

Relation between Lineal Energy Distribution and Relative Biological Effectiveness for Photon Beams according to the Microdosimetric Kinetic Model

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Our cell survival data showed the obvious dependence of RBE on photon energy: The RBE value for 200 kV X-rays was approximately 10% greater than those for mega-voltage photon beams. In radiation therapy using mega-voltage photon beams, the photon energy distribution outside the field is different with that in the radiation field because of a large number of low energy scattering photons. Hence, the RBE values outside the field become greater. To evaluate the increase in RBE, the method of deriving the RBE using the Microdosimetric Kinetic model (MK model) was proposed in this study. The MK model has two kinds of the parameters, tissue-specific parameters and the dose-mean lineal energy derived from the lineal energy distributions measured with a Tissue-Equivalent Proportional Counter (TEPC). The lineal energy distributions with the same geometries of the cell irradiations for 200 kV X-rays, ⁶⁰Co γ -rays, and 6 MV X-rays were obtained with the TEPC and Monte Carlo code GEANT4. The measured lineal energy distribution for 200 kV X-rays was quite different from those for mega-voltage photon beams. The dose-mean lineal energy of 200 kV X-rays showed the greatest value, 4.51 keV/ μ m, comparing with 2.34 and 2.36 keV/ μ m for ⁶⁰Co γ -rays and 6 MV X-rays, respectively. By using the results of the TEPC and cell irradiations, the tissue-specific parameters in the MK model were determined. As a result, the RBE of the photon beams (y_D : 2~5 keV/ μ m) in arbitrary conditions can be derived by the measurements only or the calculations only of the dose-mean lineal energy.

INTRODUCTION

In the radiotherapy using photon beams, Relative Biological Effectiveness (RBE) has been conventionally regarded as 1.0 in any energy range.¹⁾ Only physical dose has been used to design the treatment planning in the conventional photon radiotherapy. However, the photon energy distribution outside the field is different with that in the field because of a large number of low energy scattering

photons.²⁾ Consequently, the RBE outside the field becomes greater.³⁾

In microdosimetry, a lineal energy distribution is related to RBE and a distribution of energy deposited by ionizing radiations in the microscopic region,^{4,5)} which causes lethal lesions of DNA resulting in radiation-induced cell death. Thus, lineal energy is an important quantity for evaluation of radiation quality,⁶⁻⁹⁾ and has been measured with a Tissue-Equivalent Proportional Counter (TEPC) and calculated with the Monte Carlo simulation.¹⁰⁻¹³⁾

The Microdosimetric Kinetic model (MK model) is a biophysical model of cell survival after irradiations.^{6,7)} In the MK model, the increase in the RBE can be explained as the increase in energy deposited in a microdosimetric site which can be defined as a microscopic subunit referred to as a "domain". Furthermore, it is assumed that the mean number of lethal lesions in a domain can be described by a linear-quadratic function of specific energy. A survival fraction of tumor cells irradiated with low-LET radiations was mathematically derived by considering distributions of lethal lesions according to the Poisson distribution. Moreover, this

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model requires the determinations of the dose-mean lineal energy and the tissue-specific parameters to calculate RBE values. In this study, the dose-mean lineal energy for 200 kV X-rays, ^{60}Co γ -rays, and 6 MV X-rays were derived from the lineal energy distributions measured with a TEPC. Furthermore, the measured lineal energy distributions were compared with the calculations with a Monte Carlo code, GEANT4.¹⁴⁾ The tissue-specific parameters were determined from the experimental cell survival fractions after irradiations with 200 kV X-rays, ^{60}Co γ -rays, and 6 MV X-rays.

We assume that the biological response of the Human Salivary Gland (HSG) tumor cells can be expressed according to the MK model. Our purpose is to propose the method of deriving the RBE for photon beams from physical approach instead of performing the cell irradiations. By using the obtained tissue-specific parameters, the RBE of the photon beams (y_D : 2~5 keV/ μm) in arbitrary conditions can be derived by the measurements only or the calculations only of the lineal energy distributions.

