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Original Article

Impact of Breast Reconstruction on Biophysical Parameters of Mammary Skin in Patients Receiving Postmastectomy Radiotherapy for Breast Cancer

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ABSTRACT

Purpose: In this study, we examined the impact of reconstruction using tissue expander insertion (TEI) on the risk of radiation dermatitis in patients undergoing postmastectomy radiotherapy (PMRT).

Methods: Between August 2015 and March 2019, patients with breast cancer who had received systemic chemotherapy and PMRT were prospectively included. Skin parameters, including melanin, erythema, hydration, sebum, and elasticity, were measured using a multi-probe instrument at 6 time points: before the initiation of radiotherapy (pre-RT), at weeks 1, 3, and 5 during radiotherapy (weeks 1–5), and 1 and 3-month after radiotherapy (post-RT-1m and post-RT-3m). Patient-reported outcomes (PROs) were assessed at each time point. Changes in biophysical parameters and PRO were compared between patients with and without TEI (TEI+ vs. TEI−).

Results: Thirty-eight patients, including 18 with TEI+ and 20 with TEI-, were analyzed. The pattern of time-course changes in biophysical parameters and PRO did not differ between TEI+ and TEI− patients. The melanin index was highest at post-RT-1m, while the erythema index was highest at week 5. At post-RT-3m, TEI+ patients presented higher melanin values than TEI- patients, with no statistical significance (coefficient, 47.9 vs. 14.2%; $p = 0.07$). In all patients, water content decreased throughout the measurement period. At post-RT-3m, TEI+ patients demonstrated a further decrease in water content, while the TEI- group nearly recovered the water content to pre-RT status (coefficient, −17.1, −2.5; $p = 0.11$). The sebum and elasticity levels were not altered by TEI.

Conclusion: In patients undergoing PMRT, TEI did not significantly affect the changing patterns of skin biophysical parameters and PRO during radiotherapy.

Keywords: Breast neoplasms; Mammoplasty; Mastectomy; Radiodermatitis; Radiotherapy

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Park W, Cho J, Kim E; Data curation: Kim H, Kang D, Park H, Choi DH, Cho WK, Jeon BJ, Lee KT; Formal analysis: Kim H, Kang D; Investigation: Park H, Kim E; Supervision: Park W; Writing - original draft: Kim H, Kang D; Writing - review & editing: Kim H, Kang D, Park W, Cho J, Choi DH, Cho WK, Jeon BJ, Lee KT.

INTRODUCTION

Radiotherapy is a crucial component of the treatment of breast cancer. Adjuvant radiotherapy conducted after breast-conserving surgery or mastectomy improves the probability of tumor control and enables prolonged survival in patients with breast cancer [1]. Given the benefits of radiotherapy, an increasing number of patients with breast cancer have been receiving radiotherapy. However, as many as 95% of patients experience radiation dermatitis (RD) within days to weeks of breast radiotherapy [2]. In irradiated skin, symptoms, such as dryness, erythema, and hyperpigmentation, develop gradually during radiotherapy. In addition to the physical changes observed in the skin, RD negatively influences a patient's quality of life [3]. Therefore, it is necessary to identify factors that can be attributed to the development of RD.

It has been suggested that the risk of RD depends on the skin type, administration of systemic therapy, and radiotherapeutic schedules [4]. As sensitivity to radiation differs based on skin thickness, areas with thinner skin tend to be more radiosensitive than those with thicker skin [5]. Additionally, breast reconstruction and implants have been associated with severe RD [6]. In patients with breast implants, the skin overlying the implant tends to be thin because of tissue stretching caused by the placement of an implant directly beneath or over the pectoralis muscle. Based on the physiological changes induced by implants in the skin, it has been suggested that patients undergoing reconstruction with implants might present a higher risk for RD than those with no implant reconstruction [7]. However, there is a lack of clinical reports evaluating the impact of breast reconstruction on the risk of RD. Moreover, biophysical changes in the skin have not been evaluated in relation to breast reconstruction during postmastectomy radiotherapy (PMRT). Hence, this study was performed to assess the impact of reconstruction on the risk of RD in patients undergoing PMRT. The dynamics of skin biophysical parameters during radiotherapy were compared between patients with and without tissue expander reconstruction.

METHODS

Patients

Between August 2015 and March 2019, breast cancer patients receiving systemic chemotherapy and PMRT at the Samsung Medical Center were prospectively included in this study. In patients who underwent breast reconstruction, only those who underwent tissue expander insertion (TEI) at the time of mastectomy were included. Female patients who underwent other types of reconstruction, such as autologous flap reconstruction or single-stage direct-to-implant reconstruction, were excluded from this study. Additionally, patients with a history of previous breast radiotherapy or oral corticosteroid use at the time of radiotherapy were excluded.

