Cytogenetic aberrations after partial-body irradiation during fractionated radiotherapy

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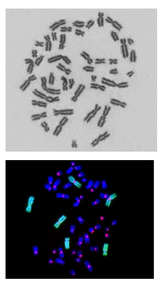
Abstract

Partial-body exposure cases are likely to occur in radiological accident, but studies on the application of biodosimetry have been relatively focused on whole-body exposure. In addition, a direct data of in vivo response to partial-body exposure are limited. In this study, we evaluated the in vivo response of cytogenetic biomarkers to localized and fractionated radiation exposure. We assessed time-dependent changes in chromosomal aberrations before, during, and after localized fractionated radiotherapy. Patients (n=12) who received adjuvant radiotherapy after breast conserving surgery were recruited for this study. Their blood samples were taken at various time points during radiotherapy, and dicentric chromosome assay and fluorescence in situ hybridization-based translocation assay were performed. Chromosome aberrations were then used to calculate whole- and partial-body biological absorbed doses of radiation. Dicentric chromosome frequencies in all study participants increased during radiotherapy ($p < 0.05$ in Kruskal-Wallis test). Increases of translocation frequencies during radiotherapy were observed in seven of the twelve patients. The increased levels of dicentric chromosomes and translocations persisted throughout our 1-year follow-up, and evidence of partial-body exposure (such as Papworth's U-value > 1.96) was observed more than 1 year after radiotherapy. We found that cytogenetic biomarkers reflected partial-body fractionated radiation exposure more than 1 year post-exposure. In addition, biological whole-body dose estimates were significantly correlated with calculated equivalent whole-body dose. The partial-body dose agreed quite well with the dose delivered to the tumor after the first fraction of radiotherapy. Taken together, our findings suggest that chromosome aberrations can be used to estimate biological absorbed radiation doses and can inform medical intervention for individuals suspected of fractionated or partial-body radiation exposure.

Background

- Biological dose estimation using chromosome aberrations such as dicentric chromosomes and translocations has been applied to assess health risks and guide medical treatment decisions in response to radiation accidents (IAEA 2011).
- Radiation biodosimetry is generally applied to whole-body exposure scenarios, but a substantial proportion of radiological incidents involve non-homogeneous partial-body exposures.(Coeytaux et al., 2015; Wang et al., 2021)
- The time-kinetics of radiation biomarkers in response to partial-body exposure have been studied primarily in animal models, due to the difficulty of obtaining radiation-exposed human samples (Herodin et al., 2012; Blakely et al., 2014).
- In this study, we evaluated the frequency of dicentric chromosomes and translocations in a homogeneous patient population that received adjuvant radiotherapy after breast-conserving surgery and followed their progress for approximately 1 year after radiotherapy.



Materials & Methods

Study subject

- Patients (n = 12) who were diagnosed with carcinoma in situ of the breast and scheduled to receive adjuvant radiation therapy were recruited for the study
- All subjects provided written informed consent prior to participation.
- Study Eligibility criteria

Inclusion criteria	Exclusion criteria
• women over the age of 19	• If pregnant or lactating at the time of study enrollment
• pathologically proven carcinoma in situ of the breast, prior breast conserving surgery	• if the radiotherapy field was a partial breast or bilateral breasts.
• an Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 2,	• if scheduled radiotherapy was discontinued,
• no previous radiotherapy or chemotherapy	• If less than 1 year of follow-up was available,
• no prescribed chemotherapy	• If chemotherapy or additional radiotherapy was administered during the study
• scheduled to receive adjuvant radiotherapy to the ipsilateral whole breast	• if the patient no longer wanted to participate in the study.

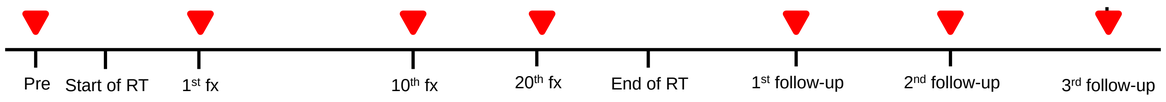
- A control population (n = 120) that was free of occupational or accidental radiation exposure was as a reference (Jang et al., 2016).