MATERIALS AND METHODS

Derivation of RBE according to the MK model

According to the paper,^{6,7)} shape of a domain is sphere, and a cell nucleus is filled with domains, although it cannot be physically realized. The meaning of domains is to set the restricted region in a cell nucleus, because a lethal lesion is produced by a pair of sub-lethal lesions which is created in a nearly distance each other. The MK model assumes that the mean number of lethal lesions L in a domain can be described by a linear-quadratic function of specific energy z , as follows.

$$L = Az + Bz^2 \quad (1)$$

The average number of lethal lesions L_n in a cell nucleus and the survival fraction S can be described by using the expected value (brackets), assuming the Poisson distribution of number of hits (ion-pairs) to a domain by a charged particles, as follows,

$$\begin{aligned} L_n &= N \langle L \rangle = N(A \langle z \rangle + B \langle z^2 \rangle) \\ &= \left(\alpha_0 + \frac{\beta y_D}{\rho \pi r_d^2} \right) D + \beta D^2 \\ &= \alpha D + \beta D^2 = -\ln S \end{aligned} \quad (2)$$

where N , $\langle L \rangle$, and y_D denote the number of domains in a cell nucleus, the average number of lethal lesions in a domain, and the single-event dose-mean lineal energy.^{4,5)} Other parameters, r_d , and ρ represent the radius of domains, the density of domains, respectively. The tissue-specific parameters, r_d , α_0 , and β were obtained from the experimental cell survival fractions after irradiations with 200 kV X-rays, ^{60}Co γ -rays, and 6 MV X-rays in this study. That is, these parameters were determined as free parameters for fitting the

experiments. The α_0 and β have replaced NA and NB , respectively. Thus, the determination of N is not necessary in the process. The domain's density ρ is assumed to be 1.0 g/cm³. Note that only α depends on radiation quality, whereas β is tissue-specific and constant irrespective of radiation quality. By using the lineal energy distribution obtained from a TEPC or GEANT4 simulation, the dose-mean lineal energy y_D can be calculated, as follows,

$$y = \frac{\varepsilon}{l} \quad (3)$$

$$y_D = \frac{\int y^2 f(y) dy}{\int y f(y) dy} = \frac{\int y d(y) dy}{\int d(y) dy} \quad (4)$$

where ε , l , y , $f(y)$, and $d(y)$ denote the energy deposited in a domain, mean chord length, lineal energy, and the probability density of a lineal energy, and dose distributions of a lineal energy, respectively. The mean chord length l of a sphere can be expressed as $2/3 \times \text{diameter}$ ($2/3 \times 1 \mu\text{m}$ water-equivalent) by assuming the uniformity of radiations emitted in a given directions.⁴⁾ In the calculation of the RBE, we defined 200 kV X-rays as a reference radiation, as the following equation,

$$\begin{aligned} RBE &= \left[\frac{D_{200\text{kV}}}{D} \right]_{\text{same effect}} \\ &= \left(\frac{\sqrt{\alpha_{200\text{kV}}^2 + 4\beta_{200\text{kV}} S^*} - \alpha_{200\text{kV}}}{2\beta_{200\text{kV}}} \right) \left(\frac{\sqrt{\alpha^2 + 4\beta S^*} - \alpha}{2\beta} \right)^{-1} \end{aligned} \quad (5)$$

where S^* is negative of the natural log of the survival fraction S . The RBE value was calculated at the 10% survival level, i.e., $S^* = -\ln(0.1)$. In the MK model, $\beta_{200\text{kV}}$ is equal to β .

Measurements of lineal energy distributions with a TEPC

A TEPC (LET -1/2, Far West Technology Inc.) was used for measurements of lineal energy distributions in the microdosimetric size for a 200 kV X-ray diagnostic apparatus (MG226/4.5, YXLON, half value layer (with filters of Cu and Al of 0.5 mm thick) = 11.9 mmAl), a ^{60}Co irradiation equipment (custom-made), and a 6 MV clinical accelerator (Varian 21EX, Varian Medical Systems). Geometrical setup of the TEPC and other conditions were similar to the cell survival experiments shown in Fig. 1. The shape of sensitive volume of the TEPC is a sphere of 1.27 cm in diameter filled with a tissue-equivalent gas which consists of C₃H₈ (55.0%), CO₂ (39.6%), and N₂ (5.4%) at a low pressure of approximately 33 Torr (1 μm water-equivalent size). A positive voltage of 640 V was applied to an anode wire of the TEPC and the signals were sent to a pre-amplifier (142PC, ORTEC) and a main-amplifier (671, ORTEC). Energy calibration was performed by α particles from ^{244}Cm source. To

