

Biological dose representation for carbon-ion radiotherapy of unconventional fractionation

Nobuyuki Kanematsu^{1,2} and Taku Inaniwa²

¹ Medical Physics Section, National Institute of Radiological Sciences Hospital, QST; 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

² Department of Accelerator and Medical Physics, National Institute of Radiological Sciences, QST; 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

E-mail: kanematsu.nobuyuki@qst.go.jp

Abstract. In carbon-ion radiotherapy, single-beam delivery each day in alternate directions has been commonly practiced for efficient operation, taking advantage of the Bragg peak and the relative biological effectiveness (RBE) for uniform dose conformation to a tumor. These treatments are generally fractionated and their plans are evaluated with total RBE-weighted dose, which is however deficient in relevance to the biological effect. In this study, we reformulate the biologically effective dose (BED) to normalize the dose-fractionation and cell-repopulation effects as well as the RBE of treating radiation, based on the inactivation of a reference cell line by a reference carbon-ion radiation. The BED distribution virtually represents the biological effect of a treatment regardless of radiation modality or fractionation scheme. We applied the BED formulation to simplistic model treatments and to a preclinical survey for hypofractionation based on an actual prostate-cancer treatment with carbon ions. The proposed formulation was demonstrated to be practical and implicative. For the prostate-cancer treatment in 12 fractions, the distributions of BED and of RBE-weighted dose were very similar. With hypofractionation, while the RBE-weighted-dose distribution varied significantly, the BED distribution was nearly invariant, implying that the carbon-ion radiotherapy would be virtually insensitive to fractionation. However, treatment evaluation with such simplistic biological dose is intrinsically limited and must be complemented in practice by clinical experience and biology experiment.

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1. Introduction

The basis of radiotherapy (RT) for cancer treatment lies in the radiobiology of human tissues and cells. Douglas and Fowler (1976) first proposed a formula for cell-survival fraction S in instant radiation exposure as an exponential linear quadratic (LQ) function of dose D ,

$$S = e^{-\alpha D - \beta D^2}, \quad (1)$$

where α and β are the LQ dose coefficients of the cell sensitivity to the radiation, based on the hypothesis that the cell inactivation by lethal or double-sublethal damage was correlated with biological response. The LQ model is generally considered as valid for fractionated RT of up to 10 Gy fractions (Fowler, 1989). As indicated by the model, the relative biological effect per unit dose increases with fraction dose, which is referred to as the dose-fractionation effect. In clinical practice, radiation oncologists evaluate the total fractionated dose for the assessment of treatment. However, the same total dose may not generally yield the same biological effect with a different number of fractions or with different fractionation into uneven doses. The concept of biologically effective dose (BED) was introduced for universal assessment of treatment by the total dose in infinite fractions for the same biological effect (Barendsen, 1982), where the BED was originally referred to as extrapolated response dose as it extrapolates the dose-fractionation effect to the limit of infinite fractionation.

Besides dose fractionation, radiation quality modifies the relative biological effect per unit dose especially of ions whose linear energy transfer (LET) rises with depth to cause the Bragg peak. The use of such ion beams for RT was pioneered in the United States, for which dose prescription incorporated depth-dependent weighting of relative biological effectiveness (RBE) against a reference radiation to give a uniform biological effect in a spread-out Bragg peak (SOBP) (Castro, 1993). Subsequently, clinical research and practice developed intensively with carbon ions in Japan and Germany. The high uniformity of the RBE-weighted dose (RWD) to a tumor facilitates the delivery of single beams with daily different dose distributions for efficient operation of carbon-ion RT. Such uneven dose fractionation except to a tumor has been commonly practiced in Japan including clinical studies to optimize dose prescription in fewer fractions, or hypofractionation (Kamada et al., 2015). In Germany, carbon-ion beams have been occasionally used as a boost in multimodal RT (Combs and Debus, 2013). Nevertheless, these treatments may still be evaluated unconsciously with the total RWD distribution despite its intrinsic deficiency in additivity.

The BED concept was extended for high-LET radiations to be an equivalent total dose in infinite fractions with a reference radiation (Dale and Jones, 1999; Jones et al., 2006; Carabe-Fernandez et al., 2007) in the form of

$$D_{\text{BE}} = \sum_{i=1}^n D_i \left(\epsilon_{\text{max}i} + \frac{\epsilon_{\text{min}i}^2 D_i}{\alpha_{\text{ref}}/\beta_{\text{ref}}} \right), \quad (2)$$

where D_i is the physical dose delivered at the i -th fraction of n total fractions,

$\epsilon_{\max_i} = \alpha_i/\alpha_{\text{ref}}$ and $\epsilon_{\min_i} = \sqrt{\beta_i/\beta_{\text{ref}}}$ are the maximum and minimum RBEs at infinitesimal and infinite dose limits and $\alpha_{\text{ref}}/\beta_{\text{ref}}$ is the α/β ratio for the reference radiation that is typically an x ray. While the $\alpha_{\text{ref}}/\beta_{\text{ref}}$ values for many tumor and normal-tissue cells have been established, the RBE limits or the LQ dose coefficients for carbon-ion radiation vary with depth of beam penetration and are not generally available. The fact that the physical dose and the radiosensitivity largely vary in a target tumor discourages the use of the BED in (2).

