RADIATION THERAPY ONCOLOGY GROUP

RTOG 0319

A PHASE I/II TRIAL TO EVALUATE THREE DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) CONFINED TO THE REGION OF THE LUMPECTOMY CAVITY FOR STAGE I AND II BREAST CARCINOMA (9/30/03)

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A PHASE I/II TRIAL TO EVALUATE THREE DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) CONFINED TO THE REGION OF THE LUMPECTOMY CAVITY FOR STAGE I AND IIA BREAST CARCINOMA

SCHEMA

R

38.5 Gy Total/10 fractions (3.85 Gy per fraction)
2 fractions/day (separated by 6 hours)

G

Given in 5 consecutive working days

I

Radiotherapy should begin within eight weeks of surgery

S

(If chemotherapy is given first, RT begins 2 weeks after the last cycle of chemotherapy)

T

E

R

Chemohormonal Therapy
Chemohormonal therapy may be done at the discretion of treating institution. Cytotoxic chemotherapy is not to be started until at least two weeks post radiation therapy, if RT is first. If chemotherapy is first, RT will begin a minimum of 2 weeks after the last cycle of chemotherapy. Tamoxifen or Arimidex® can be started at once.

Eligibility (see Section 3.0 for details) (9/30/03)
- Invasive ductal, medullary, papillary, colloid (mucinous), tubular histologies.
- AJCC Stage I or II (T_1N_0, T_1N_1, T_2N_0, T_2N_1); lesion ≤ 3 cm.
- Six surgical clips placed at time of tylectomy to delineate lumpectomy cavity.
- Unifocal breast cancer (single focus which can be encompassed by one tylectomy).
- Negative surgical margins.
- No extensive intraductal component or patients with distant metastases.
- Negative post-tylectomy mammogram (if applicable); no diffuse suspicious microcalcifications
- Patients with up to 3 positive axillary nodes.
- No prior malignancy (< 5 years prior to study entry) except non-melanomatous skin cancer; disease-free interval from any prior carcinoma must be continuous.
- No collagenous disease (systemic lupus erythematosis, scleroderma, dermatomyositis).
- No previous non-hormonal therapy including radiation or chemotherapy for current breast cancer.
- No patients with Paget’s disease of the nipple.
- No patients with co-existing medical conditions with life expectancy < 2 years.
- No pregnant or lactating women.
- Patients must be ≥ 18 years of age.
- Signed study-specific informed consent form prior to study entry.

Required Sample Size: 46
Does the patient have histologically confirmed invasive ductal, medullary, papillary, colloid (mucinous), or tubular cancer of the breast?

Is the AJCC TNM classification T1-2, N0-N1, M0?

Is the primary tumor size ≤ 3 cm?

Has the patient undergone tylectomy resulting in negative inked tumor margins > 2 mm?

If no, is re-excision planned prior to radiation? (failure to meet all criteria subsequent to re-excision will result in ineligibility).

Any evidence of pre-excision microcalcifications on the initial mammogram?

If yes, is the postoperative mammogram negative for residual suspicious microcalcifications?

Have six surgical clips been placed delineating the margins of the tylectomy cavity?

Has the patient had at least six axillary nodes sampled or a sentinel lymph node biopsy?

Are more than 3 axillary nodes/sentinel node biopsy positive?

Is there any evidence of multicentric breast tumor, an extensive intraductal component, unresolved suspicious synchronous tumors/calcifications or prior history of breast cancer?

Any evidence of Paget’s disease of the nipple, tumor involving skin, internal mammary or supraclavicular lymph nodes or distant metastasis?

Is the cosmesis of the breast following extensive tylectomy low to poor resulting in a breast technically unsatisfactory for radiotherapy?

Any evidence of collagen vascular disease including Systemic Lupus Erythematosus, Scleroderma, or Dermatomyositis?

Except for non-melanomatous skin cancer, is there history of prior malignancy within the past 5 years?

Any prior treatment, other than tylectomy or chemotherapy, including radiotherapy, or non-hormonal therapy for the current breast cancer?

If prior chemotherapy, will a minimum of 2 weeks from the last cycle have elapsed prior to the start of radiation therapy?

Is the patient pregnant or lactating?

Is the patient ≥ 18 years of age?

(continued on next page)
______(N) 18. Any co-existing medical condition with life expectancy of < 2 years?
______(N) 19. Any psychiatric or addictive disorder that would preclude informed consent?

The following questions will be asked at Study Registration:

__________ 1. Name of institutional person registering this case?
__________(Y) 2. Has the Eligibility Checklist (above) been completed?
__________(Y) 3. Is the patient eligible for this study?
__________ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
__________ 5. Patient’s Initials (Last, First) [Initials only effective 2/2/02]
__________ 6. Verifying Physician
__________ 7. Patient’s ID Number
__________ 8. Date of Birth
__________ 9. Race
__________ 10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)
__________ 11. Gender
__________ 12. Patient’s Country of Residence
__________ 13. Zip Code
__________ 14. Patient’s Insurance Status
__________ 15. Will any component of the patient’s care be given at a military or VA facility?
__________ 16. Was a stereotactic core needle biopsy done?
__________ 17. Will tamoxifen or Arimidex® be started?
__________ 18. Is chemotherapy planned? (if yes, must not start < 2 weeks after radiation therapy)
__________ 19. Treatment Start Date

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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 ___________________________
I. INTRODUCTION

This study will evaluate the technical feasibility and acute toxicity of irradiating the region of the tumor bed alone with three-dimensional conformal radiation therapy (3D-CRT) after lumpectomy. Selected patients with Stage I or IIA carcinoma of the breast will be treated with breast conserving therapy (BCT); negative surgical margins must be confirmed histologically.

Breast conserving therapy has become an accepted option in the treatment of most patients with Stage I and II breast cancer. Multiple retrospective studies as well as six prospective randomized trials have established the equivalence of this treatment approach compared to mastectomy in terms of disease-free and overall survival.\(^1\)\(^-\)\(^6\) The major advantage of BCT is related to the superior cosmetic result and reduced psychological and emotional trauma resulting from this procedure compared to mastectomy. However, BCT also has relative disadvantages. The technique is a more complex and prolonged treatment regimen, which requires approximately five to seven weeks to complete. As a result, for patients who are elderly or who live a significant distance from treatment centers, logistical problems can prove to be prohibitive. In addition, with the more frequent use of adjuvant chemotherapy in both node-negative and node-positive patients, substantial delays can be incurred prior to the initiation of either local breast irradiation (XRT) or systemic chemotherapy. Thus, despite the obvious cosmetic and potential emotional advantages of BCT, only 10% to 40% of patients who are candidates for breast conservation actually receive it.\(^7\)

Most of the logistical problems associated with BCT relate to the protracted course of external beam XRT delivered to the whole breast. Standard therapy after tumor excision generally includes five weeks of external beam XRT to the whole breast (45-50 Gy) followed by a boost to the tumor bed with either an additional 8 to 10 fractions (days) of external beam XRT or a two to three day interstitial implant. The rationale for this approach is based upon two principles. First, higher doses of XRT are given to the 'tumor bed' in an attempt to control residual small foci of cancer that may be left behind after excision alone. Second, whole breast XRT is used to eliminate possible areas of occult multicentric in situ or infiltrating cancer in remote areas of the breast. That such remote, multicentric areas of cancer exist has long been established. However, the biological significance of these areas of occult cancer is unknown and the necessity to prophylactically treat the entire breast has recently been questioned. For instance, there are now at least five prospective randomized trials that have been conducted comparing the outcome of patients treated with excisional biopsy alone or followed by whole breast XRT.\(^5\)\(^,\)\(^8\)\(^-\)\(^12\) In all of these trials, the majority of recurrences in the breast of patients who did not receive XRT occurred at or in the area of the tumor bed. Thus, it would appear that XRT after tumor excision exerts its maximal effect upon reducing breast cancer recurrence at or near the tumor site.\(^12\)

