

Correlation Between Dosimetric Parameters and Acute Dermatitis of Post-operative Radiotherapy in Breast Cancer Patients

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Abstract. *Background/Aim:* To examine the correlation between dosimetric parameters and acute radiation dermatitis in early breast cancer patients subjected to post-operative radiotherapy. *Patients and Methods:* The data of 84 patients treated with post-operative radiotherapy were analyzed. The total prescribed dose was 50 Gy in 25 fractions over 5 weeks. Radiation dermatitis was assessed according to Common Terminology Criteria for Adverse Events v4.0. We set organ at risk whole body (from neck to abdomen examined by CT images) also as surrogate skin volume (3 mm thickness). *Results:* A total of 28 patients showed radiation dermatitis grade equal or higher than 2 at the 50 Gy time point. These 28 patients were compared to 56 matched pair patients with grade 0-1 radiation dermatitis during the same treatment period. The mean of V5-20 and V40 in patient's whole volume and V40-50 in skin volume were significantly higher in patients who presented with acute radiation dermatitis Grades ≥ 2 than in the other patients who did not. The statistically most significant difference was observed for V40 for skin volume and V5 for patient whole volume. Rate of acute radiation dermatitis grade ≥ 2 was significantly higher for patients with V5 (whole body) $>1,360 \text{ cm}^3$ than those with V5 (whole body) $<1,360 \text{ cm}^3$ (47% vs. 27%, $p=0.0353$), as well as for patients with V40 (skin volume) $>45 \text{ cm}^3$ compared with

those with V40 (skin volume) $<45 \text{ cm}^3$ (50% vs. 18%, $p=0.0043$). *Conclusion:* Dosimetric parameters were useful to predict radiation dermatitis grade ≥ 2 . V5 (whole body) $1,360 \text{ cm}^3$ and V40 (skin volume) 45 cm^3 may be dose volume constrain for radiation dermatitis grade ≥ 2 .

Breast-conservation therapy (BCT) for early-stage breast cancer, involving a lumpectomy followed by whole-breast radiotherapy, has become the standard therapy for suitable breast cancer patients (1, 2). Radiotherapy reduces local recurrence and improves overall survival rate compared to lumpectomy only (3). However, radiotherapy causes several treatment-related complications (e.g. dermatitis, pneumonitis, cardiac injuries), which sometimes deteriorate patients' quality of life (1, 2). Out of those toxicities, radiation dermatitis is the most common and extensively reported toxicity (4, 5). In a previous study, erythema occurred in more than 90% of the patients after standard radiotherapy, while 10% developed erythema of grade 3 or 4 in the 20th century (6). The influential factors for severe radiation dermatitis have been reported (7-14). High dose irradiation is one of the most important predictors of severity of both acute and late dermatitis and is associated with increased breast dose inhomogeneity and a resultant high irradiated volume (hot spots) (8-11, 14). As larger breasts, and higher body weight were reported to be predictive factors for radiation dermatitis, we included body mass index (BMI) in the factors examined in this study (8-11).

After spreading of three-dimensional conformal radiotherapy (3D-CRT), field in field technique (FIF) was installed to reduce hot spot (15, 16). FIF reduced hotspot more than 107-110% at the prescribed dose (53.5-55 Gy if prescribed dose is 50 Gy), which may result in a reduction of severe radiation dermatitis. In addition, intensity modulated radiotherapy was also explored in order to reduce inhomogeneity and hotspot (17).

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Dose volume analysis is an essential part of radiation biology to predict outcome not only for tumor control but also for toxicity; *i.e.*, V20 (normal lung volume irradiated by more than 20 Gy) or mean lung dose is an important constrain to reduce radiation pneumonitis in lung irradiation (18). However, there is a paucity of literature on dosimetric parameters for radiation dermatitis (12). Therefore, in this study, the role of dosimetric parameters for the prediction of radiation dermatitis was explored. We set organ at risk the whole body because lower irradiation area also extended outside the treated volume. In addition, we set surrogate skin volume as a represented organ at risk for skin. This study's aim was to examine the predictive role of dosimetric parameter for radiation dermatitis in patients that underwent post-operative radiotherapy.