prevent the spectra from the distortion by the pileup, the TEPC should be used up to a few tens of $\mu\text{Gy}/\text{min}$. However, the lowest nominal dose rate of the 6 MV clinical accelerator is 1 Gy/min. Various techniques to extremely reduce the dose rate of the clinical accelerators down to a few tens of $\mu\text{Gy}/\text{min}$ were reported by Amols and Zellmer.^{10,11)} The gun grid voltage was decreased in this study. In adjusting the gun grid voltage, a 600 ml ionization chamber (C-110, Oyogiken) was used for monitoring the dose rate before the TEPC measurements. Consequently, the dose rate could be successfully reduced to approximately 30 $\mu\text{Gy}/\text{min}$.

Monte Carlo simulation with GEANT4

Monte Carlo simulation will be the most accurate method to calculate not only dose distributions, but also microdosimetric values, such as lineal energy distributions.^{15,16)} In order to calculate the lineal energy distributions, the simulations using the code GEANT4 (Version 4.8.2.p01) have been performed on a 16-CPU Linux cluster for a 200 kV X-ray diagnostic apparatus, a ^{60}Co irradiation equipment, and a 6 MV clinical accelerator. The GEANT4 provides a number of user-selectable physics lists for the calculations. In this study, “ElectroMagnetic (EM) standard physics” with a cut value of 0.01 μm was used to calculate the lineal energy distributions. The geometrical setup and other conditions of simulations were the same as the cell survival experiments (Fig. 1).

For a 200 kV X-ray diagnostic apparatus, energy spectra behind a tungsten target can be simplified by using a Birch’s formula,¹⁷⁾

$$I_{hv} = \frac{\rho N_A}{A} \int_{T_0}^{T_v} \left(1 + \frac{T}{m_0 c^2} \right) Q \left(\frac{dT}{dx} \right)^{-1} \exp \left(- \frac{\mu_v}{\rho C} (T_0^2 - T^2) \cot \theta \right) dT \quad (6)$$

where N_A , ρ , A , T , Q , C , θ , and μ_v are the Avogadro’s number, the density and the atomic number of the tungsten target, the electron energy, the X-ray energy intensity per unit energy interval per incident electron flux per atom, The Thomson-Whiddington constant, the target angle, and the attenuation coefficient, respectively. By using above the formula in the GEANT4 simulation, photon energy of a 200 kV X-ray diagnostic apparatus is easily determined. However, the filters and collimator were modelled in the GEANT4 simulation. A Cu and an Al filter of 0.5 mm thick were placed behind the tungsten target, and the field size was a diameter of 30 cm at source to surface distance of 57 cm.

A ^{60}Co irradiation equipment was modelled with a field of 33 cm diameter at a distance of 80 cm from the ^{60}Co source emitting γ -rays of 1.17 and 1.33 MeV.

For a 6 MV clinical accelerator, the initial electron beam parameters, i.e., the mean energy, the radial intensity distribution, and the spread of mean energy were the same as those proposed by Sheikh-Bagheri.¹⁸⁾ In order to verify the validity to use these electron beam parameters for our medical linear accelerator, the calculated data were compared with measured data for the depth dose curve of a $10 \times 10 \text{ cm}^2$ field and the dose profile curve of a $40 \times 40 \text{ cm}^2$ field. The dose distributions from the GEANT4 simulation agreed with the measured dose distributions with an averaged

