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Quantitative Evaluation of Skin Erythema Caused by Radiotherapy

Hiroshi Sekine[1], Ichiro Fukuda[2], Sayako Takagi[2], Masao Kobayashi[2], Manabu Aoki[2], and Chihiro Kanehira[2]

[1]*Department of Radiation Oncology, Saitama Medical University, School of Medicine*
[2]*Department of Radiology, The Jikei University School of Medicine*

ABSTRACT

Radiation-induced skin erythema is the most common adverse effect of external radiotherapy. The severity of the erythema can be expressed with a qualitative scale. Because this qualitative scale is vaguely defined, the assessments are not reproducible. The purpose of this study was to determine whether quantitative evaluation of radiation-induced skin erythema is possible. The subjects of the study were patients with early breast cancer who had received radiotherapy after undergoing breast conserving-surgery. Each patient received a total of 50 Gy of radiotherapy delivered with conventional fractionation and a tangential field. Quantitative measurements of skin erythemas were made using a spectrophotometer to measure the L*a*b* color space and the 560-nm reflectance over time. L* indicates the lightness, and a* (redness) and b* (yellowness) indicate the chromaticity coordinates. L* significantly decreased and a* significantly increased with the radiation dose. An increase in b* with the radiation dose was also observed, but the trend was not significant. The 560-nm reflectance corresponds to the absorption of hemoglobin ; this value decreased significantly as the radiation dose increased. In conclusion, radiotherapy-induced skin erythema can be quantitatively assessed with reflectance spectrophotometry.

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Key words : radiotherapy, radiation effect, radiation dermatitis, skin erythema, spectrophotometry

Introduction

Ionizing radiation induces cell death in highly mitotic cells by damaging the DNA and can also induce cell functional failure in well-differentiated nonmitotic cells as a result of biochemical damage. Because malignant tumor cells are highly mitotic, radiotherapy for cancer treatment generally functions via a mechanism involving DNA damage. Because cancer cells can arise from various tissues in the body, the proliferating malignant cells are surrounded by normal tissue. Ionizing radiation can easily penetrate the human body and be used as an external treatment for deeply seated malignant tumors. For successful radiotherapy, the radiation dose to normal tissue should be minimized to avoid life-threatening adverse effects. Several methods of concentrating the radiation beams to conform with tumor geometry have been developed. However, if the clinical target volume (CTV) is large and close to dose-limiting normal tissue, such as in postoperative radiotherapy for breast cancer, the skin will likely receive a large dose of radiation. Therefore, the acute effects of radiation to the skin are an important concern when administering radiotherapy to breast cancer patients.

Visual assessments of the skin in the irradiated

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関根　広，福田　一郎，高木佐矢子，小林　雅夫，青木　学，兼平　千裕
Mailing address : Hiroshi Sekine, Department of Radiation Oncology, Saitama Medical University, School of Medicine, 38, Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan.
E-mail : h_sekine@saitama-med.ac.jp

area can be scored using qualitative methods, such as the National Cancer Institute Common Toxicity Criteria scale[1]. Several factors can contribute to the severity of radiation-induced skin reactions, including the treatment site, volume of irradiated tissue, type of radiation, treatment energy, concomitant drug therapy, genetic susceptibility, and nutritional status.

Although radiation-induced skin reactions are pathophysiological conditions[2,3], the initial sign of a reaction is a change in skin color. Color is a matter of perception and subjective interpretation. Accurate verbal descriptions of skin color are too complicated and difficult and can be influenced by both intrinsic factors (e.g., hereditary skin color, exercise, diet, and mental stress) and extrinsic factors (e.g., temperature and humidity). The L*a*b* color space is a popular method for objectively measuring color and is used in many fields. Color is expressed using three variables: L* indicates lightness and a* and b* are chromaticity coordinates. Positive a* values extend in the red direction, and positive b* values extend in the yellow direction. Reflectance spectrophotometry can be used to noninvasively measure skin color. We previously attempted to quantitatively measure skin color using this method.

Although radiation-induced erythema develops in many patients, the treatment of erythema is controversial and, all too often, is based on anecdotal evidence[4,5]. Part of the reason for this seems to be uncertainty about the quality of skin erythema assessments. Therefore, an accurate and reproducible method for quantifying erythema could be used to evaluate treatments for erythema. The purpose of this study was to examine the reliability of reflectance spectrophotometry for detecting and quantitatively evaluating radiation-induced skin erythema.

