Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2016 June 1; 95(2): 590–596. doi:10.1016/j.ijrobp.2016.01.030.

The Impact of Axillary Lymph Node Dissection on Breast Skin Thickening During and After Radiotherapy for Breast Cancer

Mylin A. Torres, M.D.^{1,2}, Xiaofeng Yang, Ph.D.^{1,2}, Samantha Noreen, B.A.³, Hao Chen, Ph.D.^{1,2,4}, Tatiana Han, B.A.^{1,2}, Simone Henry, B.A.^{1,2}, Donna Mister, B.A.^{1,2}, Fundagal Andic, M.D.⁵, Qi Long, Ph.D.^{2,3}, and Tian Liu, Ph.D.^{1,2}

¹Department of Radiation Oncology, Emory University School of Medicine, Atlanta, GA, USA

²Winship Cancer Institute, Emory University, Atlanta, GA, USA

³Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, USA

⁴Provision Center for Proton Therapy, Knoxville, Tennessee, USA

⁵Department of Radiation Oncology, Cukurova University School of Medicine, Adana, Turkey

Abstract

Purpose—This prospective study was conducted to determine predictors of epidermal thickening during and after whole breast radiotherapy (XRT) using objective measurements acquired with ultrasound.

Methods and Materials—Following breast conserving surgery, 70 women received a definitive course of whole breast XRT (50 Gy plus boost). Prior to XRT, at week 6 of XRT, and 6 weeks post XRT, subjects underwent objective ultrasound measurements of epidermal thickness over the lumpectomy cavity and all four quadrants of the treated breast. A skin thickness ratio (STRA) was then generated normalizing for corresponding measurements taken of the untreated breast.

Results—Baseline measurements indicated that 87% of patients had skin thickening in the treated versus untreated breast (mean increase of 27%, SD of 0.29) prior to XRT. The STRA increased significantly by week 6 of XRT (mean 25% (SD .46) and continued to increase significantly 6 weeks post XRT (mean 33% (SD .46) above baseline measurements ($p < 0.001$ for both timepoints). In multivariable analysis, breast volume ($p = 0.003$) and surgical evaluation of the axilla with full lymph node dissection ($p < 0.05$) predicted for more severe changes in STRA 6 weeks after XRT compared with baseline. STRA measurements correlated with physician ratings of skin toxicity according to RTOG grading criteria.

Corresponding Author: Mylin A. Torres, MD, Emory University, Department of Radiation Oncology, 1365 Clifton Rd NE, Room 1307A, Atlanta, GA 30322. Telephone: (404) 778-3473; Fax: (404) 778-5520; matorre@emory.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: None

Conclusions—This is one of the first studies to objectively document that lymph node surgery impacts XRT-induced skin thickening in breast cancer patients. Surgical evaluation of the axilla with a complete lymph node dissection was associated with the most severe XRT-induced skin changes following XRT completion. These results may inform future studies aimed at minimizing side effects of XRT and surgery, particularly when surgical lymph node assessments may not alter breast cancer management or outcome.

Introduction

Whole breast radiotherapy (XRT) treatment following partial mastectomy for breast cancer reduces risk of in-breast recurrence and the need for mastectomy.(1) Nevertheless, as many as 70 to 100% of women, will develop skin erythema, desquamation, and/or cutaneous thickening and hardening within the breast during and after XRT.(2–4) These breast toxicities may be associated with pain, noncompliance with treatment, and overall poor cosmetic outcome.(5)

Although cutaneous toxicities from breast XRT are prevalent, physicians are unable to reliably predict which patients will develop these side effects and toxicity severity. Moreover, prospective, longitudinal data objectively documenting the natural history of XRT-induced skin toxicity is lacking. Studies have been limited by cross-sectional design and subjective physician grading criteria and patient reported outcomes scales with low inter-rater and intra-rater reliability.(6–8)

Nevertheless, among previous studies, breast size appears to be one of the more consistent patient-related factors associated with XRT-induced skin toxicity.(9) Other patient characteristics associated with the development of acute dermatitis during breast XRT include smoking, African American race, postmenopausal status, and a body mass index (BMI) greater than 25. (8,10)

