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Temporal Changes in Skin Erythema Induced by Fractionated Radiotherapy Simulated by Using the Time-dependent Linear-quadratic Model

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ABSTRACT

Radiotherapy with ionizing radiation for the treatment of cancer is fractionated to increase its efficacy and to decrease its adverse effects. Radiotherapy for breast cancer targets all the mammary gland tissue immediately below the skin, and therefore, broad exposure of the skin to radiation is unavoidable. Radiation-induced skin erythema results in intolerable anxiety. In order to relieve axiety, it is important to explain to patients the dermatological changes that may occur during and after radiotherapy. We used a spectrophotometer to measure the severity of the erythema caused by radiotherapy after breast conserving surgery for breast cancer. In this study, radiation-induced erythema was quantified and the values were incorporated into a newly developed generalized linear quadratic model to reproduce the temporal changes on a virtual radiation field. This simulation model will be useful not only for patients' but also for medical students' education.

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Key words : breast cancer, radiotherapy, radiation erythema, Linear Quadratic Model, GLQ model

BACKGROUND

External beam radiotherapy with ionizing radiation for the treatment of malignant tumors is fractionated to increase its efficacy and to decrease its adverse effects. In fractionated radiotherapy, irradiation is fractionated using specific criteria, and autonomous responses to radiation in tumor cells and normal tissues are evaluated as treatment effects.

Because of the way in which external beam radiotherapy is administered from out side of body, it is impossible to prevent radiation exposure to the skin. The amount of radiation exposure is expressed in terms of energy absorbed by an object. However, in the early history of radiotherapy, radiation exposure was estimated based on the severity of erythema because despite individual variations, the response of normal tissue to radiation is similar among individuals. Owing to advances in irradiation devices and techniques, modern radiotherapy techniques have been devised to reduce the amount of radiation exposure to the skin. However, radiotherapy for breast cancer targets all the mammary gland tissue immediately below the skin, and therefore, broad exposure of the skin to radiation is unavoidable. Because patients are able to observe any changes in their skin macroscopically, to relieve their anxiety, it is important to explain to them the dermatological changes that may occur during and after radiotherapy.

Physiological, biochemical, and molecular biology mechanisms are behind the various biological responses to radiation. However, even without the knowledge of an accurate mechanism, medical students, residents, technicians, and nurses will be able to understand biological responses

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to fractionated radiotherapy if the physical quantity of radiation exposure is converted to a biological effect expressed by using mathematical methods. This will also lead to the development of novel fractionation regimens.

In the 1970s and 1980s, based on the clinical observations of cancer patients undergoing radiotherapy, a function of fractionated dose, number of fractionation, and overall treatment duration was recommended for converting the physical quantity of radiation exposure to a biological effect, such as treatment efficacy. In those days, the following equation was used exclusively :

$$TDF = \sum_{i=1}^{m} n_i (100 d_i)^{1.538} \chi^{-0.169} 10^{-3}$$

The radiation tolerance dose in dose-limiting normal tissue was taken as $TDF = 100$, and the exponents were decided so that the fractionation number, single fractionated dose amount, and fractionation interval agree with n, d, and χ (in days), respectively. It should be noted here that, although rarely used today, this equation takes the irradiation period into account.

In addition, in the 1980s, to convert the physical quantity of radiation to a biological effect, some researchers started using colony formation assays, in which cultured cells are irradiated at predetermined doses and the survival probability of cells is determined by counting the number of colonies formed by the cells surviving the irradiation[1]. This relationship is mathematically well represented by using a second-order polynomial equation called a linear-quadratic (LQ) model :

$$SF_1 = Exp[-(\alpha d + \beta d^2)]$$

In this equation, SF_1 denotes the surviving fraction, α and β are tissue-specific constants, and d is the fractionated dose. The α/β ratio defines the dose at which cell killing by linear and quadratic components are equal. For early-reacting tissues, such as malignant tumor cells, the α/β ratio tends to be larger (e.g. 10 Gy) whilst for late-reacting tissue, such as normal tissue cells, the ratio tends to be smaller (e.g. 3 Gy). This equation measures colony-forming ability of cells exposed to a single irradiation. For fractionated irradiation performed n fractions, with the assumption that the cells fully recover from radiation damage during the fractionation interval, the surviving fraction $(SF_1)^n$ is expressed as follows :