MATERIALS AND METHODS

1. *Objects*

From July through November 2004, 19 patients with early breast cancer who had undergone breast-conserving surgery were enrolled. Before starting radiotherapy, all participating patients gave informed consent. The patients had a mean age of 55.3 ± 13.9 years (mean±SD) and ranged in age from 27 to 82 years. Two patients had received chemotherapy before undergoing radiotherapy, and 5 patients received concomitant hormone therapy. None of the patients who had received chemotherapy underwent concomitant hormone therapy.

2. *Radiotherapy*

The patients were positioned in the supine position with their arms elevated and their elbows fixed and supported with angled plastic braces. Therapy was delivered tangentially in 2-Gy fractions via a 4-MV photon beam generated with a Linear Accelerator (Clinac 2100C; Varian Medical Systems, Palo Alto, California); 5 fractions were administered per week until a total dose of 50 Gy had been administered.

3. *Measurements*

To quantitatively measure radiation-induced skin erythema, a reflectance spectrophotometer (CM-2500d; Konica-Minolta, Tokyo, Japan) was used. The detector measures the L*a*b* color space values and the reflectance spectra of a circle of skin with an average diameter of 8 mm. The skin area of the treated breast was divided into 4 sections (inner upper, inner lower, outer upper, and outer lower). The meter readings in 2 of the divided areas located at least 5 cm from the surgical suture were divided by those in the corresponding areas on the nonirradiated breast. The assessments were performed weekly until 2 weeks after the completion of radiotherapy.

4. *Statistical analysis*

Data for each factor were collected according to each dose range. The means and SDs of the values were then calculated. Student's t-test was performed as an unpaired, two-tailed analysis. A value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

The ratio of L* values for the irradiated and nonirradiated breasts (dL^*) was negatively correlated

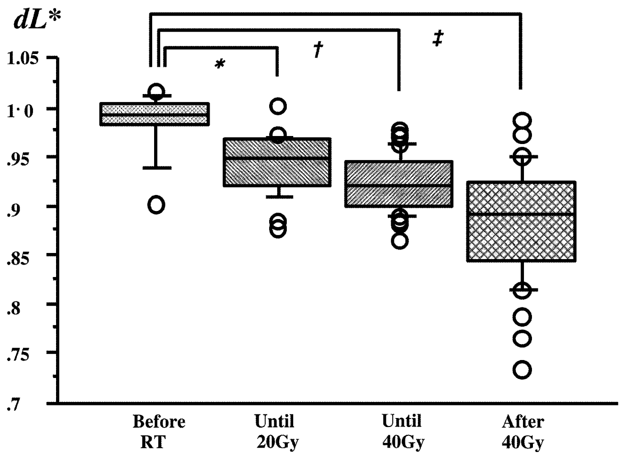

Fig. 1. Relationship between dL^* and irradiation dose. *; $p=0.0002$, †; $p<0.0001$, ‡; $p<0.0001$

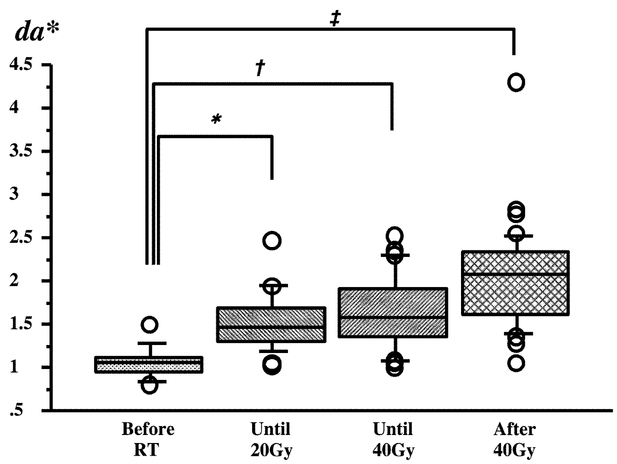

Fig. 2. Relationship between da^* and irradiation dose. *; $p<0.0001$, †; $p<0.0001$, ‡; $p<0.0001$

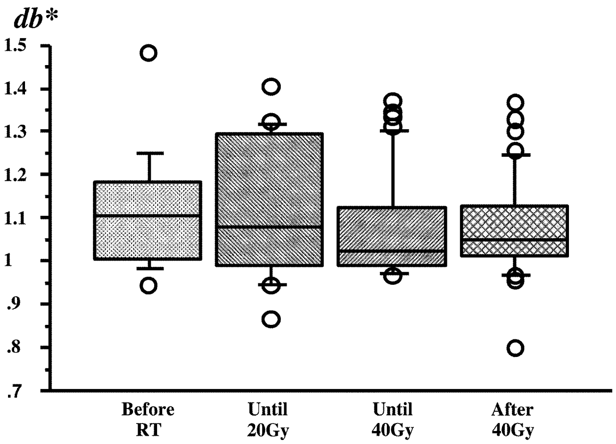

Fig. 3. Relationship between db^* and irradiation dose. No significant changes were observed.

