Alliance for Clinical Trials in Oncology
American College of Radiology Imaging Network

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Effect of Preoperative Breast MRI on Surgical Outcomes, Costs and Quality of Life of Women with Breast Cancer

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Participants
• American College of Surgeons Oncology Group members
• North Central Cancer Treatment Group members
• Cancer and Leukemia Group B members
• American College of Radiology Imaging Network (ACRIN) members
• Cancer Trials Support Unit (CTSU) members

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1. Background

Surgical planning and local-regional treatment of breast cancer relies on adequate assessment of the extent of disease in the breast including the size of the primary tumor and the presence or absence of multiple tumor foci, either within the same quadrant (multifocality) or in different quadrants of the breast (multicentricity). Macroscopic multifocal or multicentric disease is considered to result in higher rates of local recurrence and therefore is generally a contraindication to breast conservation. Estimates of the frequency of multifocality and multicentricity in breast cancer vary widely, and depending on the specific criteria used can range from 7% to 63%. With the concern for high local failure rates, women with multifocal or multicentric disease at presentation may not be ideal candidates for breast conservation. Preoperative identification of these patients is important for appropriate surgical planning and treatment.

As a diagnostic modality in breast cancer patients, MRI of the breast has been shown to have high sensitivity (94-100%). MRI has proven to be important in facilitating breast conservation in patients with unusual presentations such as nipple discharge and axillary node metastases. MRI has also shown efficacy over conventional surveillance methods for patients at high risk of developing breast cancer. However, for the majority of patients with breast cancer, the role of MRI remains controversial. Several small studies have described changes in the treatment of their patient cohorts based on MRI findings. Recently, data from a large multicenter trial of MRI in patients with breast cancer demonstrated a nearly 10% increase in detection of multicentric/multifocal disease in the index breast. Furthermore, MRI also detected clinically and mammographically occult cancer in the contralateral breast in 3.1% of patients. Such findings have led to changes in surgical management of breast cancer patients in nearly 20% of women who undergo preoperative MRI with most cases converting from breast conserving therapy to mastectomy.

Despite the enhanced sensitivity of breast MRI, its clinical application for preoperative surgical staging of breast cancer patients has remained controversial. In part, this is due to high false positive rates which lead to additional biopsy procedures. However, the primary reason for the continued debate regarding the utility of preoperative breast MRI stems from the lack of data demonstrating an oncologic benefit. Specifically, the biologic and thus clinical significance of additional foci of carcinoma detected only by MR imaging is unknown. Strikingly, the frequency of occult disease detected by MRI is 2-3 fold higher than the rates of local recurrence (LR) among women who undergo BCT without the benefit of preoperative breast MRI. Data from many clinical trials suggest that local recurrence following breast conserving surgery and adjuvant systemic therapy is low, less than 10% at 10 years. In contrast, the results of MRI based studies demonstrate 15-20% conversion rate from BCT to mastectomy on the basis of greater extent of disease or additional foci detected by MRI. Although some of this increase in mastectomy rates may be due to more accurate assessment of the size of the index carcinoma, a substantial portion is due to identification of additional foci of disease at a distance from the primary tumor. These rates of conversion from BCT to mastectomy are higher than most 10 year reports of LR rates in BCT patients. This therefore suggests that not all of the additional multifocal/multicentric disease that is detected by MRI is biologically relevant, or alternatively that it may be adequately treated with adjuvant radiation or adjuvant systemic therapy. Therefore, it is possible that too many women are undergoing mastectomy based on MR imaging. In order to assess the biologic relevance of these additional areas of carcinoma detected by MRI, long term studies that assess the impact of MRI staging on local recurrence need to be undertaken.

Two retrospective studies have attempted to address this issue but have reached opposing conclusions. Fisher and colleagues reported that among 346 breast cancer patients undergoing BCT, there was a statistically significant difference in LR rates between cohorts imaged with MRI preoperatively and those who did not undergo preoperative MRI (1.2% vs. 6.5% respectively). Unfortunately, the two groups in this retrospective series were not balanced. Specifically, patients in the no MRI arm had more advanced disease and importantly, less use of adjuvant therapies.
which are known to impact local control. In addition, more recent data from a larger retrospective cohort from the University of Pennsylvania suggested no improvement in LR among women undergoing preoperative MRI for staging.

