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ORIGINAL ARTICLE

Long-term analysis of irradiated skin after breast-conserving surgery in breast cancer patients using noninvasive imaging

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Abstract

Aims: In patients with breast cancer, skin assessment is useful for the treatment and prevention of postoperative adverse effects of radiotherapy. This study was designed to clarify the long-term changes in the irradiated skin of patients after breast-conserving surgery using visual inspection and noninvasive imaging.

Methods: We compared changes in the irradiated skin over time between evaluations, based on visual inspection and noninvasive imaging in 31 patients receiving postmastectomy radiation therapy. The condition of the skin was evaluated by visual inspection of the thermogram, and analysis of skin surface temperature, intensity of erythema, intensity of melanin, and hydration level.

Results: Skin surface temperature remained higher at the irradiation site after 11 months, despite the absence of erythema per visual inspection. The intensity of erythema was higher at the irradiated site until 17–19 months after completion of irradiation. Similarly, the intensity of melanin tended to be higher at the irradiated site compared with the nonirradiated site until 17–19 months. The hydration level at the irradiated site was lower at 6 months but recovered to match the nonirradiated site at 11–13 months. Impaired skin conditions assessed by noninvasive objective procedures persist longer than the assessment made by visual inspection.

Conclusions: Adverse effects should be treated or prevented in the long term in patients receiving postmastectomy radiation therapy.

KEYWORDS
breast cancer, erythema intensity, hydration level, radiodermatitis, skin surface temperature

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1 | INTRODUCTION

Breast cancer is the most common malignancy in women, and most patients undergo radiotherapy to prevent recurrence of the ipsilateral breast tumor after a breast-conserving surgery. The patients are irradiated with doses of radioactivity 1.8–2.0 Gy five times a week, for a total of 45–50.4 Gy. In addition, boost irradiation around 10–16 Gy is performed in the margin that is described as positive on the tumor. Radiation skin injury is a common adverse reaction. Many irradiated patients experience swelling, redness, pigmentation, burning and itching of the skin, fibrosis, ulceration, and pain.[1] During postoperative breast cancer radiation therapy, most patients develop radiation dermatitis as an acute adverse event.[2] The external radiation passes the skin, and in the case of the tumor with lesion, radiation dermatitis easily develops near the skin. Because skin basal cells undergo active cell division, their radio-sensitivity is high and 95% of breast cancer patients develop acute radiation dermatitis.[3] To date, there remains no consensus on the standard assessment or treatment for radiation-induced skin reactions in patients with breast cancer.

Early skin changes include erythema, dry desquamation, and moist desquamation, while late adverse effects include pigmentation changes, telangiectasias, atrophy, fibrosis, and ulceration.[4]

Radiation dermatitis peaks after completion of treatment at 2–3 weeks and gradually improves, followed by pigmentation that progresses after 4 weeks. Skin symptoms of dryness and desquamation peak at 2 weeks following whole-breast radiotherapy.[5] Skin hydration decreases, while skin pH, pigmentation, and cutaneous blood flow increase in irradiated breasts.[6] Radiodermatitis and breast pain decrease the quality of life (QOL) in patients, although both disappear within 2 years.[7] However, the dermato-toxicity of radiation dermatitis affects various aspects of the patient's QOL.[8,9] Overall, skin impairment after radiotherapy persists for several months. However, to our knowledge, long-term observations have not been performed in patients receiving postmastectomy radiation therapy.

Our previous research used objective assessment tools such as skin surface temperature and erythema intensity to assess skin condition during and after radiation therapy.[10] However, our previous study included only a small sample size, and those parameters were measured only at two time points.

Previous studies have shown that radiation leads to the development of cutaneous vasculature and generation of an inflammatory response, which in turn increase skin temperature.[11] The most common way to measure skin temperature is with an infrared thermography camera. Near-infrared imaging has been used for detection of melanin in pigmentation of skin disorders.[12] Thermal near-infrared imaging has been used for contactless evaluation of burn wound depths,[13] or as an adjunctive screening method for breast cancer.[14,15] Thus, this study was designed to clarify the long-term changes in the irradiated skin of patients after breast-conserving surgery.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study enrolled 31 women with breast cancer undergoing postoperative radiotherapy. Some subjects dropped out of the study and only completed earlier measurements.

