Quantifying radiation-induced breast fibrosis by shear-wave elastography in patients with breast cancer: A 12-months-follow-up data of a prospective study

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ARTICLE INFO

ABSTRACT

Purpose: To assess radiation-induced fibrosis (RIF) using shear-wave elastography (SWE) in patients with breast cancer who received radiotherapy (RT) after breast conserving surgery.

Methods: Forty-one patients were enrolled in a prospective study before RT. SWE and B-mode ultrasonography were performed to measure elasticity. For quantitative measurement, the maximum elasticity value was measured in the tumor bed and non-tumor bed of the treated breast, and contralateral breast before RT and at 3, and 12 months after RT. and RIF was recorded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: The mean $\pm$ standard deviation elasticity values for the tumor bed, non-tumor bed, and contralateral breast were 71.2 $\pm$ 74.9 kPa, 19.4 $\pm$ 9.8 kPa and 20.3 $\pm$ 10.0 kPa before RT; 28.7 $\pm$ 26.3 kPa, 15.1 $\pm$ 7.0 kPa, and 14.7 $\pm$ 6.3 kPa at 12 months after RT, respectively. The elasticity values for all three measurement areas before and 12 months after RT were significantly different (p < 0.001 for tumor bed, p = 0.002 for non-tumor bed, p = 0.001 for contralateral breast). At 12 months follow-up, the distribution of grades of RIF evaluated by CTCAE grade was grade 0 in 43.9 %, grade 1 in 48.8 %, and grade 2 in 7.3 %.

Conclusion: We demonstrated that SWE enables the evaluation of tissue stiffness to provide quantified information for the RIF of breast cancer. Further studies with long-term follow-up should provide more quantitative data.

Introduction

Radiation-induced fibrosis (RIF) is one of the most common late side effects that occur in breast cancer patients receiving radiotherapy (RT), and the reported incidence of grade 2 or higher breast fibrosis had a wide range from 1 % to 75 % [1]. RIF is an irreversible process where there is an excessive production of fibrous connective tissue or collagen which causes functional and structural changes, and may progress over time [2]. It has been reported in previous studies that RIF may affect cosmetic outcomes and quality of life of the patients, such as breast pain and edema [3,4].

The commonly used method for RIF estimation and scoring is based on clinical palpation, which has the limitations of being subjective and expressed in ordinal rather than absolute units. The subjective grading systems for RIF are the Radiation Therapy Oncology Group (RTOG)/the European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria [5], the Late Effects Normal Tissue Task Force–Subjective, Objective, Management and Analytic (LENT-SOMA) scale

[6], and the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [7].

Ultrasonic elastography is a non-invasive method that can measure and image the rigidity and elasticity of a tissue in real time. Elastic ultrasound can be classified into two types: shear-wave elastography (SWE) and strain elastography depending on the physical quantity to be measured [8]. Among these, SWE is an objective means to quantitatively measure soft tissue stiffness by measuring the shear wave speed at which a force is applied to the tissue according to the elasticity, and thus has the advantage of being less dependent on the operator and having good reproducibility [9–11].

Previous studies showed that SWE can be used for predicting the response of breast cancer to neoadjuvant chemotherapy (NAC) [12–14]. Since tumor rigidity is related to the content of collagen in the stroma, it can help predict the response to NAC by measuring the stiffness and structural abnormalities of the stroma with SWE after NAC. However, there are currently no studies using SWE to evaluate RT-induced breast fibrosis.

The aim of our study was to investigate the feasibility of using SWE to assess RT-induced breast fibrosis over time.

Materials and methods

We prospectively enrolled patients aged 19 to 70 years who are recommended to receive adjuvant RT after breast conserving surgery for unilateral invasive or non-invasive breast cancer between February 2021 and February 2022. Patients were excluded if they had previous irradiation in the same breast; had bilateral breast cancer or had a breast implant to the tumor bed. This prospective study was approved by the institutional review board (approval number: 2020–09-032 at Ewha Womans University Mokdong Hospital), and written informed consents were obtained from all participants.