Patients and Methods

Patient characteristics. Between December 2008 and March 2016, 529 patients underwent postoperative radiation therapy at Department of Radiology Kyoto Prefectural Medical University. Of them, 28 patients (5.3%) showed grade ≥ 2 radiation dermatitis (26 grade 2 and 2 grade 3). These 28 patients were compared to 56 matched pair patients with grade 0-1 radiation dermatitis during the same treatment period. To compare the influential factors for radiation dermatitis 56 matched pair (age, T, N, M, treatment periods) patients were included (2 patients with grade 0 and 54 patients with grade 1) (1:2 comparison). All patients had been traditionally treated with tangential Field's 6 MV photon beam using Linac. The median age of the patients was 54 years (range=23-84 years). Eligibility criteria were invasive or non-invasive ductal carcinoma, invasive lobular carcinoma, or malignant disease requiring post-operative radiotherapy, and ECOG (Eastern Cooperative Oncology Group) performance status 0-2. All patients had histologically proven breast malignancy. Table I shows the characteristics of patients. All patients were enrolled in the study after signing an informed consent prior to radiotherapy. The study followed the guidelines and protocol approved by the intra-institutional ethics committee (IRB permission No. RBMR-c-803-2).

Treatment. Details of radiotherapy (RT) are described elsewhere (19). In brief, radiation dose was normalized to the point of the midplane of the breast (ICRU reference point). In all cases, 50 Gy was prescribed in 25 fractions. CT images for treatment planning were taken from the middle neck to the middle abdomen using 3 mm slices at the CT - scanner (Aquilion, Toshiba Medical, Tokyo, Japan). Radiotherapy planning and dosimetric parameters were calculated with a commercial treatment planning system (TPS) (XiO, Elekta Medical Systems Inc., Stockholm, Sweden). To obtain a uniform dose distribution, a wedge filter or FIF technique was used to reduce the maximum dose to $<110\%$ of the prescribed dose (15, 19).

When FIF was applied, initially, the dose distribution was calculated using the tangential two field technique. Secondly, by viewing the dose distribution along the beam's-eye view, the subfields were optimally added to shield the areas of the breast receiving doses more than 107-110% of the prescription dose by manipulating the multi leaf collimators. The weight of additional subfields was approximately 6-10% of the total dose. All additional subfields were set not to shield the field isocenter as the dose reference point.

Dosimetric analysis. Whole body volume was delineated from neck to upper abdomen as solid organ on the CT images (Figure 1a). We set organ at risk whole body volume and also surrogate skin volume "skin volume". Skin volume was calculated by "whole body" minus "whole body minus 3 mm" volume in XiO (Figure 1b). The volumes of the "whole body" (cm^3) and "skin volume" (cm^3) receiving 5 Gy, 10 Gy, 20 Gy, 30 Gy, 40 Gy, 50 Gy, 107% of the prescribed dose=53.5 Gy (V5, V10, V20, V30, V40, V50, V107%, respectively) and maximal dosage were calculated.

Toxicity analysis. Radiation oncologists performed an assessment of radiation dermatitis according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 at 50 Gy point. Comparisons between patients with radiation dermatitis grade 2-3 and grade 0-1 were made.

Statistical analysis. All statistical analyses were carried out with the Statview-v5.0 software program. Student's *t*-tests were used for normally distributed data and the Mann-Whitney *U*-test for skewed data. For analyzing correlation coefficients *lrl*, we defined $p < 0.05$ if $|lrl| \geq 0.2$ ($0.4 \geq |lrl| > 0.2$; weak correlation, $0.7 \geq |lrl| > 0.4$; intermediate correlation, $|lrl| > 0.7$; strong correlation). The chi-square test was used to analyze percentages and considered a *p*-value of < 0.05 as statistically significant.

Results

There were no background differences in patients with grade 0-1 and grade 2-3 of radiation dermatitis. No toxicity of grade 4 \geq was detected in any patient.

