Emulsion of Olive Oil and Calcium Hydroxide for the Prevention of Radiation Dermatitis in Hypofractionation Post-Mastectomy Radiotherapy: A Randomized Controlled Trial

Imjai Chitapanarux^{a–c} Napatra Tovanabutra^d Siri Chiewchanvit^d
Patumrat Sripan^{a–c} Ausareeya Chumachote^a Wannapha Nobnop^a
Damrongsak Tippanya^a Darat Khamchompoo^a

^aDivision of Radiation Oncology, ^bNorthern Thai Research Group of Radiation Oncology (NTRG-RO),

^cChiang Mai Cancer Registry, Maharaj Nakorn Chiang Mai Hospital, and ^dDivision of Dermatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Keywords

Olive oil · Calcium hydroxide · Skin toxicity · Hypofractionation · Post-mastectomy radiotherapy

Abstract

Background: Most of the patients who have been treated by post-mastectomy radiotherapy (PMRT) experience skin toxicity. There have been few studies on acute radiation dermatitis in breast cancer patients who received hypofractionation PMRT. **Methods:** 62 patients were randomized to receive a general skin care regimen with or without the addition of an emulsion of olive oil and calcium hydroxide twice a day, from the initiation of PMRT to 2 weeks after radiotherapy. Adverse skin reactions and the Skindex-16 score were assessed. **Results:** At the 8th, 13th, and 16th fraction of PMRT, grade 1 dermatitis was found in 42, 90, and 90% of the control group and in 16, 30, and 71% of the intervention group. At the end of the study, the mean Skindex-16 score of the intervention group was significantly better than that of the control group ($p = 0.019$). **Conclusions:** Addition of an emulsion of olive oil and calcium hydroxide for patients undergoing hypofractionation PMRT yielded superior preventive results over a general skin care regimen alone, in terms of delaying skin toxicity, reducing the severity of acute radiation

dermatitis, and a better quality of life in the intervention group. However, a larger number of patients will be required to confirm this result.

© 2019 S. Karger AG, Basel

Introduction

The acute skin reaction from post-mastectomy radiotherapy (PMRT) includes erythema, epilation, dry and moist desquamation, ulceration, and skin necrosis [1–5]. These side effects have been experienced by most patients (74–100%) over the course of their PMRT [6, 7]. Porock et al. [8] reported several predictive factors for the severity of radiation dermatitis, including breast size, age, tumor stage, weight, skin cancer, smoking, lymphocele aspiration, and radiation dose. Moreover, Tucker et al. [9] found that age, genetic predisposition, chronic diseases, skin types, and skin damage from previous cytotoxic chemotherapy play a role in radiosensitivity.

The physiopathology of radiation dermatitis is known to be a combination of the production of free radicals, which is the main factor for the endothelial cell and basal layer cell injury and the inflammatory response. Deprivation of the endothelial cells produces a perivascular in-

flammatory infiltration nearby blood vessels. Deprivation of the basal layer cells involves an inflammatory cascade by the transcription of pro-inflammatory cytokines [6, 8, 9] and is related to skin erythema, which was usually seen in the first 2 weeks of irradiation. Moist desquamation, which was seen in the later weeks of irradiation, resulted from the loss of basal layer cells of the epidermis.

The most important part in the management of radiation dermatitis is prophylaxis. Based on the evidence, the Supportive Care Guidelines Group [10] has developed recommendations for the general skin care for patients receiving radiotherapy. The recommendations are: to gently wash the irradiated area with water alone, to pat dry with a soft bath towel, not to use any topical agents before receiving radiotherapy (as they may have bolus effects and increase the skin dose), to avoid exposure to sunlight and extreme temperatures, to avoid using any metallic-based topical products, e.g. aluminum-based products or zinc oxide topical pastes (as they also could increase the skin dose), to avoid tight clothing over the irradiated skin to prevent friction wounds, and to keep the irradiated skin dry and clean.

Owen et al. [11] reported the chemistry and physiological function of olive oil, which has antioxidant and anti-inflammatory properties. Ichihashi et al. [12] found that daily topical use of olive oil after sun tanning may defer and decrease ultraviolet light(UV)-induced skin cancer due to decreased levels of the reactive oxygen species-induced 8-hydroxydeoxyguanosine that is responsible for genetic mutations. Kiechl-Kohlendorfer et al. [13] also demonstrated that daily application of olive oil could decrease the risk of dermatitis during the study period in all gestational-age infants and that it was better than a water-in-oil emollient cream. The effect of olive oil in the prophylaxis of acute radiation-induced dermatitis has been reported in nasopharyngeal cancer patients treated with concurrent chemoradiotherapy, and application of this product can significantly reduce the severity of this adverse event [14].

