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Original Article

Effect of standard skin care treatments on skin barrier function in X-irradiated hairless mice

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ABSTRACT

Objective: The effectiveness of skin care to radiation dermatitis (RD) on patients who received radiotherapy for cancer has not been clarified. The purpose of this study was to investigate the effect of moisturizers and skin washing on skin barrier function possibly leading to the development of RD using X-ray irradiated hairless mice.
Methods: Nine-week-old hairless mice were irradiated with 10 Gy of X-rays, and the skin care group had moisturizers applied or skin washing with soap from the day of irradiation during observations. The condition of the skin was observed to evaluate RD. Skin barrier function was evaluated by measuring skin temperature and transepidermal water loss (TEWL) once every two days until 25 days after X-ray irradiation.
Results: RD was not observed in all groups until 25 days after X-ray irradiation. Skin temperature tended to increase in all groups regardless of irradiation or skin care. However, unlike the control group, the measured value of TEWL in the no skin care group tended to increase in the days after the X-ray irradiation. On the other hand, TEWL was increased in the skin care group compared with the no skin care group a few days after X-ray irradiation. While TEWL was constant in the moisturizer group, the skin washing groups showed an increasing tendency of TEWL and it reached a peak at 13 days after X-ray irradiation.
Conclusions: These results suggested that the decrease in skin barrier function was caused by X-ray irradiation and also that skin washing could contribute to the deterioration of skin barrier function after X-ray irradiation.

Introduction

Radiotherapy (RT) is a major treatment for many cancers. Radiation dermatitis (RD) is a well-known side effect of RT. It has been reported that 95% of women with breast cancer who received whole-breast RT experienced RD.[1]

There are a limited number of guidelines for the management of RD in patients with cancer. The evidence from **a** review of each guideline has varied and some have reached different conclusions.[2–4] This may be due to the different timing and methodologies used to develop the guidelines. However, the effectiveness of skin care for RD has not been clarified yet. According to a survey in Japan, RD care performed by certified nurses in RT differed depending on the departments or medical facilities where they worked. One of the reasons for this was considered to be a lack of standard guidelines for RD care.[5]

The skin performs various functions such as body temperature regulation and is a sensory organ, and one of its most important roles is known to be a skin barrier function. The skin barrier function is the ability to prevent water evaporation inside the stratum corneum and to prevent foreign substances such as bacteria, allergens, and chemical substances from entering the skin. In other words, when the skin barrier function is damaged, it leads to increased water loss from the skin, which is expressed as increased transepidermal water loss (TEWL). Thus, the measurement of TEWL has been demonstrated to be a reliable indicator of skin barrier function and the health of the epidermis.[6] In addition to TEWL, other indices such as skin hydration, melanin index, erythema index, and skin temperature are also used to evaluate skin barrier function.[7] In fact, it has been reported that TEWL in the lesions of patients with psoriasis and atopic dermatitis is significantly higher than in healthy individuals, and that skin temperature in the lesions of patients with atopic dermatitis is significantly higher than in healthy individuals.[8] Furthermore, the patients treated with RT for breast cancer have decreased skin water content[9,10] and sebum content.[11] Regarding the skin care for these skin symptoms, it has been reported that the use of

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moisturizers can restore skin moisture content and maintain or restore sebum content. Nevertheless, its effectiveness has not been established since the mechanism is not clear. In addition, although there are many studies related to RD in mice,[12] few studies have clarified the effects of standard care procedures like washing on mouse skin after irradiation. The purpose of this study was to examine the changes in skin barrier function in the process leading to the development of RD and the effect of moisturizers and skin washing on skin barrier function in X-irradiated hairless mice.