Although breast MRI is clearly the most sensitive imaging modality for determining the extent of the primary carcinoma, for identifying additional occult foci of multicentric and/or multifocal disease, its impact on the most relevant clinical endpoint, local control, has not been studied. Furthermore, recent data in the literature has raised concerns that routine use of preoperative breast MRI is associated with increased rates of mastectomy and delays to surgery. In a series of over 5000 patients from the Mayo Clinic, Katipamula and colleagues reported that use of MRI was significantly associated with choice of mastectomy. Similarly, data from Fox Chase Cancer Center demonstrate that mastectomy as first procedure increased from 19.5% amongst women who did not undergo breast MRI to 27.7% in the cohort of women who had preoperative breast MRI. In addition, in this latter group, time from diagnosis to surgery increased from 38.1 days to 56.9 days. Conversely, there are no studies that demonstrate that non-utilization of MRI in the staging of breast cancer patients adversely impacts clinically important outcomes such as local control and rates of re-operation. In fact, data recently made public from the COMICE trial, a multicenter, randomized clinical trial conducted in the UK, reported that women undergoing breast MRI did not have lower rates of re-excision and as already discussed there is minimal and conflicting retrospective data regarding MRI and local control. This lack of demonstrated benefit and increased awareness of potential harms has led to concerns that use of MRI is leading to an over-diagnosis of occult breast cancer and subsequently to more aggressive surgical interventions than would be otherwise warranted. In light of these recent publications, it has become even more imperative to determine whether preoperative MRI improves clinical outcomes.

A key component of this trial is the collaboration between ACRIN and the Alliance. This collaboration was undertaken for two main reasons. First, to help ensure quality control of the MRI study. Second, there are currently no standards for how MRI findings should be clinically interpreted and implemented. Thus, a major emphasis of this collaborative effort is to establish standards for structuring the image report data and creating guidelines for subsequent patient intervention.

2. Rationale for Trial Design

To distinguish whether preoperative breast MRI improves local staging and ultimately improves local regional control, we propose that women deemed eligible for BCT by standard criteria be randomized between current standard of care, clinical examination and mammography (+/- ultrasound) and current standard of care plus preoperative breast MRI. In order to maximize the probability of deriving benefit from preoperative MRI, the study will focus on women with ER/PR/HER-2 negative (triple negative) and HER-2 amplified breast cancers. Recent data has demonstrated that amongst breast cancer subtypes, these 2 groups of patients have the highest risk of local regional recurrence at 5 years following BCT with rates as high as 17-20% at 5-10 years of follow-up (see table below). In contrast women with ER/PR positive breast cancer had 5-year local recurrence rates following BCT of 0.8-1.5%. Given such low rates of in breast recurrence in the ER positive population, it would be challenging to achieve further significant lowering of local recurrence rates. Furthermore, if patients with ER/PR positive tumors are included in the trial, this will lower the risk of local recurrence in the control arm and thus require at least a doubling of the sample size to detect a meaningful reduction in local recurrence in the experimental (MRI) arm. Therefore, this multicenter trial will target women at the highest risk of local recurrence and test the hypothesis that increased rates of multifocality and multicentricity in this population accounts for the higher reported rates of local recurrence.

3. Significance

This proposed randomized trial of preoperative breast MRI in patients deemed eligible for breast
conserving surgery by conventional clinical criteria will provide important information about the clinical and biologic relevance of occult disease identified by MRI alone. Currently, the importance of these additional MRI detected foci remains controversial and there is concern that the enhanced sensitivity of breast MRI may result in unnecessary mastectomy. The results of this trial evaluating local recurrence rates in women who do and those who do not undergo preoperative MRI will therefore provide critical information about the significance of these additional MRI detected foci. If the trial results demonstrate that women who undergo BCT without the benefit of preoperative MRI have higher local recurrence rates compared to women staged preoperatively with breast MRI, then this would suggest that the occult areas of carcinoma, detected by MRI alone, are clinically relevant and if not surgically addressed, result in inferior local control. This finding would thus justify the routine use of preoperative MRI for staging of patients and selection for BCT. However, if the use of preoperative breast MRI does not improve on long term local control rates, this would suggest that the increased sensitivity of breast MRI in detecting otherwise occult disease is not clinically significant and/or these additional areas are well controlled through the use of adjuvant radiation and systemic therapies. Therefore, the use of preoperative MRI for routine staging of women prior to breast surgery would not be warranted and the increased rates of mastectomy seen with utilization of breast MRI would not be justified.