The effect of an emulsion of olive oil and calcium hydroxide on the prophylaxis of acute skin reaction from a hypofractionation radiotherapy regimen has not yet been studied. The primary objective of this trial was to investigate the effect of prophylactic use of one particular emulsion in preventing acute skin reactions in patients receiving adjuvant hypofractionation PMRT. The secondary objective was to assess the quality of life (QoL) by using the validated Skindex-16 questionnaires at the same time as the clinical assessments.

Materials and Methods

This randomized study was conducted from August 2016 to April 2017. The study protocol was approved by our institution's ethics committee. All participants had given their written in-

formed consent. The eligibility criteria included being at least 18 years old and having histologic proof of invasive breast carcinoma and undergoing adjuvant hypofractionation PMRT. The patient must also have a good (Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1). We excluded those patients who had inflammatory carcinoma of the breast as well as those with a known allergy to olive oil or calcium hydroxide. Patients with pre-existing loss of skin integrity or prior radiotherapy to the area being treated were also excluded. The patients were randomized to either the control group or the intervention group. A block randomization was conducted by computer and there was no stratification for the randomization. The randomization ratio was 1:1. After receiving a declaration of a new enrollment form from the research nurse, the study statistician referred to the list of randomized numbers and assigned the patient to the next number. Both groups of patients were advised by the protocol nurse to follow the recommendations of the general skin care regimen. For the intervention group, the patients were also instructed to use an emulsion of olive oil and calcium hydroxide on the irradiated skin every morning and evening from day 1 of the PMRT to 2 weeks after finishing the PMRT. To allow for absorption and to prevent any bolus effect of residual product on the skin, irradiation was not introduced until at least 1 h after product application. All patients were laid on a wing board (CIVCO, Coralville, IA, USA) with both arms up above the head. Images from the computed tomography (CT) simulation were transferred into the treatment planning system with Pinnacle³ version 7.6 (Philips, Andover, MA, USA) or TomoTherapy Hi-Art software, version 4.2.3 (TomoTherapy Inc., Madison, WI, USA). The patients were irradiated to the chest wall and supraclavicular lymph nodes using a 6-MV photon beam for 3-dimensional conformal radiotherapy (3D-CRT). The patients needing to receive the whole axilla irradiation were treated by helical tomotherapy. The patients were treated with a dose of 265 cGy per fraction: 5 fractions per week to a total of dose of 42.4 Gy. For 3D-CRT, a 10-mm-thick bolus (Superflab; Med-Tec, Orange, IA, USA) was used only in the first 8 treatment fractions. The maximum dose (D_{max}) in the irradiated volume, the chest wall separation, and the skin dose that was estimated from the treatment plan were recorded for each patient. Physical examination was performed once every week during the radiotherapy. At the 3rd, 8th, 13th, and 16th fraction and at 1 month after completion of the PMRT, radiation-induced skin toxicity was assessed by the physician using the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria [15]. RTOG grade 0 acute skin toxicity is described as no change, grade 1 as follicular erythema, dry desquamation, epilation, grade 2 as patchy moist desquamation confined to skin folds, grade 3 as confluent moist desquamation of other than skin folds, and grade 4 as ulceration, hemorrhage, necrosis.

All patients were assessed for QoL by using the validated Skindex-16 questionnaires (Thai version) concurrent with the clinical assessments. These questionnaires have scores ranging from 0 to 96 (for best QoL to poor QoL). In each week of evaluation for the intervention group, the amount of the product used was examined by the protocol nurse.