Radiotherapy was administered to the chest wall and regional lymph nodes with a total dose of 50 Gy in 25 fractions over 5 weeks. A bolus was administered to the mastectomy scar once every other day during radiotherapy. All patients received 3-dimensional conformal radiotherapy using 6-MV photons (**Figure 1**). In patients with TEI, the tissue expander was fully inflated before radiotherapy initiation (**Figure 1B**). Systemic treatments, including chemotherapy, hormonal therapy, or anti-human epidermal growth factor receptor 2 (HER2) agents, were performed according to tumor subtype. The mastectomy volume for each patient was calculated by multiplying the width, length, and height of the resected specimen.

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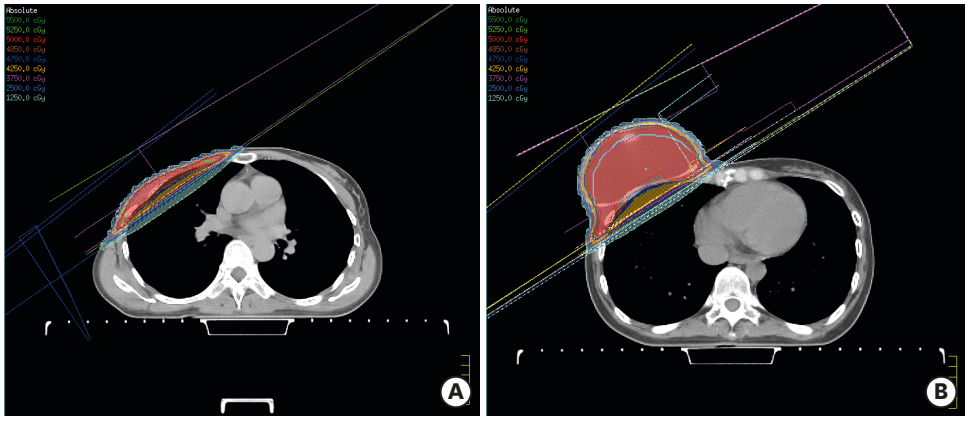

Figure 1. Example of a radiotherapy plan for patients without TEI (A) and for patients with TEI (B).
TEI = tissue expander insertion.

The timing of radiotherapy was evaluated and categorized into 4 quarters to analyze seasonality. The frequency of wound-related issues before radiotherapy was assessed in both groups. This study was approved by the Institutional Review Board of the Samsung Medical Center (SMC2015-05-062). Informed consent was obtained from all participants.

Measurement of skin biophysical parameters and patient-reported outcomes (PROs)

For each patient, hydration, sebum content, pigmentation, and skin elasticity were measured both at the irradiated chest wall and contralateral non-irradiated breast. The use of topical products was not permitted for at least 8 hours before the measurement of skin parameters. Patients were instructed to use only one type of hydration lotion once nightly. The application of anti-melanin cream, anti-histamine cream, and corticosteroid ointment was prohibited during the observation period of this study. In both breasts, the midpoint between the axilla and nipple was selected as the measurement site, and the surgical scar was avoided when selecting the measurement sites. The measurements were performed at 6 time points: before the initiation of radiotherapy (pre-RT), at weeks 1, 3, and 5 during radiotherapy (week 1, week 3, and week 5), and at 1 and 3 months after the completion of radiotherapy (post-RT-1m and post-RT-3m).

To evaluate the biophysical parameters of the skin, we used the Multi-Probe Adapter (MPA) System® (Courage-Khazaka, Köln, Germany). Hydration, sebum, pigmentation, and skin elasticity were measured using the following probes of the MPA: hydration content (arbitrary units, AU) with Corneometer®, sebum quantity (μg/cm^2) with Sebumeter®, melanin and erythema content (AU) using Mexameter®, and elasticity with Cutometer®. At each evaluation time point, all parameters, except sebum, were measured 3 times in each patient. The mean value of repeated measurements was obtained.

To assess PRO, we used the radiation dermatitis assessment for breast cancer 11 (RADA-BC 11) [8]. RADA-BC 11 is used to evaluate the severity of color changes, pain, dryness, itchiness, roughened skin, and scleroderma [9]. For each symptom, we asked patients whether a symptom was "present" or "absent." Furthermore, we ranked the symptoms using a 4-point Likert scale ("a little bit," "somewhat," "quite a lot," and "very much"). Symptom prevalence was estimated by classifying them as continuous scores, and the number of patients who reported ≥ 3 scale points for a symptom was enumerated. Additionally, the frequency of symptoms receiving ≥ 3 points was compared in association with breast reconstruction.

