

The Effect of 0.2% Hyaluronic Acid Cream on the Severity of Acute Radiodermatitis in Breast Cancer Patients: a Double-Blind Randomized Controlled Trial

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ABSTRACT

Background: Radiotherapy is an essential treatment in reducing the risk of breast cancer but can cause side effects such as acute radiodermatitis. This condition is the result of ionizing radiation damaging deoxyribonucleic acid (DNA) through reactive oxygen species (ROS) and inducing inflammatory responses, which lead to variable degrees of skin damage. Hyaluronic acid (HA) plays a role in triggering cell proliferation and keratinocyte differentiation while inhibiting lipid peroxidation caused by oxidative stress. **Purpose:** This study aims to determine the effectiveness of hyaluronic acid in reducing the degree of acute radiodermatitis using the Radiation Therapy Oncology Group (RTOG) score in breast cancer patients undergoing radiotherapy. **Methods:** This study was a double-blind randomized controlled trial. The samples were from patients diagnosed with breast cancer receiving radiotherapy. The treatment group received 0.2% HA cream, while the control group received a placebo. The clinical appearance was evaluated weekly from the beginning of radiotherapy until two weeks post-radiotherapy using the RTOG score. **Result:** A total of 41 subjects were divided into two groups. RTOG score evaluation with intention-to-treat analysis and per-protocol analysis at weeks 3, 4, and 5 showed that the hyaluronic acid cream group experienced delayed onset of acute radiodermatitis compared to the placebo group. The log-rank test showed a significant difference in effectiveness between 0.2% HA cream compared to base cream in reducing the degree of acute radiodermatitis ($p=0.035$). **Conclusion:** The use of 0.2% HA cream was effective in reducing the severity of acute radiodermatitis in breast cancer patients undergoing radiotherapy.

Keywords: breast cancer, radiotherapy, acute radiodermatitis, hyaluronic acid cream.

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BACKGROUND

Cancer is one of the leading causes of death worldwide, with breast cancer being the most common type among women. According to the Global Cancer Observatory report in 2020, there were 2.3 million new cases of breast cancer, with a mortality rate of 11.7% of total global cancer cases.¹ In Indonesia, the incidence of breast cancer reached 65,858 cases, with

22,430 deaths.² Radiotherapy is one of the primary modalities in breast cancer treatment, aiming to destroy cancer cells through ionizing radiation that damages their DNA, leading to cell death or loss of proliferative ability.³ Radiodermatitis is a side effect caused by radiotherapy on the skin, with an incidence rate of 85-95% in breast cancer patients undergoing this therapy.⁴ Acute radiodermatitis is characterized by erythema,

dry desquamation, moist desquamation, and skin ulceration, which can occur from the start of radiotherapy up to 90 days after treatment and can impact the patient's quality of life.⁵

The management of radiodermatitis currently lacks a gold standard. Several studies have shown the effectiveness of topical agents such as topical corticosteroids and non-steroids in reducing the severity of radiodermatitis.⁶ Topical corticosteroids are often used in the management of radiodermatitis due to their anti-inflammatory effects. However, long-term use of topical corticosteroids can cause side effects such as skin atrophy, hypopigmentation, and telangiectasia.⁷ Hyaluronic acid, which has anti-inflammatory properties and accelerates wound healing, is an alternative for preventing and managing radiodermatitis.⁸

HA works by binding large amounts of water, maintaining skin hydration, and having antioxidant effects that can inhibit lipid peroxidation caused by reactive oxygen species (ROS).⁹ Additionally, HA can enhance keratinocyte proliferation and differentiation, aiding in the re-epithelialization of skin damaged by radiation.¹⁰ Based on a literature review, no studies have been conducted on the effectiveness of 0.2% HA cream in delaying the onset and progression of acute radiodermatitis in breast cancer patients undergoing radiotherapy in Indonesia, particularly in Yogyakarta.