Fisher's exact test was used to compare the distribution of all baseline characteristics between the two study groups for qualitative variables and the Wilcoxon rank-sum test was used for continuous variables. Fisher's exact test was also used to see the statistical significance of the difference in proportion to the RTOG grades between the two arms of the study. A probability value of less than 0.05 was considered significant. The Skindex-16 scores at all the time points between both arms were adjusted to normal distribution by log transformation and are reported as geometric mean (GM) and 95% confidence interval. GM Skindex-16 scores

Table 1. Patient and treatment characteristics

Variable	Control group n = 31	Intervention group n = 31	p
Age, median (IQR), years	55 (47–62)	56 (51–61)	0.573 ^a
Stage			0.725 ^b
I	1 (3%)	0 (0%)	
II	17 (55%)	14 (45%)	
III	11 (36%)	15 (48%)	
IV	2 (6%)	2 (7%)	
Treatment			0.828 ^b
AC	2 (7%)	3 (10%)	
AC-T	19 (61%)	21 (68%)	
FAC	8 (26%)	6 (19%)	
No chemotherapy	2 (6%)	1 (3%)	
Techniques			0.99 ^b
3D-CRT	21 (68%)	22 (71%)	
TomoTherapy	10 (32%)	9 (29%)	
Skin dose, mean ± SD, Gy	47.99 ± 3.09	47.83 ± 3.15	0.725 ^a
D _{max} , mean ± SD, Gy	50.39 ± 3.39	49.76 ± 3.38	0.460 ^a
Chest wall separation, mean ± SD, cm	19.90 ± 2.86	19.72 ± 2.82	0.683 ^a

IQR, Interquartile range; AC, anthracycline and cyclophosphamide; T, taxane; FAC, 5-fluorouracil, anthracycline, and cyclophosphamide; 3D-CRT, 3-dimensional conformal radiotherapy.

^aWilcoxon rank-sum test.

^bFisher's exact test.

were compared using repeated-measures mixed-model analysis. The assumptions of constant variance and normality of the residuals error were examined by visual inspection. All statistical analyses were done with SPSS (version 20) and STATA (version 10.1).

Results

Patient and treatment characteristics were similar between the two study groups (table 1). 62 patients (31 in each group) met the inclusion criteria and were enrolled in this trial. The median age and interquartile range were 55 (47–62) years in the control group and 56 (51–61) years in the intervention group. All patients received 16 fractions of hypofractionation PMRT. The radiation fields covered the chest wall and supraclavicular lymph nodes in 21 patients (68%) of the control group and 22 patients (71%) of the intervention group. 10 patients (32%) and 9 patients (29%) from the control and the intervention groups, respectively, received chest wall plus supraclavicular and whole-axilla lymph node irradiation by helical tomotherapy machine. Most of the patients received previous adjuvant anthracycline-based chemotherapy, except for 3 patients who received only adjuvant hormonal treatment during PMRT. None of the patients received adjuvant trastuzumab during PMRT. At the third fraction of treatment, there were only 3 patients (10%) in the control group who developed RTOG grade

1 radiation dermatitis whereas there was none in the intervention group ($p = 0.238$). At the 8th, 13th, and at the last fraction of treatment (fraction 16), grade 1 dermatitis increased to 42, 90, and 90% for the control group and 16, 30, and 71% for the intervention group as shown in figure 1; these differences were significant with p -values of 0.049, 0.001, and 0.007, respectively. At the 6-week follow-up visit post PMRT, there was still significantly fewer grade 1 dermatitis in the intervention group than in the control group, i.e. 18 patients (58%) versus 28 patients (90%) ($p = 0.002$) (fig. 1).

Breast cancer stage, adjuvant chemotherapy before PMRT, radiotherapy technique, skin dose, maximum dose, and chest wall separation were not significant prognostic factors for acute radiation-induced skin reaction.

For the patient-reported outcomes, the GM Skindex-16 score of the intervention group was slightly higher than that of the control group, but the difference was not statistically significant, as shown in table 2. The GM Skindex-16 score of the intervention group decreased significantly from 2.42 (3rd fraction) to 1.03 (6-week visit) with a p -value of 0.002. In the control group, the GM Skindex-16 score tended to increase over the treatment period and 6-week visit. The GM Skindex-16 score of the control group at the 6-week visit (2.73) was significantly higher than at the 3rd fraction (1.28) with a p -value of 0.006. At the 6-week visit, the GM Skindex-16 score of the control group was significantly greater than

Fig. 1. RTOG scores (%) of acute skin toxicity in the control and intervention group over the treatment period and at the 6-week visit.

that of the intervention group with a p-value of 0.019 (table 2).

From the safety and tolerability aspects, none of the patients in the intervention group experienced any side

effects of this product. Only 1 patient reported a temporary tingling sensation after applying the emulsion. However, this patient continued to participate in the study.