Radiotherapy

RT was delivered with 6 and 15 megavoltage photons from a linear accelerator using either 3-dimensional conformal RT or intensity-modulated RT. According to the fractionation schedule, patients received RT using either a conventional fractionated (1.8–2 Gy/fraction) or hypofractionated (2.6–2.7 Gy/fraction) schedule. Determination of conventional or hypofractionated RT was depended on the choice of attending radiation oncologists.

Shear-wave elastography acquisition and analysis

SWE and B-mode ultrasonography were performed by one board certified radiologist XX with 12 years of experience with breast imaging and 11 years in performing SWE. Ultrasound unit with a 4–15 MHz linear-array transducer (Aixplorer system, Supersonic Imagine, Aix en Provence, France) was used for B-mode ultrasonography, color Doppler ultrasonography and SWE images. B-mode ultrasound images with transverse and longitudinal views, color Doppler image and SWE images were obtained for the tumor bed, non-tumor bed within the treated breast, and same clock quadrant as the tumor bed in the non-irradiated contralateral breast as a representative of normal breast parenchyma. The non-tumor bed was defined as a quadrant other than the tumor bed within the ipsilateral breast. For example, if there was a tumor bed in the upper outer quadrant of the breast, the elasticity of the non-tumor bed was measured in the lower inner quadrant within the treated breast. Additionally, when the tumor bed located in the subareolar area, the elasticity of non-tumor bed was not measured. The SWE probe was applied to the area to be measured and kept still for a few seconds to allow acceptable quality SWE images to be frozen and saved. The region of interest (ROI) box of the color map was set in the stiffest portion of the lesion, which was depicted on a semitransparent color map of tissue stiffness overlaid on the B-mode image with a range from dark blue, indicating the lowest stiffness, to red, indicating the highest stiffness (0–180 kPa). The maximum size of ROI box was 30 x 25 mm and a 2- to 3-mm sized circular ROI was placed over the stiffest areas of the lesion.

For quantitative measurement of SWE, ROI was placed by an investigator over the stiffest area of the tumor bed or the breast fatty tissue outside the tumor bed, including the immediate adjacent stiff tissue. A second ROI within the same ROI box was placed in the surrounding fatty tissue as the reference fat tissue. This allowed automatic calculation of quantitative elasticity parameters including maximum elasticity values (Emax) in kPa for the tumor bed or the breast fatty tissue outside the tumor bed (Fig. 1). According the Emax, elasticity was assessed as soft (Emax ≤ 72 kPa), intermediate (72 kPa < Emax ≤ 108 kPa) and hard (>108 kPa). With the method for SWE measurement as described above, SWE was performed for patients before RT and at 3, and 12 months after the completion of RT.

Clinical assessment of radiotherapy induced breast fibrosis

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 5.0) was used to evaluated RT-induced breast fibrosis at 1-year follow-up visit. The CTCAE system consists six scores: Grade 0 (no change), Grade 1 (mild induration, able to move skin parallel to plane and perpendicular to skin). Grade 2 (moderate induration, able to slide skin, unable to pinch skin), Grade 3 (severe induration; unable to slide or pinch skin), Grade 4 (generalized signs or symptoms of impaired breathing or feeding), and Grade 5 (death).

Statistical procedures

Descriptive outcomes are shown as means, medians, standard deviations and confidence intervals. To compare the elasticity values obtained at two time points, paired t-tests and Wilcoxon signed-rank tests were used. A repeated measures general linear model was used to assess the changes in elasticity values over time. The variables were compared using the chi-square test or Fisher's exact test. Statistical analyses were performed using R, version 4.1.3 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 18.0 (SPSS, Chicago IL). The significance level was set at $p < 0.05$ and all tests were two-tailed.