with the radiation dose ($r=-0.670$, $p<0.0001$). The dL^* values of all the dose ranges were significantly different from the values obtained before radiotherapy (Fig. 1). Thus, the dullness of the skin increased with the total radiation dose delivered. The ratio of a* values (da^*) was positively correlated with the radiation dose ($r=0.601$, $p<0.0001$). The da^* values of all the dose ranges were significantly different from the value obtained before radiotherapy (Fig. 2). Thus, da^* significantly increased in the positive direction as the total radiation dose increased, indicating that the redness of the skin became more vivid. However, the ratio of b* values (db^*) was not significantly correlated with the radiation dose ($r=-0.109$, $p=0.2572$; Fig. 3).

The spectral reflectance of the skin during radiotherapy of one of our patients is shown in Figure 4. As the radiation dose increased, the reflectance of the skin decreased. Wavelengths from 520 to 600 nm were particularly sensitive to radiation. This range of wavelengths corresponds to hemoglobin absorption. The ratio of the 560-nm reflectance values (*d560nm*) was negatively correlated with the radiation dose ($r=-0.588$, $p<0.0001$). The *d560nm* values of all the dose ranges were significantly different from the value obtained before radiotherapy (Fig. 5). Thus, the absorption of red blood cells circulating in the skin increased as the radiation absorption dose increased.

The effects of adjuvant therapy on radiation-induced skin erythemas were also analyzed. Concomitant hormone therapy significantly suppressed the a* direction readings after the delivery of 20 Gy or more of radiation as compared with no hormonal therapy (Fig. 6). However, the other factors (L*, b*, and 560-nm reflectance) were not significantly affected. Chemotherapy was administered to too few patients before radiation therapy for its effects on radiation-induced skin erythemas to be analyzed.

Discussion

Ionizing radiation damages the DNA of cancer cells and induces cell death. This is the underlying principle of radiation therapy. On the other hand, the

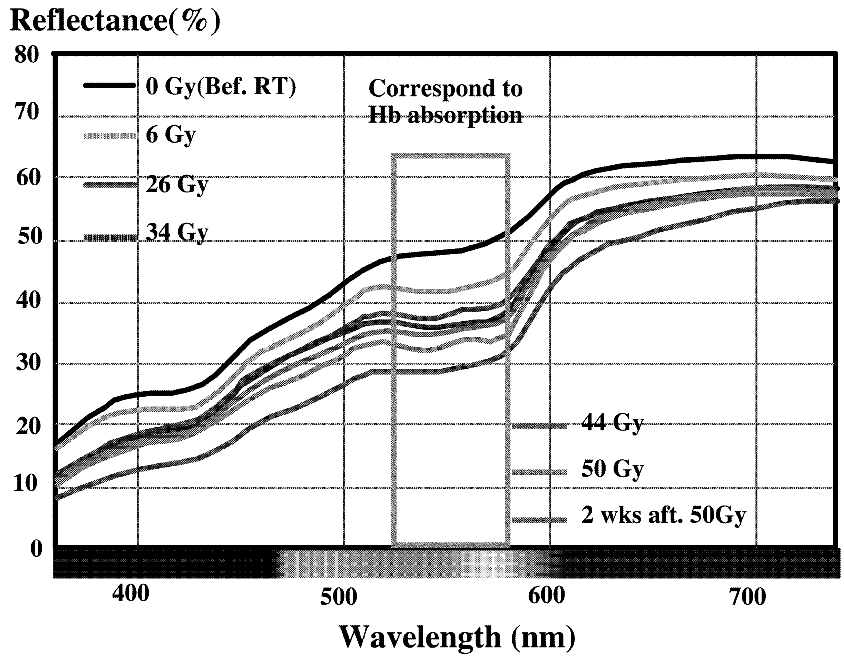

Fig. 4. Spectral reflectance of skin during radiotherapy.