In addition to patient characteristics, factors associated with treatment have also predicted for XRT-induced skin toxicity including previous and/or concurrent chemotherapy and hormone therapy.(8) Specific XRT-related factors include treatment with standard fractionation (versus hypofractionated radiotherapy), bolus, and boost dose (versus no boost), as well as higher cumulative dose to the breast.(8,11) In addition, the volume of breast receiving more than 107% of prescribed dose, dose heterogeneity, and overall maximum radiotherapy dose (Dmax) within the breast have been associated with increased cutaneous toxicity.(8,12–14)

Few studies, however, have examined the impact of breast cancer surgery on XRT-induced breast toxicity. It is well-documented that a complete axillary dissection is associated with higher rates of upper extremity morbidities including lymphedema, parasthesias, wound infections, and axillary seromas but little is written on the impact of axillary surgery on the breast itself.(15–17)

Our group has previously published on the use of ultrasound to objectively document changes within the skin of women treated with breast XRT.(18,19) In a cross-sectional study, ultrasound measurements of skin thickness strongly correlated with physician assessments

of cutaneous toxicity using RTOG grading criteria.(18) Skin thickness is also a relevant concern to patients due to its association with breast texture and appearance and if persistent, may serve as an unwanted reminder of cancer treatment. Using ultrasound tissue characterization methods to objectively measure epidermal thickness, we conducted a prospective longitudinal study of XRT-induced skin toxicity. Our goal was to document the natural history of acute changes in epidermal thickening before, during (week 6 of XRT) and 6 weeks post XRT in women who received a complete axillary lymph node dissection, sentinel lymph node biopsy or no surgical evaluation of the axilla (due to a diagnosis of DCIS). We also sought to identify additional patient and treatment related factors including those due to surgery which may predict for worse XRT-induced skin toxicity objectively measured with ultrasound.

Methods

Between January 2010 and December 2013, women between the ages of 18 and 75 with an initial diagnosis of Stage 0–III breast cancer were approached for enrollment on this XXXX IRB approved prospective study of XRT-induced skin toxicity. Patients were eligible if they received breast conserving surgery (BCS) for their breast cancer and were prescribed whole breast irradiation (50 Gy plus boost). 70 eligible women with breast cancer were enrolled and provided informed consent prior to any study procedures. At the time of BCS, the axilla was assessed with sentinel lymph node biopsy (i.e. less than 6 lymph nodes removed per the 7th edition of the American Joint Committee on Cancer Staging Manual,) in women with invasive cancer and/or full axillary lymph node dissection (i.e. 6 or more lymph nodes removed) when metastatic disease within the lymph nodes was found. Median number of lymph nodes removed from sentinel lymph node biopsy alone patients (n=30) was 3 (range 1–5), while median number of lymph nodes removed from full lymph node section patients (n=18) was 13 (range 6–23). Prior to XRT, some patients also received chemotherapy, administered neoadjuvantly (n=19) or adjuvantly (n=10), for their breast cancer based on advanced cancer stage, triple negative or Her2 positive receptor status, or high 21 Gene Recurrence Score. Patients treated with mastectomy, partial breast irradiation, electrons matched to shallow tangents, and/or whole breast hypofractionation XRT regimens were excluded.

Subjects were treated with definitive whole breast XRT to a dose of 50 Gy with 6 and/or 18MV photons followed by a 10–16 Gy sequential boost to the lumpectomy cavity depending on surgical margin width (10 Gy for ≥2mm margins, 14 Gy for <2.0mm margins, and 16 Gy for positive margins) as predicated by institutional practice. Boost was delivered to lumpectomy cavity and scar plus a 2.5cm margin with electrons. A mini photon tangent boost was used in cases when the lumpectomy cavity could not be adequately treated with electrons due to cavity depth. All patient plans were designed with heterogeneity corrections and according to ICRU guidelines.(14) A subset of patients (n=16) was also treated with supraclavicular irradiation to a dose of 50 Gy at 2 Gy per fraction due to positive lymph nodes and/or large primary tumor. Half of these patients received intentional axillary nodal (level I/II) irradiation due to extracapsular extension, incomplete nodal dissection, or greater than 20% of positive nodes. Tissue equivalent bolus was not used during any of the XRT treatments.