Kellerer and Roissi (1972) developed a microdosimetric theory of dual radiation action for the yield of elementary lesions in a micrometer-sized domain as a LQ function of dose, where the linear dose coefficient is related to single-event energy deposition while the quadratic dose coefficient is independent of radiation. The microdosimetric theory was statistically reinforced to deal with cell survival (Hawkins, 1994) and has eventually been applied to treatment planning of carbon-ion RT (Inaniwa et al., 2010), in which the LQ model is rewritten as

$$S = e^{-\alpha_0 D - \beta D(\zeta + D)} \quad \text{or} \quad \alpha = \alpha_0 + \zeta \beta, \quad (3)$$

where α_0 and β are the cell-intrinsic parameters independent of radiation and ζ is the saturation-corrected dose-mean single-event specific energy in the domain. The ζ and thus α parameters increase with LET typically below 100 keV/ μm , above which the saturation correction effectively accounts for the overkill effect.

The microdosimetric LQ model is the current basis of the clinical dosimetry system for carbon-ion RT at the National Institute of Radiological Sciences (NIRS) of Japan (Inaniwa et al., 2015). In this study, we attempt to apply the BED concept to practical and valid assessment of carbon-ion RT treatment plans. In the following sections, we review basic radiobiology to reformulate the BED to be readily obtainable in treatment planning and apply it to two simplistic model treatments and a typical prostate-cancer treatment to demonstrate its usability and to obtain theoretical implications for dose fractionation including hypofractionation.

2. Methods and Materials

2.1. Radiobiological modeling

2.1.1. Survival factor In radiobiology, survival fraction is defined as a fraction of clonogenic cells surviving a radiation exposure. In fractionated RT, the survival fraction will be modified by cell repopulation over time, which we refer to as survival factor. On the hypothesis of the constant rates for cell division and natural loss (Dale, 1989), the survival factor at time t after the delivery of i -th fraction dose D_i at time t_i is formulated as

$$S_i(t) = e^{-\alpha_i D_i - \beta_i D_i^2} 2^{(t-t_i)/T_d}, \quad (4)$$

where α_i and β_i are the LQ dose coefficients and T_d is the effective doubling time for the surviving tumorigenic cancer cells, which we assume to equal to the tumor-doubling

time. The survival factor at the end of a treatment in n fractions is formulated as

$$S = \prod_{i=1}^{n-1} S_i(t_{i+1}) S_n(t_n) = \prod_{i=1}^n e^{-\alpha_i D_i - \beta_i D_i^2} \cdot e^{T \ln 2 / T_d}, \quad (5)$$

where $T = t_n - t_1$ is the overall treatment time.

2.1.2. Biological effect The biological effect for an instant beam delivery of fraction i is defined as

$$E_{B_i} = -\ln S_i(t_i) = \alpha_i D_i + \beta_i D_i^2, \quad (6)$$

which statistically corresponds to the mean number of unrepaired lethal damages per cell. The biological effect for an overall treatment is similarly defined as

$$E_B = -\ln S = \sum_{i=1}^n \alpha_i D_i + \sum_{i=1}^n \beta_i D_i^2 - \frac{T \ln 2}{T_d}, \quad (7)$$

where the last term accounts for the cell-repopulation effect.

2.1.3. RBE-weighted dose Fraction RWD D_{RW_i} is the dose of a reference radiation with LQ dose coefficients α_{ref} and β_{ref} to cause the same biological effect,

$$E_{B_i} = \alpha_i D_i + \beta_i D_i^2 = \alpha_{\text{ref}} D_{RW_i} + \beta_{\text{ref}} D_{RW_i}^2. \quad (8)$$

This leads to the symmetric solutions of physical dose and RWD,

$$D_{\{i, RW_i\}} = \frac{\alpha_{\{i, \text{ref}\}}}{\beta_{\{i, \text{ref}\}}} \left(\sqrt{\frac{1}{4} + \frac{\beta_{\{i, \text{ref}\}}}{\alpha_{\{i, \text{ref}\}}^2} E_{B_i}} - \frac{1}{2} \right). \quad (9)$$

The RBE of the treating radiation and the total RWD are defined as

$$\epsilon_i = \frac{D_{RW_i}}{D_i} \quad \text{and} \quad D_{RW} = \sum_{i=1}^n D_{RW_i} = \sum_{i=1}^n \epsilon_i D_i. \quad (10)$$

The total RWD is widely used in carbon-ion RT although it is deficient in relevance to the biological effect against dose fractionation and against cancer-cell repopulation.