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Statistical analysis

For longitudinal data analysis, we used mixed-effects models to model the changes in skin pigmentation, hydration, sebum content, elasticity, and patient-reported skin changes over time. To control for natural changes due to weather or other unmeasured effects, the biophysical parameters of contralateral un-irradiated breast skin were included in the model. Next, we calculated the relative change in the irradiated breast compared to that in the contralateral un-irradiated breast. Furthermore, we obtained a *p*-value for the interaction to test the homogeneity of the relative changes in the irradiated breast compared to those in the contralateral un-irradiated breast between patients with TEI (TEI+) and those without TEI (TEI−).

In assessing PRO, patients who responded "quite a lot" and "very much" were grouped into the "severe symptom" category. Patients who complained of severe symptoms were counted at each measurement time point. Furthermore, the proportion of patients with severe symptoms was also calculated. As the frequency of severe symptoms at certain time points was low, Fisher's exact test was performed. All analyses were performed using Stata 15.0 (Stata Corp., College Station, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

A total of 41 patients agreed to participate in the study. All patients, except 3, underwent skin measurements at all 6 predetermined time points. Therefore, 38 patients, including 20 with TEI and 18 with TEI, were included in the final analysis. The median age of the patients was 47 years (range, 43–52 years). Additionally, TEI+ patients were more likely to be younger and to undergo neoadjuvant chemotherapy than patients with TEI. The chemotherapy regimen and extent of radiotherapy did not differ between TEI+ and TEI− patients. All patients undergoing anti-HER2 therapy received a combination of taxane, carboplatin, and trastuzumab as neoadjuvant treatment. The median time interval between mastectomy and radiotherapy initiation did not differ with respect to TEI. In addition, the timing of radiotherapy, volume of mastectomy specimens, and frequency of wound-related problems before radiotherapy did not significantly differ between the 2 groups. Details regarding patient characteristics are presented in **Table 1**.

Biophysical parameters of the skin

During the PMRT sessions, 5 biophysical parameters were assessed at 6 predetermined time points. For all biophysical parameters, the pattern of time-course changes did not significantly differ between TEI+ and TEI− patients in the irradiated skin. The changing patterns of each biophysical parameter are presented in **Table 2** and **Figure 2**.

In all patients, melanin and erythema values increased after the initiation of radiotherapy in the irradiated breast skin. The highest melanin value was recorded at post-RT-1m, while the erythema index was highest at week 5 of radiotherapy. After week 3, the melanin index increased in all patients until post-RT-1m. At post-RT-3m, TEI+ patients presented higher melanin values than TEI− patients, demonstrating no statistical significance. The erythema index increased until week 5 of radiotherapy, then decreased until post-RT-3m. At post-RT-3m, TEI+ patients showed a higher erythema index than TEI− patients, without statistical significance.

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Table 1. Patient characteristics

Variables	Tissue-expander (–) (n = 20)	Tissue-expander (+) (n = 18)	*p*-value
Age* (yr)			0.04
≤ 50	12 (60.0)	16 (88.9)	
> 50	8 (40.0)	2 (11.1)	
Clinical stage			0.32
I/II	9 (45.0)	5 (27.7)	
III/IV	11 (55.0)	13 (72.3)	
Chemotherapy sequence			< 0.01
Neoadjuvant	5 (25.0)	16 (88.9)	
Adjuvant	15 (75.0)	2 (11.1)	
Interval between surgery and RT (median, days)			
In patients with NAC	44 days	35 days	0.61
In patients without NAC	205 days	199 days	0.68
Timing of RT			0.15
3rd quarter (July, August, September)	14 (70.0)	16 (88.9)	
Others	6 (30.0)	2 (11.1)	
Volume of mastectomy specimen (length × width × height, cm^3)	1,221 ± 574	1,114 ± 641	0.59
Wound problem†			1.00
None	19 (95.0)	17 (94.4)	
Yes	1 (5.0)	1 (5.6)	
Chemotherapy regimen			0.10
AC + T	15 (75.0)	15 (83.3)	
TCH	5 (25.0)	1 (5.6)	
TC	0 (0.0)	2 (11.1)	
Extent of radiotherapy			0.11
Chest wall only	0 (0.0)	3 (16.7)	
Chest wall + SCN	15 (75.0)	13 (72.2)	
Chest wall + SCN + IMN	5 (25.0)	2 (11.1)	

Values are presented as the number of patients (%), days, or mean ± standard deviation.
RT = radiotherapy; NAC = neoadjuvant chemotherapy; AC = doxorubicin, cyclophosphamide; T = taxane; TCH = taxane, carboplatin, trastuzumab; TC = taxane, cyclophosphamide; SCN = supraclavicular lymph node; IMN = internal mammary lymph node.
*Median 47 years, range, 33–61 years; †Wound revision (n = 1, tissue-expander [+] group) and re-operation for bleeding control (n = 1, tissue-expander [–] group) were counted as wound problem.