Table II shows the correlations between the dosimetry parameters (whole body) and radiation dermatitis grade ≥ 2 . V5, V10, V20, and V40 showed statistically significant differences in patients' whole body. The lowest *p*-value was observed for V5 ($p=0.011$, Figure 2a).

Table III shows the correlations between the dosimetric parameter (skin volume) and radiation dermatitis grade ≥ 2 . Patients with grade ≥ 2 dermatitis had significantly higher values in V40 and V50 (skin volume). The lowest *p*-value was observed for skin V40 ($p=0.008$, Figure 2b).

V5 (whole body) and V40 (skin volume) were statistically significantly correlated with BMI ($p=0.0171$, $|lrl|=0.260$, $p=0.0141$, $|lrl|=0.444$, Table IV).

Rate of acute radiation dermatitis grade ≥ 2 was significantly higher for patients with V5 (whole body) $>1360 \text{ cm}^3$ than those with V5 (whole body) $\leq 1360 \text{ cm}^3$ (47% vs. 23%, $p=0.0353$), as well as for patients with V40 (skin volume) $>45 \text{ cm}^3$ compared with those with V40 (skin volume) $\leq 45 \text{ cm}^3$ (50% vs. 18%, $p=0.0043$, Table V).

Discussion

Breast conserving therapy has become a standard treatment as it helps to improve QOL of breast cancer patients. Activities of daily living, physical factors, and psy-chological status are the main criteria in assessing QOL

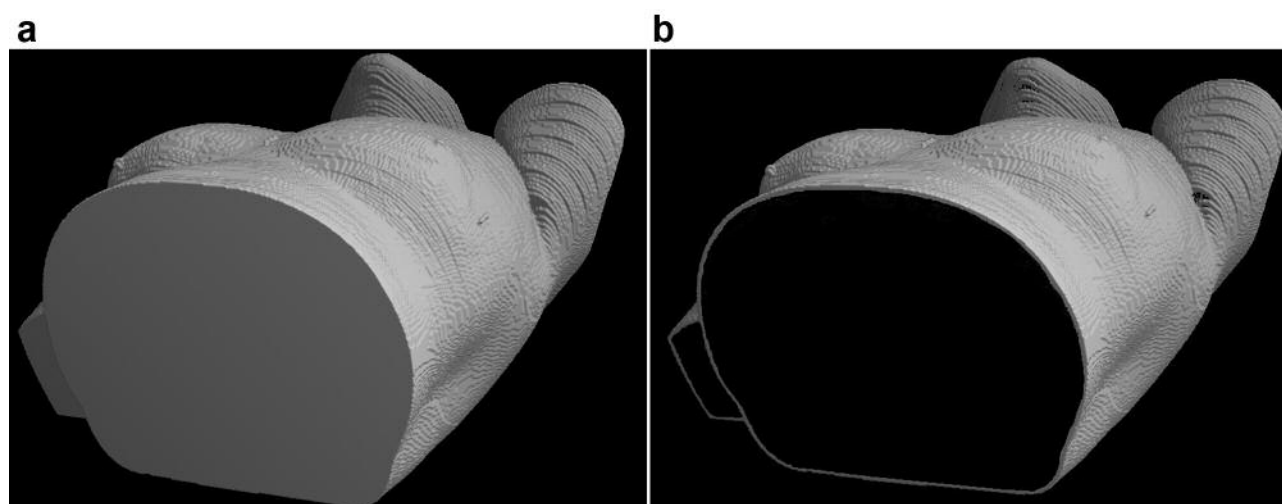


Figure 1. Represented figures of organs at risk. a) Whole body. Whole body of patient was created by contour of patient's outline. b) Skin volume. Skin volume (3 mm thickness) was calculated by "whole body" (Figure 1a) minus "whole body minus 3 mm" volume.

Table I. Characteristics and treatment factors of patients.