Methods

Mice and X-irradiation

We used 9-week-old female hairless mice, Hos:HR-1 (SLC, Shizuoka, Japan), for the experiment. Before X-irradiation, mice were injected with three kinds of mixed anesthetics. The mixed anesthetics were prepared with 0.3 mg/kg of medetomidine, 4.0 mg/kg of midazolam, and 5.0 mg/kg of butorphanol. The anesthetized mice were fixed on an acrylic plate with tape so that an area (1 cm × 1 cm) of posterior dorsal region of each mouse was irradiated with 5 Gy of X-rays twice for a total dose of 10 Gy. The interval between the first and second irradiation was 20 min. The irradiation was divided into two sessions as simulate fractional irradiation in RT. The non-irradiated area was shielded with a 1 cm thick lead plate. The mice were placed under a lead plate with a space created by styrofoam for irradiation.

All animal procedures were performed in accordance with the guidelines for animal experimentation of ARRIVE and the Oita University of Nursing and Health Sciences (Oita-NHS, Oita-city, Japan) and were approved by the Oita-NHS Research Ethics Committee (approval number: 20-91).

Dosimetry

X-rays were delivered by an X-ray generator (HF320, Shimadzu, Tokyo, Japan) with 18 mA and 180 kV. This X-ray generator was also equipped with a filter system composed of 0.5-mm copper and 0.5-mm aluminum plates. Dose measurement was carried out using RPL dosimetry system Dose Ace (AGC Techno Glass Co., Shizuoka, Japan). The aperture of the X-ray generator was 2 cm × 2 cm, and the distance between the X-ray tube and the irradiation table on which an acrylic plate was placed was set to 37 cm. To perform dosimetry, glass dosimeter elements were placed on the acrylic plate in the area (1 cm × 1 cm) of the cavity of the lead shielding plate, which was the irradiation area, and the glass dosimeter elements were placed in two diagonal directions to measure the dose. As a result, the dose rate was 1.27 Gy/min in both directions.

Standard skin care treatment

In this study, we performed moisturization or skin washing as standard skin care treatments after X-ray irradiation. Hirudoid® Lotion 0.3% (Maruho, Osaka, Japan) as a moisturizer and acidic detergent Minon®(Daiichisankyo, Tokyo, Japan)as a washing agent was used.

Three mice each were grouped for the control group (Group C), the no skin care group (Group N), the moisturizer group (Group M), and the skin washing group (Group W). Group C were non-skin care and non-irradiated. Mice without skin care after irradiation were designated as Group N. The mice in Group M had 0.2 mL of moisturizer placed on their skin post-irradiation and applied with fingers. The mice in Group W had the irradiated area moistened with 1 mL of slightly warm water, a weakly acidic detergent was whipped into the irradiated area, and the foam was completely rinsed with 2 mL of warm water. Standard skin care treatments (applied moisturizers, skin washing) and measurements (skin temperature, TEWL) were performed by the same person from the beginning to the end of the study.

These skin care treatments were performed from the day of irradiation. In addition, in order not to affect the measured values of TEWL and skin temperature, skin care on the measurement day was treated after all measurements were completed.

Evaluation of dermatitis

The dermatitis score that was used was based on previous study,[13] and the dermatitis was evaluated by photographs taken. A score of 0 was given for normal skin, 1 for erythema, 2 for dry desquamation, 3 for wet desquamation, and 4 for ulceration.

Measurement and evaluation

TEWL was measured with a VapoMeter® (Delfin Technologies, Kuopio, Finland), and skin temperature with a BIO-IRB153 thermometer for animal research (Bioseb, Vitrolles, France). The measurements of skin temperature and TEWL were performed in a room with 25 ± 1 °C and 50-70% humidity from 10:00 am to 12:00 pm. Mice were moved from the rearing room to the measurement room and allowed to acclimate for 30 min before starting the measurement. For each mouse, TEWL was measured three times and skin temperature three times, and the average value of each was used as the measurement value.

The measurements were taken from the day after irradiation (1 day later) until 25 days later. After the measurement of TEWL and skin temperature, the irradiated area was photographed with a digital camera, and the skin condition was recorded over time. The photograph was conducted under anesthesia.