Radiotherapy was performed using a linear accelerator (ClinaciX, Varian Medical Systems, Germany), employing 6 MV X-ray, at Hirosaki Central Hospital. Tangential irradiation technique with two nonparallel portals was used. The total dose was 50 Gy in 25 fractions with a conventional schedule. This study was approved by the Committee for Medical Ethics of Hirosaki University, and written informed consent was obtained from all subjects.

2.2 | Measurements

The condition of the skin in the patients was measured with a multi-skin instrument, consisting of Corneometer CM825, Maxameter MX18, and Skin-Thermometer ST500 (Courage + Khazaka Corporation, Germany), during and after radiotherapy. These instruments are noninvasive and can evaluate four parameters pertaining to skin condition: skin surface temperature, the hydration level of the skin surface, degree of melanin, and erythema. The probe of the Mexameter MX18 emits three specific light wavelengths (568, 660, and 870 nm), and the receiver measures the light reflected by the skin. After determining the quantity of emitted light, the quantity of light absorbed by the skin can then be calculated. The measurement was performed in a medical examination room where the temperature was controlled to 25.0–26.0°C by an air conditioner.

The measuring point for the irradiated breast was selected from the part of the skin within the irradiated fields, and without the markings for radiotherapy and avoiding the wound of operation. Parameters were measured in the irradiated breast and in an equivalent area of the nonirradiated breast.

Local images were taken from three directions (front, left side, and right side of the chest) using a digital single-lens reflex camera (NikonD5200). Thermogram was acquired from the front of the chest using an infrared camera (Nippon Avionics Co., Ltd.; Thermo ShotF20). The

TABLE 1 T stage is the size of breast cancer, and *N* stage is lymph node metastasis

Characteristics		Value
Age		58.3 ± 10.7
Sex		All females
Irradiation site	Right	11
	Left	20
Combination therapy	Hormonal therapy	16
	Chemotherapy	6
	Hormonal therapy and chemotherapy	7
Boost irradiation		8
T stage	Tis	4
	T1	15
	T2	10
	T3	0
	T4	
N stage	N0	23
	N1	7
	N2	0
	N3	1
Disease stage	0	4
	IA	12
	IB	1
	IIA	8
	IIB	3
	IIIB	2
	IIIC	1
Past history(+)		DM, HT, dylipidemia

images obtained were used to evaluate the skin condition in terms of redness and pigmentation; skin surface temperature between the irradiated and nonirradiated sites was also analyzed visually.

2.3 | Statistical analysis

All data were expressed as mean ± SD and analyzed using SPSS 26.0 software. Results were compared using repeated measures analysis of variance followed by Bonferroni posttest. Comparisons between the irradiated and contralateral sides at the same time-point were performed using a two-sided paired *t*-test. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study patients

Thirty-one patients with breast cancer undergoing both breast-conserving surgery and postoperative radiotherapy were enrolled in this study. The average age was 58.3 ± 10.7 years, and the stage of breast cancer was zero through IIIC (Table 1). The laterality of the primary lesion was 11 on the right side and 20 on the left side. Combination therapy was performed: 16 patients had hormone administration, six patients were subjected to chemotherapy, and seven patients received both chemotherapy and hormone administration.