Patients had ultrasound imaging of both breasts at three timepoints: Baseline (within 1 week prior to beginning XRT, mean of 67 days post surgery, range 29–208 days), during XRT (first day of week 6 and prior to boost treatment) and 6 weeks post XRT. Among patients who did not receive adjuvant chemotherapy (n=60), baseline assessment took place an average of 52 days (range 29–89 days) after surgery. At each timepoint, photographs were taken of the breasts for physician grading of toxicities. Ultrasound images were acquired from all four quadrants of the affected and unaffected breast as well as over the lumpectomy cavity and corresponding area on the normal control breast. In total, 2100 images were acquired. On each image set, the epidermal layer of the skin was demarcated as previously described.(18,20) A skin thickness ratio (STRA) was generated by normalizing the average of the five epidermal thickness measurements taken of the affected breast (one over each breast quadrant and the lumpectomy scar) to the mean of measurements taken over the unaffected breast. To determine reproducibility of these measurements acquired by three different operators, STRA measurements of the control breast were compared, and there were no significant inter- or intra-rater operator differences between measurements acquired at three different timepoints (all $p>0.05$). As mentioned previously, the STRA has correlated with RTOG grading criteria of radiotherapy-induced skin toxicity in breast cancer patients. (18,21) Therefore, STRA served as an objective measure of XRT-induced skin toxicity in our study.

Relevant patient, tumor and treatment characteristics including dosimetric data were collected at baseline.

Statistical Analysis

Analysis of variance was used to compare mean STRA measurements across different timepoints and to determine if XRT caused significant changes in epidermal thickening. To further validate the STRA measures, spearman correlation coefficients were computed to determine the relationship between the STRA and RTOG grading criteria as assessed by two independent physicians who evaluated breast photographs taken at each timepoint.

Simple linear regression analysis was performed to assess significant predictors of STRA during and after XRT as well as changes in STRA measurements taken during and after XRT relative to baseline. Multiple linear regression analysis was then performed to assess relationship between relevant variables and STRA. Patient and tumor variables that were assessed for their relationship with STRA and changes in STRA included baseline STRA, patient age, breast volume, race, history of diabetes, BMI, and smoking status (current vs. previous or none) and tumor size and stage (0/I vs. II/III). Radiotherapy treatment variables that were examined included breast volume receiving more than 107% of the prescribed XRT dose, maximum XRT dose (Dmax), supraclavicular nodal irradiation treatment, boost dose, and boost technique (photon vs. electron), boost volume, and boost to breast volume ratio. Lastly, treatment variables including prior chemotherapy, concurrent endocrine therapy, and previous axillary surgery (sentinel lymph node biopsy alone, complete axillary lymph node dissection, or no axillary surgical evaluation) were also evaluated. A p-value <0.2 was used as a cutoff for significant predictors to be included in model selection. Next,

starting with all of these significant predictors, backward model selection based on Akaike information criterion (AIC) was conducted to identify the optimal final model.(22)

Results

Patient, tumor, and treatment characteristics are listed in Tables 1 and 2.

STRA during Radiotherapy (50 Gy prior to boost)

In univariable analysis, predictors of higher STRA at week 6 of XRT were higher baseline STRA ($p<0.001$), larger breast volume ($p=0.001$), more advanced cancer stage (Stage II/III vs. 0/I) ($p<0.01$), current smoker ($p<0.01$), any axillary lymph node surgery (with full dissection associated with higher STRA than sentinel lymph node biopsy, and sentinel lymph node biopsy associated with higher STRA than no axillary surgery, $p<0.001$ for all comparisons), and supraclavicular nodal irradiation treatment ($p<0.001$). In multivariable analysis, higher baseline STRA ($p<0.001$) and breast volume ($p<0.001$) remained significant predictors of higher STRA at 50 Gy.