Data analysis

Generalized linear regression (GLR) analysis was performed on all data for skin temperature and TEWL for each group. The differences in skin temperature and TEWL values between groups were examined using the likelihood ratio test to see if the goodness of fit of the data increased with the presence or absence of skin care treatment or X-irradiation. The goodness of model fit was evaluated using Akaike's Information Criterion (AIC). In addition, TEWL measurements (at 13 time points) for each mouse were summed and a Welch's t-test was performed for each group. The statistical analysis software used was R ver3.3.3.

Results

The X-irradiated skin was photographed and observed with a digital camera until day 25 after irradiation. A photograph of the irradiated area is shown in Fig. 1. The irradiated area is within the dotted line of the square (Fig. 1). During the observation period, RD was not observed in all groups and the dermatitis score was 0.

Fig. 2 shows the data of the change in skin temperature over time for each group with the fitted models obtained by GLR analyses. Skin temperature tended to increase by +0.5 °C from the beginning to the end of the observation in all groups (Fig. 2a–d). Table 1 provides the estimates of the model parameters and the results of the likelihood ratio test for the differences between the groups according to skin care or irradiation. There was no difference in the change in skin temperature over time between Group C and Group N. The temporal changes in skin temperature in the irradiated group were also compared between Group N and Group M, and between Group N and Group W, and no differences were found in both comparisons. Fig. 3 shows the data of changes in TEWL over time for each group with the fitted models obtained by GLR analyses. The TEWL of Group C showed little change during the observation period (Fig. 3a).

Group N showed the same level of TEWL as Group C on the first day after irradiation although X-ray irradiation was performed. However, the TEWL of Group N (Fig. 3b) tended to increase gradually with time and was higher than Group C on the last day. As a result of the likelihood ratio