In addition, we have included a cost effectiveness component to this study. This will allow us to capture significant in depth data regarding the costs associated with the two treatment strategies and test the hypothesis that although preoperative breast MRI is expensive, these costs will be offset, in the short term, by reducing the number of operative interventions required to achieve margin negative BCT and, in the long term, by reduction in local recurrence events. We believe that the information obtained from this CER study will be as important as the primary and secondary endpoints. The CER study has the potential to alter clinical management even if we are unable to demonstrate oncologic benefit of routine preoperative breast MRI. It is possible that even though the rates local recurrence or re-operation between the two arms do not appear to differ (i.e. the p-value is not significant), a decrease in either parameter in the MRI arm may still be sufficient to make preoperative MRI a cost effective strategy and thus warranted for routine use in the clinic.

Registration fatigue/uniscale assessment: QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.

4. **Primary Objective**

To compare the rates of local-regional recurrence (LRR) following attempted breast conserving therapy in a cohort of women with triple negative or HER-2 amplified breast cancer randomized to preoperative staging with mammography (control arm) or mammography plus breast MRI (MRI arm).

5. **Secondary Objectives**

- To compare the re-operation rates following attempted breast conserving therapy between women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
- To compare local recurrence rates between women who undergo BCT on the control arm to women who undergo BCT on the MRI arm.
- To compare the conversion rate to mastectomy secondary to persistent positive margins or
poor comesis within the first 6 months of attempting BCT (prior to the administration of RT) between women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.

- To compare the contralateral breast cancer rates in women randomized to preoperative breast MRI to those not receiving pre-operative breast MRI.
- To compare the disease-free survival rates between women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
- To compare breast cancer specific and overall survival outcomes of women assessed preoperatively with breast MRI to those assessed without the use of breast MRI.
- To estimate the rate of MRI-guided localization assisted surgery.
- To estimate the rate of multi-centric disease in the index breast for women in the MRI arm.
- To evaluate the accuracy of index lesion characteristics and other factors in predicting multi-centricity in the cohort randomized to breast MRI.
- To assess the positive predictive values (PPV) of MRI in detecting ipsilateral multi-centric disease and contralateral disease in women with breast cancer undergoing preoperative breast MRI.

6. Correlative Science Objectives

Quality of Life

- To compare patient reported QOL parameters between women randomized to the preoperative breast MRI arm and women randomized to the no pre-operative breast MRI arm.
- To explore the impact that preoperative MRI has on patient QOL.
- To compare the QALY in patients randomized to the preoperative breast MRI arm versus those randomized to the no preoperative breast MRI arm.
- To contribute to a bank of normative data of QOL outcomes in cancer patients.

Cost Effectiveness

- To compare the estimated mean costs of breast cancer treatment between women randomized to the pre-operative breast MRI arm and women randomized to the no pre-operative breast MRI arm.
- To determine the incremental cost-effectiveness ratio of pre-operative breast MRI.
- To determine the impact of preoperative breast MRI using a net-benefit regression framework.

Translational Studies

- To determine whether clinical-pathologic variables predict LRR.
- To determine proteomic changes that correlate with LRR and disease-free survival.
- To determine alterations transcriptome that correlate with LRR and disease-free survival.
- To determine DNA mutations and copy number changes that correlate with LRR and disease-free survival.
- To determine molecular alterations that develops between primary tumors and recurrent tumors
7. **Accrual Goal**
The target accrual for this trial is 488 eligible patients. An over-accredual of at most 48 women will be allowed to account for patient withdrawals after randomization and for women deemed to be ineligible. Hence, the maximum accrual for this trial is 536 women.