2.1.4. Biologically effective dose The BED is a total physical dose of reference radiation in hypothetical infinite fractions for the same biological effect as with the actual treatment and is simply given by the ratio of the biological effect to the α parameter of interest (Barendsen, 1982). The instant BED from a fraction is therefore defined as

$$D_{BE_i} = \frac{E_{B_i}}{\alpha_{\text{ref}}} = D_{RW_i} + \frac{\beta_{\text{ref}}}{\alpha_{\text{ref}}} D_{RW_i}^2, \quad (11)$$

where the first linear dose term is independent of fractionation and the second quadratic dose term accounts for the dose-fractionation effect. The BED for an overall treatment is similarly defined as

$$D_{BE} = \frac{E_B}{\alpha_{\text{ref}}} = D_{RW} + \frac{\beta_{\text{ref}}}{\alpha_{\text{ref}}} \sum_{i=1}^n D_{RW_i}^2 - \frac{1}{\alpha_{\text{ref}}} \frac{T \ln 2}{T_d}. \quad (12)$$

Excluding the third term for cancer-cell repopulation, the RWD-based formula (12) is mathematically equivalent to (2) for the reference radiation with reassignments $\alpha_i \rightarrow \alpha_{\text{ref}}$, $\beta_i \rightarrow \beta_{\text{ref}}$ and $D_i \rightarrow D_{\text{RW}i}$ and is easy to use in the practice of carbon-ion RT, where the RWD is well defined and always available.

2.1.5. Tumor-control probability The tumor-control probability (TCP) is radiobiologically modeled as the probability of inactivating all of the N_0 tumorigenic cancer cells that originally existed in a tumor (Munro and Gilbert, 1961) and is statistically given by

$$P_{\text{TC}} = e^{-N_0 S} = \exp(-N_0 e^{-E_B}), \quad (13)$$

which should be high for a curative treatment. Inversely, when the number of tumorigenic cancer cells is reasonably estimated, a curative TCP can be translated into the biological effect of treatment,

$$E_B = \ln \frac{N_0}{-\ln P_{\text{TC}}}. \quad (14)$$

With a compensation for cancer-cell repopulation between fractions, the biological effect of treatment may be evenly divided into n fractions of an instant biological effect of

$$E_{B1} = \frac{1}{n} \left(\ln \frac{N_0}{-\ln P_{\text{TC}}} + \frac{T \ln 2}{T_d} \right), \quad (15)$$

from which fraction dose D_1 and RWD $D_{\text{RW}1}$ can be determined by (9) to prescribe optimum beam deliveries for curative RT.

2.1.6. Beam-delivery prescription A treatment fraction is normally prescribed with RWD to a tumor, which is inversely converted with RBE to a physical dose to a reference point for beam-delivery control or assessment. When multiple beams (b) are involved in a fraction, their mixed radiation is characterized by the summed dose and the dose-mean LQ dose coefficients,

$$D_i = \sum_b D_{ib}, \quad \alpha_i = \sum_b \alpha_{ib} \frac{D_{ib}}{D_i} \quad \text{and} \quad \sqrt{\beta_i} = \sum_b \sqrt{\beta_{ib}} \frac{D_{ib}}{D_i} \quad (16)$$

in the LQ model (Zaider and Rossi, 1980), with which its RBE can be calculated. To allot the intended fraction RWD to the relevant beams with arbitrary specified weights, the physical beam doses are generally derived iteratively by the LQ model or deterministically by the lesion-additivity (LA) model (Lam, 1987). These radiation-mixing models have been the basis of SOBP design and prescription of fractions each involving multiple beams, for which no significant inconsistency has been found by biology experiment (Inaniwa et al., 2010) or by clinical experience (Kamada et al., 2015).

2.2. Application to simplistic model treatments

We investigated the formulated dose representations in simplistic examples with four model radiations of two modalities: a photon radiation with $\alpha = 0.3 \text{ Gy}^{-1}$ and $\beta = 0.06$

Gy^{-2} and three carbon-ion radiations sampled in a SOBP with $\alpha = 0.5, 1.0$ and 1.5 Gy^{-1} and a common $\beta = 0.06 \text{ Gy}^{-2}$ based on a realistic radiobiology model (Inaniwa et al., 2015), for $N_0 = 10^7$ hypothetical cancer cells in a fast-growing tumor with doubling time $T_d = 30$ days. In the following model treatments, a prescribed fraction RWD taking the photon radiation for reference was assumed to be delivered once a day, seven days a week for simplicity. We generally note prescribed RWD values with postfix “(RBE)” to indicate that they are RBE-weighted.

2.2.1. Dose fractionation For a carbon-ion RT treatment of total 40 Gy (RBE), we varied the number of fractions to prescribe evenly.

2.2.2. Multimodal RT For a treatment initially with photons of 2 Gy fractions for 10 days, followed by carbon ions of 4 Gy (RBE) fractions for 6 days to total 44 Gy (RBE) in 16 days, we evaluated the accumulation of treatment dose.

2.3. Application to a prostate-cancer treatment

2.3.1. Clinical dosimetry system At NIRS, carbon-ion RT doses are prescribed in clinical dose defined as

$$D_{C_i} = f_C D_{RW_i} = f_C \epsilon_i D_i, \quad (17)$$

where clinical factor $f_C = 2.41$ was introduced for historical reasons and we note clinical-dose values with postfix “(C)” for distinction so that 1 Gy (RBE) corresponds to 2.41 Gy (C). In this system, the RBE ϵ_i is defined against the reference radiation of a typical carbon-ion beam at a central SOBP depth for the inactivation of *in vitro* tumor cells of human salivary gland (HSG), which resulted in the LQ dose coefficients of $\alpha_{\text{ref}} = 0.764 \text{ Gy}^{-1}$ and $\beta_{\text{ref}} = 0.0615 \text{ Gy}^{-2}$ (Inaniwa et al., 2015). In other words, the RWD is the dose of the reference carbon-ion radiation for an equivalent biological effect and the clinical dose further involves artificial rescaling. This definition deviates from the conventional RBE defined against an x ray with LQ dose coefficients of $\alpha_x = 0.313 \text{ Gy}^{-1}$ and $\beta_x = 0.0615 \text{ Gy}^{-2}$ (Furusawa et al., 2000). The BED of carbon-ion radiation in (12) can be readily converted with a factor of $\alpha_{\text{ref}}/\alpha_x = 2.44$ to the BED of the x ray in infinite fractions for an equivalent effect on the HSG tumor cells, for multimodal RT treatments.