The implications of these observations form the basis of the current study. Can an acceptable outcome be achieved with external beam XRT delivered only to the region of the tumor bed? If this were so, radiation therapy could be delivered in a very short period of time (one to two weeks) after tumor excision, thus significantly shortening treatment time and potentially reducing health care costs. This would significantly improve the quality of life of many patients undergoing BCT, and just as importantly, extend the conservation option to more women by reducing the time and inconvenience of radiation therapy. Additionally, toxicity to adjacent normal structures (i.e., heart, underlying chest wall, contralateral breast) should be significantly reduced with this approach.

There are currently several groups studying the efficacy of lumpectomy bed irradiation alone in the management of early stage breast cancer patients treated with BCT.\(^15\)\(^-\)\(^24\) Both interstitial brachytherapy techniques as well as external beam irradiation protocols have been implemented (See Table 1). Preliminary results from these trials are very encouraging and the techniques have been shown to be safe, tolerable, and highly reproducible. In 1993, Vicini et al. initiated a pilot trial of low dose rate (LDR) brachytherapy as the sole radiation modality with BCT.\(^15\) As of February 2001, 120 patients have been treated on this protocol. With a median follow-up of 85 months, only 3 patients have developed a local recurrence (five-year actuarial rate of 1%) and cosmetic results were judged as good to excellent in 98% patients (verbal communication). In addition, no adverse sequelae were noted on the protocol. More recently, a second protocol employing high dose rate (HDR) brachytherapy (in the same subset of patients) was also initiated.
at the same institution (Baglan et al.). Although results were preliminary, no adverse sequelae were noted.

Table 1. Breast conserving therapy with lumpectomy plus partial breast irradiation

<table>
<thead>
<tr>
<th>Institution</th>
<th># Pt</th>
<th>Median F/U (mo)</th>
<th>Scheme (cGy)</th>
<th>Total Dose (cGy)</th>
<th>% Local Recurrence</th>
<th>% Good/Excellent Cosmetic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDR Series*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ochsner Clinic</td>
<td>26</td>
<td>20</td>
<td>400 x 8</td>
<td>3200</td>
<td>0</td>
<td>67</td>
</tr>
<tr>
<td>Royal Devon/Exeter Hospital, Exeter, England</td>
<td>45</td>
<td>18</td>
<td>1000 x 2, 700 x 4, 600 x 6</td>
<td>2000</td>
<td>8.8</td>
<td>95</td>
</tr>
<tr>
<td>Orszagos Onkologiai Intezet, Budapest, Hungary</td>
<td>41</td>
<td>17</td>
<td>520 x 7, 433 x 7</td>
<td>3640</td>
<td>2.4</td>
<td>not stated</td>
</tr>
<tr>
<td>London Regional Cancer Centre, London, Ontario</td>
<td>39</td>
<td>20</td>
<td>372 x 10</td>
<td>3720</td>
<td>2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>not stated</td>
</tr>
<tr>
<td>William Beaumont Hospital&lt;sup&gt;25&lt;/sup&gt;</td>
<td>79</td>
<td>48</td>
<td>400 x 8, 340 x 10</td>
<td>3200, 3400</td>
<td>1</td>
<td>98</td>
</tr>
</tbody>
</table>

| LDR Series**                       |      |                |              |                  |                    |                                  |
| Ochsner Clinic                     | 26   | 20             | 4000         | 0                |                    | 78                               |
| Guy's Hospital<sup>13,17</sup>     | 27   | 72             | 40 cGy/hr    | 5500             | 37<sup>a</sup>      | 83                               |
| Cionini et al.<sup>21</sup>       | 90   | 27             | 5000-6000    | 4.4<sup>a</sup>   | not stated          |                                  |
| William Beaumont Hospital<sup>20</sup> | 120 | 85       | 52 cGy/hr     | 4992             | 1         | 98 |

| External Beam Series               |      |                |              |                  |                    |                                  |
| Christie Hospital<sup>14,24</sup>  | 353  | 65             | 500          | 4000             | 19.6<sup>a</sup>    | ---                             |
| William Beaumont Hospital (personal communication) | 31   | 12             | 385 x 10     | 3850             | 0                  | 100                             |
| European Institute of Oncology<sup>28</sup> | 86   | 8              | 2100 x 1     | 2100             | ---                | ---                             |

<sup>a</sup>Seven year rate

*HDR = High dose rate brachytherapy

**LDR = Low dose rate brachytherapy

The RTOG recently closed accrual of a similar protocol (RTOG 95-17) designed to test the technical feasibility and acute toxicity of brachytherapy alone confined to the region of the lumpectomy cavity in early stage breast cancer patients treated with BCT. As of March 2000, a
total of 99 patients were treated on the protocol with no adverse events reported. In the present protocol, 3D-CRT will replace interstitial brachytherapy due to the potential advantages that this technique offers. These potential advantages include:

- The potential elimination of an additional invasive procedure.
- The elimination of variability in operator experience (no surgical experience is required as with brachytherapy).
- The more precise 3-dimensional (3-D) delineation of the tumor bed volume using computerized tomography (CT).
- The more precise delivery of irradiation using 3-D radiation techniques.
- A significantly reduced amount of time to plan the radiation treatment.
- Immediate implementation of this technique in most radiation facilities (with 3D treatment capabilities) across the country, if proven successful.
- A larger proportion of potential candidates for the technique due to greater patient preference for a non-invasive procedure.

Several other groups have recently published their data exploring the possibility of shortening overall treatment time by increasing the radiation dose per fraction. Shelley et al.\(^{26}\) retrospectively reviewed their institutions' experience delivering 40 Gy in 16 daily fractions to 294 breast post-lumpectomy patients with negative resection margins (no boost was given). The median duration of follow-up of surviving patients was 5.5 years. The five year actuarial breast relapse rate was 3.5% and 77% of patients stated that they were either extremely or very satisfied with the overall appearance of the breast (19.5% moderately satisfied).

Whelan et al.\(^{27}\) recently presented results of a randomized trial comparing two fractionation schedules for breast irradiation post-lumpectomy patients with node-negative breast cancer. A total of 1234 women with clear resection margins were randomized: 622 to 42.5 Gy in 16 fractions in 22 days (Arm A) and 612 to 50 Gy in 25 fractions in 35 days (Arm B). Results for cosmetic outcome were available for 1220 patients at baseline, 987 at 3 years and 371 at 5 years. No difference was detected in global cosmetic ratings between the two treatment groups using a modified version of the EORTC Cosmetic Rating System. The five-year rate of local recurrence in both arms also was not significantly different.