STRA 6 Weeks after Radiotherapy

In univariable analysis, predictors of higher STRA 6 weeks after XRT completion were higher baseline STRA ($p<0.001$), larger breast volume ($p=0.04$), supraclavicular nodal irradiation ($p<0.001$), advanced cancer stage (Stage II, III vs. 0/I) ($p<0.001$), surgical evaluation of the axilla with either full axillary lymph node dissection or sentinel lymph node biopsy ($p<0.001$), and being a current smoker ($p=0.02$). In addition to these variables, previous chemotherapy ($p<0.01$) predicted for STRA 6 weeks post XRT.

In multivariable analysis, increased baseline STRA ($p<0.001$) and breast volume ($p=0.02$) continued to predict for more epidermal thickening not only during but also 6 weeks post XRT. However, at the later timepoint, patients treated with complete lymph node dissection also had significantly higher STRA compared to those who had no surgical evaluation of the axilla ($p=0.02$) in the multivariable model.

Impact of Radiotherapy on STRA during and after Treatment

STRA at baseline was 1.27 (standard deviation (SD) 0.29) indicating a 27% mean increase in skin thickening in the treated breast compared with the untreated breast following surgery and prior to XRT. During XRT treatment, STRA significantly increased to 1.52 (SD 0.46; $p<0.001$ compared to baseline) and continued to significantly increase six weeks post XRT to 1.6 (SD 0.46; $p=0.03$ compared to 50Gy measurement and $p<0.001$ compared to baseline measurement). These results indicated the epidermis continued to thicken several weeks after the last day of XRT (Figure 1).

STRA measurements correlated with RTOG clinical grading of breast photographs acquired at the time of ultrasound measurements among the small number of patients who developed Grade 0 and 2 toxicity. During XRT, mean STRA of patients with Grade 2 toxicity ($n=1$) was 1.94 (SD 0.55) versus 1.68 (SD 0.33) with patients who had Grade 0 toxicity ($n=4$)

($p=0.001$). At timepoint 3, mean STRA of patients with Grade 2 toxicity ($n=4$) was 1.82 (SD 0.66) versus 1.53 (SD 0.44), $p<0.03$ in patients who had Grade 0 toxicity ($n=15$) (Figure 2).

Multivariate analysis revealed that breast volume ($p<0.001$) and older age ($p=0.04$) were significant predictors of larger increases in STRA at 50 Gy of XRT relative to baseline measures. Breast volume receiving above 107% of the dose, XRT treatment to the supraclavicular fossa, evaluation of the axilla with either sentinel lymph node biopsy or full lymph node dissection, previous chemotherapy, concurrent endocrine treatment, breast cancer stage, baseline STRA and race did not predict for more XRT-induced changes in STRA at week 6 of XRT compared to baseline.

However, in a multivariable model, significant predictors of more severe and increased changes in STRA 6 weeks after XRT, relative to baseline, were breast volume ($p=0.003$) and surgical evaluation of the axilla with either sentinel lymph node biopsy or full lymph node dissection compared with no axillary surgery ($p<0.05$; Figure 3). A complete lymph node dissection was associated with more significant changes in breast epidermal thickening than sentinel lymph node biopsy alone ($p=0.04$). Clinical cancer stage, XRT treatment of the supraclavicular fossa, previous chemotherapy, concurrent endocrine therapy, volume of the breast receiving more than 107% of the prescribed XRT dose, use of photon boost, boost volume, boost to breast volume ratio, boost dose, and baseline STRA did not predict for XRT-induced changes in STRA 6 weeks post XRT compared to baseline.

STRA prior to Radiotherapy (Baseline)

Because baseline STRA was a significant predictor of STRA during and after XRT, pertinent patient, tumor, and treatment related factors were examined to determine predictors of higher baseline STRA. In a model which included smoking status (current vs. not current), tumor stage and size, previous chemotherapy (yes vs. no), presence of diabetes, patient age, race, breast volume, and number of days between surgery and first study assessment, only being a current smoker ($p<0.001$) and axillary surgery (either sentinel lymph node biopsy ($p<0.001$) or axillary lymph node dissection ($p<0.001$) predicted for a larger baseline STRA (Figure 3). Axillary lymph node dissection was associated with a higher baseline STRA than sentinel lymph node biopsy alone or no axillary surgery ($p<0.001$ for both comparisons).