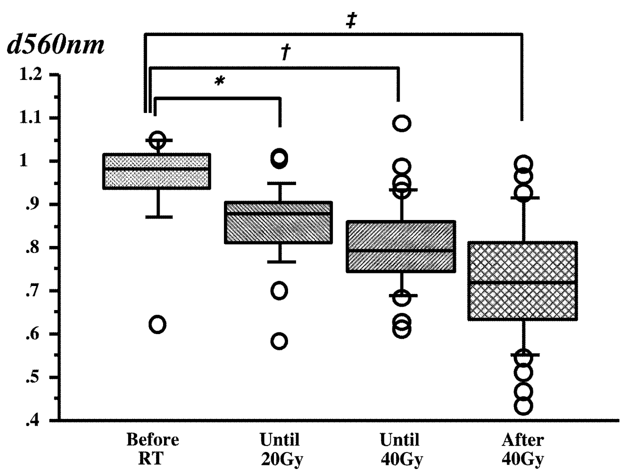

Fig. 5. Relationship between *d560nm* and irradiation dose. *; $p=0.0034$, †; $p<0.0001$, ‡; $p<0.0001$

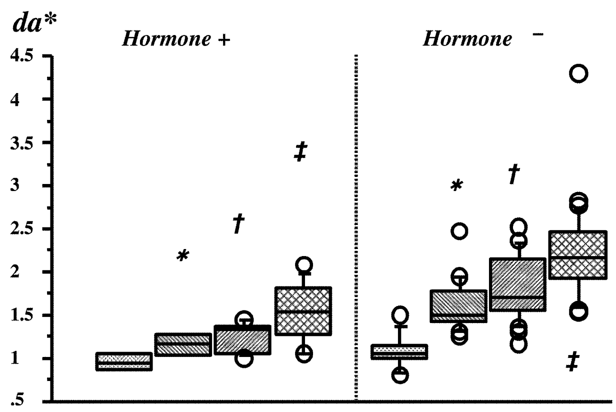

Fig. 6. Relationship between *da** and irradiation dose according to hormone therapy status. *; $p=0.0096$, †; $p<0.0001$, ‡; $p<0.0004$

functional damage to normal tissue induced by ionizing radiation is an important adverse effect. Radiation-induced skin effects are known as "radiation dermatitis," and include erythema, dry desquamation, wet desquamation, and ulcer formation, depending on the radiation dose. The histological features of these effects are well known[2,3]. However, the physiological features of these effects have rarely been described. We have studied the functional effects of radiation dermatitis from the point of view of skin temperature, skin conductance, and sweating ability[6–8]. The initial sign of erythema is a physical change in skin color. However, visual assessments of skin erythema can be complicated by the melanin pigmentation that develops during the course of radiotherapy[9].

We attempted to measure and document skin erythema quantitatively during and after radiotherapy instead of relying on visual assessments. A popular method for objectively measuring color in a reproducible and noninvasive manner is reflectance spectrophotometry. However, the small area of skin used to obtain the measurement is a shortcoming of this technique. Furthermore, measuring the same area during each evaluation can be difficult. The 'DermaSpectrometer' reflectance spectrometer illuminates an area of approximately 11 mm^2 with green or red light[10]. The detectors measure green light with a wavelength of 568 nm, which corresponds to oxyhemoglobin absorption and can be used to evaluate erythema. We used a CM-2500d spectrophotometer, which can measure the reflectance of all ranges of optical wavelengths with a 10-nm resolution. We chose a 560-nm wavelength as being representative of radiation-sensitive regions. Our results were similar to those obtained by others[10] and suggest that hemoglobin absorption increases, because the peripherally circulating blood volume of the skin increases in a dose-dependent manner. Interestingly, although anemia affects local control in patients with several kinds of carcinomas[11,12], the results of the present study indicate that a higher hemoglobin level may also be associated with more severe skin reactions.

Considering the large area of skin that is irradiated during the treatment of breast cancer, including the entire treatment field would be desirable when assessing erythema. An evaluation of the entire treatment area using a digital imaging system, comprising a digital camera and software, in conjunction with the reflectance spectrophotometry method has been attempted; results of this evaluation suggest that digital cameras could be used in a reliable and valid manner to measure radiation-induced skin erythema[10]. To obtain a consistent exposure, however, a reference gray standard color test strip and a soft halogen light in the examination room are essential for color correction.

If radiation erythema could be assessed quantitatively and reproducibly, appropriate methods of prevention or treatment would likely be developed. One study has used reflectance spectrophotometry to examine the effects of a water-based cream, a sucralfate cream, and no cream on the development of radiation-induced skin reactions during radiotherapy[13]. However, consistent differences in the severity of skin reactions between the treatment groups were not found, although differences in reactions were found among different irradiated fields. Interestingly, patients who had a higher body mass index, smoked, or received concomitant chemotherapy were more likely to have skin reactions.

In conclusion, this study has found a positive correlation of radiation dose with a^* and a negative correlation of radiation dose with L^* and the reflectance at 560 nm. In the future, we plan to enroll a larger number of patients to analyze other factors that may affect the severity of radiation erythema. We also hope to conduct a randomized study using this quantitative method to examine methods for preventing radiation erythema.

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