3.2 | Comparison of skin surface temperature between irradiated and nonirradiated sites

Skin surface temperature at the irradiated site ranged from 33.5 to 33.7°C, within 1–8 months after irradiation completion and decreased to 33°C afterwards (Figure 1). Thus, skin surface temperature at the irradiated site was higher than that at the contralateral site from 1–9 months and 11 months after irradiation completion (all $p < 0.01$). The temperature was similar between the irradiated site and the nonirradiated site after 12 months. As shown in Figure 2,

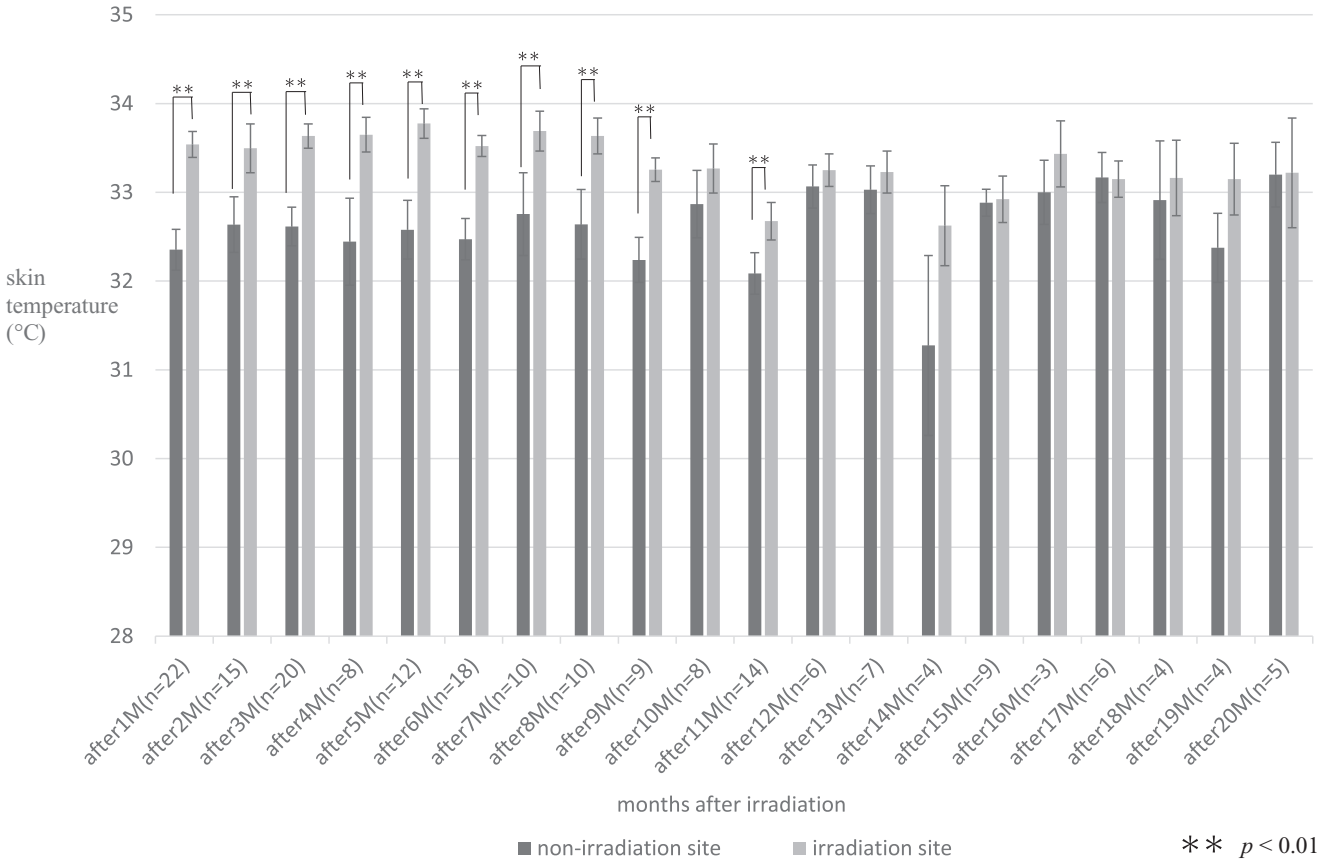

FIGURE 1 Comparison of skin surface temperature between irradiated and nonirradiated sites ($n = 31$ patients)

erythema was detected in the irradiated site at 1–2 weeks after irradiation completion and reached maximum after 1 month; redness was noted in the axillary portion. The erythema gradually changed to pigmentation, particularly around the wound, starting at 2 months after irradiation completion until 10 months. In the thermogram, skin temperature was higher at the irradiated site than at the nonirradiated site during irradiation therapy up to 13 months after irradiation completion.