8. **Schema**

9. **Eligibility Criteria**
A patient will be eligible for inclusion in this study only if ALL of the following criteria apply:

1. Female. Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.
2. Pathologically confirmed diagnosis of breast cancer, clinical stage I-II (T1-3 N0 M0, T0-2 N1 M0).
   Diagnosis must be by needle biopsy; patients diagnosed by surgical excision are excluded.
3. Patients must have either:
   a. ER negative/PR negative (<1% by IHC staining) and HER-2 negative (IHC 0, 1+ or FISH ≤ 2.2) breast cancer.
   **OR**
   b. ER negative/PR negative (< 1% by IHC staining) and HER-2 amplified tumors as determined IHC 3+ or by FISH (amplification > 2.2).
4. No patients with previous ipsilateral invasive breast cancer or DCIS.
5. No patients with bilateral breast cancer.
6. No patients with known deleterious mutations in BRCA genes.
7. No current history of receiving hormonal therapy, tamoxifen, and or aromatase inhibitors for therapeutic measures.
8. No history of chemotherapy for cancer within 6 months prior to registration.
9. No patients scheduled to receive neoadjuvant chemotherapy or partial breast irradiation following breast conserving surgery.

10. Eligible for BCT based on clinical examination, mammography and, if standard practice at a given institution, ultrasound. Women who cannot be appropriately selected for BCT based on these standard imaging studies, and for whom additional imaging is recommended to clarify local disease extent, will not be eligible for this trial.

11. No preoperative imaging with tomosynthesis.

12. No patients with multicentric or multifocal disease scheduled to undergo multiple lumpectomies.
   Multifocal disease that can be encompassed in a single operative bed can be enrolled.

13. Suitable to undergo MRI and receive the contrast agent gadolinium (exclusions follow):
   a. No history of untreated claustrophobia;
   b. No presence of metallic objects or implanted medical devices in body (i.e., cardiac pacemaker, aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, tattoos near the eye, or steel implants);
   c. No history of sickle cell disease;
   d. No contraindication to intravenous contrast administration;
   e. No known allergy-like reaction to gadolinium or moderate or severe allergic reactions to one or more allergens as defined by the American College of Radiology (ACR); patient may be eligible if willing to undergo pre-treatment as defined by the institution's policy and/or ACR guidance (see www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx for reaction definition and premedication guidance);
   f. No findings consistent with renal failure, as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m² based on a serum creatinine level obtained within 28 days prior to registration;
   g. Weight lower than that allowable by the MRI table;

14. No prior MRI of the study breast within the 12 months prior to registration.

15. Non-pregnant and non-lactating. Patients of child-bearing potential must have a negative pregnancy test within 7 days prior to registration. Perimenopausal patients must be amenorrheic > 12 months to be considered not of child-bearing potential.

16. ≥ 18 years of age.

17. Signed study-specific informed consent prior to registration.
10. Study Calendar

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* As clinically indicated; all data should be submitted for all post-operative visits.
** Every 4 months after final oncologic surgery until 2 years following registration, then every 6 months for 3 years.
*** For patients who consent to these additional studies.

A QOL questionnaires for patients on Arm 1 are to be completed at enrollment/prior to randomization, at first and last postop visit (if undergoing re-operation), and at 8 and 12 months following diagnosis. QOL questionnaires for patients on Arm 2 are to be completed at enrollment/prior to randomization, after MRI but prior to surgery, at first and last postop visit (if undergoing re-operation), and at 8 and 12 months after diagnosis.

B If more than one surgery is performed, medical care costs data is to be collected at every post-op visit.

C For patients randomized to Arm 2. MRI must be performed within 30 days following last mammographic study.
1. Within 16 days prior to registration.
2. Within 7 days prior to registration.
3. Within 21 days prior to registration

11. Treatment Arms

Arm 1 (standard): Clinical breast examination and mammography with ultrasound (US) of breast and regional nodes (if US is a standard component of institutional preoperative assessments); followed by breast conserving surgery (BCS).