Discussion

Our prospective, longitudinal study is one of the first to objectively document skin thickening in patients undergoing whole breast XRT treatment for breast cancer. Skin thickening is a clinically relevant endpoint to both patients and providers, as skin thickness is directly correlated with overall cosmetic outcome. Using ultrasound tissue characterization, we determined that the epidermal layer of the breast continues to thicken during and up to 6 weeks after XRT. With these objective measurements, we confirmed that large breast volume is one of the more consistent patient related factors associated with increased epidermal layer thickening secondary to XRT.(8,9)

In addition, we identified surgical factors not previously associated with skin toxicity during and after XRT. Baseline STRA, largely due to the impact of surgery on the breast, predicted

for worse STRA at each timepoint. Being a current smoker also predicted for worse baseline STRA. Interestingly, axillary surgery with either complete axillary lymph node dissection or sentinel lymph node biopsy was a third and novel factor which predicted for higher baseline STRA, as well as STRA after XRT. In addition, axillary surgery of any type was associated with increased XRT-induced changes in STRA 6 weeks after XRT compared to baseline measures. It is important to note, however, that complete axillary surgery, as defined by the removal of six or more lymph nodes, was associated with more severe breast skin changes, as reflected in the STRA measurements, than sentinel lymph node biopsy alone. At the longer timepoint, XRT appeared to have a synergistic effect with that of lymph node surgery on breast skin thickening. Surgical evaluation of the axilla clearly disrupts the draining lymphatics which may lead to lymphatic congestion and increased breast edema that is reflected in our ultrasound STRA measurements. It is also possible that the edema secondary to normal tissue injury caused by XRT is not able to decompress in a patient with disrupted lymphatics secondary to surgery.

Among XRT related factors, use of a photon boost, boost volume, and boost to breast volume ratio were not significant predictors of change in STRA 6 weeks after XRT completion compared to baseline. In addition, other dosimetric parameters did not significantly predict for STRA or changes in STRA during our study timepoints, possibly due to the low number of patients with hotspots greater than 107% (33%) or the possibility that breast size rather than dosimetry is the dominant risk factor for XRT-induced skin toxicity. Indeed, a previous study has suggested that adipose tissue in women with large breast size is particularly radiosensitive.⁽⁹⁾ All patients in our study used a calendula-based cream during treatment but silvadene was held until treatment completion. Therefore, differences in skin toxicity could not be explained by skin care regimens.

Of note, our study did not find that race, BMI, smoking status, supraclavicular XRT with or without intentional level I/II treatment, previous chemotherapy, or concurrent endocrine therapy predicted for more XRT-induced skin toxicity when controlling for the impact of surgery and other factors.^(8,10) Admittedly, the relatively small number of patients in some of these subgroups limits conclusions regarding these factors (Tables 1–2). However, a significant strength of our study was that objective ultrasound measurements were taken of the breast with high intra-rater and inter-rater reliability. Using ultrasound tissue characterization, we determined the significant impact of axillary lymph node surgery on breast skin thickening and XRT-induced skin changes. Our study included a large number of African American and Caucasian patients, and our results seemed to be independent of race. Follow-up studies are needed to determine the long-term impact of lymph node surgery on breast thickening and to determine if these results remain true in a group of women who are treated with hypofractionation. These studies are currently underway at our institution.

In conclusion, surgical evaluation of the axilla has a significant impact on breast thickening before and up to 6 weeks after XRT. If these findings are confirmed in long-term follow-up, our results may be used in clinical management decisions to justify less axillary surgery, particularly in circumstances where lymph node evaluation and dissection will not impact adjuvant treatment or overall breast cancer outcome. Given the results of the recent AMAROS trial, additional studies are also warranted to determine if treatment of the axilla

with radiotherapy rather than surgery not only leads to lower rates of arm edema but also less breast skin thickening.(17)

Acknowledgments

This work was supported by National Institutes of Health (NIH), National Cancer Institute (NCI) grants R21 CA155511, R03CA173770, R03CA183006, and P30CA138292. A seed Grant also provided by the Radiation Therapy Oncology Group Community Clinical Oncology and Symptom Management Group. Funding was also provided by the Fred Cooper Family Foundation Breast Cancer Initiative and Robbins Scholar Award from the Winship Cancer Institute of Emory University.