2.3.2. Clinical case For demonstration, we took a case of prostate-cancer patient who received carbon-ion RT in 12 fractions of 4.3 Gy (C) over 3 weeks (Nomiya et al., 2014). In the planning CT of the patient immobilized in a supine position, the clinical target volume (CTV) included the prostate and the seminal vesicles. The planning target volume (PTV) additionally included anterior and lateral margins of 10 mm each and a posterior margin of 5 mm. Lateral opposing carbon-ion beams were used alternately for the initial 8 fractions to cover the original PTV with more than 95% of the prescribed fraction dose, or cumulatively with about 2/3 of the prescribed total dose. To care

against the risk of complication, the posterior margin of the PTV near the rectum was cut away to derive a restricted PTV, for which similar opposing beams with shrunk fields were used alternately for the remaining 4 fractions. The daily single-beam delivery was conducted with pencil-beam scanning (Furukawa et al., 2010) to conform 4.3 Gy (C) to either PTV. The physical-dose and clinical-dose distributions per fraction were calculated and stored in the treatment plan while the total clinical-dose distribution was primarily used for clinical assessment of the plan.

2.3.3. Plan dose distributions Applying the microdosimetric implication of $\beta = \beta_{\text{ref}}$ to (8), the α/β ratio for each fraction can be obtained from a set of RWD $D_{\text{RW}i} = D_{\text{C}i}/f_{\text{C}}$ and physical dose D_i as

$$\frac{\alpha_i}{\beta_{\text{ref}}} = \frac{D_{\text{RW}i}}{D_i} \left(\frac{\alpha_{\text{ref}}}{\beta_{\text{ref}}} + D_{\text{RW}i} - D_i \right). \quad (18)$$

Using the distributions stored in the plan, we calculated the distributions of total physical dose by $\sum_i D_i$, total dose-mean α/β ratio by $\sum_i (\alpha_i/\beta_{\text{ref}}) D_i / \sum_i D_i$, total clinical dose by $\sum_i D_{\text{C}i}$ and BED by (12), where we ignored the cell-repopulation effect on the assumption of slow-growing prostate cancer with $T \ll T_d$.

2.3.4. Field fusion Aside from the actual treatment, we reduced the number of beams from four to two to simplify the fractionation while conserving the total dose. In fact, the field-shrinking approach was originated from the historical limitations of passive broad-beam delivery. The field-modulation approach with pencil-beam scanning for multiple target volumes and doses will improve the operational efficiency with fewer beams. To simulate scanning beams of stepped target dose, we fused the original-field beams by 2/3 and the shrunk-field beams by 1/3 per direction into the left and right beams and obtained their physical-dose and dose-mean α/β -ratio distributions. In addition, to simulate even fractionation with the left and right beams delivered successively each day, we further fused them by 1/2 each and obtained its physical-dose and dose-mean α/β -ratio distributions.

2.3.5. Hypofractionation simulation We attempted a survey toward hypofractionation, in which we virtually varied the number of fractions for each of the successive and alternate delivery schemes. For the same BED of $D_{\text{BE}} = 24.49$ Gy to the prostate as with 12 fractions of 4.3 Gy (C) by (12), we additionally prescribed fraction clinical doses of 6.124, 10.83 and 18.31 Gy (C) by (9) with $E_{\text{B}1} = (D_{\text{BE}}/\alpha_{\text{ref}})/n$ for $n = 8, 4$ and 2 fractions, respectively. Accordingly, we rescaled the respective fraction physical-dose distributions by the same factors as for the prescribed clinical doses, or by 1.424, 2.519 and 4.258, based on the fact that the reference radiation quality with an invariant RBE of 1 was in the prostate somewhere. We then obtained the BED distribution for each n from the fraction physical-dose and dose-mean α/β -ratio distributions using (8)–(12).