Radiotherapy and Physical whole body dose calculation

- All patients underwent adjuvant radiotherapy after breast-conserving surgery.
- The planning target volume included the ipsilateral whole breast and was prescribed at 50 Gy in 25 fractions.
- Physical whole-body dose = The mean dose of CT scanned body (D_{mean_BVCT}) x body volume in the planning CT scan (BVCT) / total body volume (TBV)

Blood collection

- Peripheral blood samples were collected before treatment, during the course of radiotherapy and after treatment (approximately 3, 6, and 12 months).



Cytogenetic analysis and Biological dose estimation

- Dicentric chromosome assays (DCA) and FISH-based translocation assays were performed according to guidelines recommended by IAEA (IAEA 2011).
- Whole-body dose estimates and 95% confidence intervals were calculated using the results of DCA and translocation assay.
- Papworth's U-value, a normalized unit of dispersion (the variance/mean ratio), was calculated to determine the heterogeneity of irradiation.
- The contaminated Poisson method proposed by Dolphin was applied to estimate partial-body dose and the fraction of the body irradiated

Result

Table 1. Characteristics of the study cohort.

Patient code	Age	ECOG	Duration of RT (day)	Height (cm)	Weight (cm)	BSA (m^2)	TBV (litre)	BVCT (litre)	D_{mean_BVCT} (Gy)	Physically estimated whole-body dose (Gy)
#1	49	0	39	164	65.7	1.73	62.12	14.67	5.49	1.296
#2	48	1	33	162	53.2	1.55	49.90	11.35	4.19	0.953
#3	44	0	33	158	63.5	1.67	60.08	14.73	5.46	1.339
#4	44	0	33	158.5	52.8	1.52	49.30	10.36	4.59	0.965
#5	52	0	33	150	56.7	1.54	53.40	13.62	5.16	1.316
#6	52	0	37	165	59.6	1.65	55.90	13.38	5.11	1.223
#7	55	0	37	152.1	84.7	1.89	83.06	18.23	5.12	1.124
#8	60	0	39	159.6	57.4	1.6	54.08	13.26	4.46	1.094
#9	75	1	33	143.1	59.3	1.54	56.39	12.81	4.47	1.015
#10	40	0	40	168.5	55.3	1.61	51.51	10.25	3.85	0.766
#11	61	0	40	160.1	66.3	1.72	62.96	15.00	5.28	1.258
#12	46	0	33	160.6	52.3	1.53	49.04	10.54	4.69	1.008
CV (%)	-	-	8.6	4.4	14.8	6.8	16.4	17.8	10.9	16.0

ECOG, Eastern Cooperative Oncology Group performance status; BSA, body surface area; TBV, total body volume; RT, radiation therapy; BVCT, total body volume according to the planning CT scan; D_{mean_BVCT}, mean dose of total body volume according to the planning CT scan.