In TEI+ patients, the water content in the irradiated skin decreased throughout the measurement period and continuously decreased until post-RT-3m. Additionally, TEI- patients demonstrated a decline in water content during the PMRT sessions; however, the water content increased during post-RT-1m and post-RT-3m. At post-RT-3m, the water content in the irradiated skin approached the pre-RT value in patients with TEI.

In TEI- patients, the sebum level was elevated at week 1 and post-RT-1m, while lower levels were observed at weeks 3, 5, and post-RT-3m. However, TEI+ patients demonstrated decreased sebum levels over the PMRT course, except for week 5. At post-RT-1m, the sebum level in irradiated skin differed between patients with and without TEI. Patients with TEI presented significantly lower sebum content than those without TEI (coefficient, 0.09 vs. 22.73; $p = 0.05$). However, no statistical significance was observed at other measured time points regarding differences in sebum content between TEI+ patients and TEI- patients.

In all patients, the elasticity values decreased over the measured period. However, the degree of change was relatively small compared to the other biophysical parameters. Furthermore, the use of TEI did not influence the change in elasticity patterns in irradiated skin.

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Table 2. Changes in skin biophysical parameters during the course of post-mastectomy radiotherapy according to breast reconstruction

Parameters	Pre-RT	Week 1	Week 3	Week 5	Post-RT-1m	Post-RT-3m	Overall *p* for interaction*
Melanin							
TEI+	Reference	14.13 (−12.80, 41.06)	8.96 (−18.15, 36.06)	8.37 (−18.97, 35.72)	72.27 (45.16, 99.38)	47.93 (21.21, 74.64)	
TEI−		−11.1 (−35.07, 12.87)	−11.07 (−35.04, 12.90)	18.48 (−5.49, 42.45)	48.19 (23.91, 72.48)	14.23 (−9.74, 38.20)	
p for interaction		0.18	0.29	0.60	0.21	0.07	0.17
Erythema							
TEI+	Reference	44.32 (−0.06, 88.71)	59.91 (15.87, 103.94)	121.73 (77.05, 166.41)	74.10 (29.42, 118.78)	59.00 (14.96, 103.04)	
TEI−		34.58 (−7.69, 76.86)	61.42 (19.14, 103.69)	109.9 (67.63, 152.17)	66.72 (23.89, 109.55)	12.82 (−29.46, 55.09)	
p for interaction		0.75	0.96	0.71	0.81	0.14	0.67
Hydration							
TEI+	Reference	−1.93 (−14.93, 11.07)	−4.43 (−17.43, 8.57)	−13.96 (−27.15, −0.77)	−13.49 (−26.68, −0.30)	−17.10 (−30.10, −4.10)	
TEI−		0.11 (−13.05, 13.27)	−6.15 (−19.31, 7.01)	−7.35 (−20.51, 5.81)	−11.37 (−24.7, 1.96)	−2.55 (−15.71, 10.61)	
p for interaction		0.82	0.85	0.47	0.82	0.11	0.53
Sebum							
TEI+	Reference	0.11 (−16.05, 16.27)	2.83 (−13.33, 18.99)	9.64 (−6.76, 26.04)	0.09 (−16.45, 16.63)	−4.86 (−21.31, 11.58)	
TEI−		13.15 (−6.06, 32.36)	3.00 (−16.21, 22.21)	6.12 (−13.22, 25.46)	22.73 (3.12, 42.34)	0.1 (−19.11, 19.31)	
p for interaction		0.25	0.99	0.76	0.05	0.67	0.21
Elasticity							
TEI+	Reference	−0.08 (−0.17, 0.01)	−0.19 (−0.27, −0.10)	−0.09 (−0.18, 0.00)	−0.09 (−0.18, 0.00)	−0.09 (−0.17, 0.00)	
TEI−		−0.08 (−0.16, 0.00)	−0.14 (−0.22, −0.06)	−0.09 (−0.17, −0.01)	−0.10 (−0.18, −0.01)	−0.11 (−0.19, −0.03)	
p for interaction		0.99	0.46	0.98	0.97	0.72	0.93

Values are presented as Coefficient† (95% confidence interval). Adjusted for age and chemotherapy sequence.
Pre-RT = before the initiation of radiotherapy; week 1 = at 1 week of radiotherapy; week 3 = at 3 weeks of radiotherapy; week 5 = at 5 weeks of radiotherapy; Post-RT-1m = post-1-month of radiotherapy; Post-RT-3m = post-3-month of radiotherapy; TEI+ = patients with tissue expander insertion; TEI− = patients without tissue expander insertion.
*The *p*-values for homogeneity of relative change of irradiated breast compared to the change of contralateral un-irradiated breast between TEI+ and TEI−;
†Relative change of irradiated breast compared to the change of contralateral un-irradiated breast.