Results

A total of 41 patients were enrolled in this study, and Table 1 shows the baseline characteristics of patients, tumors and treatments. The median age was 52 years and ranged from 39 to 70 years. The median dose of whole breast RT was 50.4 Gy (range, 50–50.4 Gy) in conventional RT and 40.5 Gy (range, 40.5–41.6 Gy) in hypofractionated RT. An additional tumor bed boost was sequentially delivered up to 9–14 Gy in 5–7 fractions for conventional RT and 9.6–15 Gy in 4–5 fractions for hypofractionated RT. Total median dose was 59.4 Gy (range, 50.0–64.4 Gy) in conventional RT and that of hypofractionated RT was 50.5 Gy (range, 50.5–55.5 Gy). Most patients were node negative (n = 27), and only 5 patients received regional nodal irradiation. The administered systemic treatments in patients were chemotherapy alone in 8 (19.5 %), chemotherapy followed by endocrine therapy in 14 (34.1 %), and endocrine therapy alone in 19 (46.3 %). The median interval from surgery to the start of RT was 1.8 months (range, 0.9–7.9 months), with 46.3 % (n = 19) of patients starting RT within 2 months after surgery. Three patients with involved resection margin underwent re-excision after primary BCS.

The elasticity values before RT and at 3, and 12 months after RT were shown with a box-and-whisker plot in Fig. 2. The means ± standard deviation (SD) elasticity values before RT were 71.2 ± 74.9 kPa (range, 2.4–298.5 kPa) for the tumor bed, 19.4 ± 9.8 kPa (range, 5.3–50.2 kPa) for the non-tumor bed, and 20.3 ± 10.0 kPa (range, 5.9–46.1 kPa) for contralateral breast. At 3 months after RT, the means ± SD elasticity values for the tumor bed, non-tumor bed, and contralateral breast were
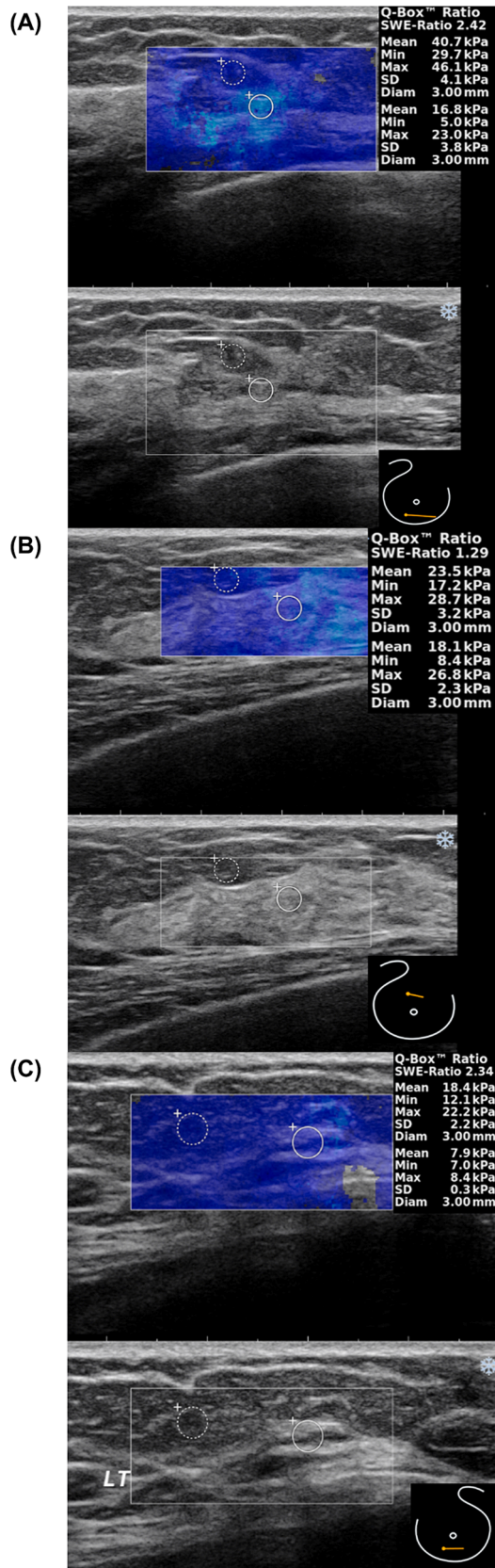
Fig. 1. A 56-year-old woman with a pathologically proven invasive ductal carcinoma in the right breast lower center who underwent shear wave elastography (SWE) before radiotherapy. (A) SWE (top) and B-mode (bottom) images on split screen mode performed on the tumor bed. The SWE image shows that the lesion is soft (blue) and the maximum elasticity values (Emax) was 46.1 kPa. (B) SWE (top) and B-mode (bottom) images on split screen mode performed on the non-tumor bed within the ipsilateral breast. The SWE image shows that the lesion is soft (blue) and the Emax was 28.7 kPa. (C) SWE (top) and B-mode (bottom) images on split screen mode performed on the contralateral breast of the tumor bed. The SWE image shows that the lesion is soft (blue) and Emax was 22.2 kPa. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