METHODS

This study is a double-blind randomized controlled trial. The research was conducted at the Tulip Integrated Cancer Center, Dr. Sardjito Hospital Yogyakarta, and the Department of Dermatology and Venereology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. Patients aged 18 years or older who received radiotherapy for breast cancer and signed an approved informed consent form were eligible for the study. Exclusion criteria comprised history of radiotherapy to same areas, concurrent chemotherapy, and other skin disorders that could influence the study's outcome. Pregnant or lactating women, as well as patients with a history of allergic reactions or known hypersensitivity to any of the ingredients in HA or base cream, were not included in the study. Subjects were then divided into two groups: the treatment group receiving 0.2% HA cream and the control group receiving a base cream, based on randomization. An appropriate quantity of HA cream or base cream (1 Finger Tip Unit/0.5 gr) was applied to the irradiated skin area twice daily using the flat part of a stainless steel spatula. The first application was made 2 hours after the morning radiotherapy session, and the second was made in the evening. The patients were told to apply the cream on their own on the weekends.

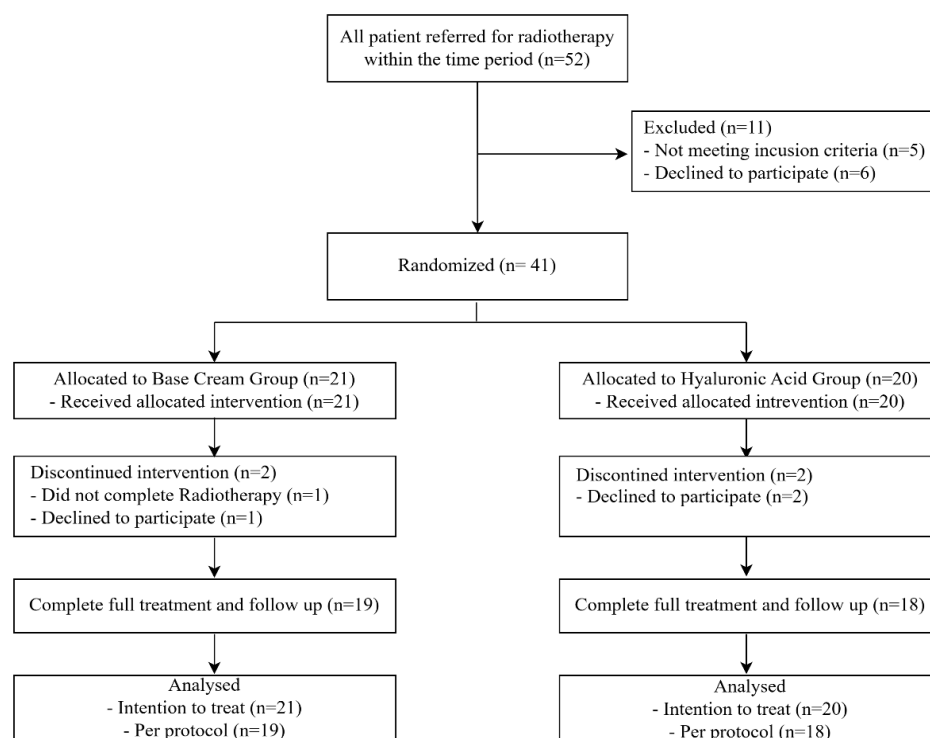


Figure 1. CONSORT diagram

When the patients did not receive any radiotherapeutic treatment, the creams were applied every day in the morning and in the evening. The degree of acute radiodermatitis was evaluated weekly from the baseline until two weeks after the completion of radiotherapy using the Radiation Therapy Oncology Group (RTOG) score (grade 0: no change over baseline; grade 1: follicular, faint, or dull erythema, epilation, dry desquamation, decreased sweating; grade 2: tender or bright erythema, patchy moist desquamation, moderate edema; grade 3: confluent, moist desquamation, other skin folds, pitting edema; and grade 4: ulceration, hemorrhage, necrosis). The difference in the degree of acute radiodermatitis using

the RTOG score was analyzed using Intention-to-Treat (ITT) and per-protocol analysis with the Mann-

Whitney test. The time progression of acute radiodermatitis to grades 2, 3, and 4 was analyzed using the Kaplan-Meier curve, and the difference between the two groups was analyzed using the log-rank test. A *P* value < 0.05 was considered statistically significant. The study ensured the reliability of the assessment with Cohen's Kappa test, which showed a high level of agreement among observers. This research has been reviewed by the Medical and Health Research Ethics Committee Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada (MHREC number: KE/FK/0920/EC/2023).