Table 2. Skindex-16 scores of all time points between control and intervention

Visit	Control, GM (95% CI)	Intervention, GM (95% CI)	p
3rd fraction	1.28 (0.57–2.31)	2.42 (1.36–3.95)	0.103
8th fraction	0.93 (0.46–1.56)	2.09 (1.23–3.27)	0.058
13th fraction	1.44 (0.68–2.54)	1.46 (0.75–2.46)	0.970
16th fraction	1.89 (0.94–3.29)	1.52 (0.63–2.89)	0.662
6-week	2.73 (1.45–4.66)	1.03 (0.44–1.87)	0.019

GM, Geometric mean; CI, confidence interval.

Discussion

Radiation-induced dermatitis is the common consequence in patients receiving radiation therapy. Acute radiation dermatitis changes are a result of direct tissue injury along with local inflammation [6, 8, 9]. The clinical manifestation ranges from mild erythema to moist desquamation and ulceration. Chronic skin injury usually develops more than 3 months after radiotherapy and includes alterations of the vessels and connective tissue of the dermis and underlying subcutaneous tissue [16]. Apart from basic skin care provided in the guideline [10], several topical medications and skin care products had been investigated for the prophylaxis and amelioration of acute radiation dermatitis. Salvo et al. [17] investigated the studies of products for the prevention and treatment of acute skin reaction from radiotherapy. Most of the studies were categorized as prophylactic trials. The intensity of radiation dermatitis was significantly decreased by several corticosteroids in topical form, but there was no definite suggestion of any favorite corticosteroid [18–21]. There were many studies of non-steroidal skin creams, e.g. hyaluronidase-based creams, Biafine cream, and *Aloe vera* cream [22–28]. The evidence for the use of these topical products is inconsistent. Until now, there is no sufficient evidence to suggest the use of any individual agent for the prophylaxis of acute radiation dermatitis.

The main mechanism of radiation skin injury involves the production of free radicals and the reduction of antioxidant capacity [29]. Antioxidant agents have been studied in the management of radiation dermatitis in breast cancer [30, 31]. Aysan et al. [30] revealed that the application of a boron-based gel significantly diminished the radiation dermatitis compared to placebo in breast cancer patients. Zhao et al. [31] also demonstrated that topical epigallocatechin-3-gallate was well tolerated and effective in treating radiation dermatitis in patients receiving PMRT. Olive oil was selected for our study because it has been used as a skin care product for a long time. Not only does it moisturize the skin by preventing transepidermal water loss, but it also has antioxidant properties [11]. The

antioxidative components of olive oil include phenolic compounds, tocopherol, squalene, and triterpenic acids [32]. However, the antioxidant properties of olive oil diminish with time and are markedly decreased after the refining process [33, 34]. Neutralization is one of the refining methods that remove undesirable free fatty acids, caused by the hydrolysis of triacylglycerols. Sodium hydroxide has been used as a neutralizing agent to eliminate free fatty acids. Nevertheless, this process also removes natural antioxidants. Using calcium hydroxide instead of sodium hydroxide revealed that oil neutralized with calcium hydroxide had a higher amount of α -tocopherol and phytosterols compared to oil neutralized with sodium hydroxide [33]. Our study used an emulsion of virgin olive oil neutralized with calcium hydroxide, which contained high amounts of antioxidants. This emulsion also had no fragrance and preservatives, ensuring a low risk of skin irritation as well as contact allergy.

Topical olive oil was studied by Cui et al. [14] in the prophylaxis of acute radiation toxicity in nasopharyngeal cancer patients treated with radiotherapy plus chemotherapy. Their results indicated that olive oil is an effective and safe prophylactic treatment for radiation-induced dermatitis. Our results match their findings.

Focusing on the 2 patients who had grade 2 toxicity in the last fraction of PMRT, both of them were in the control group and received the 3D-CRT technique with bolus to the whole chest wall area in the first half of the treatment. 1 patient still had grade 2 radiation dermatitis at the time of follow-up. However, she had much recovered, with only a small area of moist desquamation being seen in her axilla region. Skin dose, maximum dose, and chest wall separation in these 2 patients were reviewed, and they were not different from those of the other patients in the study. Placing the bolus at the last session of the treatment or omitting it at any fraction, based on a clinical decision, were the options to reduce the skin toxicity. Although our study used a hypofractionation regimen that was supposed to instigate more skin toxicity, we observed a lower incidence of radiation dermatitis compared to the 100% of all patients in the study of Cui et al. [14], which reported some degree of erythema, dry or wet desquamation, or edema, by the end of treatment. One of the explanations could be the higher-dose radiotherapy (70 Gy) and the implementation of concurrent chemotherapy in their study. Comparable to the study of Cui et al. [14], we found the RTOG grade 1 radiation dermatitis in the group treated with the emulsion of olive oil and calcium hydroxide to be statistically significantly lower than in the general skin care recommendation group at the 6-week follow-up visit after PMRT. The effectiveness of the olive oil emulsion in protection against skin toxicity might be explained by the study of Owen et al. [11], where the antioxidative and anti-inflammatory effects of olive oil were