**Intra-operative Partial Breast Irradiation Experience**

Intra-operative external beam irradiation has also recently been explored as an additional method of delivering post-lumpectomy partial breast irradiation in an accelerated fashion. Veronesi et al from the European Institute of Oncology in Milan, Italy recently published their preliminary results from a phase I/II dose escalation study of single-fraction irradiation given immediately after quadrantectomy.\(^{28}\) With minimal toxicity in the first 86 patients treated with dose levels of 17-19-21 Gy per fraction using 3 - 9 MeV electrons, the authors have now proceeded with a phase III trial comparing standard whole breast irradiation (50 Gy plus a 10 Gy boost) to a 21 Gy intra-operative single fraction. As of February 2002, > 250 patients have been enrolled in this equivalency trial with an accrual goal of over 800 patients (verbal communication).

Vaidya et al recently published their experience with intra-operative partial breast radiation therapy as boost treatment.\(^{29}\) In a pilot study of 35 patients, the post-operative tumor bed boost was replaced with an intra-operative 5 Gy fraction of radiation therapy delivered with the Photon Radiosurgery System. This device emits soft X-rays from a ball-shaped applicator applied directly against the lumpectomy cavity. With a median follow-up of 24 months, there have been no major complications. A phase III trial has recently been initiated.

**3D-CRT Partial Breast Irradiation Experience**

3D-CRT techniques have also been tested in two other phase I/II trials. Formenti et al recently published their experience treating nine patients with early stage breast cancer after lumpectomy with 3D-CRT using various fraction sizes and total doses.\(^{30}\) Patients received five fractions over ten days (total dose range, 25-30 Gy): Three received 5.0 Gy per fraction; four, 5.5 Gy; and two
At a minimum follow-up of 36 months (range, 36-53 months), all patients were alive with good-to-excellent cosmesis.

In addition, Vicini et al. also initiated a pilot study of 3D-CRT in 1999 using similar selection criteria as RTOG 95-17. As of March 2003, 31 patients have been treated with 10 fractions of radiation (3.4 Gy or 3.85 Gy per fraction-bid-separated by 6 hours) to total doses of 34 Gy or 38.5 Gy. Patients were treated in the supine position and the clinical target volume (CTV) was specified as the lumpectomy cavity (as outlined by surgical clips) plus a 1.5 cm margin. The planning target volume (PTV) consisted of the CTV plus 1.0 cm. This PTV margin was added for breathing motion and treatment set-up uncertainties that were analyzed prospectively. No adverse sequelae were noted (verbal communication).

Patients enrolled in this protocol will be selected to insure that their cancers have been adequately excised and that tumor bed irradiation alone will be adequate (as per the same selection criteria employed in RTOG 95-17). Shortly after surgery, patients will undergo a CT scan of the breast. 3D treatment planning will be used to outline the clinical target volume (CTV), defined as the quadrant of the breast tissue to be irradiated (as defined by surgical clips plus a margin). Using 3-D software already developed for other disease sites, the planning target volume (PTV) will then be defined. The optimal prescription plan (beam angles, intensity, etc.) to homogeneously treat only the 3-D defined region of breast tissue will then be constructed. Ten treatments of radiation will then be given to the PTV. The dose per fraction will be 385 cGy. This should provide a biologically equivalent dose (BED) of 45 Gy in 1.8 Gy fractions assuming an α/β ratio of 10. Each treatment will be separated by a minimum of six hours. This dosing schedule is considerably more conservative than that used in similar protocols and is designed to produce the highest local control rate with the least amount of cosmetic deterioration. Similar radiation schedules have been used at other institutions. For example, the Christie Hospital and Holt Radium Institute randomized 708 patients with lesions 4 cm or less in diameter and without axillary dissection to receive either: (1) tumor bed (quadrant) irradiation alone, typically 10 MeV electron beam to an average field size of 6 X 8 cm, 42.50 Gy in 8 fractions (531 cGy per fraction), or (2) tangential whole breast irradiation (standard therapy). Results between the two treatment arms were similar with respect to local recurrence in patients with infiltrating ductal carcinoma. More importantly, complication rates were also similar between the two groups (< 3%).

If feasible, this technique will also offer an alternative treatment for selected patients with early stage breast cancer, which is intermediate between observation alone (after excisional biopsy) and full breast irradiation. There are currently several trials attempting to identify subsets of patients that may do well without added XRT following excisional biopsy alone. At the present time, however, no consistent subgroup of patients has been identified that has achieved a high enough rate of local control to justify elimination of all XRT. The treatment proposed in this pilot trial, if successful, may give an alternative to be used in these selected low risk patients who may not require five to seven weeks of external beam XRT but who would do significantly better than excisional biopsy alone with less comprehensive XRT.

Patient selection criteria in this RTOG protocol have been chosen to minimize the risk of multicentricity and a remote breast cancer recurrence. The key factors are the exclusion of patients with microscopic extension of tumor cells to within 2 mm of the inked surgical margins, lobular histologies, tumors larger than 3 cm, and patients having an extensive intraductal component (EIC). Even with these strict selection criteria, approximately 71,000 women per year in the United States would be potential candidates for this protocol.

**2.0 OBJECTIVES**

This study will evaluate the technical feasibility and reproducibility, cosmetic results, complication rates, and local control rate of 3D-CRT confined to the region of the lumpectomy cavity for patients with Stage I and II (≤ 3 cm) carcinoma of the breast (non-lobular histology) treated with tylectomy with histologically assessed negative surgical margins (> 2 mm), up to 3 nodes positive at axillary dissection or sentinel lymph node biopsy, with no extensive intraductal component (EIC) by the Harvard definition.

**2.1 Hypotheses**
2.1.1 For selected patients with Stage I and II breast carcinoma, 3D-CRT delivered to the region of the lumpectomy cavity is technically feasible and reproducible with acceptable complication rates in a multi-institutional trial.

2.1.2 Cosmetic results after partial breast irradiation therapy following tylectomy will be comparable to that obtained after whole breast external beam radiation therapy.

2.1.3 The local tumor control rate in the breast after partial breast irradiation therapy following tylectomy will be comparable to that of conventional external beam radiation therapy, with less inconvenience and potentially less cost to the patient, given the selection criteria which minimize the risk of clinically significant multicentric or extensive residual carcinoma following tylectomy.

2.2 End Points

2.2.1 Evaluation of the prescription isodose curves, dose inhomogeneity, and coverage of the volume as defined by surgical clips placed at the time of tylectomy to delineate the target volume.

2.2.2 The evaluation of cosmetic results as judged by the patient, surgeon, and radiation oncologist at stated follow-up intervals and by an independent panel who will judge cosmesis from serial photography.

2.2.3 Assessment of patient satisfaction with the procedure as measured by a questionnaire.

2.2.4 The evaluation of tylectomy wound healing and the overall complication rate.

2.2.5 Ipsilateral breast recurrence rate. Disease status will be evaluated at routine patient follow-up appointments, including yearly mammography.

2.2.6 Freedom from mastectomy.

2.2.7 Cost benefit analysis of this treatment method compared with standard external beam treatment at the discretion of the participating institution. (planned for future Phase III trial).