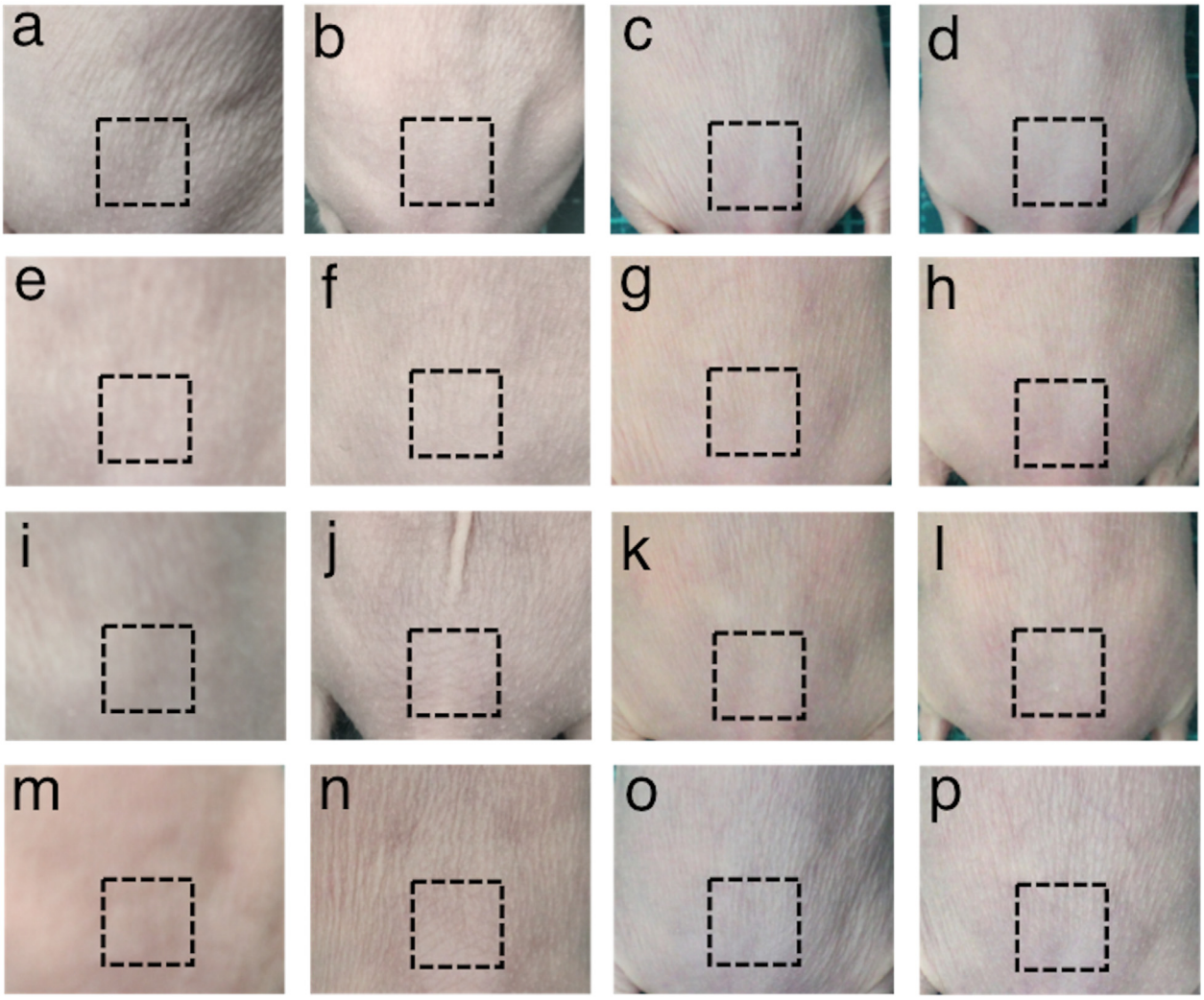

Fig. 1. Photography images of irradiated area after X-irradiated day 1, 5, 15, and 25; (**a–d**): control group (Group C), (e–h): no skin care group (Group N), (i–l): moisturizer group (Group M), and (m–p): skin washing group (Group W).

test, there was a difference in the TEWL between Group C and Group N ($P < 0.05$). Group M (Fig. 3c) showed an increase in TEWL, but the TEWL in some individual mice appeared to be higher than Group N on the third to the ninth day after irradiation. According to the results of GLR analysis, there was no change in the TEWL of Group M over time. However, there were significant differences of TEWL change over time between Group M and Group N in a likelihood ratio test.

Group W (Fig. 3d) showed a higher TEWL value than the other groups from the first day after irradiation. As a general trend, the TEWL increased with time and reached a peak on day 13 after irradiation, and then decreased with time. The temporal changes were markedly different from those in the other groups. Non-linearity was shown by the evidence that the GLR analysis provided **a** better fit for the quadratic model (AIC = 120.14) than for the linear model (AIC = 142.73). When TEWL are compared between Group M and Group W, Group W shows a higher value on the first day after irradiation. However, the TEWL of Group W and Group M tended to be similar at the end of the observation.

The TEWL values were summed for each mouse to obtain the cumulative TEWL, and the results of the Welch's t-test are shown in Table 3. The results showed significant differences between Group C and Group N, Group N and Group W, but there were no significant differences between Group N and Group M.

Discussion

This study examined the changes in skin barrier function in the process leading to the development of RD and the effect of moisturizers and skin washing in X-irradiated hairless mice on skin barrier function. Skin temperature showed a trend toward an increase of +0.5 °C in all groups, but there was no significant difference between Group C and Group N, Group N and Group M, or Group N and Group W. Miyamae et al reported that the skin temperature of patients with breast cancer and with symptoms of erythema, who received postoperative RT, significantly increased compared with before RT started.[14] In an experiment using female B6CF1 mice, Saegusa et al measured the skin temperature for 14 days in the same environment and showed that the mean value of the skin temperature on the back fluctuated in the range of 36.6–37.8 °C.[15] There was no dermatitis observed in this study, and the increase in skin temperature was only +0.5 °C. Therefore, it is most likely that this was a diurnal variation rather than an effect of irradiation or skin care.