46.7 ± 37.1 kPa (range, 6.2–160.6 kPa), 16.3 ± 9.3 kPa (range, 6.5–53.4 kPa), and 20.2 ± 6.9 kPa (range, 8.6–40.3 kPa), respectively. At 12 months after RT, the means ± SD elasticity values for the tumor bed, non-tumor bed, and contralateral breast were 28.7 ± 26.3 kPa (range, 3.3–108.2 kPa), 15.1 ± 7.0 kPa (range, 6.7–38.2 kPa), and 14.7 ± 6.3 kPa (range, 4.1–33.3 kPa), respectively. Significant differences were observed at two or more time points in all sites where breast tissue elasticity was measured. There were significant decreases in tumor bed and non-tumor bed between before RT and 3 months after RT ($p = 0.008$ for tumor bed, $p = 0.043$ for non-tumor bed). Statistically significant reductions in elasticity values were seen in tumor bed and contralateral breast between 3 and 12 months after RT ($p = 0.009$ for tumor bed, $p < 0.001$ for contralateral breast). In all three measurement areas, statistically significant decreases in elasticity values were shown between before RT and 12 months after RT ($p < 0.001$ for tumor bed, $p = 0.002$ for non-tumor bed, $p = 0.001$ for contralateral breast). The change of elasticity value in the tumor bed between before RT and 3 months after RT increased in 14 of 41 patients (34.1 %) and decreased in 27 of 41 patients (65.9 %). The change of elasticity value in the tumor bed between before RT and 12 months after RT increased in 12 of 41 patients (29.3 %) and decreased in 29 of 41 patients (70.7 %) (Fig. 3).

The distribution of grades of RT-induced fibrosis evaluated by CTCAE grade was grade 0 in 18 (43.9 %), grade 1 in 20 (48.8 %), and grade 2 in 3 (7.3 %). The means ± SD elasticity values in the tumor bed before RT were 56.3 ± 49.9 kPa (range, 5.5–163.3 kPa) for grade 0, 79.1 ± 78.9 kPa (range, 2.4–294.1 kPa) for grade 1, and 108.9 ± 164.2 kPa (range, 11.6–298.5 kPa) for grade 2. At 12 months after RT, the means ± SD elasticity values in the tumor bed were 17.5 ± 16.4 kPa (range, 3.4–67.0 kPa) for grade 0, 34.0 ± 26.2 kPa (range, 3.3–108.2 kPa) for grade 1, and 60.4 ± 45.9 kPa (range, 7.5–89.3 kPa) for grade 2.

The tumor location in the inner quadrants was also associated with a significantly higher incidence of ≥ grade 1 RT-induced fibrosis (88.9 % for inner quadrants vs. 35.0 % for outer quadrants or 66.7 % for central portion, $p = 0.018$) (Table 2). Patients receiving a boost dose of 10 Gy or more had a higher incidence of ≥ grade 1 RT-induced fibrosis, but the difference was statistically insignificant (33.3 % for boost dose < 10 Gy vs. 60 % for boost dose ≥ 10 Gy, $p = 0.377$). There was no correlation of RT-induced fibrosis with diabetes, hypertension, body mass index, alcohol, re-excision, fractionation, RT technique, chemotherapy, or endocrine therapy.

Discussion

To our knowledge, this is the first prospective study to assess RIF with SWE in breast cancer. In this study, we investigated the application of SWE for measuring the elasticity value of breast before RT and at 3, and 12 months after RT. The results of this study showed that breast stiffness parameters on SWE imaging were increased for the tumor bed area of patients compared with the non-tumor bed of the treated breast or the contralateral breast.