$$SF_n = Exp[-n(\alpha d + \beta d^2)]$$

Although the fractionation number (n) is incorporated into this model, the interval between two fractions is not defined. For example, the survival rate remains constant regardless of whether the interval between the two fractions is long or short, even though local control rates have been shown to decrease after a long interval[2-6]. This suggests that strict rules should be established for the proper use of the LQ model in fractionated radiotherapy because the model does not consider irradiation time.

We therefore attempted to develop a novel LQ model that considers fractionation intervals. The following points were incorporated into the new model :

1. Cancer cells grow during the waiting period between radiotherapy planning and the start of irradiation.
2. The irradiation period is calculated by using the fractionation interval and fractionation number.
3. Radiation-induced cell death is classified as either mitotic death or interphase (non-mitotic) death.
4. Cancer cells that do not undergo cell death will continue to grow.
5. Normal cell population that do not undergo cell death will grow back to steady state levels.

A model that incorporates these points is a generalized linear-quadratic (GLQ) model.

$$SF_n = \frac{1}{p+k}\left\{ p \prod_{i=1}^{n} Exp\left[-(\alpha d + \beta d^2) f_{cont}(t, t_i)\right] + k \prod_{i=1}^{n} Exp\left[-(\alpha d + \beta d^2) f_{apo}(t, t_i)\right] \right\} g(t)$$

The letter "t" denotes observed day, and day 1 represents the first day of radiotherapy. Treatment duration is t_i, where i represents the fractionation number.

$$t_i = i + 2\left\{ Ceiling\left[\frac{i-5}{5} \right] \right\} \qquad (i = 1 \ldots n)$$

Ceiling[x] gives the smallest integer ≥ x. In conventional fractionation, treatment is carried out five times a week from Monday to Friday.

Assuming that the proportion of mitotic death and interphase death within the total cell death after irradiation is p and k, respectively, total cell death is $p+k$ (100%). In addition, k is set to ≈0 based on the assumption that 2 Gy/fraction used in regular fractionated radiotherapy seldom induces interphase death in the case of normal skin tissue. Mitotic death is described as an exponential decay function of time, as follows :

$$f_{cont}(t, t_i) = 0, \qquad (t < t_i)$$

$$f_{cont}(t, t_i) = 1 - Exp\left[\frac{-(t-t_i)Log(2)}{t_{1/2}}\right] \qquad (t \geq t_i)$$

The half-life of the cells after irradiation is defined as $t_{1/2}$.

Interphase death is expressed by using a unit step function.

$$f_{apo}(t, t_i) = 0, \ (t < t_i)$$

$$f_{apo}(t, t_i) = 1, \ (t \geq t_i)$$

In the present simulation, interphase death is ignored based on the assumption that it does not occur at 2 Gy/fraction.

Proliferation is assumed to happen in tumor and normal cells.

・The number of tumor cells is assumed to grow exponentially, and therefore, the doubling time is defined as t_{dt}.

$$g(t) = Exp\left[\frac{t \cdot Log(2)}{t_{dt}}\right]$$

・Because the number of cells does not exceed the original number N_∞ in normal tissue, a sigmoid function is used.

$$g(t) = \frac{N_\infty}{1 + (N_\infty - 1)Exp[-t/t_{dt}]}$$

In a previous study, we used a spectrophotometer to measure the severity of erythema caused by radiotherapy conducted after breast-conserving surgery for breast cancer, and have shown that the change in skin color correlated well with radiation dose[7]. The purpose of this study was to try to reproduce the time-dependent changes in erythema by using the GLQ model described above.