3.0 PATIENT SELECTION CRITERIA

3.1 Eligibility Criteria

3.1.1 Invasive ductal, medullary, papillary, colloid (mucinous), or tubular histologies.

3.1.2 AJCC Stage I or II (T1N0, T1N1, T2N0, T2N1) histologically confirmed invasive carcinoma of the breast with a lesion ≤ 3 cm treated with tylectomy and axillary node dissection with at least 6 nodes sampled or sentinel node biopsy. Patients with up to 3 positive axillary nodes are eligible (see Section 8.0). (9/30/03)

3.1.3 Six surgical clips in place delineating the margins of the tylectomy cavity.

3.1.4 Unifocal breast cancer (single focus which can be encompassed by one tylectomy).

3.1.5 Negative, inked histologic margins of tylectomy (> 2 mm) or reexcision specimen to be confirmed prior to radiation. Margins are unacceptable if there is invasive or non-invasive tumor within 2 mm of the inked margin.

3.1.6 Negative post-tylectomy or post-excision mammography if malignancy-associated microcalcifications were initially present.

3.1.7 Tamoxifen or Arimidex® therapy is allowed. If chemotherapy is planned, it must begin no earlier than two weeks following completion of radiation therapy. If chemotherapy is first, a minimum of 2 weeks from the last cycle must elapse prior to the start of radiation therapy.

3.1.8 Patients must be ≥ 18 years of age.

3.1.9 Pretreatment evaluations required for eligibility include: Post-tylectomy ipsilateral mammogram (prior to start of radiation) if microcalcifications were initially present, to confirm complete removal (See Section 3.1.6)

3.1.10 Signed study-specific informed consent form prior to study entry.

3.2 Ineligibility Criteria

3.2.1 Evidence of suspicious microcalcifications in the breast prior to the start of radiation.

3.2.2 Four or more positive axillary nodes/sentinel biopsy with at least six axillary lymph nodes sampled (if an axillary dissection is performed).

3.2.3 Patient with distant metastases.

3.2.4 Patients with invasive or extensive in-situ lobular carcinoma or pure ductal carcinoma in-situ or non-epithelial breast malignancies such as sarcoma or lymphoma.

3.2.5 Patients with proven multicentric carcinoma (tumors in different quadrants of the breast or tumor separated by at least 4 cm) with other clinically or radiographically suspicious areas in the ipsilateral breast unless confirmed to be negative for malignancy by biopsy.
3.2.6 Palpable or radiographically suspicious contralateral axillary, supraclavicular, infraclavicular or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.

3.2.7 Extensive intraductal carcinoma by the Harvard definition, i.e. 1) more than 25% of the invasive tumor is DCIS and there is DCIS in adjacent breast tissue; or 2) an intraductal carcinoma with microinvasion.

3.2.8 Any previously treated contralateral breast carcinoma or synchronous ipsilateral breast carcinoma.

3.2.9 Prior non-hormonal therapy or radiation therapy for the current breast cancer; prior chemotherapy if administered less than 2 weeks from start of radiation therapy.

3.2.10 Patients with Paget’s disease of the nipple.

3.2.11 Patients with skin involvement, regardless of tumor size.

3.2.12 Patients with a breast technically unsatisfactory for radiation therapy.

3.2.13 Patients with tylectomies so extensive that the cosmetic result is low or poor prior to radiation.

3.2.14 Patients with collagenous diseases, specifically systemic lupus erythematosis, scleroderma, or dermatomyositis.

3.2.15 Patients with co-existing medical conditions with life expectancy < 2 years.

3.2.16 Patients with psychiatric or addictive disorders that would preclude obtaining informed consent.

3.2.17 Other malignancy, except non-melanomatous skin cancer, < 5 years prior to participation in this study; the disease-free interval from any prior carcinoma must be continuous.

3.2.18 Patients who are pregnant or lactating due to potential exposure of the fetus to RT and unknown effects of RT to lactating females.

4.0 PRETREATMENT EVALUATIONS
(In addition to required evaluations in Section 3.0)

4.1 History including family history of breast carcinoma and method of detection of the breast tumor (clinical, mammographic or both).

4.2 Physical examination with the location and palpable size of the tumor in cm.

4.3 Mammogram of both breasts with a careful measurement of the lesion size in cm.

4.4 Chest x-ray, CBC, platelets, alkaline phosphatase, AST, serum calcium; pregnancy test (if applicable) within one week of study entry.

4.5 Breast CT for treatment planning.

4.6 Bone scan if the alkaline phosphatase is elevated and/or the patient complains of bone pain or has other symptoms suggestive of skeletal metastases.

4.7 Abdominal CT if the liver function blood tests are elevated.

4.8 Photographs of the patient’s breast prior to radiation therapy (Digital images or 35 mm slides are preferred; polaroids are acceptable). The first photo should be a close-up encompassing only the breast to be treated at a 45° oblique with arms elevated over the patient’s head. The second photo should be a straight frontal view of both breasts taken in either a standing or seated position with the patient’s hands on her hips, taking care to exclude her face. Label each slide or photograph with the date and RTOG patient case number.

5.0 REGISTRATION PROCEDURES

5.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in Appendix IV may enter patients to this study. The Facility Questionnaire is to be sent to the Image-Guided Therapy Center (ITC) for review prior to entering any cases. Upon review and successful completion of a “DRY RUN” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. Institutions that have previously been credentialed and enrolled patients on RTOG 93-11, RTOG 94-06, or RTOG 98-03 do not need to repeat the credentialing procedure.

5.2 Patients can be registered only after eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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.
After the patient is registered, the institution will submit the required data (both hardcopy and digital) to the ITC (See Section 12.2) and to the RTOG (See Section 12.1) as appropriate.

### 6.0 RADIATION THERAPY

**Note: Intensity Modulated RT (IMRT) is not allowed.**

#### 6.1 Treatment Planning & Imaging (9/30/03)

Treatment planning and delivery should be performed with the patient in the supine position. A treatment planning CT scan will be required to define the clinical target volume (CTV) and planning target volume (PTV). The clinical target volume will be defined by uniformly expanding the excision cavity volume by 10-15 mm. Surgical clips should be used to help define the boundaries of the CTV. However, the CTV will be limited to 5 mm from the skin surface and lung-chest wall interface (see Section 8.1.11). The CT scan should start at or above the mandible and extend several cm below the inframammary fold (including the entire lung). The following structures will be contoured: CTV, PTV (see below), ipsilateral breast, thyroid, contralateral breast, ipsilateral and contralateral lung, and heart. The shoulders, chin, and contralateral breast should be included in the scan. A CT scan thickness of ≤ 0.5 cm should be employed. The CTV and PTV and normal tissues must be outlined on all CT slices.

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 patient (especially for superficial cavities) the PTV is then copied to a PTV for Evaluation (PTV_EVAL), which is edited: This PTV is limited to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excluding (if applicable) the PTV expansion within the lung. This PTV_EVAL is the structure used for DVH constraints and analysis (see Section 6.8.2). This PTV for evaluation CANNOT be used for beam aperture generation.

#### 6.2 Designing the Planning Target Volume

The planning target volume will provide a margin around the CTV to compensate for the variability of treatment setup and motion of the breast with breathing. Ideally, a breathing motion study should be performed to define the degree of excursion of the breast (with respiration) to determine its impact on dose delivery and portal images will be acquired with each fraction to evaluate set-up uncertainty. If these data have not been collected, a minimum of 10 mm around the CTV is required (superior, inferior, medial and lateral dimension).