Focusing on TEWL as the skin barrier function that was the primary endpoint, a change in TEWL was observed. It would be due to the effects of X-ray irradiation and skin care. In this study, the TEWL of Group N tended to increase over time and was significantly different from Group C. The increase in TEWL associated with X-ray irradiation has been reported in previous studies. Meimeti et al measured the level of TEWL in

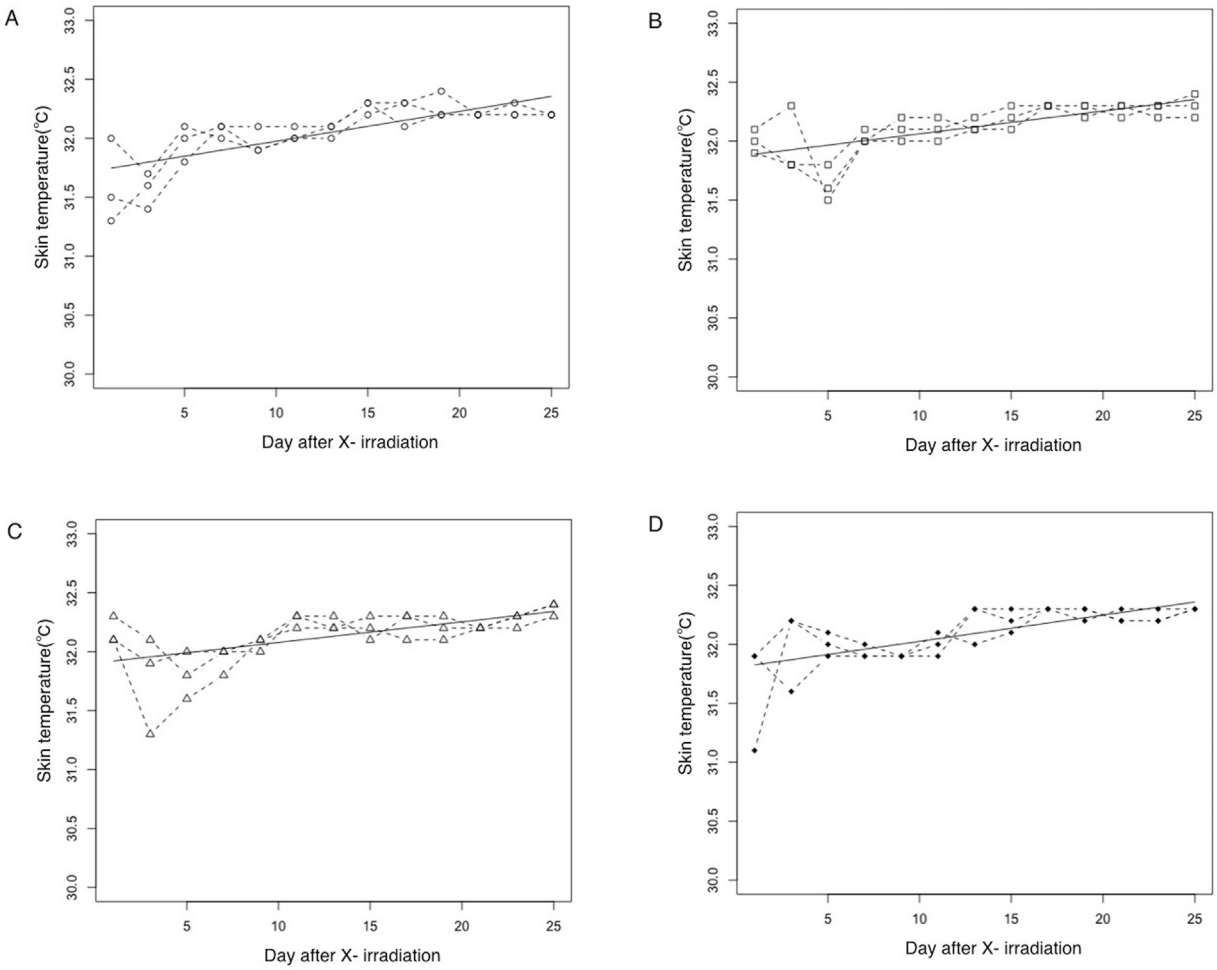

Fig. 2. Skin temperature on day 1–25 after irradiation and the fitted line by generalized linear regression analysis; (**A**) control group (Group C), (**B**) no skin care group (Group N), (**C**) moisturizer group (Group M), and (**D**) skin washing group (Group W).