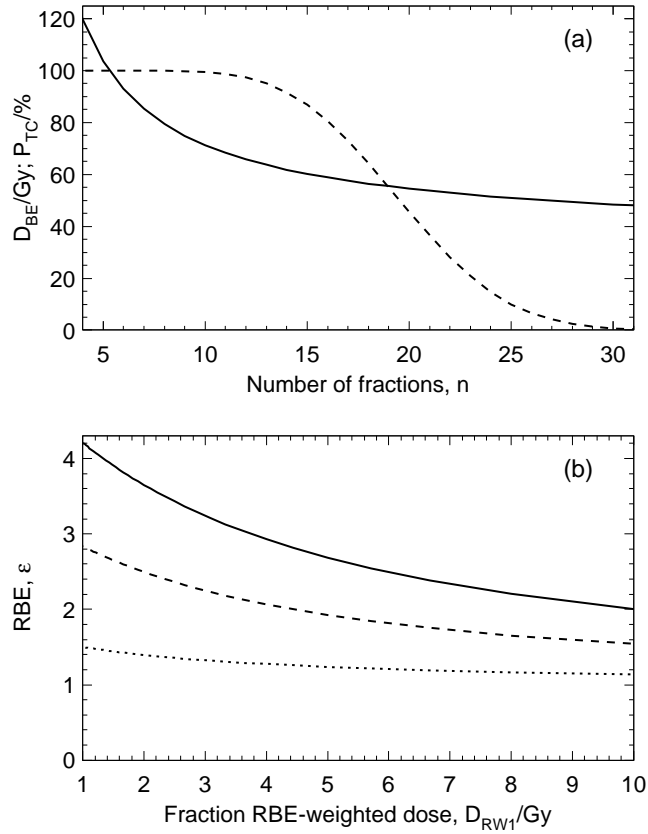


Figure 1. Dose fractionation effect calculated for a model treatment of total 40 Gy (RBE) with carbon ions: (a) BED (D_{BE} , —) and TCP (P_{TC} , - - -) as functions of number of fractions. (b) RBEs for low- α (·····), mid- α (- - -) and high- α (—) carbon-ion radiations as functions of fraction RWD.

3. Results

3.1. Application to simplistic model treatments

3.1.1. Dose fractionation Figure 1(a) shows the BED and the TCP for the model treatment of total 40 Gy (RBE). The BED decreased with number of fractions due to dose fractionation and cancer-cell repopulation and correlated with the TCP. Figure 1(b) shows the RBEs of the three carbon-ion radiations in a SOBP. The RBE values and their variation decreased with the fraction RWD, which implies that the SOBP should be designed differently for uniform treatment according to the prescribed fraction RWD.

3.1.2. Multimodal RT Figure 2 shows the representations of daily cumulative dose for the model treatment of multimodal RT. After day 10, the change in prescribed fraction dose from 2 Gy to 4 Gy (RBE) by a factor of 2 changed the BED slope by a larger factor of 2.62 due to the quadratic term. On day 16 at the end of the treatment, the cell-repopulation term reduced the BED by 1.16 Gy or 1.7%, while the TCP of 99.2% may still be reasonably curative. If the same total RWD of 44 Gy (RBE) were evenly delivered

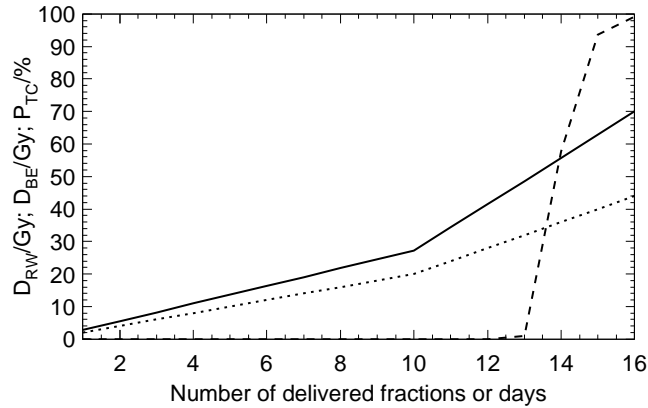


Figure 2. A model treatment of multimodal RT in 10 fractions of 2 Gy with photons and 6 fractions of 4 Gy (RBE) with carbon ions over 16 days: cumulative RWD (D_{RW} , \cdots), BED (D_{BE} , —) and TCP (P_{TC} , - - -) as functions of number of delivered fractions or days.

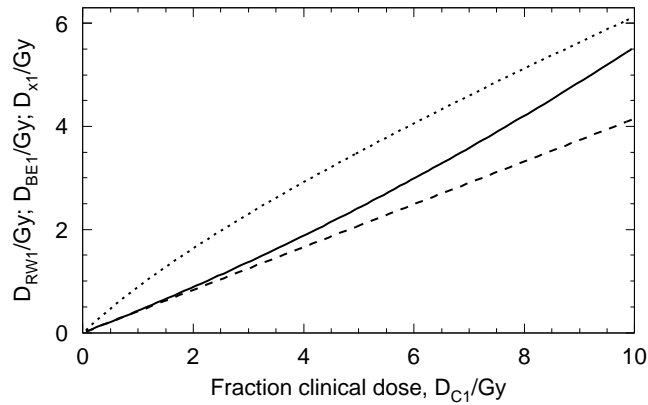


Figure 3. Relation between fraction clinical dose (D_{C1}) and fraction RWD (D_{RW1} , - - -), instant BED (D_{BE1} , —) and the photon-equivalent fraction dose (D_{x1} , \cdots) in the NIRS clinical dosimetry system.

in 16 fractions of 2.75 Gy (RBE), the TCP would be reduced to 98.1% according to the formulas in section 2.1, indicating the deficiency of RWD-based prescription against the change of dose fractionation. To obtain the same TCP of 99.2% with 16 even fractions, the required RWD would be 2.83 Gy (RBE) per fraction or 45.3 Gy (RBE) in total.