Table 1. Baseline characteristics of the subjects

Baseline characteristics		Cream, n (%)		Total (n=41)	P-value
		Base cream (n=21)	HA (n=20)		
Age, (mean $\pm$ SD), years		51.61 $\pm$ 10.48	50.55 $\pm$ 10.43	51.09 $\pm$ 10.34	0.745
Gender	Female	21 (100)	20 (100)	41 (100)	-
Education level	Elementary school	4 (19)	5 (25)	9 (21)	0.537
	Junior High School	4 (19)	2 (10)	6 (14.63)	
	Senior High School	4 (19.05)	7 (35)	11 (26.83)	
	University	9 (42.86)	6 (30)	15 (36.59)	
Ethnics	Javanese	20 (95.24)	19 (95)	39 (95.12)	0,367
	Sundanese	0 (0)	1 (5)	1 (2.44)	
	Malay	1 (4.76)	0 (0)	1 (2.44)	
Marital status	Married	21 (100)	19 (95)	40 (97.56)	0.488
	Single	0(0)	1(5)	1(2.44)	

HA= Hyaluronic Acid, SD= Standard Deviation

RESULT

This research was conducted from July to December 2024, and during that period, 52 breast cancer subjects received radiotherapy. A total of 41 subjects met the inclusion and exclusion criteria and were divided into two treatment groups: the base cream group and the 0.2% HA cream group, based on randomization. The subject recruitment details, allocation, therapy, and assessment are presented in the CONSORT diagram (Figure 1).

Table 1 presents the baseline characteristics of the subjects, including age, education level, ethnicity, and marital status. The characteristics showed that all subjects were female (100%), with 97.56% being married and predominantly of Javanese ethnicity (95.12%). The mean age of the subjects was 51.09 $\pm$ 10.34 years, with the base cream group having a mean age of 51.61 $\pm$ 10.48 years and the HA cream group having a mean age of 50.55 $\pm$ 10.43 years. The majority

of subjects in the base cream group had a university education (42.86%), while the majority in the HA cream group had a senior high school education (35.00%). The analysis of baseline characteristics showed that the initial data distribution between the two groups was homogeneous (*p*>0.05).

The clinical characteristics describe the data obtained through anamnesis and physical examination during the first visit (week 0). The clinical characteristics assessed included body mass index (BMI), history of mastectomy, history of chemotherapy, family history of breast cancer, smoking and alcohol consumption habits, breast cancer stage, radiotherapy area, and total radiotherapy dose administered. The mean BMI of all subjects was 24.09 $\pm$ 4.49, with the base cream group having a mean BMI of 23.42 $\pm$ 3.86 and the HA cream group having a mean BMI of 24.79 $\pm$ 5.07. Most subjects were diagnosed

with stage II breast cancer (48.78%), followed by stage III (39.02%).

Almost all subjects had undergone chemotherapy (97.56%) and mastectomy, with the most common technique being modified mastectomy (63.41%), followed by partial mastectomy (19.51%) and total mastectomy (17.07%). The main comorbidity was hypertension (26.83%), followed by diabetes, anemia, atopy, and COPD, each at 2.44%, but the majority of

subjects had no comorbidities (63.41%). Radiotherapy characteristics showed a predominance of irradiation in the left breast area (56.1%) compared to the right breast area (43.9%), with the most common total dose administered being >50 Gy (46.34%). The data analysis showed no significant differences in the clinical characteristics of the subjects between the two treatment groups ($p>0.05$).

Table 2. Clinical characteristics of the subjects

Clinical characteristics		Cream, n(%)		Total (N=41)	P-value
		Base cream (n=21)	HA (n=20)		
BMI (mean $\pm$ SD)		23.42 $\pm$ 3.86	24.79 $\pm$ 5.07	24.09 $\pm$ 4.49	0.333
History of mastectomy	Partial	3 (14.29)	5 (25)	8 (19.51)	0.414
	Modified	13 (61.90)	13 (65)	26 (63.41)	
	Total	5 (23.81)	2 (10)	7 (17.07)	
History of chemotherapy	Yes	21 (100)	19 (95)	40 (97.56)	0.488
	No	0 (0)	1 (5)	1 (2.44)	
Family history of breast cancer	Yes	5 (23.81)	6 (30)	11 (26.83)	0.655
	No	16 (76.19)	14 (70)	30 (73.17)	
Comorbidities	None	12 (57.14)	14 (70)	26 (63.41)	0.518
	Hypertension	6 (28.57)	5 (25)	11 (26.83)	
	Diabetes	0 (0.00)	1 (5)	1 (2.44)	
	Anemia	1 (4.76)	0 (0)	1 (2.44)	
	Atopy	1 (4.76)	0 (0)	1 (2.44)	
	COPD	1 (4.76)	0 (0)	1 (2.44)	
Smoking/alcohol habits	Yes	0 (0)	0 (0)	0 (0)	1.000
	No	21 (100)	20 (100)	41 (100)	
Breast cancer stage	I	1 (4.76)	0 (0)	1 (2.44)	0.389
	II	10 (47.62)	10 (50)	20 (48.78)	
	III	10 (47.62)	6 (30)	16 (39.02)	
	IV	0 (0)	4 (20)	4 (9.76)	
Radiotherapy area	Right breast	8 (38.10)	10 (50)	18 (43.9)	0.433
	Left breast	13 (61.90)	10 (50)	23 (56.1)	
Radiotherapy dose (Gy)	50 Gy	10 (47.62)	8 (40)	18 (43.9)	0.623
	>50 Gy	11 (52.38)	12 (60)	23 (46.34)	