Table 1
The estimates of the model parameters and the results of the likelihood ratio test in skin temperature for the differences between the groups according to skin care or irradiation.

	Coefficients		
	linear term (95%CI)	constant (95%CI)	
Group C	0.03	31.72	
	(0.02; 0.03)	(31.62; 31.83)	
Group N	0.02	31.87	*[a]
	(0.01; 0.03)	(31.77; 31.96)	
Group M	0.02	31.90	*[b]
	(0.01; 0.03)	(31.79; 32.02)	
Group W	0.02	31.80	*[b]
	(0.01; 0.03)	(31.69; 31.92)	

[a] There was no difference in the change in skin temperature over time compared with Group C.
[b] There was no difference in the change in skin temperature over time compared with Group N.

treated SKH-HR2 mice after X-irradiation. It was reported that the value of TEWL increased during the period of X-rays irradiation, and that the level of TEWL did not return to the pre-irradiation level after 60 days.[16] Furthermore, in an experiment using SKH1 mice irradiated with a single dose of 20 Gy or 40 Gy, Jang et al reported that RD was observed from 10 days after irradiation, and also showed that the TEWL of irradiated groups increased compared with the control from 4 days after irradiation prior to the onset of RD.[17] Clinical studies have also reported an increase in TEWL with RT. Schmuth et al reported that 12 of 15 patients with breast cancer who received RT had an increased level of TEWL during RT and that the onset of TEWL increase was observed on average 11 days after the start of RT.[18] It was earlier than the onset of RD. They also reported that TEWL peaked at an average of 27 days after the start of RT. Nevertheless, the reports from medical facilities in Japan have shown different results for the changes in TEWL due to RT. A multi-center clinical study of RT patients with breast cancer has revealed that the TEWL ratio (irradiated side breast/non-irradiated side breast) decreased from the second week of RT ($P < 0.01$).[7] Given these facts, the association between changes in TEWL and the development of RD has not been fully elucidated experimentally and clinically.

In this study, our result revealed that 10 Gy of X-irradiation increased TEWL. It was not possible to directly discuss the relationship between RD development and changes in TEWL since RD was not observed even in 10 Gy. However, the increase of TEWL would be a process leading to the development of detectable RD.

Regarding the effect of skin care on TEWL variation after X-ray irradiation, there were markedly different trends in Group M and Group W compared to Group N. These trends were quite different than expected. The projection beyond observation periods may indicate the suppressive effects of moisturizing care and skin washing care of TEWL.

We used the heparinoid moisturizer, Hirudoid®. It has been widely used in Japan to treat dry skin, and especially for the treatment of atopic dermatitis.[19] The effects of moisturizers on RT patients have been reported to include increased stratum corneum water content and increased sebum production.[9–11].