reported. However, to the best of our knowledge, there are no guidelines on skin toxicity stating that the second layer of the skin cannot be protected by any cream or oil.

In our study, the Skindex-16 was used to measure health-related QoL with skin conditions. This questionnaire is a standard, validated instrument for assessing health-related QoL and is commonly used in dermatologic research [35]. It also has more details to evaluate skin symptoms of patients compared to the more widely used Dermatology Life Quality Index (DLQI). The patient-reported outcome of our study revealed that application of the emulsion of olive oil and calcium hydroxide had an impact on the acute radiation-induced skin injury compared to the patients who used a general skin care recommendation.

Our randomized prospective study was the first study using the emulsion of olive oil in hypofractionation radiotherapy. However, there are a few limitations to our study. First, this study was unblinded and non-placebo controlled, which may have affected the QoL results. Another limitation was the small sample size to explain individual differences in skin radiosensitivity. A larger

number of patients and a confirmatory randomized control trial are required to determine the efficacy of this regimen.

In conclusion, using an emulsion of olive oil in addition to general skin care recommendations is associated with a significant reduction in the intensity of acute radiation-induced skin reaction, deferment of the skin toxicity, and enhancement of a better QoL for breast cancer patients treated with hypofractionation PMRT.

Acknowledgement

The emulsion of olive oil in this study was supported by Ouiheng International Healthcare Company, Bangkok, Thailand. The authors acknowledge the contributions of the patients and radiation therapists' teams at Chiang Mai University for their assistance.

Disclosure Statement

No conflicts of interest.

References

- Berthelet E, Truong PT, Musso K, et al: Preliminary reliability and validity testing of a new Skin Toxicity Assessment Tool (STAT) in breast cancer patients undergoing radiotherapy. *Am J Clin Oncol* 2004;27:626–631.
- Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
- Harper JL, Franklin LE, Jenrette JM, Aguero EG: Skin toxicity during breast irradiation: pathophysiology and management. *South Med J* 2004;97:989–993.
- Knobf MT, Sun Y: A longitudinal study of symptoms and self-care activities in women treated with primary radiotherapy for breast cancer. *Cancer Nurs* 2005;28:210–218.
- Wengström Y, Häggmark C, Strander H, Forsberg C: Perceived symptoms and quality of life in women with breast cancer receiving radiation therapy. *Eur J Oncol Nurs* 2000;4:78–88, discussion 89–90.
- Hymes SR, Strom EA, Fife C: Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol* 2006;54:28–46.
- Porock D, Kristjanson L: Skin reactions during radiotherapy for breast cancer: the use and impact of topical agents and dressings. *Eur J Cancer Care* 1999;8:143–153.
- Porock D, Kristjanson L, Nikolett S, Cameron F, Pedler P: Predicting the severity of radiation skin reactions in women with breast cancer. *Oncol Nurs* 1998;25:1019–1029.
- Tucker SL, Turesson I, Thames HD: Evidence for individual differences in the radiosensitivity of human skin. *Eur J Cancer* 1992;28A:1783–1791.
- Bolderston A, Lloyd NS, Wong RKS, Holden L, Robb-Blenderman L: Supportive Care Guidelines Group of Cancer Care Ontario Program in Evidence-Based Care: The prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. *Support Care Cancer* 2006;14:802–817.
- Owen RW, Mier W, Giacosa A, Hull WE, Spiegelhalter B, Bartsch H: Identification of lignans as major components in the phenolic fraction of olive oil. *Clin Chem* 2000;46:976–988.
- Ichihashi M, Ahmed NU, Budiyo A, et al: Preventive effect of antioxidant on ultraviolet-induced skin cancer in mice. *J Dermatol Sci* 2000;23(suppl 1):S45–S50.
- Kiechl-Kohlendorfer U, Berger C, Inzinger R: The effect of daily treatment with an olive oil/lanolin emollient on skin integrity in preterm infants: a randomized controlled trial. *Pediatr Dermatol* 2008;25:174–178.
- Cui Z, Xin M, Yin H, Zhang J, Han F: Topical use of olive oil preparation to prevent radio-dermatitis: results of a prospective study in nasopharyngeal carcinoma patients. *Int J Clin Exp Med* 2015;8:11000–11006.
- Pires AMT, Segreto RA, Segreto HRC: RTOG criteria to evaluate acute skin reaction and its risk factors in patients with breast cancer submitted to radiotherapy. *Rev Lat Am* 2008;16:844–849.
- Hegedus F, Mathew LM, Schwartz RA: Radiation dermatitis: an overview. *Int J Dermatol* 2017;56:909–914.
- Salvo N, Barnes E, van Draanen J, et al: Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Curr Oncol* 2010;17:94–112.
- Boström A, Lindman H, Swartling C, Berne B, Bergh J: Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study. *Radiother Oncol* 2001;59:257–265.
- Omidvari S, Saboori H, Mohammadianpanah M, et al: Topical betamethasone for prevention of radiation dermatitis. *Indian J Dermatol Venereol Leprol* 2007;73:209.
- Schmuth M, Wimmer MA, Hofer S, et al: Topical corticosteroid therapy for acute radiation dermatitis: a prospective, randomized, double-blind study. *Br J Dermatol* 2002;146:983–991.
- Shukla PN, Gairola M, Mohanti BK, Rath GK: Prophylactic beclomethasone spray to the skin during postoperative radiotherapy of carcinoma breast: a prospective randomized study. *Indian J Cancer* 2006;43:180–184.
- Elliott EA, Wright JR, Swann RS, et al: Phase III trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99–13. *J Clin Oncol* 2006;24:2092–2097.
- Fenig E, Brenner B, Katz A, et al: Topical Bifine and Lipiderm for the prevention of radiation dermatitis: a randomized prospective trial. *Oncol Rep* 2001;8:305–309.