HA= Hyaluronic Acid, BMI= Body Mass Index, SD= Standard Deviation, Gy=Gray

Table 3 shows that from the initial week (baseline) until week 2, no cases of acute radiodermatitis were observed in either group ($p=1.00$). By week 3, a significant difference in the occurrence of grade 1 acute radiodermatitis was observed, with 61.91% in the base cream group and 15% in the HA cream group ($p=0.002$). Significant differences were also observed in week 4 ($p=0.026$) and week 5 ($p=0.024$). The RTOG score assessment in the last three weeks showed no significant difference between the two groups (week 6 $p=0.05$, week 7 $p=0.414$, and week 8 $p=0.285$).

The time progression from baseline to grade 2 acute radiodermatitis was assessed using the Kaplan-Meier curve (Figure 2).

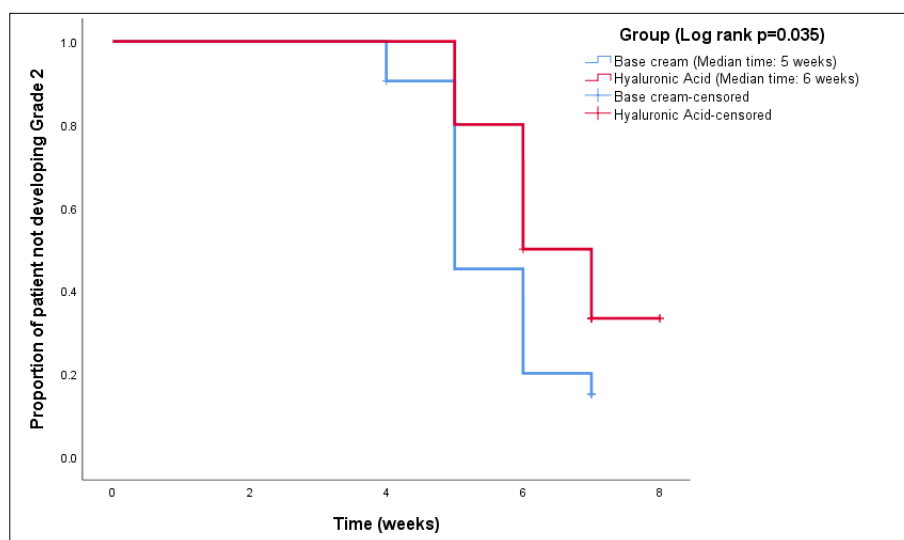
The curve showed that subjects in the base cream group (blue line) developed grade 2 radiodermatitis faster, starting at week 4, compared to the HA cream group (red line), which started at week 5. Additionally, the log-rank test showed a significant difference in the effectiveness of 0.2% HA cream compared to the base cream in preventing the severity of acute radiodermatitis ($p=0.035$).