RIF is usually assessed by palpation and inspection, and classified based on the severity as those in RTOG/EORTC toxicity criteria [5], LENT-SOMA system [6], and CTCAE version 5.0 [7], etc. However, these

Table 1
Patient, tumor and treatment characteristics.

		All patients(n = 41)	
		n	(%)
Age (yr)*		52	(39–70)
Body mass index (kg/m^2)*		23.4	(17.0–30.8)
Histology			
	DCIS	7	(17.1)
	IDC	31	(75.6)
	Others	3	(7.3)
Tumor size (cm)*		1.6	(1.0–4.0)
(y)pT stage			
	ypCR, Tis	9	(22.0)
	T1	25	(61.0)
	T2	7	(17.0)
(y)pN stage			
	N0	27	(65.9)
	N1	7	(17.1)
	N2	1	(2.4)
	Nx	6	(14.6)
No. of examined LN*		3	(0–27)
Total RT dose (Gy)*		50.5	(50.0–64.4)
RT technique			
	3D	9	(22.0)
	IMRT	32	(78.0)
RT field			
	whole breast alone	36	(87.8)
	whole breast + supraclavicular LN	5	(12.2)
Tumor bed boost			
	No	2	(4.9)
	Yes	39	(95.1)
Chemotherapy			
	No	19	(46.3)
	Neoadjuvant	4	(9.8)
	Adjuvant	18	(43.9)
Adjuvant endocrine therapy			
	Tamoxifen	16	(39.0)
	AI	17	(41.5)
	None	8	(19.5)

*Median (range).

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; CR, complete response; LN, lymph node; RT, radiotherapy; 3D, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; AI, aromatase inhibitor.

measures are subjective, with the potential for marked inter-observer variation [15]. In the present study, we used SWE to evaluate the degree of fibrosis objectively. There are other studies evaluating RIF using SWE at sites other than the breast parenchyma [16–18]. A recent study of 56 consecutive patients with nasopharyngeal cancer found that both mean and maximum elasticity values of the bilateral sternocleidomastoid muscles were significantly higher when measured at 1.5 years after RT than before [16]. Wolfram et al. showed the results of measuring pectoralis major stiffness using SWE [18]. They reported that muscle stiffness increased at 6 months after RT and continued at 12 months after RT, and there was the usefulness of using SWE in the screening of patients who need rehabilitation after RT. In this regard, SWE may potentially be an objective, useful and specific tool in quantifying soft tissue stiffness and then help classify the severity of breast fibrosis.

Radiation-induced breast fibrosis is one of the late toxicities of breast RT affecting cosmetic results and breast symmetry, and is characterized by a progressive induration of the breast tissues [19]. Immink et al. described a comparison of differences in breast fibrosis according to tumor bed boost or no boost in breast cancer patients who received whole-breast irradiation [20]. In their study, the incidence of moderate fibrosis was 1.8 % in the no boost group and 15.6 % in the boost group after 6 years. Several studies have shown that RIF was associated with irradiated dose, and the tumor bed received the highest dose due to the additional boost delivery [21–24]. Brouwers et al. demonstrated that the high boost dose group (n = 1210, 26 Gy) had a higher rate of severe fibrosis in the boost area compared to the standard boost dose group (n