Patient-reported symptoms

During the study period, changes in skin color were the most frequently reported patient-reported symptoms. The most severe symptoms were recorded at week 5 of RT and post-RT-1m. No statistically significant differences were observed in patient-reported symptoms between TEI+ and TEI- patients. The details of patient-reported symptoms are presented in **Table 3**.

Severe hyperpigmentation and erythema were reported in 22% of TEI+ patients. Hyperpigmentation was documented between week 5 and post-RT-3m, while erythema was reported at weeks 3 and 5 of radiotherapy. At week 5, approximately 16% of the patients reported a burning sensation in the irradiated breast. Dryness, scaly skin, breast pain, and itching sensation were noted at post-RT-1m in 5%–11% of patients. At post-RT-3m, TEI+ patients reported no symptoms, except for hyperpigmentation in the irradiated skin.

DISCUSSION

In this prospective observational study, we analyzed the dynamics of the biophysical parameters of irradiated breast skin during PMRT in patients with breast cancer. Skin parameters, including melanin, erythema, hydration, sebum, and elasticity, were measured at 6 time points, both during and after radiotherapy sessions. The changing patterns of biophysical parameters differed according to the receipt of breast reconstruction. However, no statistically significant difference was observed in the dynamics of skin parameters between TEI+ and TEI− patients. Furthermore, we observed no significant differences in patient-reported symptoms of RD with TEI. These findings suggest that, in patients receiving

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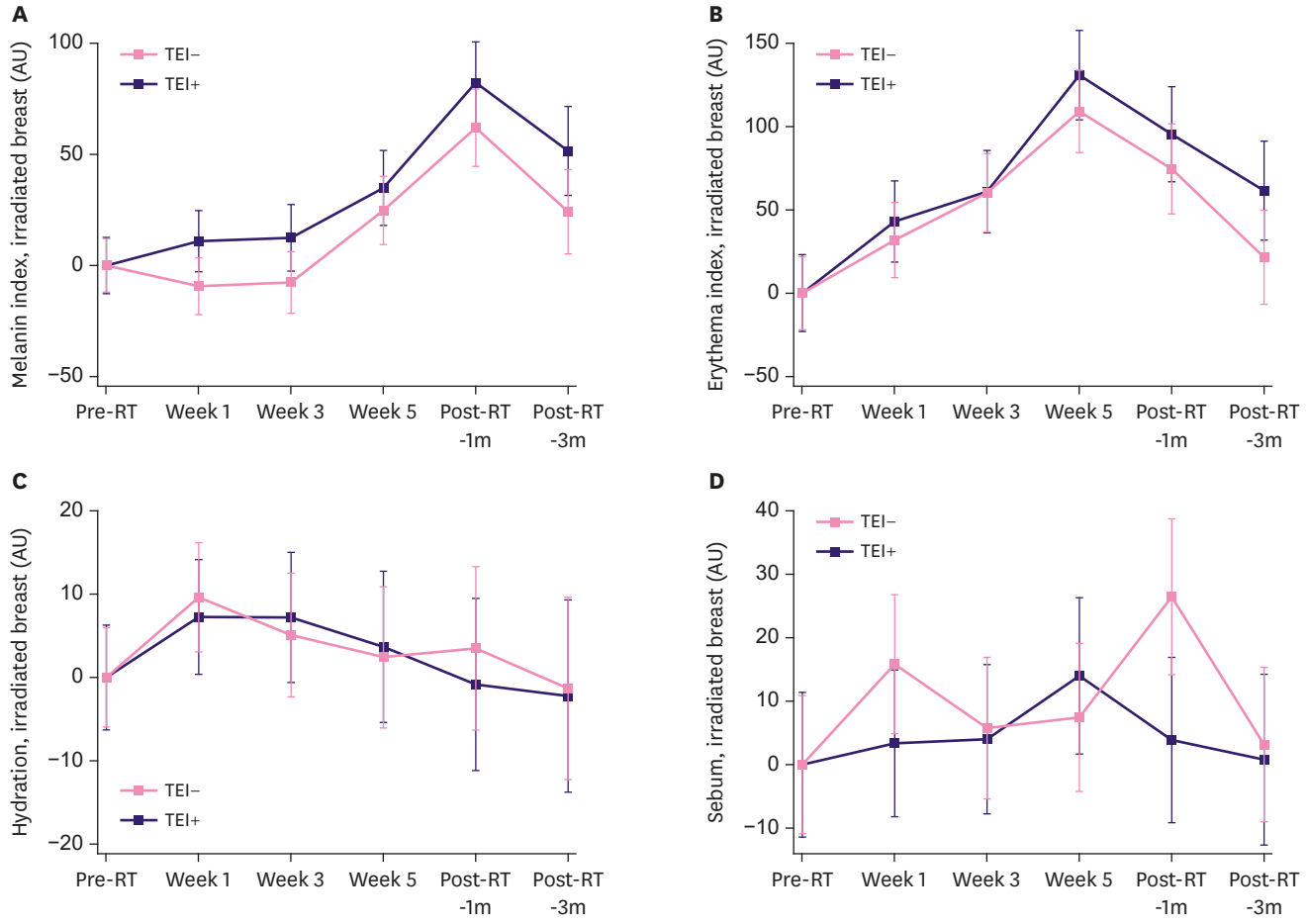