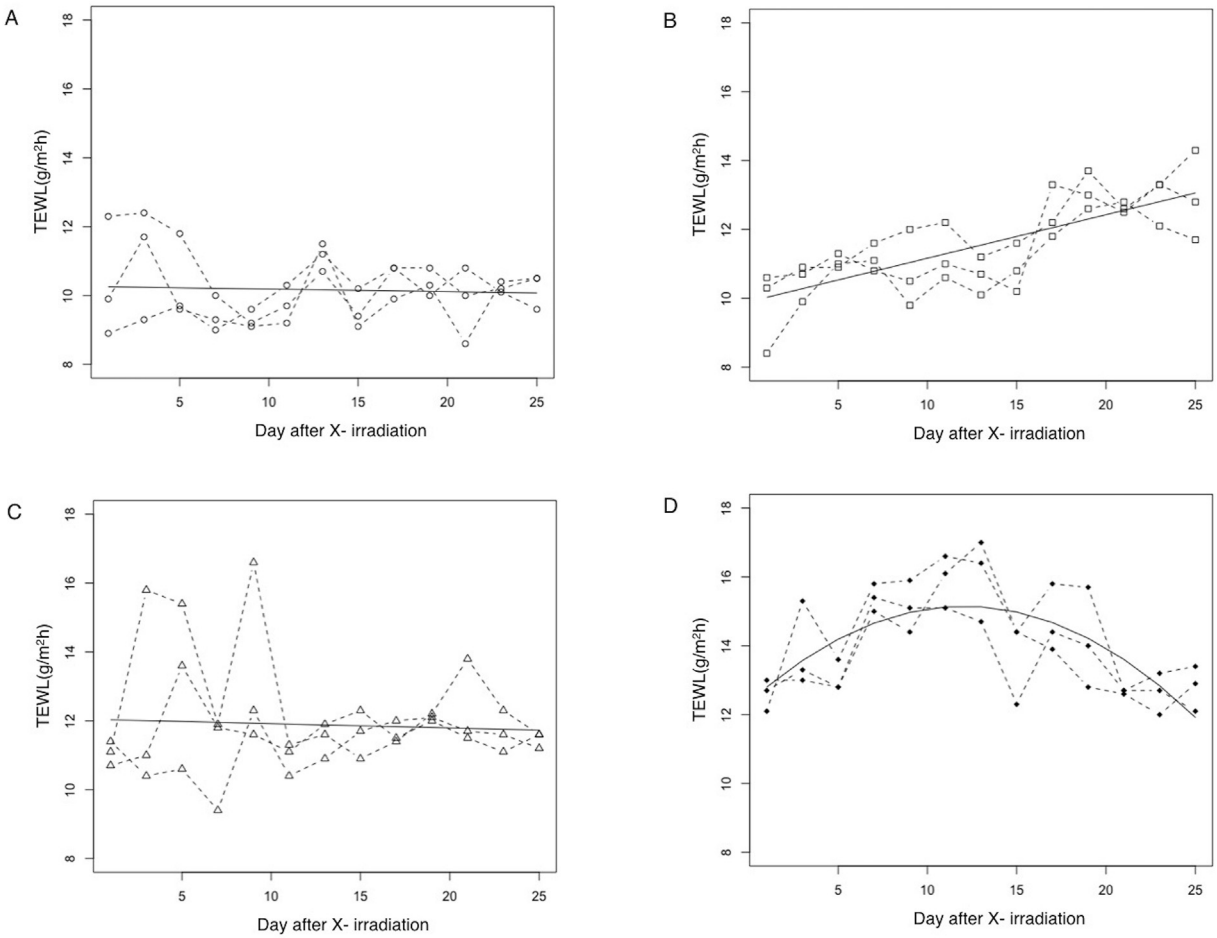

Fig. 3. TEWL on day 1–25 after irradiation and the fitted line by generalized linear regression analysis; (**A**) control group (Group C), (**B**) no skin care group (Group N), (**C**) moisturizer group (Group M), and (**D**) skin washing group (Group W). TEWL, transepidermal water loss.

Table 2
The estimates of the model parameters and the results of the likelihood ratio test in TEWL for the differences between the groups according to skin care or irradiation.

	Coefficients			
	Linear term (95%CI)	Constant (95%CI)	Quadratic term (95%CI)	
Group C	−0.01 (-0.05; 0.03)	10.26 (9.67; 10.85)		
Group N	0.13 (0.09; 0.16)	9.90 (9.37; 10.43)		*[a]
Group M	−0.01 (-0.08; 0.05)	12.04 (11.10; 12.98)		*[b]
Group W	0.46 (0.28; 0.65)	12.36 (11.31; 13.40)	−0.02 (-0.03; −0.01)	*[c]

[a] There was significant difference in the change in TEWL over time compared with Group C ($p < 0.05$).
[b] There was significant difference in the change in TEWL over time compared with Group N ($p < 0.05$).
[c] There was a significant difference in TEWL change over time between Group W (linear model) and Group N ($p < 0.05$).

Table 3
Cumulative TEWL (Mean ± SD) for each group and results of Welch's t-test.