(A) Tumor bed

(B) Counter-lateral quadrant
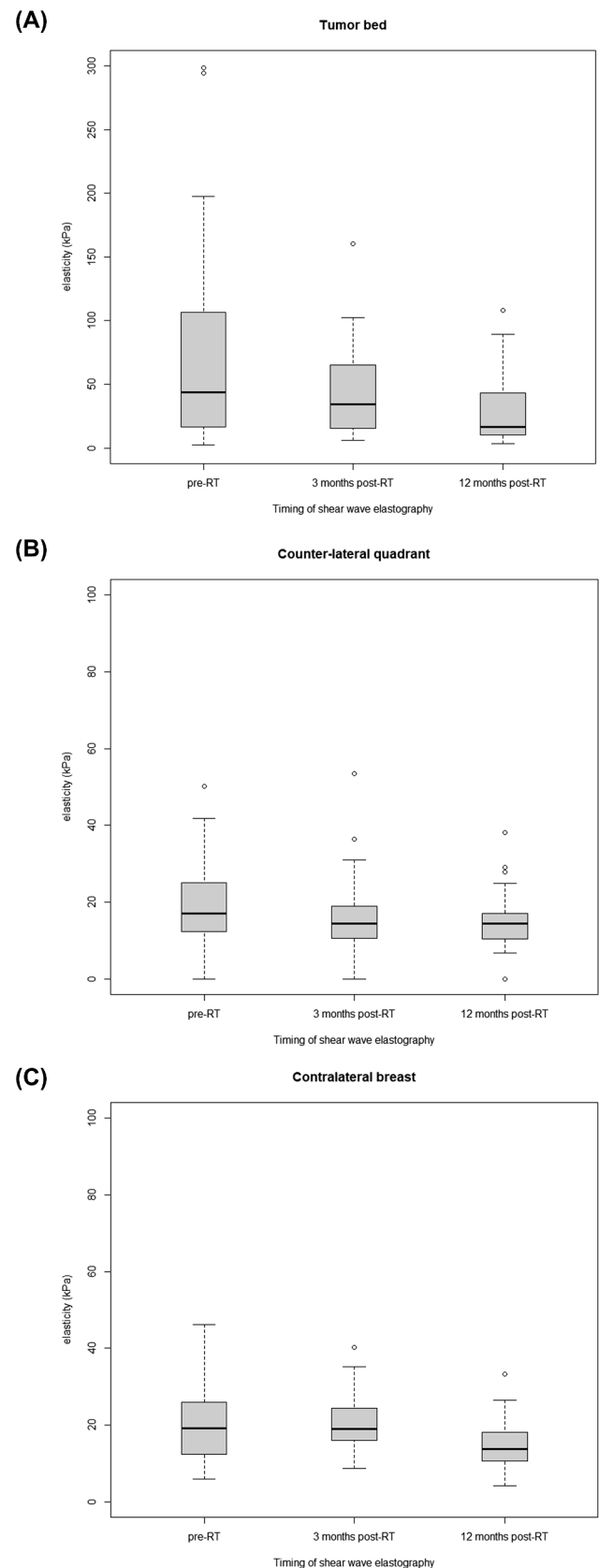
(C) Contralateral breast

Fig. 2. Box plots of the median, maximum, and minimum elasticity values before radiotherapy (RT) and at 3 and 12 months after RT in (A) tumor bed, (B) non-tumor bed, and (C) contralateral breast. Boxes, values from lower to upper quartiles; central lines, medians; whiskers, from minimal to maximal values; dots, outliers.
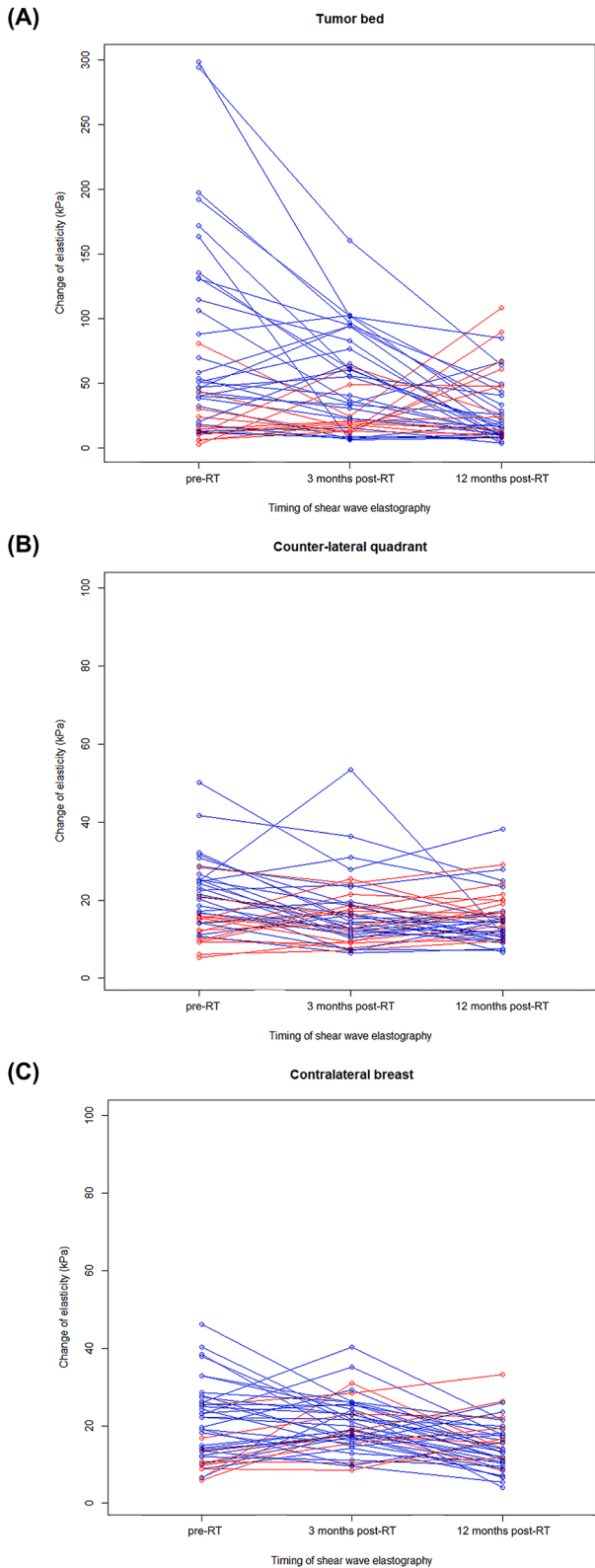
(A)