Subjects

The subjects were 118 breast cancer patients who were undergoing radiotherapy after breast-conserving surgery at Saitama Medical University Hospital between June 2005 and March 2008 and had provided written consent to participate in the study. This study was performed in compliance with the Declaration of Helsinki, and was approved by the Ethics Committee of Saitama Medical University School of Medicine (approval number 408).

Radiotherapy with 6-MV X-rays was conducted as tangential breast irradiations of 2 Gy/fraction/day for 5 days/week (Monday–Friday) up to a total of 50 Gy. A small number of breast cancer patients who had received 1.8 Gy/fraction were excluded from the study. Some of the 118 patients received a boost of radiation after receiving the total dose of 50 Gy. In these patients, the area of the boost was excluded from the measurement of skin color. Measurement was performed a total of 731 times.

Methods

1. Measurement of skin color : A spectrophotometer (CM2500-D, Konica Minolta, Tokyo, Japan) that can coordinate with the CIE L*a*b* color space (defined by Commission Internationale de l'Éclairage in 1976) was used to measure skin color at 2 points (5 cm away from the incision site) selected from different breast regions on the ipsilateral side. The vertical L* axis represents Lightness, ranging from 0-100. The other (horizontal) axes are represented by a* and b*. The a* axis is red at one extremity (represented by +a), and green at the other (−a ; it cannot be human skin color). The b* axis has yellow at one end (+b), and blue at the other (−b ; it cannot be human skin color). In theory, there are no maximum values for a* and b*, but in practice they usually range from −128 to +127 (256 levels). Two points on the contralateral healthy side were also measured as controls. The average of the values of the 2 points on each side was used as the measurement value. The ratios of the irradiated side divided by the contralateral side are defined as dL*, da*, and db*, respectively.

2. Timing of measurement : Measurement was performed once before radiotherapy, weekly during radiotherapy, and once at each outpatient visit after radiotherapy.

3. Color space conversion : dL*, da* and db* values were plotted in 3-dimensional (3-D) coordinates to investigate the relations between L*, a*, and b*.

4. Conversion of L*a*b* values to the HSB color space : Saturation (S) was calculated by using the weighted 2-norm equation $S = C\sqrt{(da^*)^2 + (db^*)^2}$, where the conversion factor (C) is 17.7/60 (the average S value of non-irradiated breast skin = 17.7, and the estimated maximum S value of the irradiated side = +60). Hue (H) was calculated by using the equation $H = Tan^{-1}[db^*/da^*] \cdot \frac{180}{\pi}$.

Brightness (B) is the same as L* (L*=dL*×0.697 ; Average L* of non-irradiated side is 0.697).

5. A graph of H, S, or B versus days after the start of radiotherapy was generated for each dose, and the values of the constants were calculated by using a least squares method to develop a GLQ model for H, S, and B. However, because S increases after irradiation, the reciprocal value of S was used to develop a GLQ model, and the function was subsequently reversed to obtain a GLQ model of S.

6. Time-dependent colorimetric changes in the H-S-B system were reproduced on the radiation field in the 3-D breast model created by using the function.

This analysis was performed by using Mathematica version 9.0.1.

RESULTS

Time-dependent colorimetric changes in the L*a*b* color space were plotted by using the ratio of the measurement values between the ipsilateral and contralateral sides to create a 3-D plot with a regression plane. The 3-D plot revealed a negative correlation between dL* and da*, but no correlations between dL* and db* or da* and db* (Fig. 1).