Arm 2 (experimental): Clinical breast examination, mammography with ultrasound (US) of breast and regional nodes (if US is a standard component of institutional preoperative assessments) and breast MRI; followed by breast conserving surgery (BCS) or mastectomy.

12. Interventions

Breast Conserving Therapy

Patients randomized to Arm 1 will proceed directly to breast conserving surgery (BCS).

Patients randomized to Arm 2 who remain eligible for breast conserving surgery after MRI (see Section 5.2), will similarly proceed to BCS.

For quality control purposes, surgery must be performed at the registering institution or at an affiliated site with IRB approval for the study.

Oncoloplastic techniques can be utilized at the surgeon’s discretion.

A margin negative excision, defined as no tumor identified at the inked surgical margin, is required.
For patients with positive margins after initial attempt at BCS, decision regarding re-excision vs. completion mastectomy will be made at surgeon’s discretion.

Management of the axilla
Patients with clinically negative nodes should undergo staging using standard sentinel node techniques.

Patients with clinically positive nodes, as determined by preoperative US/FNA of axillary nodes, should undergo axillary nodal dissection.

In patients with clinically negative nodes, but positive sentinel node, and who otherwise conform to ACOSOG Z0011 entry criteria, axillary nodal dissection may be omitted in favor of axillary radiation at the discretion of their treating physician.

13. Postoperative Therapy
Postoperative Radiation Guidelines
Radiation treatment decisions will be determined by the treating multidisciplinary team. The following guidelines may be used to aid in radiation treatment decisions for patients treated on this protocol.

All patients treated with radiation may be simulated on a conventional simulator or CT-simulator, but CT- simulation and dose planning is encouraged.

Breast Conserving Surgery
All patients undergoing breast conserving surgery should receive whole breast radiation therapy using tangential fields with appropriate dose compensation techniques to optimize dose homogeneity, at a dose of 180-200 cGy daily to a total median dose of 4500-5040 cGy. Patients should routinely receive a dose to the tumor bed of 1000-1600 cGy to a total dose of between 6000 and 6600 cGy.

Given recent results demonstrating equivalent local control, survival and cosmetic outcomes with hypofractionated whole breast radiation, patients may at the discretion of the radiation oncologist, be treated using the Canadian Hypofractionation scheme of 4250 cY in 16 fractions to the whole breast. A boost to the tumor bed of 1000 cGy in 5 fractions of 200 cGy or 1000 cGy in 4 fractions of 250 cGy may be employed at the discretion of the treating radiation oncologist. If regional nodal irradiation is planned, patients should receive conventional radiation of 180 -200 cGy per fraction as above.

For patients treated with either conventional whole breast or hypofractionated whole breast dose homogeneity should be kept at +/- 7% at the central breast axis.

Mastectomy
For those patients who undergo mastectomy, the decision for post-mastectomy radiation should be made by the radiation oncologist in collaboration with the other treating physicians. All patients with 4 or more nodes should be treated with postmastectomy radiation and selected high risk patients with node negative disease and patients with 1-3 positive nodes may receive postmastectomy radiation. Patients treated with postmastectomy radiation should receive treatment to the chest wall using tangential fields or en-face electron fields at a dose of 180-200 cGy daily to a total dose of 4500-5040 cGy. Dose compensation techniques should be used to optimize dose homogeneity and bolus should be used at the discretion of the treating physician to assure adequate skin dose. A chest wall/scar boost may be administered at the discretion of the treating physicians, to a total dose not to exceed 6600 cGy.

Regional Nodal Irradiation
Patients undergoing radiation for node negative disease following BCS will not undergo RNI.

Patients undergoing radiation post mastectomy or post lumpectomy with more than 3 positive nodes or selected patients with 1-3 nodes involved nodes may undergo regional nodal irradiation as follows:

**Supraclavicular Radiation**

Patients should receive radiation to the supraclavicular fossa (without axillary radiation except as described below), using standard AP or APPA fields, with a daily dose of 180-200 cGy daily, to a total dose not to exceed 4500-5040 cGy. Standard matching techniques to minimize overlap with the breast/chest wall fields, and standard blocking techniques should be employed. Except when intentionally treating the full axilla as described below, the lateral border of the supraclavicular field is recommended to be placed at the coracoid process or no further lateral than the medial border of the humeral head.