3.3 | Change in breast skin parameters

To further analyze the effect of radiotherapy on skin surface temperature, the intensity of erythema, melanin, and hydration levels were compared between the irradiated and nonirradiated sites at 6 months, 11–13 months, and 17–19 months after irradiation completion. Although the intensity of erythema at the nonirradiated site was unchanged from 6 to 17–19 months, in the irradiated site erythema intensity decreased from 11–13 months to 17–19 months ($p < 0.01$). The intensity of erythema was higher at the irradiated site than at the nonirradiated site at 6, 11–13, and 17–19 months after irradiation completion ($p < 0.01$, $p < 0.01$, $p < 0.05$, respectively; Figure 3A).

The intensity of melanin in both irradiated and nonirradiated sites was stable from 6 to 11–13 months after irradiation completion and then decreased at 11–13 months and 17–19 months ($p < 0.01$, $p < 0.05$). However, this was higher at the irradiated site than at the nonirradiated site at 6, 11–13 months, and 17–19 months ($p < 0.05$, $p < 0.01$, and $p < 0.05$, respectively; Figure 3B).

The hydration level was lower at the irradiated site than at the nonirradiated site at 6 months after irradiation completion ($p < 0.05$). Despite the absence of chronological changes in the nonirradiated site, the hydration level at the irradiated site recovered to the baseline level of the nonirradiated site, thereby showing no difference between the irradiated and nonirradiated sites at 11–13 months and 17–19 months after irradiation completion (Figure 3C).

4 | DISCUSSION

The major findings of the present study were as follows. Skin surface temperature was maintained at a higher level at the irradiation site during the 9 months, despite the absence of erythema per visual inspection. The intensity of erythema declined at 11–13 months and 17–19 months, while that of melanin tended to be higher in the irradiated