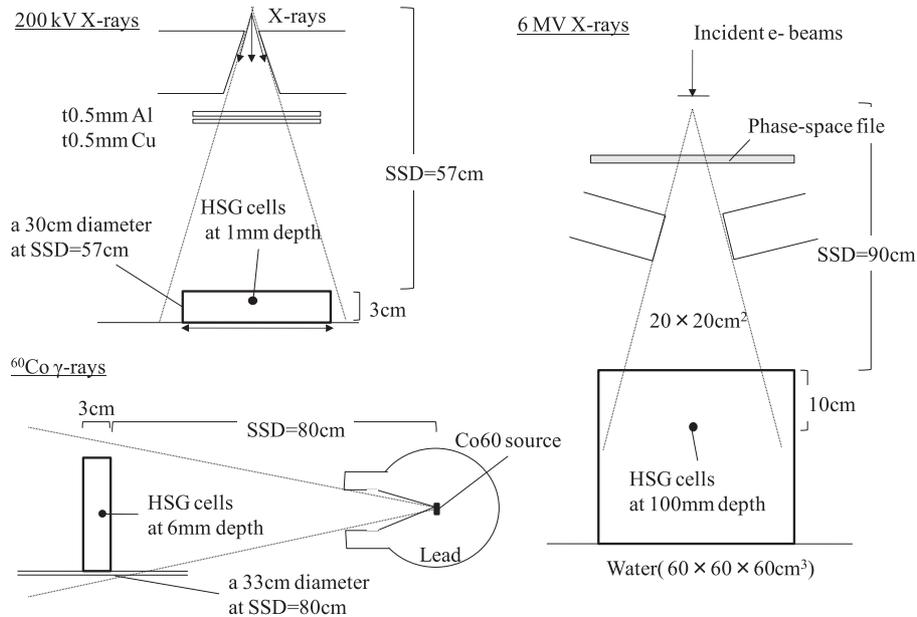


Fig. 1. The schematic of the irradiation geometry for 200 kV X-rays, ^{60}Co γ -rays, and 6 MV X-rays. The depths from the phantom surface to the HSG tumor cells for 200 kV X-rays, ^{60}Co γ -rays, and 6 MV X-rays were 1, 6, and 100 mm water equivalent depth, respectively.

difference of 1.0% (1SD of 1.6%) and 0.9% (1SD of 1.9%) for the depth dose and the dose profile, respectively. By using these electron beam parameters, the distributions of position, the kinetic energy, and the charge of all particles created at the treatment head were stored as a phase-space file above the field-defining jaws. The stored phase-space file was repeatedly used to calculate the lineal energy distributions of different conditions. This technique can effectively reduce the calculation time.¹⁹⁾

Cell culture and irradiations

Human Salivary Gland tumor cells (HSG, JCRB1070: HSGc-C5) were used for the measurements of the survival curves in this study.^{20,21)} The HSG is a standard reference cell line for the inter-comparison of RBE among proton facilities in Japan, Korea, etc.^{22,23)} Eagle's minimum essential medium (M4655, Sigma) supplemented with 10% fetal bovine serum and antibiotics (100 U/ml penicillin and 100 µg/ml streptomycin) was used at cell culture. Harvested cells were seeded in T25 flasks at about 2.0×10^5 cells/flask with 5 ml of the medium, and incubated in a 5% CO₂ incubator at 37°C for 2 days prior to irradiation. The differences of the biological responses for different radiation quality are investigated in this study. Hence, for masking Oxygen Enhancement Effect (OER), the HSG were cultured in the monolayer (hypoxic fraction of 0%), although it is not the same as condition of the in-situ tumor cells. The flasks were filled with additional medium one day before the experiment and then returned to the incubator. The irradiated cells were rinsed twice with PBS⁻, soaked once with 0.05% trypsin with 0.02% EDTA, and kept at 37°C with a bit of remaining trypsin for 4 minutes to harvest the cells. The cells were collected with 5 ml of fresh medium. Concentrations of the cells in suspension were measured with a particle analyzer (Coulter Z1). The suspensions were diluted by medium, seeded in three 6 cm culture dishes (Falcon 3002) expected to be approximately 100 surviving cells per dish, and incubated in the incubator for 13 days. The dishes were rinsed with PBS⁻, fixed with a 10% formalin solution in PBS⁻ for 10 minutes, rinsed with tap water, stained with a 1% methylene blue solution for 10 minutes, rinsed again with tap water, and dried in air. Colonies consisting of more than 50 cells were counted under a stereomicroscope as the number of viable cells. Considering the dose rate dependence of cell inactivation, a dose rate at the cell position was fixed at 0.8 Gy/min for all cases by adjusting the distance from the source to the cells. The depths from the phantom surface to cells for 200 kV X-rays, ⁶⁰Co γ-rays, and 6 MV X-rays were 1, 6, and 100 mm water equivalent depth, respectively (Fig. 1). The irradiation doses were measured with the thimble chamber according to the protocol of TRS 277²⁴⁾ (in-Air method) for 200 kV X-rays and Japanese standard dosimetry 01²⁵⁾ for ⁶⁰Co γ-rays and 6 MV X-rays. The setup of the chamber has the uncertainty of 1–2 mm (change of dose rate