(B)

(C)

Fig. 3. Changes of elasticity before radiotherapy (RT) and at 3 and 12 months after RT in (A) tumor bed, (B) non-tumor bed, and (C) contralateral breast. Patients with an increased elasticity are shown in red, and those with a decreased elasticity are shown in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2

Association between risk factors and development of radiotherapy-induced breast fibrosis following radiotherapy for breast cancer.

Variables	Subgroups	≥ grade 1 RT-induced breast fibrosis		*p*-value
Tumor location		n	(%)	0.018
	Outer quadrants	7	/20	(35.0 %)	
	Inner quadrants	8	/9	(88.9 %)	
	Central portion	8	/12	(66.7 %)	
Diabetes				0.579
	No	21	/37	(56.8 %)	
	Yes	1	/3	(33.3 %)	
	Unknown	1	/1	(100.0 %)	
Hypertension				1.000
	No	19	/33	(57.6 %)	
	Yes	4	/7	(57.1 %)	
	Unknown	0	/1	(0.0 %)	
BMI				0.228
	<23 kg/m^2	12	/18	(66.7 %)	
	≥23 kg/m^2	11	/23	(47.8 %)	
Alcohol consumption				1.000
	No	21	/35	(60.0 %)	
	Yes	1	/2	(50.0 %)	
	Unknown	1	/4	(25.0 %)	
Fractionation				0.679
	Conventional	3	/7	(42.9 %)	
	Hypofractionated	20	/34	(58.8 %)	
Boost dose				0.377
	<10 Gy	2	/6	(33.3 %)	
	≥10 Gy	21	/35	(60 %)	
RT technique				1.000
	3D	5	/9	(55.6 %)	
	IMRT	18	/32	(56.3 %)	
Chemotherapy				0.678
	No	10	/19	(52.6 %)	
	Yes	13	/22	(59.1 %)	
Endocrine therapy				1.000
	No	5	/8	(62.5 %)	
	Yes	18	/33	(54.5 %)	

Abbreviations: RT, radiotherapy; BMI, body mass index; 3D, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

= 1211, 16 Gy) at 4 years after completion of radiation in patients with early breast cancer (39 % vs. 19 %, p < 0.0001) [23]. Our results were consistent with those of previous studies in that the elasticity value of the tumor bed was higher than those of the other sites evaluated at the same time in most patients at 12 months follow-up, but there was no significant association between the boost dose ≥ 10 Gy and the incidence of grade 1–2 RT-induced fibrosis. In the current study, re-excision surgery was done in 7.3 % (n = 3) of patients with positive resection margin. Although it is difficult to analyze the correlation between re-excision and RIF due to the small patient number, re-excision of the breast tissue adjacent to the primary involved site may have a worse cosmetic outcome or increase fibrosis of the tumor bed.