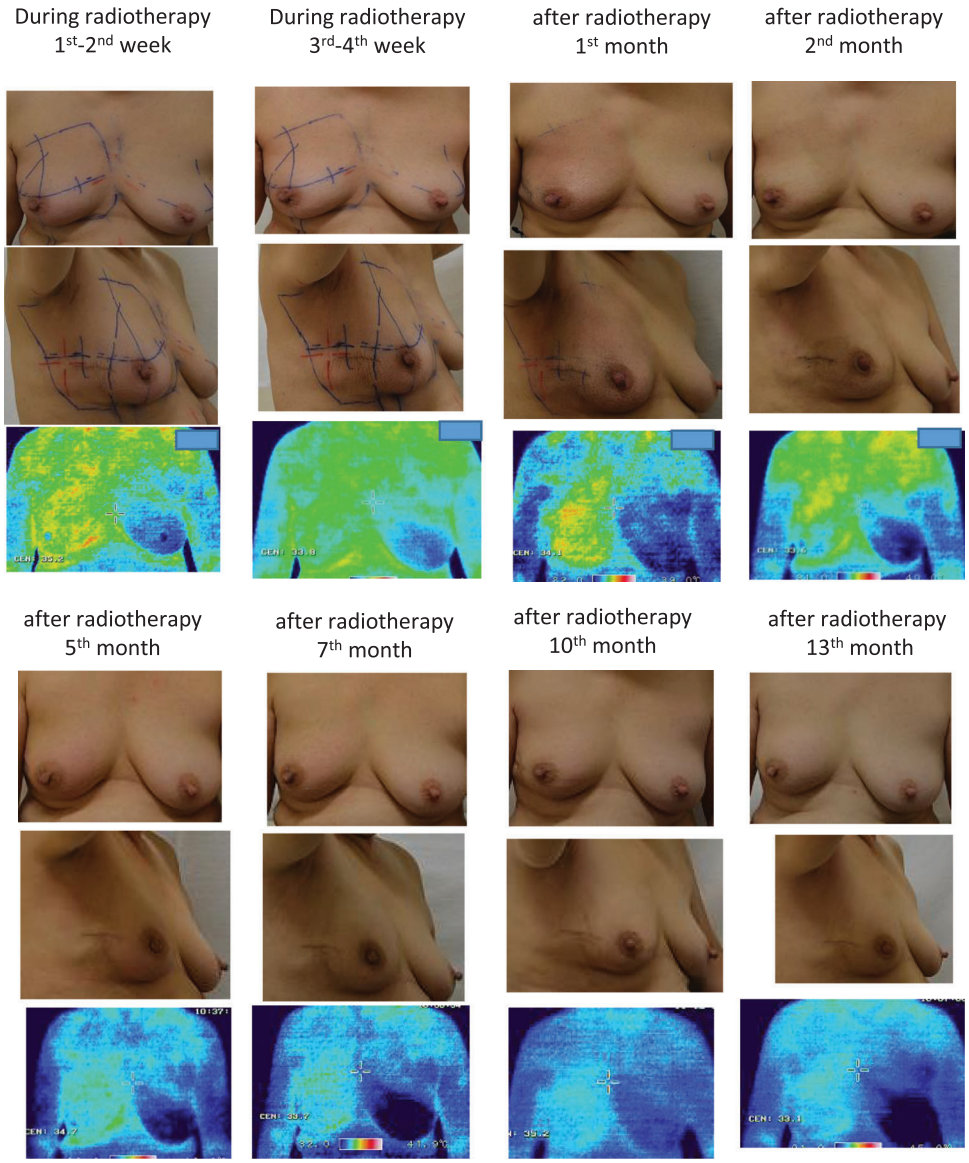

FIGURE 2 Representative chronological changes in skin states. Local images were taken from two directions (front, irradiation side of the chest), and thermography was acquired from the front only

site than in the nonirradiated site until 17–19 months. In contrast, the hydration level at the irradiated site decreased at 6 months but recovered to the baseline level of the nonirradiated site at 11–13 months. Skin surface temperature was higher at the irradiated site than at the nonirradiated site until 9 and 11 months after irradiation completion, but no differences were measured after that.

4.1 | Visual images and thermograms

More erythema intensity and hyperpigmentation have been shown to occur after 2–3 weeks of treatment.[16] According to the images of the breasts, skin redness was fading and changed to pigmentation 1 month after irradiation completion. However, there were not only acute reactions during and after radiotherapy, as skin redness changed to the pigmentation that is observed around the wound and in the axillary or upper portions of the breast. Patients have a higher risk for skin reactions in two skin surfaces: one is the epidermis, that is thin and smooth, and the other is the place where skin integrity is already disrupted from surgery, burns, or lesions.[17] This may result from the high mobility of the skin at the axillary portion, and friction with clothing; the breast upper portion also tends to be dose increased in the radiation-dose distribution surface. However, late effects such as depigmentation, hyperpigmentation, and dry skin may occur.[18] In the present study, the intensity of erythema persisted at a higher level at the irradiated site than at the nonirradiated