Figure 2. Comparison of time-course of changes in values for melanin (A), erythema (B), hydration (C), and sebum (D) in irradiated skin according to breast reconstruction performed.
The measurements were performed at 6-time points: pre-RT, week 1, week 3, and week 5, and at post-RT-1m and post-RT-3m.
AU = arbitrary units; Pre-RT = before the initiation of radiotherapy; week 1 = at 1 week of radiotherapy; week 3 = at 3 weeks of radiotherapy; week 5 = at 5 weeks of radiotherapy; Post-RT-1m = post-1-month of radiotherapy; Post-RT-3m = post-3-month of radiotherapy; TEI+ = patients with tissue expander insertion; TEI− = patients without tissue expander insertion.

PMRT for breast cancer, reconstruction using tissue expanders has a minimal impact on the biophysical changes in irradiated skin.

For surgical treatment of breast cancer, mastectomy has been performed in more than one-third of patients with breast cancer [10]. Among patients undergoing mastectomy, approximately 20%–36% of patients elect to undergo breast reconstruction [11]. In recent years, the number of patients who opt to undergo reconstruction has increased [11]. Regarding implant-based surgery, 2-stage tissue expander reconstruction is currently the most frequently practiced technique [11]. In this method, to create a space for the permanent implant, the tissue expander was inserted into the mastectomy site at the time of breast surgery. The retained skin envelope is gradually stretched with subsequent inflation of the expander [12]. Mechanical expansion of the skin during expander inflation leads to cellular responses, altering the physiological conditions of the skin [13]. Epidermal thickening, along with dermal and subcutaneous tissue thinning, is observed in response to mechanical tissue expansion [14]. These skin changes induced by the tissue expander can potentially impact the patient's symptoms. Moreover, in cases where other types of external stress are encountered,

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Table 3. A comparison of patient-reported outcomes according to breast reconstruction

Variables	Week 1	Week 3	Week 5	Post-RT-1m	Post-RT-3m
Skin color change					
Hyperpigmentation					
TEI+	0 (0.0)	0 (0.0)	4 (22.2)	4 (22.2)	1 (5.6)
TEI−	0 (0.0)	1 (5.0)	2 (10.0)	2 (10.0)	2 (10.0)
p-value	1.00	0.99	0.40	0.40	0.99
Erythema					
TEI+	0 (0.0)	2 (11.1)	4 (22.2)	0 (0.0)	0 (0.0)
TEI−	0 (0.0)	1 (5.0)	3 (15.0)	1 (5.0)	1 (5.0)
p-value	1.00	0.99	0.69	0.99	0.99
Skin characteristic change					
Dryness					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
TEI−	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)
p-value	1.00	1.00	1.00	0.47	0.49
Scleroderma					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
TEI−	1 (5.0)	1 (5.0)	2 (10.0)	2 (10.0)	1 (5.0)
p-value	0.99	0.99	0.49	0.99	0.99
Roughen					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)
TEI−	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
p-value	1.00	1.00	1.00	0.47	0.99
Scaly skin					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)
TEI−	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)
p-value	1.00	1.00	0.99	0.22	0.99
Discomfort					
Pain					
TEI+	0 (0.0)	1 (5.6)	2 (11.1)	2 (11.1)	0 (0.0)
TEI−	1 (5.0)	2 (10.0)	2 (10.0)	0 (0.0)	1 (5.0)
p-value	0.99	0.49	0.99	0.22	0.99
Itchy					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (5.6)
TEI−	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	1 (5.0)
p-value	1.00	1.00	0.99	0.47	0.99
Skin irritation					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEI−	0 (0.0)	1 (5.0)	2 (10.0)	0 (0.0)	0 (0.0)
p-value	1.00	0.99	0.49	1.00	1.00
Burning					
TEI+	0 (0.0)	1 (5.6)	3 (16.7)	0 (0.0)	0 (0.0)
TEI−	0 (0.0)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)
p-value	1.00	0.99	0.33	1.00	1.00
Swelling					
TEI+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEI−	1 (5.0)	1 (5.0)	1 (5.0)	0 (0.0)	1 (5.0)
p-value	0.99	0.99	0.99	1.00	0.99