Table 3. The difference in the degree of acute radiodermatitis between the two groups

Degree of acute radiodermatitis (RTOG)		Cream		P-value
		Base cream n (%)	HA n (%)	
Week 0 (N=40)	0	21 (100)	20 (100)	1.000
Week 1 (N=40)	0	21 (100)	20 (100)	1.000
Week 2 (N=40)	0	21 (100)	20 (100)	1.000
Week 3 (N=40)	0	8 (38.09)	17 (85)	0.002*
	1	13 (61.91)	3 (15)	
Week 4 (N=40)	0	0 (0)	3 (15)	0.026*
	1	19 (90.48)	17 (85)	
	2	2 (9.52)	0 (0)	
Week 5 (N=40)	0	0 (0)	0 (0)	0.024*
	1	9 (45)	16 (80)	
	2	11 (55)	4 (20)	
Week 6 (N=40)	0	0 (0)	0 (0)	0.050
	1	4 (20)	10 (50)	
	2	16 (80)	10 (50)	
Week 7 (N=39)	0	0 (0)	0 (0)	0.414
	1	4 (20)	6 (31.57)	
	2	16 (80)	13 (68.43)	
Week 8 (N=19)	0	0 (0)	0 (0)	0.258
	1	3 (33.33)	6 (60)	
	2	6 (66.67)	4 (40)	

P-values were determined by Mann-Whitney test.

RTOG = Radiation therapy oncology group; HA = hyaluronic acid

**Figure 2.** Proportion of subjects not developing grade 2 acute radiodermatitis over time

DISCUSSION

Radiotherapy is an important modality in the management of breast cancer, but the side effect of acute radiodermatitis remains a significant clinical challenge.¹¹ Prevention and management of acute

radiodermatitis in breast cancer patients using various modalities such as topical steroids, non-steroidal topical agents, Mepilex dressing, laser therapy, and other methods have shown mixed results in previous studies.⁶ Hyaluronic acid has been reported to be

effective in managing acute radiodermatitis. A study by Liguori et al. reported that prophylactic use of HA cream reduced the incidence of radiodermatitis in patients with head and neck, breast, and pelvic cancers, demonstrating the role of HA cream as a supportive treatment to improve compliance and quality of life in cancer patients undergoing radiotherapy.¹²

The baseline characteristics of this study showed that all subjects were female, with a mean age of 51.09 ± 10.34 years. The mean age of the subjects in this study is consistent with previous studies reporting that the mean age of women with breast cancer is 51.9 ± 7.6 years, with 52.8% being under 50 years old.¹³ The majority of subjects in the base cream group had a university education (42.86%), while the majority in the HA cream group had a senior high school education (35.00%). A study by Ganjali et al. found no statistically significant difference in education level between the intervention and control groups regarding the effectiveness of radiodermatitis treatment protocols.¹⁴ The majority of subjects were married (97.56%) and of Javanese ethnicity (95.12%). Certain genetic factors in different ethnic groups may influence skin response to radiation and the development of radiodermatitis. It has been reported that 14.7% of the Japanese population carries the ABCA1 and IL12RB2 genes, which are associated with the occurrence of radiodermatitis, this indicates that genetic factors influence susceptibility.¹⁵

The body mass index (BMI) of all subjects was normal, with a mean value of 24.09 ± 4.49 kg/m². Previous studies have reported that higher BMI is significantly associated with increased skin toxicity and the severity of radiodermatitis.¹⁶ In this study, hypertension was the most common comorbidity, accounting for 26.83%. A retrospective study indicated that the most common comorbidities in breast cancer patients were hypertension and diabetes mellitus.¹⁷ This study also observed a history of chemotherapy (97.56%) and mastectomy. Chemotherapy was not significantly correlated with the occurrence of acute radiodermatitis in breast cancer patients.¹⁸ Mastectomy may influence the occurrence of radiodermatitis through changes in vascularization.¹⁹ No subjects in this study had a history of smoking or alcohol consumption. Smoking is a significant risk factor for radiodermatitis, especially in patients undergoing radiotherapy for cancer.¹⁸ The most common total radiotherapy dose administered was >50 Gy (46.34%). Higher total radiation doses are consistently associated with an increased incidence of radiodermatitis.²⁰

In this study, both ITT and per-protocol analyses showed a significant difference in RTOG scores at weeks 3, 4, and 5 between the HA cream group and the base cream group ($p < 0.05$). The Kaplan-Meier curve showed that the base cream group developed grade 2 radiodermatitis faster than the treatment group, with a significant difference ($p = 0.035$). Liguori et al. reported that the application of HA-based cream significantly delayed the onset of grade 1 and 2 acute radiodermatitis in cancer patients undergoing radiotherapy.¹² Previous studies conducted by Pinnix et al. and Rahimi et al. showed differing results. The use of HA-based gel and HA serum formulation did not prevent or reduce the severity of radiodermatitis.^{21,22} Differences in product formulations, application frequency, and the characteristics of the studied populations may account for these variations in results.