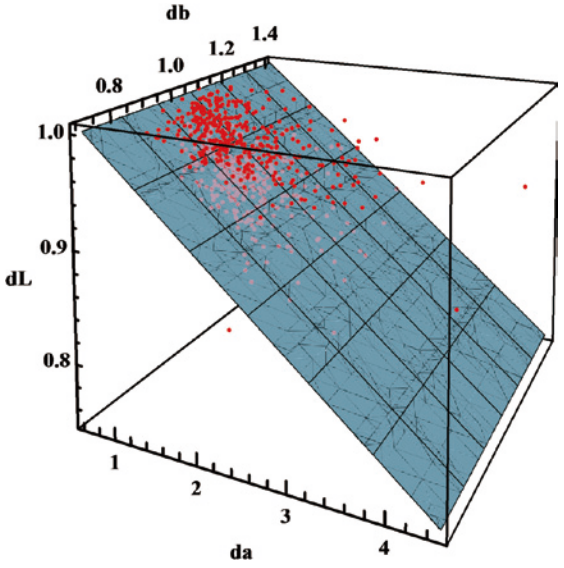

Fig. 1. Three-dimensional (da*-db*-dL*) plots for measured data of all patients. The oblique plane is calculated using regression analysis.

Table 1. Correction constant of Hue, Saturation, and Brightness

	Correction Constant ^(−1)	α	β	α/β
Hue	9.483	0.0109	0.003	3.67
Saturation	10.293	0.01	0.0027	3.67
Brightness	25.637	0.004	0.0011	3.67

In the non-linear regression model, the correction coefficient of the color space was calculated so that the value of α/β could be set to 3.67.

In LQ models, α and β are constants representing the radiosensitivity of the irradiated tissue. Although no data on the survival curve of skin cells were available, α/β was estimated to be 3-4 based on clinical data[8-10]. We therefore used a α/β *ratio* ≈ 3.67 ($\alpha = 0.103$, $\beta = 0.0281$) derived from the cultured cells SQ20B and a least squares method to determine a correction constant for α and β (Table 1).

The values of hue, saturation, and brightness, and their GLQ models generated by using a least squares method are shown in Figure 2. Although the peak skin reaction comes in about 2 weeks after irradiation, the skin visibly recovers in about three months. The skin recovery process was difficult to measure via spectrophotometry by using this

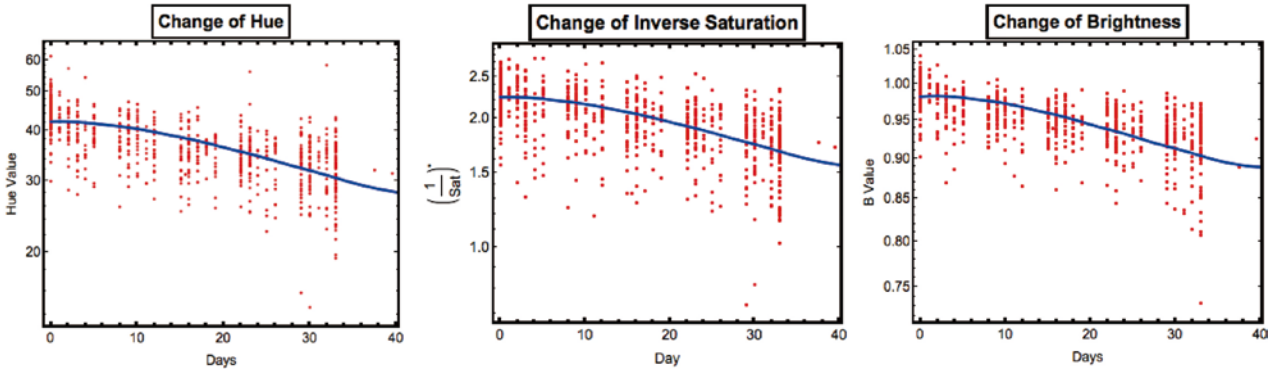

Fig. 2. Fitting curves of color space (Hue, Saturation, and Brightness) analyzed by using the non-linear least square method.