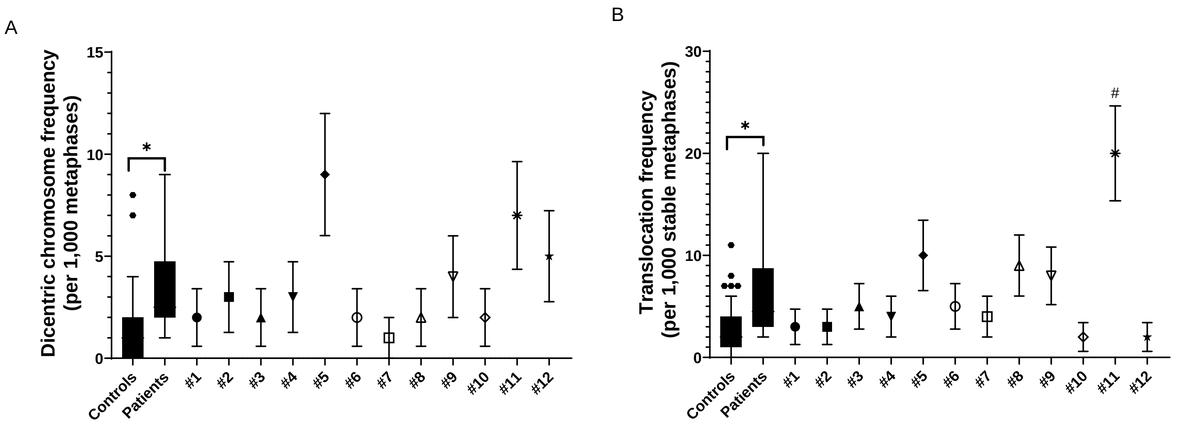


Figure 1.. Chromosomal aberrations in patients prior to radiotherapy. (A) Dicentric chromosome frequencies of the control population, the patient cohort, and each patient individually. (B) Translocation frequencies of the control population, the patient cohort, and each patient individually. * $p < 0.05$ when comparing all controls to all patients (Mann-Whitney U test). # $p < 0.05$ when comparing patient 11 to patients 1, 2, 3, 4, 6, and 7 (Kruskal-Wallis test followed by post-hoc Dunn's multiple comparison test). The control population (n = 120) was previously described in Jang et al (2016).

Result

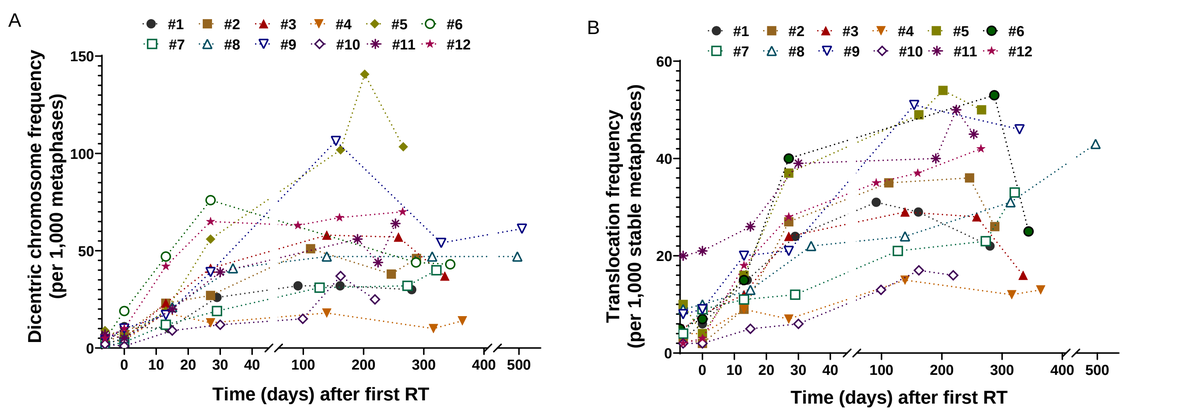


Figure 2. Chromosome aberration dynamics during and after the initiation of radiotherapy. The frequencies of dicentric chromosomes (A) and translocations (B) at time points ranging from –7 to 507 days, where day 0 indicates the first fraction of radiotherapy was received. Each symbol represents individual values of 12 patients.