**Volume and ICRU Reference Point Definitions**

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

#### 6.3 3D Treatment Planning

Treatment will be given only to the PTV using three-dimensional conformal fields. Intensity modulated radiation therapy (IMRT) is not allowed. At the present time, the use of the multi-leaf collimator (MLC) to facilitate the delivery of intensity-modulated distributions derived from constraints-based computer optimization (i.e., inverse planning) is excluded. 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 (see below). 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 and critical normal tissues.

#### 6.4 Dose Prescription

Radiotherapy should begin within eight weeks of surgery, if no chemotherapy is given. If chemotherapy is given first, RT must not begin until a minimum of 2 weeks after the last cycle of chemotherapy. A total of 38.5 Gy will be prescribed to the ICRU 50 reference point dose (usually isocenter). Two fractions per day, each of 3.85 Gy, separated by at least six hours, given in five consecutive working days (Monday-Friday) will sum to 10 fractions and 38.5 Gy. **Dose calculations with tissue inhomogeneity correction must be used.**

#### 6.5 Dose Limitations for Normal Tissues

**Uninvolved Normal Breast:** Ideally, < 50% of the whole breast should receive ≥ 50% of the prescribed dose and < 25% of the whole breast should receive the prescribed dose. For these calculations, the breast volume is defined as follows: no attempt should be made to delineate the breast tissue per se, in order to avoid the inherent uncertainties in its definition on CT scan.
slices. Instead, an irradiated volume is identified with the superior and inferior borders defined by the placement of the superior and inferior edges of the tangent beams that would have been used to treat the whole breast. The skin on each axial CT slice is delineated as the superficial boundary while the deep edge of the chest wall and tangential borders of the medial and lateral beams form the posterior boundary of the irradiated volume, excluding the lung.

6.5.2 Ipsilateral Lung: At most, < 10% of the lung can receive 30% of the prescribed dose.

6.5.3 Contralateral Breast: The contralateral breast should receive < 3% of the prescribed dose to any point.

6.5.4 Contralateral Lung: At most, < 10% of the lung should receive 5% of the prescribed dose.

6.5.5 Heart (right-sided lesions): At most, < 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 < than the V5 for treatment using conventional whole breast radiation with tangential fields.

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

6.6 Beam Angles/Treatment Position

The participating institution may choose whatever beam arrangement, number of beams they desire as long as the necessary dose volume constraints mentioned above can be met. Typically, a 3, 4, or 5-field non-coplanar beam arrangement utilizing high-energy photons can be used. Patients should be treated in the supine position unless otherwise pre-approved by the Radiation Oncology and Physics Study Chairs.

6.7 Treatment Verification

Portal films or portal images of each beam and an orthogonal pair (AP and lateral) must be obtained for the first fraction. Subsequent films or images must be obtained on fraction numbers 2, 5, and 9 including an orthogonal pair. Additional individual port films may be taken at the investigators discretion.

6.8 Quality Assurance of Dose Distribution

6.8.1 The ITC will compare submitted DVHs for the PTV for Evaluation (see definition of the PTV for Evaluation, Section 6.1), designated critical structures, and unspecified tissues. (9/30/03)

6.8.2 Each treatment plan shall be judged as:

1. No variations (total coverage), 95% isodose surface covers 100% of the PTV. All specified critical normal tissue DVH limits have been met.

2. Minor variation (marginal coverage); 95% isodose surface covers between ≥ 95% to < 100% of the PTV. No portion of PTV receives < 93% of prescription (isocenter) dose. All specified critical normal tissue DVH limits fall within 5% of the guidelines.

3. Major variations (miss); 95% isodose surface covers < 95% of the PTV. Portion of PTV receives < 93% of prescription isocenter dose. Any critical normal tissue DVH limit exceeding 5% of the specified value.

6.8.3 Dose Homogeneity

Maximum dose to PTV should not exceed the prescription dose by > 10% (no variation, ≤ 10%; minor variation, >10 to ≤ 20%; major variation, >20%).

6.9 External Beam Equipment

6.9.1 Megavoltage equipment is required with effective photon energies of ≥ 6MV.

6.9.2 3D-CRT capabilities are required as defined and confirmed by the ITC. See Appendix IV for 3D-CRT QA guidelines.

6.10 Anticipated Toxicities

6.10.1 Fatigue is the anticipated systemic reaction to radiation treatment. Skin erythema and desquamation also may occur. Breast edema and tenderness and myositis also are acute side effects. Possible long-term complications include radiation pneumonitis, rib fractures, and for left-sided lesions, cardiac complications.

6.11 Toxicity Reporting

6.11.1 Acute and late radiation effects will be evaluated and scored using the NCI CTCAE v. 3.0. A copy of the CTC version can be downloaded from the CTEP homepage (http:ctep.info.nih.gov). Please note that this study will not be using separate toxicity scales for acute and late radiation effects.

6.11.2 Fatal Events: All deaths with attribution of definite, possible or probable resulting from protocol radiation therapy must be reported by telephone to the RTOG Headquarters dedicated AE line
at (215) 717-2762 or 1-800-227-5463 ext. 4189, to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB. **All deaths** during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone within 24 hours of discovery to RTOG Headquarters at the numbers given above.

### 6.11.3 Life Threatening and Grade 4 Events

All life-threatening (an event that in the view of the investigator places the patient at immediate risk of death from the reaction) and Grade 4 events that are related, possibly related or probably related to protocol treatment using *non-standard fractionated radiation therapy* must be reported by telephone to the RTOG Headquarters AE telephone line (given above), to the RTOG Group Chair, and to the protocol Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

Grade 4 events from standard fractionated radiation therapy do not require telephone reporting unless specified otherwise in the protocol. This information is reported on the study case report forms.

Expected Grade 4 adverse events from non-standard radiotherapy may be excluded from telephone reporting if explicitly stated in the protocol.

*Standard fractionated radiotherapy is defined as 1.8 – 2.0 Gy once daily radiation to a total dose of 70.2 Gy or less, including 2D and 3D-CRT. Non-standard fractionated radiation therapy is treatment administered using brachytherapy, radiopharmaceuticals, high LET radiation, radiosurgery, intensity modulated radiation therapy (IMRT) and conventional radiotherapy with fraction size or total dose not within the parameters specified above.*

### 6.11.4 Documentation

All applicable data forms and if requested, a written report from the site principal investigator must be submitted to RTOG Headquarters (FAX 215-928-0153) within 10 working days of the telephone report of any fatal adverse event with the attribution of **definite, possible, or probable** relation to protocol radiotherapy and for Grade 4 or life-threatening events as specified in Section 6.10.3.

### 7.0 DRUG THERAPY

Not applicable to this study.

### 8.0 SURGERY-TYLECTOMY GUIDELINES

8.1 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.

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

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

8.1.3 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.

8.1.4 The initial biopsy should be performed as if it was 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 reexcision of breast tissue if biopsy is positive for cancer and the final margins are histologically negative. A frozen section should be done to confirm the diagnosis of cancer, and surgical clips should be placed to define the margin of the excision cavity (see Section 8.1.11). Margins generally are deemed unacceptable if there is invasive or non-invasive tumor within 2 mm of the inked margin, and negative if the tumor is at least 2 mm from the inked edge.

8.1.5 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.
8.1.6 Following excision of the tumor, it is urged that the breast tissue not be reconstructed or approximated. The use of breast sutures to obliterate the dead space can result in unnecessary deformity.

8.1.7 Drainage of the breast wound, either with Penrose drains or suction catheters, is not recommended. Drainage of the axilla, however, is recommended.