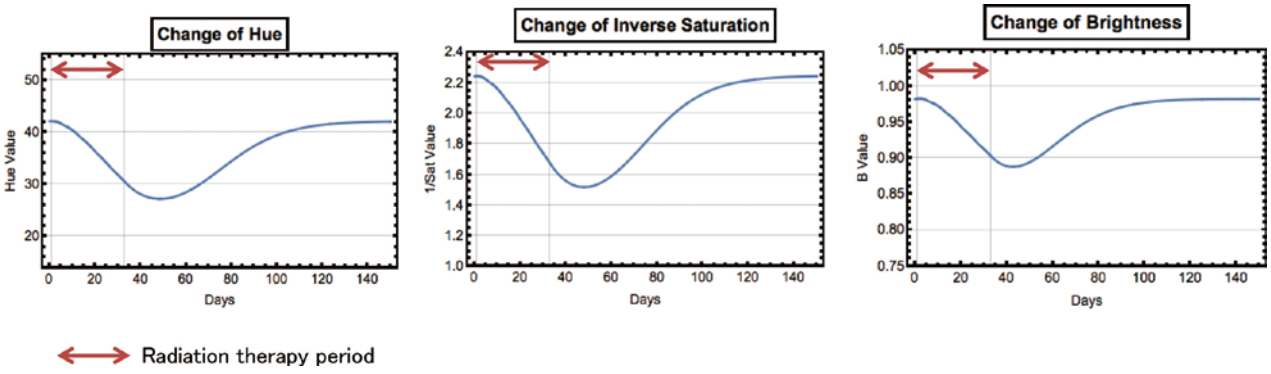

Fig. 3. Estimated temporary changes of skin erythema in color space during and after radiotherapy. The radiation period is indicated with an arrow.