Values are presented as number (%). Adjusted for age and chemotherapy sequence.
Number of patients who present symptoms with ≥ 3 points on the scale was counted.
Week 1 = at 1 week of radiotherapy; week 3 = at 3 weeks of radiotherapy; week 5 = at 5 weeks of radiotherapy; Post-RT-1m = post-1-month of radiotherapy; Post-RT-3m = post-3-month of radiotherapy; TEI+ = patients with tissue expander insertion; TEI− = patients without tissue expander insertion.

more severe skin changes can occur. Radiotherapy induces skin inflammation through direct cellular injury and subsequent inflammatory responses [15]. Therefore, patients receiving PMRT with an expander-inserted breast are expected to present a higher risk for severe RD. Considering that an increasing number of patients undergo PMRT with reconstructed breast tissues, it is necessary to analyze the impact of reconstruction on the risk of RD.

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Grading systems for assessing the RD severity have been previously developed [16,17]. However, these systems score RD severity only based on visual skin features, which is highly subjective. To objectively assess dermal changes and RD severity during RT, it is necessary to measure the biophysical properties of the skin. The MPA System® includes several measurement devices that are connected to a single main unit. By employing the connected multi-probe, the device enables measuring different physical skin parameters [18]. As several parameters, including hydration, sebum levels, pigmentation, and skin elasticity, can be measured by the device, the system has been used to assess burn severity, wound healing status, and the skin scarring process in diverse clinical situations [18]. Given the usefulness of this device, we aimed to analyze the dynamics of skin biophysical changes in the skin during radiotherapy in patients who underwent PMRT.

The first sign of RD typically presents as erythema, which occurs within 10–14 days after treatment initiation with a cumulative skin dose of 6–20 Gy [19]. In response to irradiation, dermal edema and capillary dilatation occur, leading to erythematous changes in the skin [15]. Furthermore, radiotherapy damages melanocytes in the dermis, thus inducing melanin extravasation and causing pigmentation in the irradiated skin. These acute radiation effects usually resolve 3–4 weeks after the end of radiotherapy; however, hyperpigmentation can persist for several months [19]. Similarly, in our study, we observed that melanin and erythema indices increased throughout the course of radiotherapy. The melanin index was highest at post-RT-1m, while the erythema index peaked at week 5 of radiotherapy. At post-RT-3m, melanin and erythema indexes were reduced compared to their peak values; however, they failed to fully recover to the pre-RT status. Moreover, TEI+ patients showed higher melanin and erythema values than TEI− patients at post-RT-3m, with no statistical significance. Considering that melanin expression is upregulated and angiogenesis is enhanced following tissue expansion [13], the delayed recovery of melanin and erythema levels in TEI+ patients could be attributed to the mechanical skin stretching induced by the tissue expander. These biophysical consequences should be considered when PMRT is administered to patients with TEI+.

In this study, we observed that the hydration levels of irradiated skin continuously decreased until 1 month after radiotherapy. At post-RT-3m, hydration in the irradiated breast tended to increase in TEI− patients, presenting similar hydration levels to the pre-RT status. In contrast to the alleviated symptoms observed in TEI- patients, TEI+ patients tended to demonstrate consistently decreasing hydration levels in irradiated skin. In this study, Corneometer® analyzed the skin hydration content by measuring the capacitance difference of a dielectric medium [20]. As the device measures a depth of less than 20 μm, the hydration value reflects the water content in the stratum corneum, the outermost layer of the epidermis [20]. The stratum corneum functions as a barrier that prevents water loss and protects the body from external stressors [21]. Ionizing radiation impairs the skin barrier functions of the stratum corneum, resulting in increased transepidermal water loss and decreased water content [22]. Consistent with our findings, previous investigations have shown that the water content in irradiated skin continuously decreases as radiotherapy sessions proceed over time. Moreover, several weeks to months are needed to recover hydration levels after completion of radiotherapy [22]. Considering that TEI+ patients demonstrated incomplete recovery in terms of water content even 3 months post-radiotherapy, it should be considered that the physiological consequences induced by the tissue expander might contribute to the prolonged decrease in hydration levels. Although the skin hydration level was not statistically

altered following TEI, the insufficient water content recovery in TEI+ patients raises the need for specialized treatment during radiotherapy in this patient group.