3.2. Application to a prostate-cancer treatment

Figure 3 shows the relation between fraction clinical dose and fraction RWD, instant BED and the photon-equivalent dose, in the NIRS clinical dosimetry system. The similarity between BED and RWD at small fraction sizes is due to the minor contribution of the quadratic term, or $D_{RW1} \ll \alpha_{\text{ref}}/\beta_{\text{ref}}$ in (11).

Figure 4 shows the dose distributions calculated for the actual prostate-cancer treatment: Both of the (a) dose-mean α/β -ratio and (b) physical-dose distributions

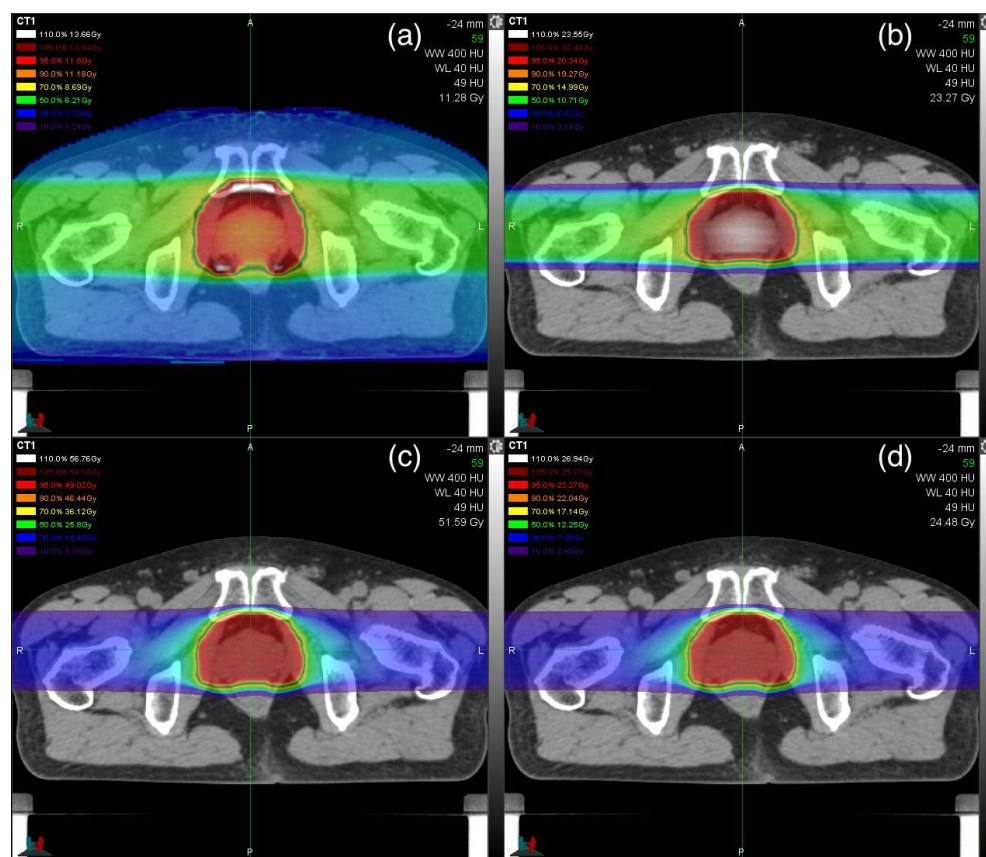


Figure 4. A planning CT image of the prostate-cancer patient in the isocenter plane with green crosshairs for the right–left and anterior–posterior axes and color-wash scales (10%, 30%, 50%, 70%, 90%, 95%, 105% and 110%) for the calculations of: (a) dose-mean α/β ratio relative to 12.42 Gy, (b) total physical dose relative to 21.41 Gy, (c) total clinical dose relative to 51.6 Gy (C) and (d) BED relative to 24.49 Gy.

were moderated in the opposing beam arrangement with concurrent enhancement in the PTV, where the α/β ratio was high on the anterior and posterior sides and the physical dose was high in the central region. The relative difference between the (c) clinical-dose and (d) BED distributions was minor due to the small quadratic-term contribution at the level of 4.3 Gy (C) or 1.78 Gy (RBE) as consistent with figure 3.

Figures 5(a) and 5(b) show the profiles of dose-mean α/β ratio and total physical dose, where the two opposing beams were designed for the treatment plan of 12 fractions of 4.3 Gy (C) and were also reused for the hypofractionated treatment plans with rescaling to conserve the BED to the point of reference radiation quality with $\alpha_{\text{ref}}/\beta_{\text{ref}} = 12.42$ Gy. The RWD distribution in figure 5(c) deformed with hypofractionation while the BED distribution in figure 5(d) was nearly invariant. The RWD distribution could give misleading impression for hypofractionated treatments. The degraded BED uniformity in the SOBP with hypofractionation was caused by the forced reuse of the beams designed for 4.3 Gy (C) fractions and would not have happened if they had been designed for each fraction dose. Outside the SOBP, as compared to the