However, the elasticity value of the tumor bed may have reflected the combination effects of postoperative fibrosis and RIF, especially during the short-term follow-up period. Bosma et al. noted the fibrosis in the tumor area over time after preoperative accelerated partial breast irradiation [25]. Since the breast tissue receiving a high dose radiation is

surgically excised, it is possible to assess the change of postoperative fibrosis over time. The proportion of patients with any grade induration in the treated area of the breast gradually decreased from 79 % at 12 months after treatment to 58 % at 2 years and 43 % at 5 years. In the current study, the elasticity value in the tumor bed decreased continuously at 3 months and 12 months after RT compared to before RT, and this finding might suggest that the postoperative fibrosis gradually decreases over time. On the other hand, approximately 30 % of patients showed increased elasticity at 3 and 12 months follow-up. Thus, long-term follow-up is needed to distinguish RIF from postoperative change based on the elasticity values. Moreover, Wen et al. compared the elasticity indices measured before and after RT in nasopharyngeal cancer [16]. In their study, there was no significant difference between mean and maximum elasticity values before RT and 3 months after RT, but there was a significant increase in the values measured at 18 months. Therefore, temporal changes over time should be monitored over a longer follow-up period.

Skin fibrosis measured by CTCAE was a subjective assessment of the cutaneous change of breast by assessing whether the skin can slide or pinch. Polat et al. compared the breast cancer-associated lymphedema in the affected and contralateral limbs by measuring the stiffness of the cutaneous and subcutaneous tissue using SWE [26]. Their study reported that the stiffness and thickness measurements of the cutaneous and subcutaneous tissue of the upper extremity lymphedema were significantly larger than those of the normal upper extremity among 16 patients with clinical lymphedema, and SWE was effective in detecting changes in the cutaneous and subcutaneous tissue. Additionally, the study by Lee et al., which evaluated the severity of lymphedema in breast cancer using SWE, demonstrated that SWE can effectively assess skin fibrosis between the affected and normal upper extremities [27]. The current study showed a correlation between quantitative elasticity value and the subjective CTCAE grade of RT-induced breast skin fibrosis. At 12 months follow-up, the mean elasticity values in the tumor bed for grade 0 group (17.5 kPA) were lower than grade 1 or 2 groups (34.0 kPa and 60.4 kPa). These findings showed that the results of this study were similar to those of previous studies and SWE can be effective for the assessment of RIF severity, but there is still a limitation that it is difficult to distinguish between RIF and postoperative fibrosis.

The limitations of this study are the small number of patients and the insufficient follow-up period of 12 months. Given prior studies have demonstrated that RIF progresses slowly over months to years in patients with breast cancer, inclusion of more patients and longer follow-up period are required. With the additional follow-up, we believe that it is possible to conduct an analysis to determine the appropriate SWE examination interval and evaluate potential risk factors affecting the cosmetic outcome.

In conclusion, our results suggest that SWE is feasible in evaluating the elasticity of breast tissues and the severity of radiation-induced breast fibrosis, but it is difficult to distinguish RIF from postoperative change within the insufficient follow-up period. Further studies with mature follow-up times should provide more qualitative and quantitative data.

Funding

Author contribution

Kyubo Kim and Jin Chung conceived and designed the research. Wonguen Jung analyzed the data and wrote the manuscript with support from Kyubo Kim and Jin Chung. Kyubo Kim supervised the findings of this study. All authors discussed the results and commented on the manuscript.

CRediT authorship contribution statement

Wonguen Jung: Data curation, Writing - original draft, Writing - review & editing, Visualization, Investigation, Formal analysis, Methodology. **Jin Chung:** Conceptualization, Writing - review & editing, Investigation, Resources, Software. **Jihae Lee:** Writing - review & editing, Investigation. **Kyubo Kim:** Conceptualization, Funding acquisition, Writing - review & editing, Investigation, Supervision, Project administration

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kyubo Kim reports financial support was provided by National Research Foundation of Korea. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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