of approximately 1%).

Parameter derivation from cell survival curves

In the MK model, the β value is assumed to be constant irrespective of radiation quality, i.e., $\beta_{MK} = \beta_{200\text{ kV}} = \beta$ in Eq. 5. However, by using a linear-quadratic function with two free parameters (α, β) to fit the survival fraction, the β takes different values for 200 kV X-rays, ⁶⁰Co γ-rays, and 6 MV X-rays, because there were experimental uncertainties for the survival fraction in a high dose region. Consequently, the β value was obtained by the following method in this study. First, experimental survival curves were fitted by linear-quadratic functions with two free parameters (α, β). Secondly, the β_{MK} value was regarded as an averaged value of three β values from the different photon beams. Thirdly, survival curves were re-fitted by linear-quadratic functions using averaged β value (β_{MK}) with α alone as a free parameter. Finally, the resulting α values were fitted by a linear function of y_D measured with the TEPC for determination of tissue-specific parameters, r_d and α₀.

RESULTS

Microdosimetric distributions y - $yd(y)$

The energy deposited in a domain under the irradiations was experimentally simulated with a TEPC and calculated using the code GEANT4. The energy deposit ε was converted into lineal energy y using Eq. 3. Furthermore, lineal energy distributions y - $f(y)$ were re-formed for the style of the standard representation of microdosimetric distribution y - $yd(y)$. Figure 2 shows the y - $yd(y)$ distributions from the TEPC and the GEANT4 simulation. The y - $yd(y)$ distribution for 200 kV X-rays was quite different from those of the other megavoltage-photon beams. However, y - $yd(y)$ distribution for

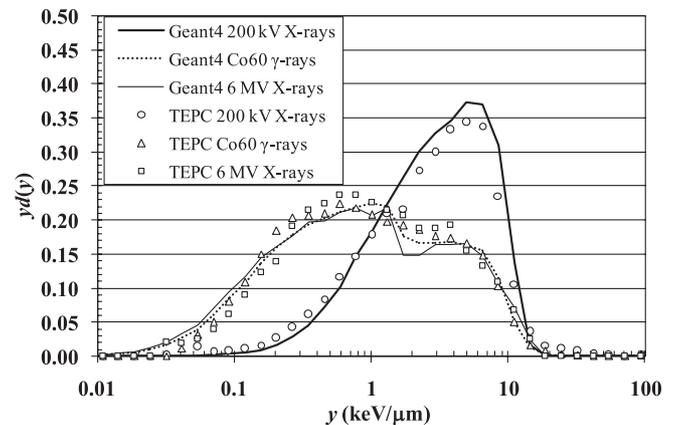


Fig. 2. Microdosimetric distributions y - $yd(y)$. Calculations for 200 kV X-rays (bold line), ⁶⁰Co γ-rays (dotted line), and 6 MV X-rays (solid line) by the code GEANT4, and measurements for 200 kV X-rays (open circle), ⁶⁰Co γ-rays (open triangle), and 6 MV X-rays (open square) with the TEPC.

Table 1. The y_D values obtained from the lineal energy distributions in the TEPC measurements and the GEANT4 simulations using Eq. 4.

Photon Beams	Single-event dose-mean lineal energy y_D (keV/ μm)		
	TEPC	GEANT4 simulation	Published data
200 kV X-rays	4.51 ± 0.05	4.41 ± 0.03	$4.2^{26)}$
^{60}Co γ -rays	2.34 ± 0.03	2.24 ± 0.01	$2.34^{27)}$
6 MV X-rays	2.36 ± 0.04	2.27 ± 0.08	No data

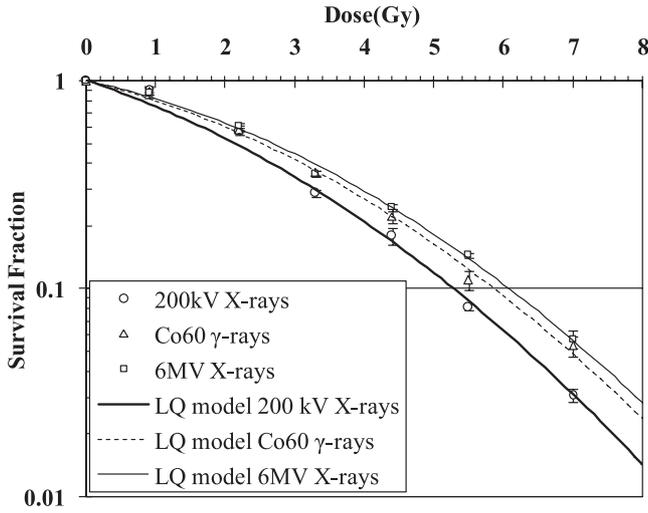


Fig. 3. Survival curves of the HSG tumor cells for 200 kV X-rays (open circle), ^{60}Co γ -rays (open triangle) and 6 MV X-rays (open square). All curves are linear-quadratic functions with two free parameters (α , β) by a method of least-squares. Error bars show \pm 1SE of each measurement.

^{60}Co γ -rays was similar to that for 6 MV X-rays.

Table 1 shows dose-mean lineal energy y_D obtained from the lineal energy distributions using Eq. 4. The y - $y_D(y)$ distribution for 200 kV X-rays showed the greatest y_D value, 4.51 and 4.41 keV/ μm for the TEPC and the GEANT4 simulation, respectively. The y_D value for ^{60}Co γ -rays agreed with that for 6 MV X-rays in both TEPC measurements and GEANT4 simulation. Furthermore, the y_D values for 200 kV X-rays and ^{60}Co γ -rays were close to the published data.^{26,27)}

Cell irradiations

Figure 3 shows the experimental survival curves of the HSG tumor cells irradiated with 200 kV X-rays, ^{60}Co γ -rays, and 6 MV X-rays. All curves are linear-quadratic functions fitted to the experimental survival fraction by a method of least-squares. As shown in the Fig. 3, 200 kV X-rays have the lowest survival fraction among the three photon beams at the same irradiation dose. From this result, RBE depends on photon energy.

Table 2. The fitting of the survival fraction of the HSG tumor cells with a linear-quadratic function with two free parameters (α , β) and one free parameter (α alone).

Photon Beams	LQ model (α , β)		LQ model (α , β_{MK})	
	α (Gy^{-1})	β (Gy^{-2})	α (Gy^{-1})	β_{MK} (Gy^{-2})
200 kV X-rays	0.205	0.043	0.241	0.036
^{60}Co γ -rays	0.197	0.033	0.179	0.036
6 MV X-rays	0.175	0.033	0.157	0.036

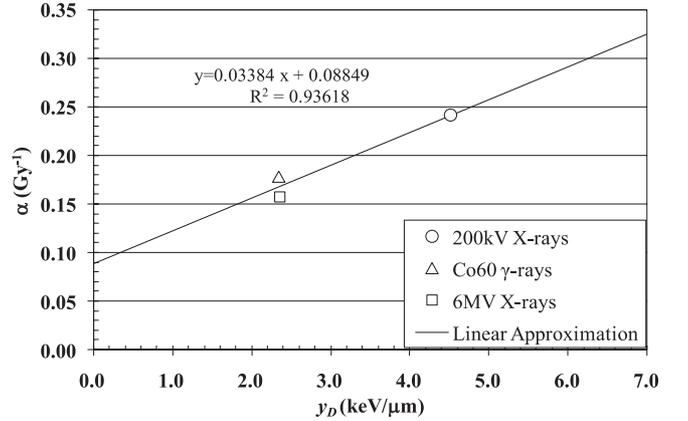


Fig. 4. The resulting α value in the linear-quadratic function with a fixed β_{MK} was fitted by a linear function of y_D obtained with the TEPC. The r_d and α_0 were derived from the slope and the y-intercept of the linear function, respectively.