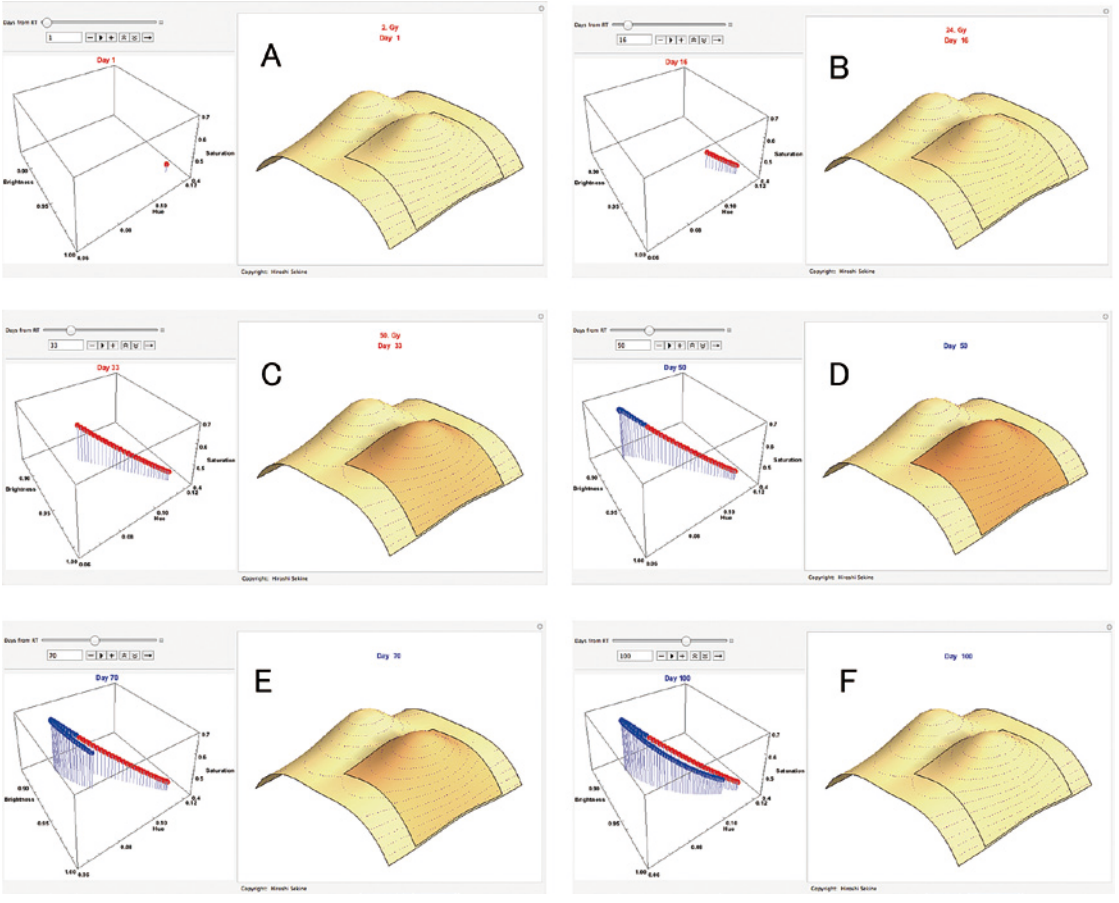

Fig. 4. Temporary color change of the skin during and after radiotherapy is projected on a body surface model and in corresponding color space. A : Day 1 (2 Gy), B : Day 16 (24 Gy), C : Day 33 (50 Gy), D : Day 50, E : Day 70, F : Day 100

study design. Therefore, in order to estimate the recovery process, we mathematically explored quantitative change by g(t) in the GLQ model. The graphs generated are shown in Figure 3.

The list of *H*, *S*, and *B* for treatment days 1–151 was created, and the values were reproduced on the radiation field in the body surface model (http://www.radbiolog.jp/Contents : Virtual Simulation using the GLQ model). As it was difficult to catch a dynamic simulation on paper, captures of the simulation were sampled and shown in Figure 4.

DISCUSSION

The effect of irradiation on the skin is collectively known as radiation dermatitis, and its symptoms and signs include erythema, dryness, and an increase in the temperature and blood amount in the irradiated skin[11–13]. Among these, the most recognizable symptom for the patient and physician is skin color change, that is, erythema. An accurate prediction of temporal changes in erythema will help the patient undergoing radiotherapy establish peace of mind and confidence. A preliminary study of measurement of skin color change by using spectrophotometry showed a pattern of color change during radiotherapy[7].

In this study, we therefore quantified and visually displayed the changes in radiation-induced erythema in the breasts of Japanese breast cancer patients. Usually, Japanese people have relatively small variations in skin color as compared with other races. Nevertheless, variations in skin color were found in this study after quantitative measurement.

Four-dimensional (4-D) simulation was used to reveal time-dependent changes in measurement values. To mathematically express the changes in the H, S, and B values, the changes were integrated into individual GLQ models, and a least squares method was used to obtain the constants.

When we showed the 4-D simulation (using QuickTime Movie on an iPad) to patients who were about to undergo radiotherapy after breast-conservation surgery, they were more understanding than the patients who did not watch the simulation. Furthermore, when shown the simulation and provided with an explanation of the principle behind it, medical students and residents who were on clinical rotation for radiotherapy were able to better understand the relationship between time, dose, and fractionation in radiation-induced erythema.

The present method should not be used to predict the severity of erythema in individual patients. However, the method can demonstrate that the severity of erythema depends on breast size. Some reports have shown that the skin reaction caused by radiotherapy is stronger in large breasts[14–16]. This conclusion is supported by the results of a study comparing acute toxicity of whole-breast irradiation in prone and supine positions in patients with large breasts[17]. This is because treatment in the prone position improves dose coverage, and reduces over-dosage volume and acute skin desquamation. In radiotherapy, breast size may be represented by depth of irradiation during treatment. Our research also suggests that severity of erythema is linked to breast size. (Data not shown)

We believe that the present method will be useful for developing GLQ models according to breast size, and for displaying the severity of erythema by breast size in a 4-D simulation.

CONCLUSION

Various symptoms and signs of radiation-induced dermatitis have been described qualitatively and quantitatively. In this study, erythema was quantified and the measurement values were incorporated into GLQ models to reproduce the temporal changes on a virtual radiation field. The conventional LQ model is not useful for representing changes over time. Furthermore, this is the first study to generate a simulation model by using measurement values. Simulation models generated by using the method described above will be useful for educating patients, medical students, residents, and nurses about the effects of radiation.

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