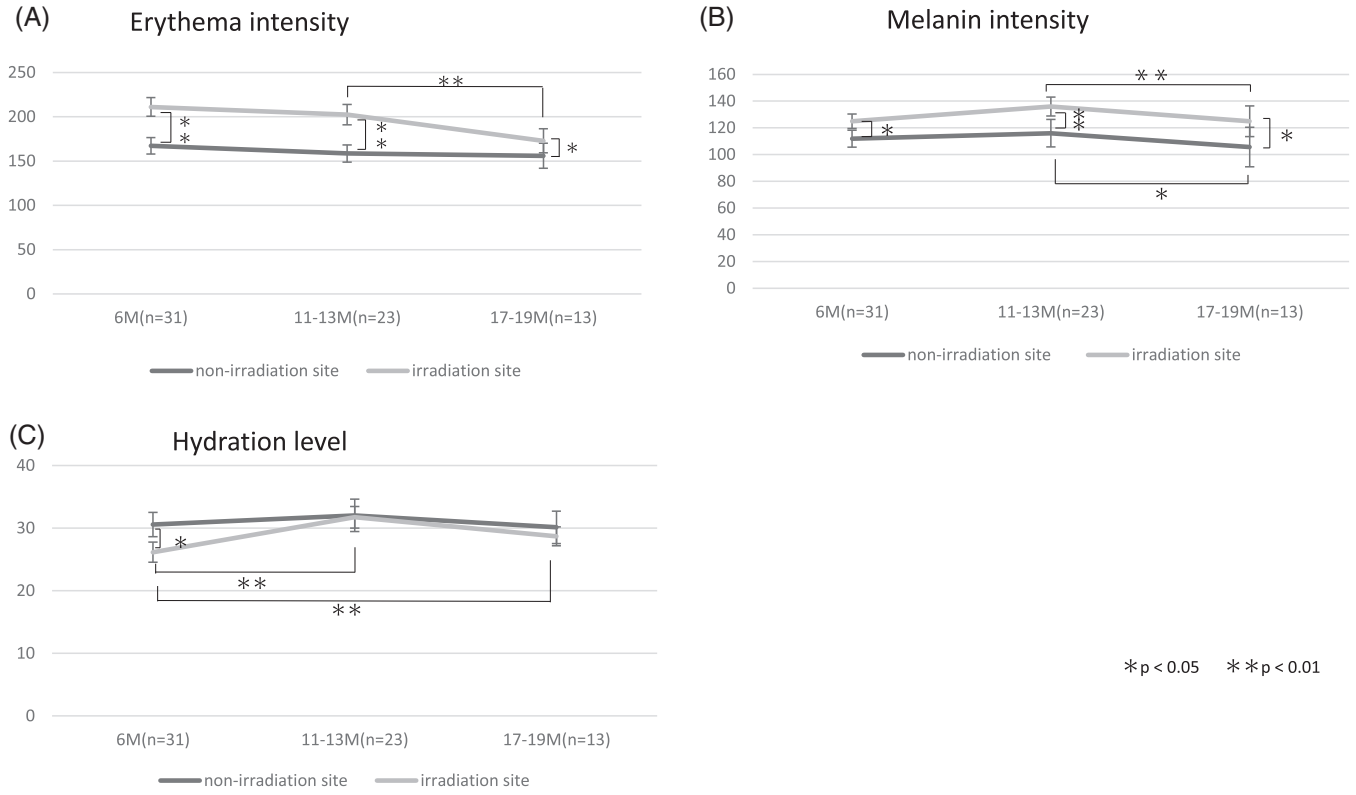

FIGURE 3 Chronological changes in breast skin parameters ($n = 31$ patients): (A) Intensity of erythema, (B) intensity of melanin, and (C) hydration level

site until 17–19 months after irradiation completion. There was no difference in skin temperature when analyzing visual images, but the skin temperature on the irradiated side was higher than on the nonirradiated site 13 months after radiotherapy in the thermogram. Therefore, even if skin redness had disappeared visually, noninvasive procedures showed that this remains observable at the irradiated site. Radiation skin injury is associated with thermographic response.[19] Long-term radiation-induced skin injury could be measured with thermography and other noninvasive and objective measurements.

4.2 | Skin surface temperature, erythema intensity, hydration level, and melanin intensity

The present study investigated the changes in skin condition in patients with breast cancer undergoing postoperative radiotherapy during 17–19 months after irradiation completion. We showed that skin surface temperature persisted longer than visible morphological damages. Skin surface temperature remained higher at the irradiated site 1 year after irradiation completion and then declined to the level of the nonirradiated site.