Moisturizers with cream-based vehicles have a thicker texture due to higher viscosity compared to lotions and contain less oil than ointment bases.²³ Additionally, their effectiveness may be influenced by several factors, including receptor interactions, skin hydration capabilities, bioadhesive properties on epithelial cells, hydrophobic interactions with the stratum corneum, and viscoelastic characteristics.¹⁰ A study by Liguori et al. on a more heterogeneous population of cancer patients (head and neck, breast, and pelvic cancer) showed that applying HA cream evenly using the flat part of a tongue depressor to the radiotherapy area twice a day was more effective.¹² Pinnix et al. and Rahimi et al., who applied HA more than twice a day using a different formula (gel and serum), found no benefit of HA in reducing skin reactions after adjuvant radiotherapy for breast cancer. A notable trend is that large-breasted patients seemed to experience more severe acute radiodermatitis, which made the treatment more challenging.^{21,22}

This study demonstrates that 0.2% HA cream is more effective in delaying the onset of grade 2 radiodermatitis compared to a base cream. Our results support the conclusions of the study by Liguori et al., which show that HA cream provides benefits in reducing acute skin reactions during breast radiotherapy. The topical application of HA shows promising potential in addressing the side effects of radiotherapy, particularly in cases of radiodermatitis. Hyaluronic acid possesses immunoregulatory and rehydration properties that can assist patients undergoing radiotherapy.⁸ The benefit is evident from the delayed onset of grade 2 radiodermatitis in the HA cream group, which occurred at week 5, whereas in the base cream group, it appeared earlier at week 4. The

log-rank test further supports this effectiveness, revealing a significant difference with a p-value of 0.035. These findings align with previous research conducted by Kirova et al., which reported that the use of HA demonstrated a trend of improvement in pain levels and skin colorimetry measurements.²⁴

Hyaluronic acid also plays a crucial role as an antioxidant in the management of radiodermatitis through its ability to protect cells from oxidative damage caused by free radicals. Exposure to ionizing radiation generates ROS such as O_2^- , OH^- , and H_2O_2 , which cause oxidative damage to lipids, proteins, and cellular DNA in the skin, ultimately triggering inflammation and tissue damage.^{25,26} Hyaluronic acid functions as an antioxidant by binding to OH^- and protecting cells from oxidative damage. It has the ability to neutralize free radicals and reduce oxidative stress. Additionally, HA protects fibroblasts from damage caused by H_2O_2 , which is one of the ROS produced during radiotherapy.²¹ Overall, HA acts as an antioxidant in radiodermatitis by neutralizing free radicals, reducing oxidative stress, and protecting cells from DNA and protein damage. The ability of HA to regulate inflammatory responses and accelerate wound healing also contributes to its effectiveness in reducing the severity of radiodermatitis.^{10,27}

Another important aspect of this study is the evaluation of the safety of HA use. From the beginning to the end of the treatment, no side effects were reported in either group. This finding is consistent with existing literature, which shows a satisfactory safety profile for topical HA. A study by Cosentino and Piro in 2018 showed that out of 134 subjects who received HA, only 4 adverse events were reported (2.98% of cases). Hyaluronic acid has been proven effective in reducing inflammation, improving tissue health, and alleviating related symptoms.⁸ Another meta-analysis showed that compared to other topical agents, HA demonstrated higher efficacy in treating acute radiodermatitis, lower incidence of desquamation, and no significant side effects in breast cancer patients.²⁸ Considering the results of this study, HA has the potential to be integrated into clinical guidelines as a supportive therapy for breast cancer patients undergoing radiotherapy. Hyaluronic acid cream is effective in preventing the severity of acute radiodermatitis and can be recommended as a moisturizer to be used during radiotherapy.

Despite providing good results, this study has several limitations that need to be considered. The majority of research subjects came from a single ethnicity, which limits the evaluation of genetic

variation's effects on skin responses to radiation and HA effectiveness. Additionally, this study only evaluated the observation of HA effectiveness up to 2 weeks after completion of radiotherapy. Long-term assessment is required to evaluate the effects of HA on acute radiodermatitis and patients' quality of life post-radiotherapy. This study also did not measure skin conditions using biophysical skin parameters to confirm the assessment results.

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