**Axillary Radiation**

If the treating physicians feel axillary radiation is warranted, the lateral border of the supraclavicular field may be extended laterally to cover the full axilla and a posterior axillary field may be employed as clinically indicated to assure full dosimetric coverage of the axilla. Dose to the axilla should follow the guidelines for supraclavicular radiation as above.

**Internal Mammary Radiation**

Radiation of the internal mammary field is left at the discretion of the treating physicians. If treated, CT Simulation and planning is required to assure minimum dose to underlying cardiac and pulmonary structures and adequate coverage of the internal mammary chain. Dose to the internal mammary chain should follow the guidelines for supraclavicular radiation noted above.

14. **Follow-up**

All registered patients will be monitored for relapse and survival for 5 years from the date of surgery, as required by the Study Calendar. Patients will be followed a minimum of every 4 months for the first 2 years from diagnosis and a minimum of every 6 months during years 3-5. Patients will be monitored for local, regional and distant relapse, and vital status.

15. **Study Design**

This is a randomized phase III superiority trial. The trial hypotheses are as follows:

**Null hypothesis:** The 5 year local-regional recurrence rate for women who undergo pre-operative breast MRI will be the same as the local-regional recurrence rate for women who do not undergo pre-operative breast MRI.

**Alternative hypothesis:** The 5 year local-regional recurrence rate for women who undergo pre-operative breast MRI will be at least 8 percentage points less than the local-regional recurrence rate for women who do not undergo pre-operative breast MRI; this is equivalent to a HR of 0.19.

16. **Sample Size and Monitoring Plan**

The primary aim is to assess whether the use of pre-operative breast MRI as part of breast cancer diagnosis procedures confers lower LRR rates compared to conventional diagnostic procedures (that do not include pre- operative breast MRI). Specifically, this is a superiority trial designed to determine whether the LRR rate for women randomized to Arm 2 (use of pre-operative breast MRI) is lower than the LRR rate for women randomized to Arm 1 (control arm with no pre-operative breast MRI).

A sample size of 244 eligible patients in the control arm (Arm 1) and 244 patients in the MRI arm (Arm 2) who are deemed to be BCT candidates prior to randomization is required given the null
and alternative hypotheses and using the parameter values and assumptions listed above. The necessary number of LRR events is 23. Assuming that approximately 10% of patients are ineligible or lost to follow-up, the (maximum) target accrual for the study is 536 women.

17. Study Duration
It is anticipated that 20 patients will be accrued per month. Hence, accrual will be completed in a little over 2 years. Final analysis will occur after study closure when the data have matured and been cleaned, which would likely happen about 3 years after the completion of accrual.

18. Regulatory Considerations
Registering Physician
The registering physician must be a member in good standing of a cooperative group.

All enrolling investigators must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to the Pharmaceutical Management Branch.

Registering Institution
Patients must be enrolled at clinical sites that have a valid assurance number from the United States Office for Human Research Protections (OHRP). Most institutions have a Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA) number or Federalwide Assurance (FWA). If the clinical site does not have such an assurance, the clinical site must apply and obtain an assurance before patients can be enrolled to this study.

Unaffiliated Investigator Agreements (UIAs) are needed from investigators who independently accrue patients on ambulatory protocols outside an institution (e.g., in private practice) but who rely on an institution’s IRB for review of protocols.

Submission of IRB Approval
Documentation of IRB approval must be submitted to CTSU for entry into the Regulatory Support System (RSS) before patient registration will be allowed. Submission instructions and coversheets are available at http://www.ctsu.org/rss/.

19. Inclusion of Women and Minorities
This study will be available to all eligible female patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of this protocol in subsets defined by race or ethnicity; and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in accuracy based on racial groupings, the sample size is not increased in order to provide additional power for such subset analyses.

Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer.

Race and Ethnicity Table

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<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
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