Variables	Strata	All n=84		Grade 0-1 n=56		Grade 2-3 n=28		p-Value
		No. or Median (range)	(%)	No. or Median (range)	(%)	No. or Median (range)	(%)	
Age		54 (23-77)		56 (26-77)		48 (23-73)		
Primary site	Right	37	(44%)	23	(41%)	14	(50%)	0.5865
	Left	47	(56%)	33	(59%)	14	(50%)	
Histology	Invasive Ductal Ca.	57	(68%)	39	(70%)	18	(64%)	0.7596
	DCIS	23	(27%)	14	(25%)	9	(32%)	
	Other	4	(5%)	3	(5%)	1	(4%)	
pT category	is	18	(21%)	12	(21%)	6	(21%)	0.5667
	0	3	(4%)	2	(4%)	0	(0%)	
	1	44	(52%)	27	(48%)	17	(61%)	
	2	15	(18%)	11	(20%)	4	(14%)	
	3	2	(2%)	2	(4%)	0	(0%)	
	4	1	(1%)	2	(4%)	0	(0%)	
	Other	1	(1%)	0	(0%)	1	(4%)	
Body mass index	(kg/m ²)	21.5 (15.9-38.9)		21.4 (15.9-30.0)		21.4 (16.3-38.9)		0.8199

DCIS: Ductal carcinoma *in situ*.

(19) and cosmetic assessment is one of the factors of interest to women. Radiation-induced skin changes were recognized soon after the discovery of x-rays and were scientifically reported as early as in 1902 (5). This is a consequence of the well-known fact that sensitivity to radiation varies between individuals and underlines the necessity of finding an objective and predictive assessment method. Therefore, we made a dose volume analysis in skin volume to find useful objective parameters to predict severe radiation dermatitis.

Several influential factors have been reported for radiation dermatitis. Larger breast volume, lower radiotherapy energy, larger irradiated volume, boost irradiation, and absence of skin care elevated severe radiation dermatitis (8-14). Inhomogeneity of radiation dose distribution also caused severe radiation dermatitis. With conventional breast radiotherapy, a portion of the breast tissue receives 110% of the prescription dose, occasionally up to 120% (20). Chen *et al.* reported that such hotspot with over 110% of the

Table II. Correlations between dosimetric parameters of whole body and radiation dermatitis grade 2 or more.

Variables		Grade 0-1 (n=56) Mean±SD	Grade 2-3 (n=28) Mean±SD	p-Value
V5	(cm ³)	1412±531	1645±475	0.011
V10	(cm ³)	1263±482	1458±437	0.027
V20	(cm ³)	1096±437	1266±403	0.035
V30	(cm ³)	968±398	1123±378	0.107
V40	(cm ³)	804±346	936±347	0.040
V50	(cm ³)	248±185	320±231	0.100
V107 %	(cm ³)	4.12±11	23±76	0.145
Maximal dosage	(Gy)	53.76±0.88	54.18±1.11	0.154

Bold depicted statistically significant values.

Table III. Correlations between dosimetric parameters of skin volume and radiation dermatitis grade 2 or more.

Variables		Grade 0-1 (n=56) Mean±SD	Grade 2-3 (n=28) Mean±SD	p-Value
V5	(cm ³)	162.7±29.2	167.6±29.8	0.471
V10	(cm ³)	152.1±27.8	156.9±26.9	0.488
V20	(cm ³)	135.7±25.1	140.0± 22.7	0.471
V30	(cm ³)	103.9±20.0	111.4±18.6	0.107
V40	(cm ³)	43.8±11.7	51.4±12.7	0.008
V50	(cm ³)	0.9±1.4	1.6±2.1	0.049
V107 %	(cm ³)	0.02±0.1	0.03±0.1	0.195
Maximal dosage	(Gy)	52.42±1.08	53.00±1.37	0.135

Bold depicted statistically significant values.

Table IV. Correlations among influential factors on radiation dermatitis grade 2 or more and body mass index.

Variables		V5 (whole body)	V40 (skin volume)	Body mass index
V5 (whole body)	(cm ³)		<0.0001	0.0171
V40 (skin volume)	(cm ³)	0.611		0.0141
Body mass index	(kg/m ²)	0.260	0.444	

p-Value depicted in upper right columns, and lrl value depicted in lower left columns. Bold depicted statistically significant values.