8.1.8 Careful approximation of the skin incision is essential. It is recommended that subcuticular closure be utilized in most cases.

8.1.9 In the majority of instances, it is recommended that the incision for the tylectomy and for the axillary dissection be separate. A single continuous incision is to be avoided. An exception to this recommendation is a lesion in the axillary tail where a continuous incision could be utilized.

8.1.10 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.

8.1.11 Surgical clips should be placed by the surgeon at the time of tylectomy 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 guides the radiation oncologist. It is recommended that small surgical clips be used to delineate the lateral edges of the volume and large surgical clips be used for the superficial and deep edges to simplify radiologic evaluation.

8.1.12 If margins are positive (<2 mm) or unknown, a reexcision is required prior to study entry. It is mandatory to evaluate the reexcision margins histologically and to confirm that they are negative. In some cases, a second reexcision may be required to achieve negative surgical margins.

8.1.13 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.

8.1.14 Measurement of the anteroposterior (AP), transverse, and superior-inferior (SI) dimensions of the resected breast specimen should be obtained and recorded.

8.1.15 The pathologist must find the dominant mass in the resection specimen and measure the tumor in three dimensions.

8.1.16 If the diagnosis has not been previously established, a small central portion of the dominant mass or suspicious area should be removed for frozen section. If the lesion is benign, the patient is not eligible for study entry.

8.1.17 If the tumor is of adequate size, tissue should be harvested for estrogen and progesterone receptor determination. Immunohistochemical staining is an alternative.

8.1.18 Multiple blocks of the primary tumor and of breast tissue from the inked margins should be taken, the latter to confirm six negative margins: 1) anterior; 2) posterior, 3) medial, 4) lateral, 5) superior, 6) inferior. Margins generally are positive if there is invasive or non-invasive tumor within 2 mm of the inked margin, and negative if the tumor is at least 2 mm from the inked edge.

8.2 The Axillary Dissection

As defined by this protocol, the axillary dissection consists of the excision of the axillary contents at levels I and II. An anatomic delineation of the scope of dissection is the latissimus muscle medially. The nerves to the serratus anterior and latissimus dorsi muscles should be identified and preserved. The axillary vein should be visualized and followed under the pectoralis major muscle to the medial border. These are minimal limits for dissection. The extent of axillary dissection should not vary with the operative procedure performed for the resection. Axillary sampling, i.e., partial, non-anatomic removal of axillary contents, is not in compliance with the study criteria. At least six nodes must be identified by the pathologist.

8.3 Sentinel Node Biopsy

Sentinel node biopsies (SNB) can be used as a substitute for a formal axillary dissection if the SNB team has documented experience with this technique in breast cancer patients. The SNB team includes the surgeon, radiologist, nuclear medicine physician, pathologist, and prior discussion with medical and radiation oncologists on the use of SNB for treatment decisions. Sentinel node involvement should be defined by multilevel node sectioning with hematoxylin and eosin (H & E). Immunohistochemical (IHC) staining may be used for equivocal cases on H & E. Routine IHC to define node involvement is allowed but controversial.
9.0 OTHER THERAPIES

9.1 Tamoxifen or Arimidex® are allowed at any time after biopsy or tylectomy, prior to, during or immediately after radiation therapy at the discretion of the patient’s medical oncologist or other physicians.

9.2 The use of chemotherapeutic agents 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 two weeks after the completion of radiation.

10.0 PATHOLOGY

Central pathology review will not be done.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (4/2/04, 5/21/04)

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<th>Assessment</th>
<th>Pre- Entry</th>
<th>During Radiation</th>
<th>At 6 weeks(^g)</th>
<th>At 3 months(^g)</th>
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a. Post-tylectomy ipsilateral mammogram if microcalcifications were initially present to confirm complete removal
b. If alkaline phosphatase is elevated and/or the patient complains of bone pain or has other symptoms suggestive of skeletal metastases
c. If LFT’s are elevated
d. As clinically appropriate
e. Yearly thereafter
f. Clinical examination and disease status assessment at 3 month intervals for the first year, every 4 months for the 2nd year, every 6 months (years 3 to 5), and yearly thereafter
g. Time points are from the start of radiation therapy
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 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 extrafield 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 **Definitions of Levels of Cosmetic Outcome (4/2/04, 6/15/04)**

11.3.1 Cosmesis will be graded by the patient, the radiation oncologist, and the surgeon three, six, and twelve months from the start of therapy and at yearly intervals thereafter. Cosmeses will also be evaluated from the photographs submitted to Dr. Vicini at required intervals; however, the Cosmesis Forms will be sent only to RTOG Headquarters.

11.3.2 **Excellent** – when compared to the untreated breast, there is minimal or no difference in the sizes, shape or texture of the treated breast. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.

11.3.3 **Good** – there is mild asymmetry in the size or shape of the treated breast as compared to the normal breast. The thickening or scar tissue within the breast causes only mild change in the shape.

11.3.4 **Fair** – there is obvious difference in the size and shape of the treated breast. This change involves ¼ or less of the breast.

11.3.5 **Poor** – marked change in the appearance of the treated breast involving more than ¼ of the breast tissue.

11.4 **Photographs**

11.4.1 Routine photographs must be taken of the post-surgical breast prior to radiation therapy. At least one photograph of the breast prior to radiation therapy is required. Photographs should also be taken and sent to Dr. Vicini at William Beaumont Hospital at three and six months, one year and yearly thereafter; also, they should be sent when any visible complication, degradation, or improvement of cosmesis or local/regional treatment failure occurs for documentation purposes. Digital images or 35 mm slides are preferred; polaroids are acceptable. Post-surgical and all follow-up photographs should always follow the guidelines specified in Section 12.

11.4.2 The first photograph should be a close-up encompassing only the treated breast at a 45° oblique angle with arms elevated over the head. The second photograph should 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 or focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry. Label each photograph with the date and RTOG patient case number and submit directly to Dr. Vicini:

Frank Vicini, M.D.
William Beaumont Hospital
Dept. of Radiation Oncology
3601 W. 13 Mile Road
Royal Oak, Michigan 48073

11.5 **Patient Enrollment Data**

11.5.1 Complete history and physical examination
11.5.2 Mammographic report(s)
11.5.3 Pathology reports
11.5.4 Initial radiation therapy consult note

11.6 **Patient Treatment Data**

11.6.1 Operative reports, including tylectomy, any reexcisions, and axillary dissection
11.6.2 Toxicity reports: skin reaction(s) to radiation therapy including erythema, desquamation, etc., and any acute radiation complications or unusual or severe side effects of treatment

11.6.3 Radiation treatment prescription

11.6.4 Copies of dosimetry calculations

11.6.5 At least one photograph of the breast showing the breast prior to initiation of radiation therapy

11.6.6 Explanation of any deviation in technique or administered dose of radiation

11.6.7 Surgical cosmesis form

11.7 Patient Follow-Up

11.7.1 Vital status. If patient has expired, a data form must be submitted

11.7.2 Disease status, classified local, regional, or distant

11.7.3 Site(s) and date of first failure in each category above

11.7.4 Relationship of breast recurrence to irradiated volume (infield, peripheral, extrafield, see Section 11.2.2)

11.7.5 Cosmetic evaluation

11.7.6 Effects of treatment

11.7.7 Follow-up physical examination and mammographic results

11.7.8 Photographs (preferably 35 mm slides, polaroids are acceptable) at least 3 and 6 months, 1 year and yearly thereafter (see Section 11.4)