In our study, the sebum content in irradiated skin fluctuated throughout the PMRT. During the measurement period, TEI+ patients showed a decreasing trend, while TEI- patients presented a mixed pattern in sebum content. Surface lipids in the skin are derived from 2 main cutaneous sources, sebum and epidermal lipids, derived from the sebaceous glands and the stratum corneum, respectively [23]. As radiotherapy damages the sebaceous gland and impairs the function of the stratum corneum [24], the amount of skin surface lipids may be altered by radiotherapy. Nonetheless, data regarding changes in sebum content during radiotherapy remain inconsistent [25,26]. In a study measuring the biophysical parameters before and after radiotherapy for breast cancer, sebum levels were not significantly altered following radiotherapy [25]. In contrast to this report, another study observed that sebum content is significantly reduced with radiotherapy. This study further reported that the application of a moisturizer could increase sebum levels in patients undergoing radiotherapy [26]. Both reports, like our study, used a photometric method for sebum measurement, evaluating the amount of sebum by analyzing the degree of light transmission in the measured area. Using this instrument, the deposition of oily materials can be reflected in sebum quantification. In our study, patients were not allowed to apply topical agents for at least 8 hours before the measurements. However, oily materials could be present on the skin at the time of measurement. Therefore, it is possible that our finding, demonstrating altered sebum content, was induced by the presence of oily products in the irradiated skin.

In addition, we observed that patient-reported dermatitis symptoms did not significantly differ according to breast reconstruction. Dermatitis-related severe symptoms were mostly reported after 5 weeks of radiotherapy. At week 5 and post-RT-1m, issues associated with skin color changes were more frequently reported by TEI+ patients than TEI− patients, without statistical significance. The findings regarding patient-reported symptoms are consistent with the results of biophysical parameter changes, given that melanin and erythema indices tended to be higher in TEI+ patients than in TEI- patients during the period between week 5 and post-RT-3m. Symptoms such as dryness, scaly skin, itching, and pain were reported at post-RT-1m. The frequency of severe symptoms did not significantly differ between patients with and without TEI. Considering that approximately 5%–22% of patients receiving PMRT reported severe discomfort associated with RD, appropriate management strategies are needed in patients receiving PMRT.

In patients with HER2-overexpressing tumors, anti-HER2 agents are concomitantly prescribed with radiotherapy. During early investigations assessing the toxicity of anti-HER2 agents in patients with breast cancer, more than half of the patients undergoing radiotherapy and receiving concurrent anti-HER2 agents experienced grade 2 or higher RD [27]. However, no statistical association was observed between the use of anti-HER2 agents and the risk of developing RD [27]. Moreover, a previous study that compared the RD frequency between patients simultaneously administered an anti-HER2 agent and those without the agent reported that the addition of an anti-HER2 agent during the course of radiotherapy was not associated with an increased risk of RD [28]. In the present study, 6 patients underwent anti-HER2 therapy. All anti-HER2 agents were employed as neoadjuvant and concurrent therapies. Furthermore, given the insignificant association between anti-HER2 agent administration and RD severity, it is likely that the use of anti-HER agents did not affect the dermal biophysical change in both groups in our study.

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Our study has a few limitations. First, this study included a relatively small number of patients. The small patient number might decrease the statistical significance in examining the impact of reconstruction on changes in biophysical parameters in irradiated skin. Additionally, as we located the measurement site at the midpoint between the axilla and the nipple, only a small portion of the breast skin was evaluated for biophysical features. Given that the most frequently involved site for RD is the axilla and inframammary fold, the severity of RD could have been underestimated. Further studies are crucial to overcoming these limitations.

In conclusion, breast reconstruction using a tissue expander did not significantly affect the changing patterns of biophysical parameters in the irradiated skin of patients undergoing PMRT. Patient-reported symptoms did not depend on reconstruction. Although statistical significance was absent, TEI+ patients tended to demonstrate prolonged elevated values for some biophysical parameters compared with TEI− patients. This phenomenon could be attributed to the physiological changes in the skin induced by the tissue expander. Therefore, specific treatments, including prophylactic topical corticosteroids [29] or photobiomodulation therapy [30], might benefit patients with TEI and PMRT.

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