Table V. Correlation between dosimetric parameter and radiation dermatitis grade 2 or more.

Variables	Strata	Grade 0-1 n=56		Grade 2-3 n=28		p-Value
		No.	(%)	No.	(%)	
V5	-1360 cm ³	37	(77%)	11	(23%)	0.0353
(Whole body)	1360 cm ³ -	19	(53%)	17	(47%)	
V40	-45 cm ³	36	(82%)	8	(18%)	0.0043
(Skin volume)	45 cm ³ -	20	(50%)	20	(50%)	

Bold depicted statistically significant values.

prescribed dose may be an important predictor for radiation dermatitis (12). In addition, smoking, absence of allergies, use of chemotherapy were also reported to be potential influential factors for radiation dermatitis (10, 11).

Erythema after standard 3D-CRT was observed at an average of 90% of the patients, while 10% developed erythema grade 3 or 4 (6). However, recent breast cancer treatment includes several chemotherapy agents, antihormonal therapies and improved radiation therapy techniques. Kraus-Tiefenbacher *et al.* reported lower skin toxicity rate of 70% erythema [Grade 1 (62.2%), grade 2 (8.5%), and no grade 3] in 211 patients with careful skin care (11). Also, in a previous study, we found that around 30 % of patients developed grade ≥2 radiation dermatitis using two-dimensional planning and 3D-CRT wedge technique (19). On contrast, only less than 5% of grade ≥2 radiation dermatitis was found in the present study after installing FIF technique. Nakamura *et al.* also reported that FIF technique offered excellent target coverage and homogeneity (16).

Sasaoka *et al.* reported that FIF significantly reduced Radiation Therapy Oncology Group (RTOG) grade 2 acute skin toxicity compared with the tangential field technique (3.1 vs. 10.6%) which concurred to our data (15). This could be due, in part, to the fact that Japanese women have smaller breasts than Caucasian women, which results in decreased irradiated volume and toxicity. Ding *et al.* also reported lower rate of grade 2 toxicity (grade 1=68.9%, grade 2=11%), in the Chinese population (9).

This is the first report analyzing dosimetric parameters for radiation dermatitis using organs at risk “whole body” and “skin volume”. Chen *et al.* reported that TV-V110% > 5.13% (percent volume receiving 110% of prescribed dose within treated volume (TV)) may be an important predictor for radiation induced dermatitis and TV-V110% related to the location of moist desquamation (12). Treated volume was considered the volume enclosed within the prescribed dose and radiation hot spot the areas receiving excessive dose, especially >110% of the prescribed dose. We agree that