Determination of the r_d and the α_0 value in the MK model

The second and the third column of Table 2 show the results of fitting to the experimental survival fraction of the HSG tumor cells with a linear-quadratic function (α , β). The β_{MK} value is assumed to be constant irrespective of radiation quality, and an averaged value (0.036 Gy^{-2}) of three experimental β values from different photon beams was used. The resulting α values are shown in the fourth column of Table 2.

Equation 2 is used to determine the tissue-specific parameters, r_d and α_0 . The resulting α values in the linear-quadratic functions with the fixed β_{MK} were fitted with a linear function of y_D obtained with the TEPC using a method of the least squares (Fig. 4). The coefficient of determination R^2 is 0.936 in terms of the accuracy of the fitting. The value of r_d can be obtained from the slope of the linear function, as $\beta/(\rho\pi r_d^2) = 0.03384$, i.e., $r_d = 0.23 \pm 0.03$ μm , where the density of a domain ρ was assumed to be 1.0 g/cm^3 . Furthermore, the α_0 value was derived from the y-intercept of the linear function, i.e., $\alpha_0 = 0.088 \pm 0.023$ Gy^{-1} .

DISCUSSION

The dose-mean lineal energy y_D for 200 kV X-rays and ^{60}Co γ -rays have been reported in many papers.^{4,5,10,11,26-28)}

However, the published data show different results, because the y_D value strongly depends on measurement conditions such as volume size and the geometry of the detector. For instance, it was reported that the y_D value for 200 kV X-rays measured by a spherical proportional counter of walled type with a simulated diameter of 0.97 μm was 4.2 keV/ μm , whereas one with the simulated diameter of 2.06 μm was 3.3 keV/ μm .²⁶⁾ In this study with the simulated diameter of 1.0 μm , we obtained the y_D values of 4.51 ± 0.05 (TEPC) and 4.41 ± 0.03 keV/ μm (GEANT4), which were close to the y_D value of 0.97 μm . For ^{60}Co γ -rays, we obtained the y_D values of 2.34 ± 0.03 (TEPC) and 2.24 ± 0.01 keV/ μm (GEANT4) with the simulated diameter of 1.0 μm , which were close to the published data of 2.34 keV/ μm with the simulated diameter of 0.95 μm .²⁷⁾

In the spectrum shape (Fig. 2), there exist the quite difference between 200 kV X-rays and mega-voltage photon beams, and little difference between ^{60}Co γ -rays and 6 MV X-rays in both the TEPC measurements and the GEANT4 simulation. These results can be understood through considering the stopping power of recoil electrons by Compton scattering. Figure 5 shows the collision mass-stopping power of electrons in water as a function of kinetic energy.²⁹⁾ As can be seen in the figure, the stopping power of electrons is drastically increasing in the region of lower than approximately 200 keV. For example, averaged photon energy of 200 kV X-rays is approximately 80 keV. In such a lower energy region, the energy deposited in the microscopic region becomes greater. Consequently, probability of incidence of the lethal lesion in DNA is expected to be higher, which results in the increase in the RBE. On the other hand, there is little difference in both the spectrum shape and the y_D values between ^{60}Co γ -rays and 6 MV X-rays, because collision stopping power is almost constant in the range of mega-voltage kinetic energy. For 6 MV X-rays, averaged photon energy at a depth of 10 cm in water is approximately 1.7 MeV.

In the determination of α value in the MK model, experimental survival fraction was fitted by a linear-quadratic function with one free parameter (α alone). However, the differences of fitting between with one free parameter and with two should be evaluated. Figure 6 represents the comparison between two methods for 200 kV X-rays. We can see a little difference in the range of high irradiation dose > 8 Gy. However, it was not serious within the scope of our purpose, because a dose of 2 Gy per fraction is well-used for the conventional radiation therapy using photon beams. The coefficients of determination R^2 were 0.997 and 0.998 for one parameter and two, respectively. The results were similar for 6 MV X-rays and ^{60}Co γ -rays. Thus it does not matter that the linear-quadratic function with the fixed β_{MK} value is used in terms of the accuracy of the fitting.