References

1. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011; 378:1707–16. [PubMed: 22019144]
2. Wengstrom Y, Haggmark C, Strander H, et al. Perceived symptoms and quality of life in women with breast cancer receiving radiation therapy. *Eur J Oncol Nurs*. 2000; 4:78–88. discussion 89–90. [PubMed: 12849634]
3. Knobf MT, Sun Y. A longitudinal study of symptoms and self-care activities in women treated with primary radiotherapy for breast cancer. *Cancer Nurs*. 2005; 28:210–8. [PubMed: 15915066]
4. Freedman GM, Li T, Nicolaou N, et al. Breast intensity-modulated radiation therapy reduces time spent with acute dermatitis for women of all breast sizes during radiation. *Int J Radiat Oncol Biol Phys*. 2009; 74:689–94. [PubMed: 19362779]
5. Lilla C, Ambrosone CB, Kropp S, et al. Predictive factors for late normal tissue complications following radiotherapy for breast cancer. *Breast Cancer Res Treat*. 2007; 106:143–50. [PubMed: 17221151]
6. Hoeller U, Tribius S, Kuhlmeier A, et al. Increasing the rate of late toxicity by changing the score? A comparison of RTOG/EORTC and LENT/SOMA scores. *Int J Radiat Oncol Biol Phys*. 2003; 55:1013–8. [PubMed: 12605981]
7. Neben-Wittich MA, Atherton PJ, Schwartz DJ, et al. Comparison of provider-assessed and patient-reported outcome measures of acute skin toxicity during a Phase III trial of mometasone cream versus placebo during breast radiotherapy: the North Central Cancer Treatment Group (N06C4). *Int J Radiat Oncol Biol Phys*. 2011; 81:397–402. [PubMed: 20888137]
8. De Langhe S, Mulliez T, Veldeman L, et al. Factors modifying the risk for developing acute skin toxicity after whole-breast intensity modulated radiotherapy. *BMC Cancer*. 2014; 14:711. [PubMed: 25252713]
9. Goldsmith C, Haviland J, Tsang Y, et al. Large breast size as a risk factor for late adverse effects of breast radiotherapy: is residual dose inhomogeneity, despite 3D treatment planning and delivery, the main explanation? *Radiother Oncol*. 2011; 100:236–40. [PubMed: 21296441]
10. Wright JL, Takita C, Reis IM, et al. Racial variations in radiation-induced skin toxicity severity: data from a prospective cohort receiving postmastectomy radiation. *Int J Radiat Oncol Biol Phys*. 2014; 90:335–43. [PubMed: 25304794]
11. Wells M, Macmillan M, Raab G, et al. Does aqueous or sucralfate cream affect the severity of erythematous radiation skin reactions? A randomised controlled trial. *Radiother Oncol*. 2004; 73:153–62. [PubMed: 15542162]
12. Pignol JP, Olivetto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol*. 2008; 26:2085–92. [PubMed: 18285602]
13. Mukesh MB, Harris E, Collette S, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol*. 2013; 108:293–8. [PubMed: 23953408]
14. Prescribing RaRPBTMI. , editor. ICRU Report No. 50. Bethesda, MD: 1993.

15. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg.* 2010; 252:426–32. discussion 432–3. [PubMed: 20739842]
16. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011; 305:569–75. [PubMed: 21304082]
17. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol.* 2014; 15:1303–10. [PubMed: 25439688]
18. Yoshida EJ, Chen H, Torres M, et al. Reliability of quantitative ultrasonic assessment of normal-tissue toxicity in breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012; 82:724–31. [PubMed: 21435799]
19. Yoshida EJ, Chen H, Torres MA, et al. Spectrophotometer and ultrasound evaluation of late toxicity following breast-cancer radiotherapy. *Med Phys.* 2011; 38:5747–55. [PubMed: 21992389]
20. Gao Y, Tannenbaum A, Chen H, et al. Automated skin segmentation in ultrasonic evaluation of skin toxicity in breast cancer radiotherapy. *Ultrasound Med Biol.* 2013; 39:2166–75. [PubMed: 23993172]
21. Liu T, Zhou J, Yoshida EJ, et al. Quantitative ultrasonic evaluation of radiation-induced late tissue toxicity: pilot study of breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010; 78:811–20. [PubMed: 20171811]
22. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions.* 1974; 19:716–723.