12.0 DATA COLLECTION

12.1 Summary of Data Submission

Data should be submitted to:
RTOG Headquarters
1101 Market Street, 14th Floor
Philadelphia, PA 19107

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<tr>
<th>ITEM (3/1/04, 5/21/04)</th>
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<tr>
<td>Demographic Form (A5)</td>
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<td>Initial Evaluation Form (I1)</td>
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<td>Pathology Report (P1)</td>
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<tr>
<td>Surgical Operative Report (S2)</td>
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<td>Surgical Pathology Report (S5)</td>
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<tr>
<td>Radiotherapy Form (T1) (copy to ITC)</td>
<td>Within 1 week of RT end</td>
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<tr>
<td>Daily Treatment Record (T5) (copy to ITC)</td>
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<tr>
<td>Follow-up Form (F1)</td>
<td>At 6 weeks; every 3 months for first year; every 4 months for the second year, every 6 months for the next 3 years and yearly thereafter. Also at progression/relapse and at death.</td>
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<td>Cosmesis Questionnaires:</td>
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<td>Patient Evaluation Form (PQ)</td>
<td>At 3, 6, and 12 months, then yearly.</td>
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<td>Surgical Oncologist Evaluation Form (FS)</td>
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<td>Radiation Oncologist Evaluation Form (QP)</td>
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<tr>
<td>Photographs (See section 11.4.2)</td>
<td>Prior to start of radiation but after surgery; at 3, 6 and 12 months; yearly thereafter.</td>
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<tr>
<td>Autopsy Report (D3)</td>
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### 12.2 Summary of RT QA Requirements (ITC) (9/30/03)

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<tr>
<td><strong>Preliminary Dosimetry Information</strong></td>
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<td>Digital patient data (CT scans, critical normal structures, all GTV/CTV/PTV contours, doses for all fraction groups, DVHs for total dose plan) (Beams, in digital form, are required for 3D-CRT treatment delivery and optional for IMRT delivery.)</td>
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<tr>
<td>Prescription (DRR or Simulation films) and port films as defined in Section 6.6 and Appendix IV</td>
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<tr>
<td>Hard copy isodoses for total dose plan as defined in Appendix IV</td>
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<td>Digital Patient Submission Information Form (T2)</td>
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<td><strong>Final Dosimetry Information</strong></td>
<td>Within 1 week of end of RT</td>
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<td>Digital patient data for any modified or changed planning data (contours, doses or DVHs)</td>
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<td>Hard copy isodoses for total dose plan if any changes made after initial submission.</td>
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<tr>
<td>Simulation and port films for boost and/or field changes as defined in Appendix IV</td>
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<tr>
<td>Daily Treatment Record (T5)</td>
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#### 12.2.1 For Mail or Federal Express: (9/30/03)

Image-guided Therapy Center (ITC)
4511 Forest Park Avenue, Suite 200
St. Louis, MO 63108
Tel. 314/747-5415  Fax # 314/747-5423

#### 12.2.2 To send over Internet or using magnetic tape:
Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the ftp account assigned to the submitting institution shall be used and e-mail identifying the data set(s) being submitted shall be sent to:

itc@castor.wustl.edu

For tape submission, please contact the ITC about acceptable tape types and formats.

#### 12.2.3 See the ITC web site at http://itc.wustl.edu for additional helpful information, including the current Facility Questionnaire, and the Quality Assurance and Dry Run Guidelines.

#### 12.3 Timely Data Submission for Toxicity Evaluation
Timely data submission is critical in order to meet the study’s objectives for toxicity evaluation.
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Reproducibility of Radiation Techniques
Reproducibility is the primary endpoint because whether or not the technique is widely applicable in a multicenter setting must be demonstrated prior to undertaking a Phase III trial. Specific tools to measure the quality of the radiation technique have been developed in Section 6. The ability of various clinical sites to perform 3D-CRT within the guidelines delineated in this protocol will provide a measure of feasibility for this technique. Since patient treatments from William Beaumont Hospital (the study chair’s institution) are most likely to be scored acceptable, the accrual from William Beaumont Hospital will be capped at 25% (see Section 13.2).

13.1.2 Toxicities
Toxicities resulting from radiation treatment will be collected and graded. Any grade 3, 4, or 5 will be promptly reported as specified in Section 6.9.

13.1.3 Cosmesis (5/21/04)
Cosmetic results will be assessed by the radiation oncologist, the surgeon, and the patient at three, six, and twelve months, then annually. Photographs are to be taken at these time points according to the specifications in Section 11.4 and sent to Dr. Vicini at William Beaumont Hospital. To maintain confidentiality of results of patient’s cosmesis assessment, copies of the Cosmesis Forms will not be sent to Dr. Vicini with the photographs.

13.1.4 Disease-Free Survival and Mastectomy-Free Survival
All disease recurrences and surgical interventions will be recorded. In disease-free survival, any tumor recurrence or death is considered a failure. In mastectomy-free survival, the failures are mastectomy and death. Ipsilateral breast recurrence rate, subdivided by in-field, peripheral and extra-field locations as defined in Section 11.2.2, ipsilateral nodal recurrence rate and distant metastases rate will be calculated.

13.1.5 Overall Survival
Death from any cause is considered a failure.

13.2 Study Design
The sample size will be determined by the first endpoint in Section 13.1, namely, the reproducibility of the radiation technique. There will be a central review by the study chair after the treatment is delivered. The radiation therapy will be scored by the study chair as acceptable, marginally acceptable, or unacceptable, using the criteria in Section 6.8.2. If, during this initial review, a treatment plan is graded unacceptable or marginally acceptable, the study chair will ask the institution to make appropriate changes. All eligible patients will be included in the analysis. The optimal two-stage design by Simon will be used. Let p be the true probability that the final review is acceptable or marginally acceptable. A p close to 1 implies that the radiation therapy is reproducible in a multi-center setting. If p is less than or equal to 80%, the goal is to have at most a 5% probability of concluding that the technique is reproducible. On the other hand, if p is greater than or equal to 95%, the desired level, the goal is have at most a 10% probability of concluding that the technique is not reproducible. With these specifications, 19 eligible patients will be required in the first stage. If 3 or more treatments are scored unacceptable, then early stopping will be recommended to the study chair. Otherwise, the trial will continue until a total of 42 eligible patients are accrued. The maximum number that William Beaumont Hospital can enter is 10 eligible patients. If 5 or more of the 42 treatments are scored unacceptable, the technique will be considered not reproducible, and a Phase III study will not be pursued. Otherwise, we will consider a further randomized Phase III study comparing radiation therapy with standard external beam radiation therapy. Under the null hypothesis of an 80% reproducibility rate, this two-stage design has an expected sample size of 24.4. When p is 80%, this design minimizes the expected sample size among all designs satisfying the same specifications.

13.3 Patient Accrual
After the accrual of the first stage of 19 eligible patients is completed, the two-stage design calls for suspension of patient accrual until the results of the first stage are known. However, after the initial reviews of treatment plans and partial reviews of final treatments, if the study chair is certain that the early stopping boundary will not be crossed, then no suspension of accrual will
occur. For the maximum sample size of 42 eligible patients, we will accrue 46 patients, taking into account the ineligible cases. Based on RTOG 9517, monthly accrual will be approximately three patients.