In the final analysis, we obtained the tissue-specific parameters, $r_d = 0.23 \pm 0.03$ μm , $\alpha_0 = 0.088 \pm 0.023$ Gy^{-1} ,

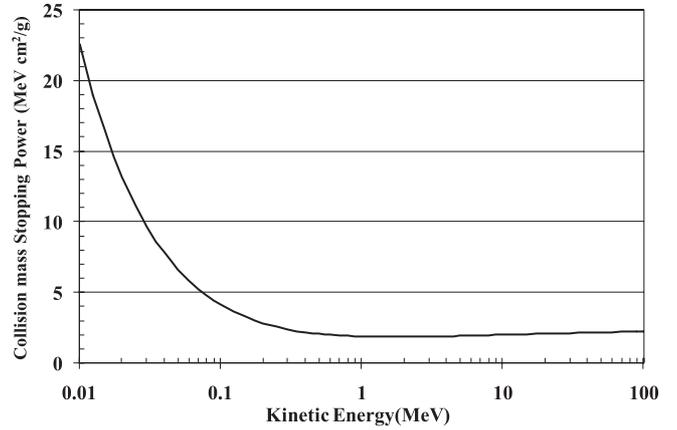


Fig. 5. Collision mass-stopping power of electrons in water as a function of kinetic energy.²⁹⁾

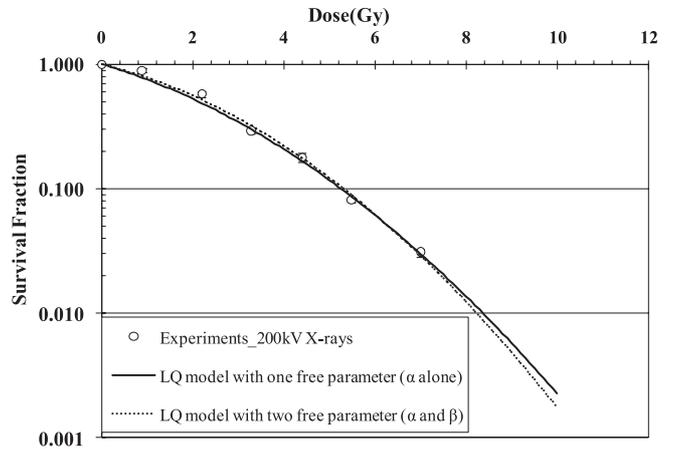


Fig. 6. Comparison between the two methods of the fitting to survival fraction of the HSG tumor cells for 200 kV X-rays.

and $\beta = 0.036$ Gy^{-2} . As a matter of fact, these values are slightly different from those in the previously reported paper.³⁰⁾ In that paper, the tissue-specific parameters were $r_d = 0.42$ μm , $\alpha_0 = 0.13$ Gy^{-1} , and $\beta = 0.05$ Gy^{-2} , which were derived from the experimental survival fraction of same kind of cells irradiated with carbon beams. When these parameters are used, the MK model gives disagreement with our experimental RBE for photon beams. This shows that the MK model cannot reproduce the experimental survival fraction of the HSG tumor cells for both low-LET radiations like photon beams and high-LET radiations like carbon-ion beams by the same tissue-specific parameters. The reason is not clear.

In conclusion, since we obtained the tissue-specific parameters, the r_d , α_0 and β value of the HSG tumor cells from the experimental survival fraction and the experimental y_D values, the α value of the HSG tumor cells can be expressed as a linear function of the y_D value: $\alpha = 0.0338 \times y_D + 0.0885$. Finally, we obtained the RBE of the HSG tumor

cells at the 10% survival level using Eq. (5), as follows,

$$RBE(y_D) = 5.299 \cdot \left(\frac{\sqrt{\alpha^2 + 4 \times 0.036 \times (-\ln(0.1))} - \alpha}{2 \times 0.036} \right)^{-1} \quad (7)$$

where $\alpha = 0.0338 \times y_D + 0.0885$. At present, the y_D values outside the field for 6 MV X-rays have been measured with the TEPC, and an increase in the RBE outside the field has been investigated by using the above equation.

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