Summary

This prospective cohort study of 70 breast cancer patients treated with partial mastectomy and whole breast radiotherapy was conducted to determine predictors of breast skin thickening during and after radiotherapy using objective measurements with ultrasound tissue characterization. Complete axillary lymph node dissection was associated with significantly more radiotherapy-induced changes in breast epidermal thickness 6 weeks after radiotherapy treatment than sentinel lymph node biopsy alone or no axillary surgical evaluation.

Figure 1. Skin Thickness Ratio before, during and after Breast Radiotherapy

A skin thickness ratio (STRA) was generated by averaging five epidermal thickness measurements taken on ultrasound B images of the affected breast (one over each breast quadrant and lumpectomy scar) and normalizing these measurements to those taken of the unaffected breast. Mean STRA 6 weeks after radiotherapy was significantly larger than both baseline mean STRA ($p<0.001$) and STRA at 50 Gy ($p=0.03$).

Figure 2. Ultrasound B images of the Breast in Breast Cancer Patients who developed Grade 0, 1, and 2 toxicity during and after Radiotherapy

Representative ultrasound B images of the breast acquired from three different breast cancer patients with Grade 0, 1, and 2 skin toxicity during and after XRT are shown. Yellow lines demarcate the epidermis of the breast. The patient with Grade 2 skin toxicity has an appreciably thicker epidermal layer 6 weeks post XRT relative to baseline, whereas the epidermal layer of the patient with Grade 0 toxicity does not appear to change.

Figure 3. The Influence of Axillary Surgery on the Skin Thickness Ratio before, during, and after Breast Radiotherapy

The skin thickness ratio among women who received full axillary lymph node dissection was significantly higher at baseline and 6 weeks post radiotherapy than women who had no surgical lymph node evaluation ($p < 0.05$ at both timepoints).

Table 1

Patient and Tumor Characteristics

Characteristic	N=70
Age	
Mean (range)	57 (26–75)
Body Mass Index (BMI)	
Mean (range)	29.3 (19.1–60.2)
Breast Volume (cm ³)	
Mean (range)	1819.9 (223.3–6988.3)
Diabetes	
No	59 (84%)
Yes	11 (16%)
Race	
Caucasian	40 (57%)
African American	30 (43%)
Smoking	
No	56 (80%)
Previous Smoker	9 (13%)
Current Smoker	5 (7%)
Cancer Group Stage	
0	20 (29%)
I	19 (27%)
IIA	20 (29%)
IIB	10 (14%)
IIIA	1 (1%)
Tumor size (cm)	
Mean (range)	1.85 (0.1–6.0)
Node Positive	
No	50 (71%)
Yes	20 (19%)

Table 2

Treatment Characteristics

Characteristic	N=70
Axillary Surgery	
Sentinel Lymph Node Biopsy Alone	30 (43%)
Full Axillary Lymph Node Dissection	18 (26%)
None	22 (31%)
Chemotherapy	
Neoadjuvant	19 (27%)
Adjuvant	10 (14%)
None	41 (59%)
Endocrine Therapy	
Concurrent	8 (11%)
Adjuvant	42 (60%)
None	20 (29%)
Radiotherapy	
Dmax	
Mean (range)	107.6% (103.5% – 115.6%)
Breast Volume receiving >107% of whole breast dose (cm ³)	
Mean (range)	71.7 (0 – 1697.9)
2cm ³ of Breast Tissue Receiving > 107% of whole breast dose	
No	47 (67%)
Yes	23 (33%)
Supraclavicular Nodal Irradiation	
No	54 (77%)
Yes	16 (23%)
Boost	
10 Gy	57 (82%)
14 Gy	12 (17%)
16 Gy	1 (1%)
Boost Technique	
Electrons	46 (66%)
Photons	24 (34%)