institutions only ship Monday-Tuesday as customs usually delays shipment by one extra day.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with dry ice (5-10 lbs/2.5-5kg minimum). **Add padding to avoid the dry ice from breaking the tubes.**
- Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- Ship ambient specimens in a separate envelope/cooler.
- **Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag. Add padding to avoid the dry ice from breaking the tubes.**
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864

**Shipping Address**

**FedEx/UPS/Courier address (all courier packages & frozen samples except CellSave tube for CTCs)**
RTOG Biospecimen Resource
UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact # 415.476.7864

CTCs: (CellSave tube)

- Using a CellSave tube, label it with the RTOG study and case number, collection date and time, and clearly mark “CTC”.

  Process:
  1. Place tube in biohazard bag.
  2. Wrap with packing material to prevent breaking during shipment.
  3. Ship overnight at room temperature within 24 hours of collection (Monday-Wednesday to ensure immediate processing).

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Shipping Address**

**FedEx/UPS/Courier address (CellSave tube for CTC Analysis)**
Wendy Woodward
c/o Summer Jackson
Breast Medical Oncology
1155 Pressler St
Unit 1354  ACB5.2320
Houston, TX 77030

For questions related to CTC collection/CellSave tubes, please email wwoodward@mdanderson.org
APPENDIX VIII

RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label punch tool with proper specimen ID. DON’T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or email us if you have any questions or need additional specimen plug kits.

Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the address below:

US Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu