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Reliability of quantitative ultrasonic assessment of normal-tissue toxicity in breast cancer radiotherapy

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Abstract

Purpose—We have recently reported that ultrasound imaging, together with ultrasound tissue characterization (UTC), can provide quantitative assessment of radiation-induced normal-tissue toxicity. This study's purpose is to evaluate the reliability of our quantitative ultrasound technology in assessing acute and late normal-tissue toxicity in breast cancer radiotherapy.

Method and Materials—Our ultrasound technique analyzes radio-frequency echo signals and provides quantitative measures of dermal, hypodermal, and glandular-tissue toxicities. To facilitate easy clinical implementation, we further refined this technique by developing a semi-automatic ultrasound-based toxicity assessment tool (UBTAT). Seventy-two ultrasound studies of 26 patients (720 images) were analyzed. Images of 8 patients were evaluated for acute toxicity (<6 months post radiotherapy) and those of 18 patients were evaluated for late toxicity (≥6 months post radiotherapy). All patients were treated according to a standard radiotherapy protocol. To assess intra-observer reliability, one observer analyzed 720 images in UBTAT and then repeated the analysis 3 months later. To assess inter-observer reliability, three observers (two radiation oncologists and one ultrasound expert) each analyzed 720 images in UBTAT. An intraclass correlation coefficient (ICC) was used to evaluate intra- and inter-observer reliability. Ultrasound assessment and clinical evaluation were also compared.

Results—Intra-observer ICC was 0.89 for dermal toxicity, 0.74 for hypodermal toxicity, and 0.96 for glandular-tissue toxicity. Inter-observer ICC was 0.78 for dermal toxicity, 0.74 for hypodermal toxicity, and 0.94 for glandular-tissue toxicity. Statistical analysis found significant changes in dermal ($p < 0.0001$), hypodermal ($p = 0.0027$), and glandular-tissue ($p < 0.0001$) assessments in the acute toxicity group. Ultrasound measurements correlated with clinical RTOG toxicity scores of patients in the late toxicity group. Patients with RTOG grade 1 or 2 had greater ultrasound-assessed toxicity percentage changes than patients with RTOG grade 0.

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Conclusion—Early and late radiation-induced effects on normal tissue can be reliably assessed using quantitative ultrasound.

Keywords

breast cancer; radiation toxicity; ultrasound; tissue characterization

INTRODUCTION

Radiation-induced normal-tissue toxicities are common morbidities in breast cancer radiotherapy (1). Despite technological advances, the majority of patients continue to suffer from acute or late radiation toxicities. Over 90% of women who receive radiation for breast cancer will develop skin changes during the course of treatment (2). European Organisation for Research and Treatment of Cancer (EORTC) reported a 10-year follow-up study of over five thousand post-radiation breast cancer patients (trial 22881-10882), and found that 26.9% developed moderate to severe fibrosis (3). Currently, radiation toxicity is exclusively evaluated by visual observation and physical examination making it highly susceptible to inter-observer variability (4, 5). Objective, noninvasive, imaging assessments of radiation toxicity, particularly those assessments that can be identified as measures of treatment outcome and quality of life, would provide a valuable adjunct to post-radiotherapy care.

We developed an ultrasound-based technique for toxicity assessment that combines conventional ultrasound with ultrasound tissue characterization (UTC) (6). The major difference between conventional ultrasound and UTC is that conventional ultrasound focuses on visualization of anatomical structures (7) while UTC provides quantitative measures of tissue integrity (8–10). Based on the phenomenon that healthy and diseased tissues have different biomechanical properties and subsequently generate different ultrasound echo signals, UTC parameters extracted from these echo signals can be used to quantify the condition of the tissue. With our quantitative ultrasound technique, we are able to produce a more sensitive, reliable, and comprehensive evaluation of radiation-related tissue injuries.

The benefit of our ultrasound technique is the provision of a continuous scale for objective evaluation of normal-tissue injury at a specific location and depth of the breast. In our previous report, we demonstrated the feasibility of our ultrasound technology in a clinic setting (10). We measured radiation-induced injury to the three layers at five different positions on the breast (12:00, 3:00, 6:00, 9:00 and the tumor bed), as shown in Figure 1. We developed three toxicity parameters that each quantified injury at a particular tissue layer: dermis, hypodermis, or glandular tissue (Table 1). In contrast to the subjective EORTC/RTOG-common toxicity criteria that are limited to 4 or 5 grades (11), our technique offers a significantly greater level of specificity and reproducibility.

This study was conducted to evaluate the reliability of our ultrasound technique. For clinical implementation of our quantitative technique, we further developed a semi-automatic, ultrasound-based, toxicity assessment tool (UBTAT) that can be easily integrated into clinical scanners. As shown in Figure 2, the UBTAT enables physicians to contour regions of interest (ROI) on B-mode breast images and then uses this information to quantify tissue properties from the digital RF echo signals. The reliability study consisted of three components: 1) intra-observer reliability, 2) inter-observer reliability, and 3) correlation between UBTAT measurements with clinical assessment.

METHODS AND MATERIALS

Patients

This study was conducted with ultrasound data from 26 patients acquired between January and December 2007 (Table 2). Eight patients were enrolled in an acute toxicity study at the time of their initial radiotherapy consultation and received ultrasound studies prior to, during, and up to 6 months post radiation treatment. Eighteen patients were enrolled in a late toxicity study after treatment completion and received one ultrasound study ≥ 6 months post radiotherapy. Patient characteristics of both subgroups are illustrated in table 2.

All patients received 50.0–50.4 Gy to the whole breast (1.8 or 2.0 Gy fractions) followed by an electron boost of 10.0–16.0 Gy at the lumpectomy site. Dose was delivered using parallel and opposed 6-MV tangential fields. Beams were modulated using wedges to assure dose homogeneity according to standard International Commissions on Radiation Units & Measurements 50 (ICRU-50) guidelines (12).

Ultrasound Data Acquisition

Ultrasound scans were performed using a clinical ultrasound scanner, Sonix RP (Ultrasonix Medical Corporation, BC, Canada), with a 12-MHz linear probe. Patients were scanned in the supine position. A thin layer of ultrasound gel was used to ensure good coupling between the breast and the ultrasound probe. The probe was placed perpendicular to the scan surface with minimal pressure applied to the breast. Ultrasound B-mode images and radio-frequency (RF) echo signals were obtained from ten locations: five on the treated (irradiated) breast (12:00, 3:00, 6:00, 9:00, and tumor bed), and five corresponding locations on the untreated (contralateral) breast (Fig. 1). Measurements from the contralateral breast served as controls to account for patient baseline variation. Each ultrasound study (10 scans) required no more than 5 minutes. A radiation oncologist used an RTOG Radiation Morbidity Scoring Scheme to perform a clinical toxicity assessment prior to each ultrasound study.

UTC Toxicity Parameters

To quantify radiation-induced late toxicity, we used three toxicity parameters derived from ultrasound RF data that each characterizes the properties of a breast tissue layer. Skin thickness was used to characterize the dermis, Pearson correlation coefficient was used to characterize the hypodermal surface, and spectral midband fit was used to characterize glandular tissue. Since breast tissue is highly variable due to compositional heterogeneity and responsiveness to biological changes, accurate evaluation of toxicity mandates comparison of irradiated tissue with an untreated baseline from the same patient (13). Measurements from the untreated breasts were used for calibrations to control for baseline patient variability.

The dermal toxicity parameter is defined as the difference between skin thickness of the treated breast and that of the untreated breast at the mirror location. Skin thickness is measured as the distance between the entry ultrasound echo signal to the border between the dermis and hypodermis (Fig. 3). The hypodermal toxicity parameter is defined as the difference between 1 minus the Pearson correlation coefficient of the hypodermal surface on the treated breast and that at the mirror location on the untreated breast. Pearson correlation coefficient is a method of measuring correlation between two variables and is defined as the covariance of the two variables divided by the product of their standard deviations. In this study, the variables are the adjacent scan lines along a segment of the hypodermal surface. Average Pearson correlation coefficient of the hypodermis is used to characterize its integrity (Fig. 4). A decrease in Pearson correlation coefficient indicates a decrease in hypodermal integrity and an increase in toxicity. The glandular-tissue toxicity parameter is

defined as the difference between spectral midband fit of the treated breast and that of the untreated breast at the mirror location. Spectral midband fit is the intensity value at the midpoint of the linear regression of the calibrated tissue spectrum. The calibrated tissue spectrum is achieved by taking the Fourier transform of the digital RF data from a region of interest minus the calibration spectrum to remove the system factors (Fig. 5).

Our software UBTAT allows physicians to select an area for toxicity analysis on a conventional B-mode image and calculates toxicity parameters (Fig. 2). To evaluate dermal and hypodermal properties, the physician contours the skin and hypodermal surfaces. Subsequently, UBTAT calculates dermal toxicity and hypodermal toxicity parameter values from the corresponding RF echo signals. Glandular toxicity is calculated from a 2D region-of-interest (ROI) located deep to the hypodermal surface. For this parameter, UBTAT has two modes: a semi-automatic mode in which the ROI of a pre-specified size is automatically generated at a pre-specified location and depth for all ultrasound images, and a manual mode in which the physician specifies the location and size for each image. Finally, UBTAT quantifies tissue toxicity from the RF data within the ROI.

Reliability study

Ultrasound data analysis using UBTAT was conducted between January and May 2010. To evaluate intra-observer reliability, one observer was asked to assess 720 ultrasound images using UBTAT at two time points. The skin surface and hypodermal surface were contoured on all images. From these contours, dermal and hypodermal toxicities were calculated. To assess the glandular tissue, UBTAT's semi-automatic mode was employed to generate a 5×30 mm ROI located 1 mm below the hypodermis contour. From each contoured ultrasound image, UBTAT calculated values for the three toxicity parameters: dermal toxicity, hypodermal toxicity, and glandular-tissue toxicity. The same observer was asked to repeat this assessment 3 months later. The time interval between assessments was chosen on the order of months to reduce memory bias. An intra-class correlation coefficient (ICC) was calculated for assessment of consistency among measurements by the same observer.

To evaluate inter-observer reliability, three observers (two radiation oncologists and one ultrasound physicist) were asked to independently assess dermal, hypodermal, and glandular-tissue toxicities on 720 ultrasound images using UBTAT. Each observer contoured the skin and hypodermal surfaces on all 720 images. In semi-automatic mode, UBTAT generated a 5×30 mm ROI located 1 mm below the hypodermis contour from which glandular-tissue toxicity was calculated. Each observer was blinded to the contours and parameter values of the other observers. An intra-class correlation coefficient (ICC) was calculated for assessment of consistency among the three observers.

In the acute toxicity group of 8 patients (46 ultrasound studies), we investigated the longitudinal trend of ultrasound-measured toxicity. This study was conducted to establish the sensitivity of quantitative ultrasound in detecting early-radiation dose response and to determine its ability to predict late radiation toxicity. In the late toxicity group of 18 patients, we compared UBTAT measurements with clinical assessments using RTOG late-toxicity scores to validate our ultrasound technique. In this paper, we focused on reliability evaluation. Findings of the radiation dose response in the acute toxicity group will be reported in a future manuscript.

Statistical analysis

Intraclass correlation coefficient (ICC) is a statistical method for measurement of intra-observer and inter-observer reliability. ICC assesses the consistency of multiple measurements of the same quantity. In general, an ICC value of 0.7–0.8 indicates strong

agreement and an ICC value >0.8 indicates excellent agreement (14). The ICC equation is based on a linear model (two-way random effects, interaction absent):

$$x_{ij} = \mu + r_i + c_j + e_{ij},$$

where μ is the overall population mean, r_i represents the patient effect, c_j represents the observer effect, and e_{ij} represents the random error effect. All effects are assumed to be normally distributed with means of zero and variances of σ_r^2 , σ_c^2 , and σ_e^2 . ICC measures the proportion of the variance that is attributed to different observers:

$$ICC = \frac{\sigma_r^2}{\sigma_r^2 + \sigma_c^2 + \sigma_e^2}.$$

A 95% confidence interval was estimated for each ICC to estimate the precision and the range of the correlation. A Mixed model was further employed to test whether observer was a significant factor affecting dermal toxicity, hypodermal integrity, and glandular-tissue toxicity parameters. In order to estimate the correlation between the ultrasound parameters and clinical assessment, a General linear model (GLM) was used to compare the difference in dermal, hypodermal, and glandular-tissue toxicities between patients with RTOG grade 0 and patients with RTOG grades 1 or 2. In this study, no patients experienced toxicity of RTOG grades 3 or 4. The significance levels were set at 0.05 for all tests. All statistical analyses were conducted in SAS statistical software (SAS institute Inc, Atlanta, GA, USA).

RESULTS

Percent differences of repeated radiation toxicity measurements by observer 1 are shown in Table 3. From the 720 images analyzed, average percent difference was 1.1% for dermal toxicity, 4.4% for hypodermal toxicity, and 0.1% for glandular-tissue toxicity. Intra-observer ICC values and 95% confidence intervals (CI) of observer 1's toxicity measurements at the five scan locations are shown in table 4. Average ICC values for dermal and glandular-tissue toxicity parameters were 0.89 and 0.96, respectively, indicating high intra-observer reliability. An average ICC value for the hypodermal toxicity parameter was 0.74, which suggests good intra-observer reliability.

Percent differences of radiation toxicity measurements among three observers are shown in Table 3. For dermal toxicity measurements, average percent difference was 9.6% between observers 1 and 2, -5.7% between observers 2 and 3, and -3.9% between observers 1 and 3. For hypodermal toxicity measurements, average percent difference was 1.2% between observers 1 and 2, 3.0% between observers 2 and 3, and -4.2% between observers 1 and 3. For glandular-tissue toxicity measurements, average percent difference was -0.6% between observers 1 and 3, 1.0% between observers 2 and 3, and 3.9% between observers 1 and 3. Inter-observer ICC values and 95% CI are shown in table 5. Average ICC values for dermal and glandular-tissue toxicity parameters are 0.78 and 0.94, respectively. The average ICC of the hypodermal toxicity parameter is 0.74. These ICC values suggest the high inter-observer reliability of dermal and glandular-tissue toxicity parameters and the moderate reliability of the hypodermal toxicity parameter.

Early radiation-induced normal-tissue changes were detected in the acute toxicity group of 8 patients (46 ultrasound studies). Statistical analysis found significant changes in dermal toxicity ($p < 0.0001$), hypodermal toxicity ($p = 0.0027$) and glandular-tissue toxicity ($p < 0.0001$) over time. Longitudinal change trends indicated that our ultrasound technique was

able to monitor the trajectory of toxicity development. For the late toxicity group of 18 patients, we compared our ultrasound evaluations with clinical assessment. Clinical assessment determined 6 patients (33%) with grade-0, 10 patients (56%) with grade-1, and 2 patients (11%) with grade-2 skin toxicity. Patients with RTOG grade 1 or 2 have greater ultrasound-assessed toxicity percentage changes than patients with RTOG grade 0 (Table 6). Dermal and glandular-tissue toxicity changes were significant ($p < 0.05$) between the two groups but hypodermal toxicity change was not significant ($p = 0.22$).

DISCUSSION

This study demonstrated that our quantitative ultrasound technique was able to reliably evaluate normal-tissue injury in breast cancer radiotherapy. Dermal- and glandular-toxicity parameters were found to be highly reliable while the hypodermal-toxicity parameter was found to be moderately reliable. Our UBTAT software program further facilitated quantitative ultrasound's clinical application by providing a user-friendly interface that allowed physicians to contour onto ultrasound B-mode images from which dermal, hypodermal, and glandular-tissue toxicities were calculated.

Glandular-tissue toxicity, with the highest ICC among the ultrasound parameters, was the most consistent at every location on the breast. The hypodermal toxicity parameter demonstrated the lowest ICC and was moderately consistent between the three observers. For dermal and hypodermal injury, the tumor bed location had a lower ICC value compared with other locations. Lack of consistency at the tumor bed location may be attributed to the surgical scar whose presence led to poor visualization of the skin and hypodermal surfaces on the ultrasound image (Figure 6). We recommend exclusion of the tumor bed location; however, since the tumor bed receives the largest radiation dose, proximal locations may be optimal for toxicity evaluation.

In the longitudinal study of the acute toxicity group, ultrasound toxicity measurements revealed significant changes over time demonstrating quantitative ultrasound's ability to document radiation dose response. Such study may be crucial for a more precise understanding of the trajectory of normal-tissue toxicity development. Further comparison was investigated between toxicity measures from our late toxicity group and clinical assessment. Statistical analysis found UBTAT evaluations to be consistent with clinical RTOG late toxicity scores. A limitation of this analysis is the use of RTOG scoring scheme as a clinical endpoint. Despite the scoring scheme's inherent subjectivity, clinical assessment of toxicity is the current standard of care and is therefore an important evaluation to which any objective/quantitative technique should correlate.

With advances in breast cancer treatment, radiotherapeutic strategies are continuously refined (15). Changes in treatment technique (16–18), such as radiation energy (19), dose (20), fractionation (13), and chemoradiation influence radiation side effects (21) and pose a significant challenge to the systematic study of the morbidity profile. Our objective imaging technique has the potential to provide radiation oncologists with a more accurate and reliable imaging tool to assess acute and late radiation-induced toxicity. Provision of a continuous scale for toxicity measurement affords greater specificity and facilitates comparison of treatment strategies in breast cancer radiotherapy across multiple institutions. Quantitative ultrasound, facilitated by UBTAT software, provides an alternative toxicity assessment tool that is easy to use and reliable. Furthermore, quantitative ultrasound may be adapted to measure toxicity at other sites, such as the head and neck or prostate.

CONCLUSION

Ultrasound imaging together with ultrasound tissue characterization provides a reliable quantitative evaluation of normal-tissue injury from radiotherapy. Facilitated by UBTAT software, physicians are able to measure acute and late toxicities as well as determine the location and extent of radiation injury using quantitative ultrasound. Our technique provides an objective and effective method of documenting the trajectory of normal-tissue toxicity development and radiation-dose response.

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Figure 1. Diagram showing 10 ultrasound scan locations: upper, medial, lower, lateral and tumor bed locations on the treated and untreated breasts. The untreated (contralateral) breast is served as the control.

Figure 2.

Ultrasound-based, toxicity assessment tool (UBTAT) provides a user-graphic interface. The user can contour the skin surface (blue line), the hypodermis (green) and glandular tissue (red region of interest). The UBTAT software computes three ultrasound parameters that each corresponds to a layer of tissue. Radio-frequency (RF) echo signals located from the skin surface and hypodermis contours correspond to skin thickness. RF echo signals located from the hypodermis contour correspond to Pearson correlation coefficient, and those located within the ROI correspond to spectral midband fit.

Figure 3.

Measurement of skin thickness is illustrated using ultrasound images of the 3:00 location on a 55 year-old woman with RTOG late toxicity score of 2. Ultrasound images were acquired 9 months post radiotherapy. Ultrasound B-mode images of the untreated breast (a) and treated breast (b) were used to contour the skin surface (purple) and the hypodermis surface (green) to assess dermal toxicity.

Figure 4.

Measurement of hypodermal toxicity is illustrated using the same ultrasound images as in Fig. 3. Ultrasound B-mode images of the untreated breast (a1) and treated breast (b1) were used to contour the hypodermis (purple). The corresponding 2D Pearson correlation coefficient matrices (a2 and b2) were generated from RF echo signals within the hypodermis region (43 pixels and 220 scan lines) to characterize hypodermal integrity. One minus the mean value of each matrix was 0.73 for the irradiated breast and 0.59 for the untreated breast. Hypodermal toxicity was defined as the difference in these values and was calculated to be 0.14.

Figure 5.