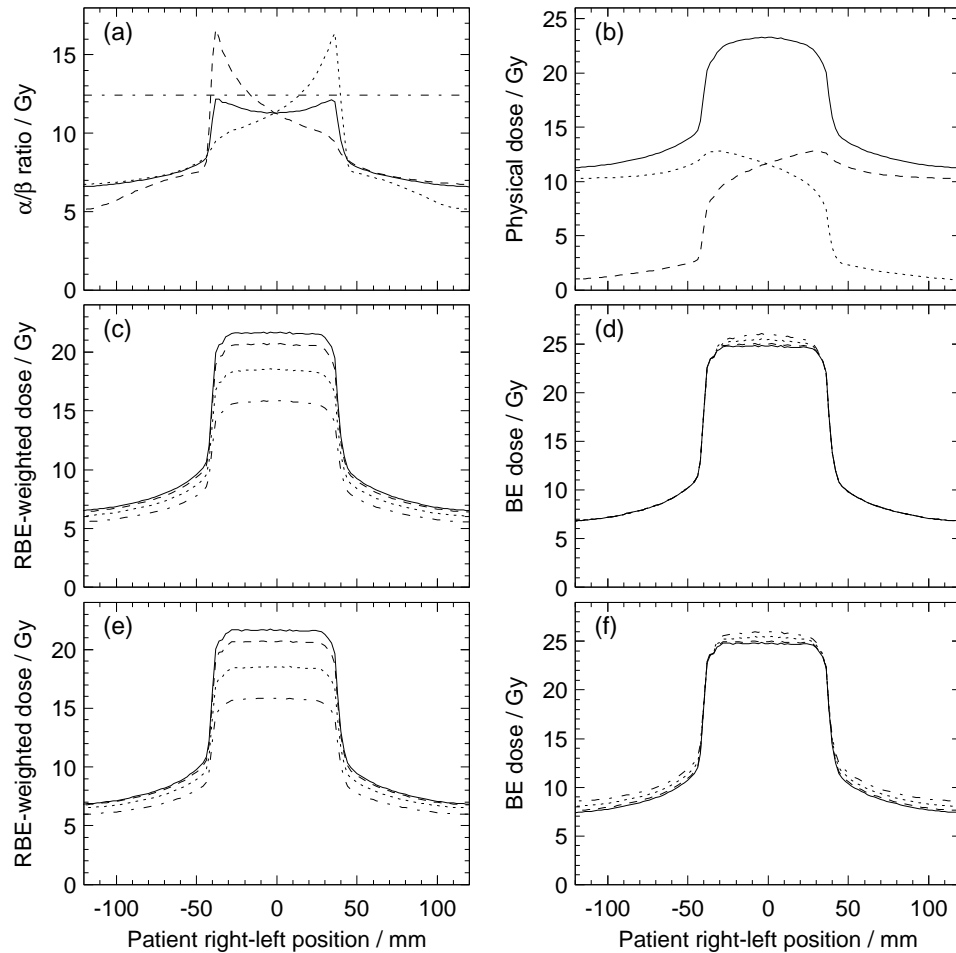


Figure 5. Calculated profiles on the patient right-left axis for the prostate-cancer treatment plans: (a) dose-mean α/β ratio, (b) total physical dose for 12 fractions, (c) total RWD and (d) BED with successive beam delivery and (e) total RWD and (f) BED with alternate beam delivery. In (a) and (b), the contributions of the left (---) and right (·····) beams and their total (—) are separately shown with the reference 12.42 Gy level (-·-·-). In (c)–(f), the treatments were prescribed with the BED of 24.49 Gy in 12 (—), 8 (---), 4 (·····) and 2 (-·-·-) fractions.

successive beam delivery in figures 5(c) and 5(d), the alternate beam delivery in figures 5(e) and 5(f) slightly increased the RWD and BED themselves and the BED variation with hypofractionation.

4. Discussion

Biological dosimetry is a concept of radiation dose measurement by consequential response of a reference biological system. The NIRS clinical dose as well as its relevant RWD and BED is a theoretical dose that offers virtual *in vivo* biological dosimetry with the HSG tumor cell, which is a cancer cell of moderate radiosensitivity (Matsufuji et al., 2007), later turned out to be of HeLa-contaminant origin (JCRB1070 HSGc-C,

JCRB Cell Bank, National Institutes of Biomedical Innovation, Health and Nutrition, Ibaraki, Osaka). While the reference to a single cell line is a conceptual limitation or arbitrariness of the biological dosimetry, an experimental study showed small variation among cell lines in RBE of carbon-ion beams against x ray at 10% survival level (Suzuki et al., 2000), which may partially support its clinical validity. The BED is a universal dose that may be useful for preclinical and retrospective studies involving various radiation modalities or dose fractionations.

The fraction of cancer cells may vary from tumor to tumor and within each tumor volume. If the initial cancer-cell population-density distribution $\rho_0(\vec{r}) = d^3N_0/d\vec{r}$ as well as the BED distribution is somehow known, the TCP in (13) is modified to

$$P_{\text{TC}} = \exp\left(-\iiint \rho_0(\vec{r}) e^{-\alpha_{\text{ref}} D_{\text{BE}}(\vec{r})} d\vec{r}\right) \quad (19)$$

for dose-distribution assessment under the hypothesis that the relevant cancer cells have the same radiosensitivity as that of the *in vitro* reference model cell.