- 24 Fisher J, Scott C, Stevens R, et al: Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys* 2000;48:1307-1310.
- 25 Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X: Phase III randomized trial of *Calendula officinalis* compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer *J Clin Oncol* 2004;22:1447-1453.
- 26 Primavera G, Carrera M, Berardesca E, Pinnaró P, Messina M, Arcangeli G: A double-blind, vehicle-controlled clinical study to evaluate the efficacy of MAS065D (XClair), a hyaluronic acid-based formulation, in the management of radiation-induced dermatitis. *Cutan Ocul Toxicol* 2006;25:165-171.
- 27 Ribet V, Salas S, Levecq JM, et al: Interest of a sterilised anti-burning gel in radiation dermatitis: results of a comparative study (Article in French). *Ann Dermatol Venereol* 2008;135:5-10.
- 28 Szumacher E, Wighton A, Franssen E, et al: Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *Int J Radiat Oncol Biol Phys* 2001;51:81-86.
- 29 Benderitter M, Isoir M, Buard V, et al: Collapse of skin antioxidant status during the subacute period of cutaneous radiation syndrome: a case report. *Radiat Res* 2007;167:43-50.
- 30 Aysan E, Idiz UO, Elmas L, Saglam EK, Akgun Z, Yucel SB: Effects of boron-based gel on radiation-induced dermatitis in breast cancer: a double-blind, placebo-controlled trial. *J Invest Surg* 2017;30:187-192.
- 31 Zhao H, Zhu W, Jia L, et al: Phase I study of topical epigallocatechin-3-gallate (EGCG) in patients with breast cancer receiving adjuvant radiotherapy. *Br J Radiol* 2016;89:20150665.
- 32 Kalogeropoulos N, Tsimidou MZ: Antioxidants in Greek virgin olive oils. *Antioxidants (Basel)* 2014;3:387-413.
- 33 Essid K, Trabelsi M, Frikha MH: Effects of neutralization with lime on the quality of acid olive oil. *J Am Oil Chem Soc* 2006;83:879-884.
- 34 Rastrelli L, Passi S, Ippolito F, Vacca G, De Simone F: Rate of degradation of alpha-tocopherol, squalene, phenolics, and polyunsaturated fatty acids in olive oil during different storage conditions. *J Agric Food Chem* 2002;50:5566-5570.
- 35 Both H, Essink-Bot M-L, Busschbach J, Nijsten T: Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol* 2007;127:2726-2739.