13.4 Schedule of Analyses
While patients are being accrued to this study, there will be semi-annual reports published in the RTOG Group Meeting Reports. These reports will give the updated information on patient accrual and toxicity. After 19 eligible patients have finished their treatment, the study chair will review the dosimetry together with other data. If three or more radiation treatments are unacceptable, early stopping will be recommended. Three to five years after the early stopping, an analyses on all the endpoints will be made. Without early stopping, the first analysis will be made one year after the completion of accrual of 42 eligible patients. This first analysis will focus on the first three endpoints in Sections 13.1.1 through 13.1.3. The results will be used to determine whether a further Phase III study is appropriate. Analysis on all the endpoints will be made three to five years after completion of accrual, possibly together with initial analysis of the Phase III study.

13.5 Inclusion of Minorities
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, the possible difference in any of the above endpoints among the racial groups will be investigated. Summary statistics such as percentage of minorities entered, estimates of the endpoints by the racial groups will be reported. Based on RTOG breast study 9517, we project that 90% of women in the study will be white, 8% will be black (not of Hispanic origin), and 2% will be Hispanic. With the proposed 42 evaluable patients, there will not be enough statistical power to detect the difference in the primary endpoint between race groups. Nonetheless, the descriptive statistics for each of these groups will be reported.

GENDER AND MINORITY ACCRUAL ESTIMATES

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<td>*46</td>
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<td>46</td>
<td>0</td>
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REFERENCES


33. Simon, Richard: Optimal Two-Stage Designs for Phase II Clinical Trials; Controlled Clinical Trials. 10:1-10, 1989.
APPENDIX I

RTOG 0319

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE I/II TRIAL TO EVALUATE THREE DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) CONFINED TO THE REGION OF THE LUMPECTOMY CAVITY FOR STAGE I AND II BREAST CARCINOMA

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have breast cancer and have had a lumpectomy.

WHY IS THIS STUDY BEING DONE?

Radiation therapy after surgery to remove breast cancer improves control of the breast cancer. Standard therapy after breast conservation surgery is five to six weeks of radiation to the entire breast. Recent studies using radiation therapy directed only to the area in the breast where the lumpectomy was performed have produced good breast cancer control rates. These studies have used a type of radiation therapy called brachytherapy. Brachytherapy consists of temporarily placing a series of needles or catheters around the lumpectomy site, which are later temporarily filled with radiation seeds to deliver the effective dose over 5 days.

This clinical trial will find out what effects (good and bad) three-dimensional conformal radiation therapy (3D-CRT) has on you and your cancer. The 3D-CRT is an investigational treatment that will be given only to the area in the breast where the lumpectomy was performed. It will be used as a replacement for brachytherapy. 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 doctor thinks may have cancer cells. The radiation therapy will be given over a five-day period.

This study is being done to find out if the 3D-CRT can be done correctly and safely not just where it was first used but at many hospitals. The results of this study will help decide whether a much larger study should be done that would show how the 3D-CRT therapy works in preventing
cancer from coming back compared with how well standard radiation therapy works.

The study will also gather information about the safety and effects (good and bad) this radiation has on you and your satisfaction with the appearance of your breast.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 46 people will take part in this study.

**WHAT IS INVOLVED IN THE STUDY?**

If you take part in this study, you will have the following treatment: radiation therapy will be delivered to the area of the lumpectomy two times per day for five consecutive working days. The radiation will be given six hours apart on each of the five days. This treatment should begin within eight weeks of your surgery, unless chemotherapy is given first. If you receive chemotherapy, radiation treatment will begin two weeks after your last cycle of chemotherapy.

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.

If you take part in this study, you will have the following tests and procedures:

**Prior to study entry:**
- History and physical
- Mammograms
- Chest X-ray
- Blood tests (pregnancy test if applicable)
- Bone scan or X-rays if indicated by your physician
- Photographs of the breast

**During radiation:**
- Blood tests if indicated
- Bone scan or X-rays if indicated
During follow-up (5/21/04):

- History and physical – 6 weeks, 3 months, and every 3 months for first year, every 4 months for second year, every 6 months years 3-5, and yearly thereafter
- Mammograms – 6 months, 12 months, and yearly thereafter
- Blood tests, CT scans, and X-rays as appropriate
- Photographs – 3 months, 6 months, and 12 months, then yearly
- Cosmetic evaluations – 3 months, 6 months, 12 months, and then yearly

**HOW LONG WILL I BE IN THE STUDY?**

This study will take approximately one week to complete. Follow-up visits will be scheduled at 6 weeks and 3 months and then every 3 months for the first year; every four months for the second year; every 6 months for years 3-5 and then yearly thereafter.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests that the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent. The study treatment may be less effective than standard treatment in controlling the tumor and/or limiting the return of cancer.

**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

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 doctor immediately. Ask about counseling and more information about preventing pregnancy.

Risks Associated with Blood Drawing

You may experience some discomfort, bruising and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with breast cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose not to participate in this study. Other treatments that could be considered for your condition may include the following: (1) standard radiation therapy; (2) chemotherapy; (3) hormonal therapy; (4)
surgery; or (5) no treatment. Treatments could be given either alone or in combination with each other.

Your 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.

Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.
WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in breast cancer from the RTOG Breast Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

For information about your disease and research-related injury, you may contact:

__________________________   ______________________
Name   Telephone Number

For information about this study, you may contact:

__________________________   ______________________
Name   Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)

__________________________   ______________________
Name   Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_________________________________________     ____________
Patient Name        Patient Signature Date

_________________________________________     ____________
Name of Person Obtaining Consent        Signature Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of 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 any self-care. Totally confined to bed or chair (Karnofsky 10-20).
DEFINITION OF TNM

Primary Tumor (T)
Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

TX Primary tumor cannot be assessed
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 with no tumor

Note: Paget’s disease associated with a tumor is classified according to the size of the tumor.

T1 Tumor 2 cm or less in greatest dimension
T1mic Microinvasion 0.1 cm or less in greatest dimension
T1a Tumor more than 0.1 but not more than 0.5 cm in greatest dimension
T1b Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below.
T4a Extension to chest wall, not including pectoralis muscle
T4b Edema (including peau d’ orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c Both T4a and T4b
T4d Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical
NX Regional lymph nodes cannot be assessed (e.g., previously removed)
N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral axillary lymph node(s)
N2 Metastasis in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a Metastasis in ipsilateral infraclavicular lymph node(s)
N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c Metastasis in ipsilateral supraclavicular lymph node(s)
APPENDIX III (cont’d)

AJCC STAGING SYSTEM
BREAST, 6th Edition

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Pathologic (pN)*

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0 No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

pNO(i-) No regional lymph node metastasis histologically, negative IHC
pNO(i+) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pNO(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)b
pNO(mol+) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)b

a Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pNO(i+) (sn).
b RT-PCR: reverse transcriptase/polymerase chain reaction.

pN1 Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1mi Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a Metastasis in 1 to 3 axillary lymph nodes
pN1b Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1c Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden).
pN2 Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN3c Metastasis in ipsilateral supraclavicular lymph nodes
**Clinically apparent** is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

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

### Distant Metastasis (M)

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### STAGE GROUPING

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* Note: T1 includes T1mic

Note: Stage designation may be changed if post-surgical 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.
APPENDIX IV

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 and hard copy 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.