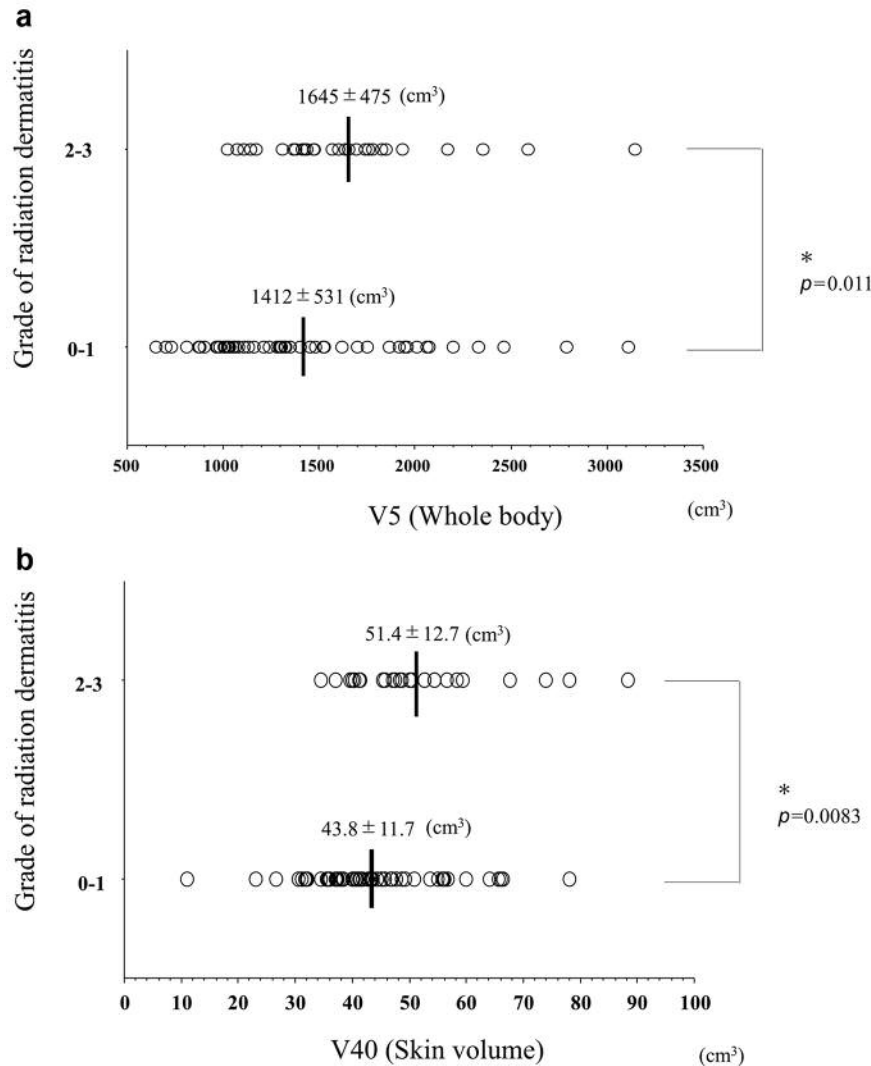


Figure 2. Correlations between dosimetric parameters and radiation dermatitis. a) V5 (whole body), b) V40 (skin volume).

hotspot is an important factor for prediction of radiation dermatitis. However, with the introduction of FIF technique, the subfields are added to the main section, hotspots were reduced at 110% of prescribed dose or more. Therefore, we thought that “whole body” or “skin volume” estimation could be useful for assessment of skin toxicity because irradiated area may spread outside breast volume or treated volume in radiotherapy planning. In fact, lowest dose constrain V5 revealed significant for radiation dermatitis. Then, treatment volume is not restricted within the organ at risk requiring larger volume. At present, no consensus on organ at risk for assessment of dermatitis has reached. This issue (optimal organ at risk for radiation dermatitis) could be left for further investigation. Actually, until now, larger breast has been identified as an important predictor of radiation dermatitis (8-

14). Also, in this study, V5 (whole body) and V40 (skin volume) showed strong correlations to body mass index. However, BMI was not found to be significant for radiation dermatitis. Which implies that FIF technique could reduce the significance of V110% and BMI for prediction of radiation dermatitis by diminishing the hotspot.

Our study had several limitations. First, this was a preliminary study with a small number of patients. Next, our data did not contain the subjective evaluation of symptoms by the patients, which would be important because several studies found significant differences between patients and clinicians when assessing toxicities following radiotherapy or chemotherapy (21, 22). At last, it does not contain the analysis on maximal color alteration which could occur even after completion of radiotherapy. In a Canadian prospective

trial, Drost *et al.* reported that ratio of grade ≥ 2 dermatitis peaked at 2 weeks after completion radiotherapy at 61.9%, which is higher than 36.3% (Grade 2=38.5%, grade 3=4.5%) at the 50 Gy timing (9). Therefore, rate of grade ≥ 2 dermatitis varies according to timing of assessment.

In conclusion, our present data showed that dosimetric parameters were useful to predict radiation dermatitis grade ≥ 2 . V5 (whole body) 1,360 cm³ and V40 (skin volume) 45 cm³ may be dose volume constraints for radiation dermatitis grade ≥ 2 .

Conflicts of Interest

The Authors state no conflicts of interest regarding this study.

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