	Cumulative TEWL *[a] Mean ± SD (g/m^2)	*P*-value
Group C	132.1 ± 4.2	
Group N	150.0 ± 6.4	< 0.05 *b
Group M	154.4 ± 10.4	0.58 *c
Group W	182.6 ± 7.2	< 0.05 *d

[a] Based on the measured TEWL value multiplied by 1 h, the average value over 1-h, the cumulative TEWL was calculated by the total of the values at each observation point.
[b] There was significant difference in cumulative TEWL compared with Group C.
[c] There was no significant difference in cumulative TEWL compared with Group N.
[d] There was significant difference in cumulative TEWL compared with Group N.

Furthermore, some animal studies reported that the use of moisturizers inhibited the increase in TEWL[20,21] and that it conversely showed no difference in TEWL from the control group.[22] Our study showed that there was a significant difference between Group N and Group M in terms of the change in TEWL over time (Table 2). However, there was no significant difference between Group N and Group M (Table 3) in terms of summation of TEWL values during observation (cumulative TEWL). These results suggest that moisturizers can affect the changes in TEWL after X-irradiation, but temporal variation could be related with different results. Further verification of the inhibitory effect of moisturizers on TEWL elevation is needed.

There are a limited number of reports that have studied the effects of washing and bathing after radiation on the skin. In a randomized study that compared the severity of RD in patients with breast cancer undergoing RT between a washing group and a non-washing group, moist desquamation was observed in 33% of non-washing patients, but in only

14% of washing patients.[23] From this result, they concluded that washing the irradiated skin during RT for breast cancer was not associated with increased skin toxicity.

In a study investigating the effects of standard washing and drying practices on the skin in healthy subjects, however, the use of soap with a single wash disrupted skin barrier function, as evidenced by the increase in TEWL.[24] Furthermore, it was also reported that towel drying using a rubbing method caused a significant increase in TEWL either with the use of soap or plain water. These results suggested that skin washing and the skin friction caused by towel drying may have caused sebum removal or damage to the stratum corneum, resulting in an increase in TEWL that can lead to a decrease in skin barrier function. In this study, there was also a tendency in Group W for TEWL to increase early after irradiation and then decrease (Fig. 3d). These temporal changes were clearly different from those in the other groups. In particular, we believe that the decrease in TEWL after 13 days may be due to skin recovery through turnover of the skin damaged by irradiation. These results suggest that skin washing after X-irradiation could temporarily deteriorate the skin barrier function. Group M and Group W also showed a different change in TEWL from Group N. It is possible that post-irradiation skin care may have some effect on TEWL. However, whether this effect is due to skin care alone or to the interaction between X-irradiation and skin care needs to be verified in the future.

A limitation of this study is that it had a lack of histological and molecular biological analysis. In the future, it is necessary to examine the effects of standard skin care, such as the use of moisturizers and skin washing, on changes in skin barrier function after irradiation, including histological and molecular biological analyses, and to clarify the relationship between changes in skin barrier function and the onset and severity of RD. Mechanical-based studies can contribute to clinical practice and provide useful information about skin care to nurses engaged in oncology nursing who provide skin care advice to patients undergoing RT and patients who have developed RD.

Conclusions

In this study, an increase in TEWL was observed in the irradiated groups. Our results suggested that the skin barrier function could be impaired by 10 Gy of X-rays, and also that standard skin care after X-ray irradiation, such as the use of moisturizers and skin washing, could contribute to the change in TEWL.

Author contributions

Designed the analysis: Keiko Iwashita, Mitsuaki Ojima, Michiaki Kai.

Collected the data and performed whole experiments: Keiko Iwashita, Reo Etani, Mitsuaki Ojima.

Performed the analysis: Keiko Iwashita, Michiaki Kai.

Wrote the paper: Keiko Iwashita.

Declaration of competing interest

None declared.

Funding

Nil.

Ethics statement

All animal procedures were performed in accordance with the guidelines for animal experimentation of ARRIVE and the Oita University of Nursing and Health Sciences (Oita-NHS, Oita-city, Japan) and were approved by the Oita-NHS Research Ethics Committee (Approval No. 20-91).

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