Since dermatitis peaked at 1 week after radiotherapy completion, and the acute phase of dermatitis passes within 1 month, it is likely that the higher skin surface temperature at the irradiation side is due to vasodilatation, as a result of a radiation-induced inflammatory reaction. As a consequence of sweat glands becoming impaired and local body temperature hard to regulate, sweat production was less at the irradiation site than at the nonirradiation site. Based on our results, the hydration level was lower at the irradiated site than at the nonirradiated site, which is consistent with previous evidence and seems to account in part for the elevation of skin surface temperature at the irradiated site. Skin thermal conductivity and variations in thickness may lead to further changes in the skin surface temperature. These also influence the detectability in dynamic IR imaging and thermal wave imaging.[20] Therefore, thermal conductivity and structural changes may have a higher influence upon skin surface temperature at the irradiated site.

We showed that the hydration level tended to be lower at the irradiated site than at the nonirradiated site 6 months after irradiation completion, and hydration level at the irradiated site recovered to nonirradiated site level at 11–13 months. Melanin intensity tended to be higher at the irradiated site than at the nonirradiated site at 6, 11–13,

and 17–19 months after irradiation completion. Skin color returned 1 year after radiotherapy,[21] even if the erythema was not observed in photos, erythema intensity was significantly elevated at the irradiation site by objective measurements. In addition, melanin intensity remained objectively higher even if not recognized visually.

The present study clearly demonstrated that skin surface temperature is elevated at the irradiated site and persists longer than visible changes in photos and hydration level. Despite the obvious absence of skin erythema at the irradiated site, skin surface temperature and intensity of erythema remained higher until 11–13 months after radiotherapy, and the intensity of melanin persisted longer than both parameters. The sweating ability of the irradiated skin decreased at 6 months after radiotherapy but returned to baseline promptly. Overall, functional impairments, such as skin temperature and sweating ability of irradiated skin, persist longer than readily visible morphological changes. Thus, objective assessment tools seem to be useful for the standard assessment of irradiation-induced skin reactions.

4.3 | Clinical implications

Skin toxicity affects numerous dimensions of QOL and physicians should consider it to improve treatments.[22] Thus, it is important to explain the skin condition to patients using objective parameters such as skin surface temperature, hydration level, and intensity of erythema and melanin. Assessment of objective parameters might contribute to maintain or improve their QOL and allow patients to recognize their own skin condition.

Meta-analysis showed that there is no clinical evidence that topical aloe vera prevents or decreases irradiation-induced skin reactions.[23,24] However, dressings decrease the extent of the irradiation-induced erythema without affecting skin surface temperature. Thus, dressings are superior to topical aloe vera in decreasing the severity of irradiation-induced erythema in patients with breast cancer treated with radiation therapy. It is likely that dressings protect irradiated skin from friction from clothes and lessen the severity of irradiation-induced skin reactions. Irradiation of the skin causes sublethal damage to the stem cells that make up the basal layer of the skin. Additional stimuli may cause more physical damage to the fragile damaged skin.

In conclusion, impaired skin conditions assessed by noninvasive objective procedures persist longer than those by visual inspection. Therefore, adverse effects should be treated or prevented in the long term in patients undergoing postmastectomy radiation therapy. The skin condition should be assessed by noninvasive objective procedures in order to advise patients with the appropriate care.

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CONFLICT OF INTEREST

The authors declare conflict of interest.

AUTHOR CONTRIBUTIONS

Kasumi Mikami: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; validation; and writing-original draft. Maiko Kitajima: Data curation; formal analysis; funding acquisition; investigation; methodology; and writing-review and editing. Yuka Noto: Conceptualization; data curation; formal analysis; investigation; methodology; supervision; and writing-review and editing. Chieko Itaki: Investigation and writing-review and editing. Yasuyo Fukushi: Investigation. Yoshiko Hirota: Investigation and methodology. Yasushi Mariya: Investigation; methodology; supervision; and writing-review and editing. Megumi Tsushima: Investigation and writing-review and editing. Keiichi Kattou: Investigation; methodology; and writing-review and editing. Tomohiro Osanai: Formal analysis; supervision; writing-original draft; and writing-review and editing.

DATA AVAILABILITY STATEMENT

Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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