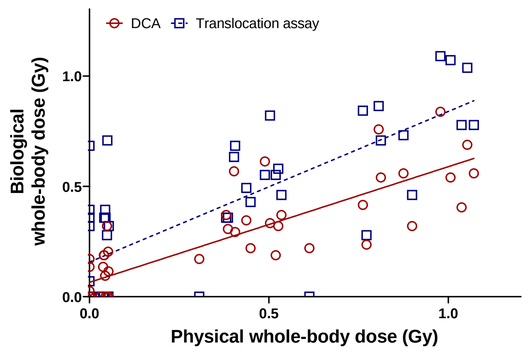


Figure 3. Correlation between physically and biologically estimated whole-body radiation doses. Physically estimated whole-body doses were calculated by dividing the integral dose by the total body volume of each patient. Biological whole-body doses were calculated using the results of the dicentric chromosome assay (DCA) or the FISH-based translocation assay. Circles and rectangles represent dose estimates derived from DCA and translocation assays, respectively.

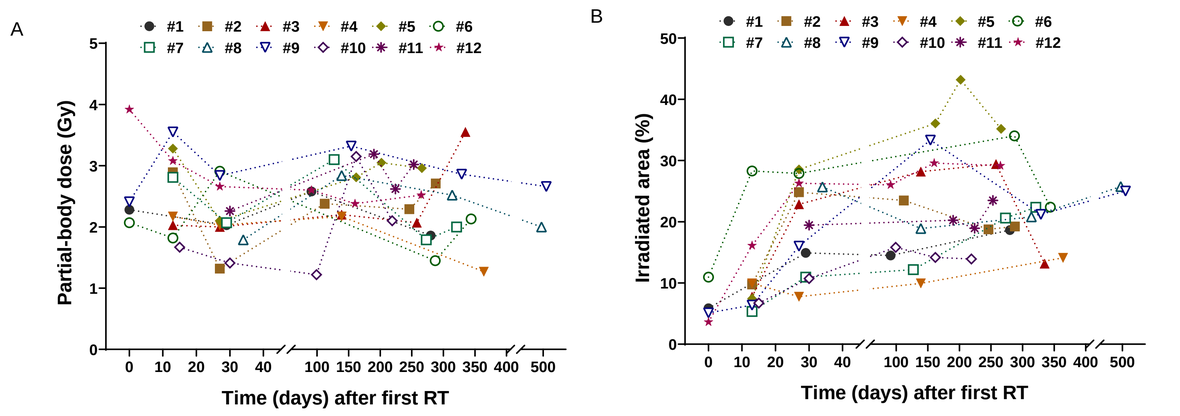


Figure 4. Partial-body radiation exposure during and after the initiation of radiotherapy. Partial-body doses (A) and irradiated areas (B) were calculated using the results of the DCA based on the contaminated Poisson method. Each symbol represents individual dose estimates of 12 patients at various time points (-7 to 507 days), where day 0 indicates the first fraction of radiotherapy was received.

Table 1. Partial-body exposures estimated by dicentric chromosome assay.

	Radiation exposure during radiotherapy	Partial-body exposure estimated by DCA	
	Tumor dose (Gy)	Local dose (Gy) ± SEM	Irradiated volume (%)
#1	2.0	2.28 ± 0.35	5.88
#6	2.0	2.08 ± 0.33	10.95
#9	2.0	2.42 ±0.37	5.12
#12	2.0	3.91 ± 0.45	3.64

[1]Partial-body dose was estimated by contaminated Poisson method (mean lethal dose = 2.70 Gy).
DCA, dicentric chromosome assay; SEM, standard error of the mean.

Conclusions

- We established a well-defined study population and investigated longitudinal partial-body radiation exposure and resulting chromosome aberrations. .
- Radiotherapy-induced dicentric chromosome and translocation frequencies were stable within approximately 1 year. Evidence of partial-body exposure was also observed during the 1-year follow-up period.
- Our findings suggest that chromosome aberrations can be used to estimate biological absorbed radiation doses and can inform medical intervention for individuals suspected of fractionated or partial-body radiation exposure.

References

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This study was supported by grants from the Korea Institute of Radiological and Medical Sciences (No. 50445-2021) and the National Research Foundation of Korea Grant (No. NRF2019R1A2C208741613), funded by the Ministry of Science and ICT, Republic of Korea.

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