Measurement of subcutaneous toxicity is illustrated using the same ultrasound images from the patient characterized in Fig. 3 and Fig. 4. The B-mode ultrasound images of the untreated breast (a1) and treated breast (b1) were used to assess subcutaneous tissue (ROI). The corresponding 1-D power spectra (a2 and b2) were computed from RF echo signals within the ROI (140 pixels and 250 scan lines). The midband fit value was 1.74 dB for the irradiated breast and -0.30 dB for the untreated breast. Subcutaneous toxicity 2.05 dB was calculated as the difference in of the treated and untreated breasts.

Figure 6.
Ultrasound B-mode image at the tumor bed location.

Table 1

Summary of ultrasound parameters

Ultrasound Parameters	Regions of Interest
Skin thickness	Epidermis and dermis
Pearson coefficient	Hypodermis
Spectral midband fit	Glandular tissue

Table 2

Patient characteristics

Characteristics	Number
Age (year)	
Mean	55
Range	42 to 74
Race	
Asian	1 (4%)
African American	4 (15%)
Caucasians	7 (27%)
Hispanics	14 (54%)
Tumor Stage	
Stage 0	6 (23%)
Stage I	14 (54%)
Stage II	6 (23%)
Tumor Location	
Right breast	16 (62%)
Left breast	10 (38%)

Table 3

Intra-observer and inter-observer variations in percent change of ultrasound parameters measurements

	Intra-observer difference	Inter-observer difference		
	Dates 1 vs 2	Observers 1 vs 2	Observers 2 vs 3	Observers 3 vs 1
Dermal toxicity	1.1% $\pm$ 18.2%	9.6% $\pm$ 39.1%	-5.7% $\pm$ 41.3%	-3.9% $\pm$ 18.1%
Hypodermal toxicity	4.4% $\pm$ 23.9%	1.2% $\pm$ 22.3%	3.0% $\pm$ 17.2%	-4.2% $\pm$ 15.1%
Glandular toxicity	0.1% $\pm$ 13.1%	-0.6% $\pm$ 19.1%	1.0% $\pm$ 18.4%	3.9% $\pm$ 13.9%

Table 4

Intra-class correlation coefficient of quantitative ultrasound evaluation of breast toxicity

Location	Dermis	Hypodermis	Glandular tissue
12:00	0.92 (0.88 – 0.95)	0.72 (0.57 – 0.82)	0.98 (0.96 – 0.99)
3:00	0.91 (0.86 – 0.94)	0.79 (0.68 – 0.87)	0.93 (0.89 – 0.96)
6:00	0.93 (0.89 – 0.95)	0.76 (0.63 – 0.85)	0.98 (0.97 – 0.99)
9:00	0.82 (0.72 – 0.88)	0.71 (0.57 – 0.82)	0.96 (0.94 – 0.98)
Tumor Bed	0.89 (0.83 – 0.93)	0.74 (0.60 – 0.83)	0.95 (0.92 – 0.97)
Average	0.89	0.74	0.96

Table 5

Inter-class correlation coefficient of quantitative ultrasound evaluation of breast toxicity

Location	Dermis	Hypodermis	Glandular tissue
12:00	0.79 (0.71 – 0.86)	0.75 (0.64 – 0.83)	0.97 (0.95 – 0.98)
3:00	0.82 (0.74 – 0.88)	0.77 (0.67 – 0.85)	0.93 (0.89 – 0.95)
6:00	0.75 (0.66 – 0.83)	0.83 (0.75 – 0.88)	0.93 (0.90 – 0.96)
9:00	0.80 (0.72 – 0.87)	0.68 (0.56 – 0.78)	0.95 (0.92 – 0.97)
Tumor Bed	0.75 (0.62 – 0.83)	0.69 (0.57 – 0.79)	0.92 (0.87 – 0.95)
Average	0.78	0.74	0.94

Table 6

Ultrasound measured toxicity between patients with and without toxicity

	Patients without toxicity RTOG score = 0	Patients with toxicity RTOG score = 1 or 2	<i>p</i> -value
Dermal toxicity	28.5% ± 26.6%	69.7% ± 39.7%	0.04
Hypodermal toxicity	5.4% ± 35.8%	19.2% ± 26.2%	0.22
Glandular-tissue toxicity	27.2% ± 43.5%	163.6% ± 127.0%	0.04