In reality, actual cancer and normal cells in a patient may be substantially different from the reference in intrinsic radiosensitivity and in environmental conditions including oxygen and biochemical concentrations, various cell interactions in tissues, etc. The radiosensitivity may also be influenced by the time structure of radiation exposure (Inaniwa et al., 2013). Furthermore, the relevance of clinical response to cell response may vary among diseases and individuals. As a result, these biological doses may not directly be related to the prognosis of treatment. Nevertheless, carbon-ion RT has been conducted according to disease-specific treatment protocols with abundant clinical experiences (Kamada et al., 2015). The clinically determined curative doses per disease and organ tolerance doses should thus be reflecting all the differences between the reference biology experiment and the actual cancer treatments of carbon-ion RT in its own dose scale.

Another major arbitrariness exists with the reference radiation, which should be chosen to minimize the overall inaccuracy of cancer treatment. For example, a few percent inconsistency between the LQ and LA models was found in conventional RBE of a mixed carbon-ion radiation against an x ray (Kanematsu et al., 2002), which should have been minimized if the RBE had been defined only to relate similar-radiation doses. The NIRS clinical dosimetry system, which is based on the RBE defined against a typical treating radiation, is therefore advantageous for accurate prescription of tumor doses in the modality-specific scale, excluding potentially inaccurate translation to conventional photon doses. In other words, the LQ model is used here only to correct variations of radiation quality within carbon-ion beams. This system has been successful in fractionated carbon-ion RT (Kanai et al., 2006). However, for single-fraction treatment of non-small-cell lung cancer, the curative dose clinically resulted in 50 Gy (C) (Takahashi et al., 2014) and deviated from an initial LQ-model estimation of 28 Gy (C) or 12 Gy (RBE), which may have been beyond its valid dose range.

The microdosimetric implication of β invariance, which is assumed in this study as well as in the NIRS clinical dosimetry system (Inaniwa et al., 2015), may however

be controversial. In fact, there was a trend that β increased for fast neutrons from for photons by factor 1.82 in average (Jones, 2010) and similarly with LET of ions typically below 100 keV/ μm (Friedrich et al., 2012). However, the fluctuations of the data points comprising the trend were quite large, as it is generally difficult to determine β values accurately in cell-survival experiments. To mitigate the influence of β errors, application of the LQ model should be limited to small fraction doses with $D \lesssim \alpha/\beta$ so that the quadratic term will remain minor. In the preclinical survey for hypofractionation of the prostate-cancer treatment, the fraction doses at the reference-radiation point in the SOBP with the α/β ratio of 12.42 Gy were 1.78, 2.54, 4.49 and 7.60 Gy for equally curative 12-, 8-, 4- and 2-fraction treatments, respectively. The fraction doses at a point outside the SOBP with the α/β ratio of 6.6 Gy were 0.9, 1.3, 2.3 and 3.9 Gy, respectively. Therefore, the hypofractionation analysis should have been reasonably valid.

In the prostate-cancer treatment, the BED distribution was very similar to the clinical-dose distribution with 12 fractions of 4.3 Gy (C), which happens to be a typical practice of carbon-ion RT (Kamada et al., 2015). In such a case, the clinical-dose distribution can be approximately interpreted as the BED distribution with rescaling,

$$D_{\text{BE}}(\vec{r}) \approx \left(1 + \frac{\beta_{\text{ref}}}{\alpha_{\text{ref}}} \frac{\check{D}_{\text{C1}}}{f_{\text{C}}}\right) \frac{D_{\text{C}}(\vec{r})}{f_{\text{C}}}, \quad (20)$$

where \check{D}_{C1} is the fraction clinical dose prescribed to a tumor. The hypofractionation attempted for the prostate-cancer treatment apparently degraded the dose concentration of the total RWD distribution, which was inconsistent with the BED distribution and thus may indicate a deficiency of RWD for hypofractionated treatments. The observed invariance of BED may have been caused by cancelation between the SOBP (high dose, high α/β) and its outside regions (low dose, low α/β) in the relative dose-fractionation effect $(1 + D_i \beta_i/\alpha_i)$. The cancellation may generally be valid for carbon-ion beams because their physical dose and LET are naturally correlated, implying that carbon-ion RT may tend to be insensitive to fractionation. This fact may rationalize the use of uneven fractionation such as with alternate single-beam delivery for efficient operation. In reality, however, the therapeutic gain by fractionation should be evaluated with accurate differentiation between cancer and normal cells in radiosensitivity (Yoshida et al., 2015), or could be learned from clinical experiences retrospectively (Fukahori et al., 2016).

5. Conclusions

The BED is a representation of treatment dose that normalizes the effects of dose fractionation, inherent tumor growth and the RBE of treating radiation. For assessment of carbon-ion RT treatment, we simplified the RBE concept to be biological dose for a reference cell line and reformulated it as a derivative of the clinical dose used in practice. The BED will theoretically be useful for preclinical and retrospective studies when variation in fractionation is involved. For a prostate-cancer treatment of carbon-ion RT, we found that the BED and RWD distributions were very similar

at a normal fraction size, that the BED distribution was nearly invariant against fractionation, that uneven fractionation was only slightly inferior to even fractionation in dose concentration and that the RWD would not suffice for dose-distribution assessment with radical hypofractionation. The BED can be converted to that of any radiation of known α value, which will theoretically enable universal assessment of RT treatments of various modalities. However, treatment evaluation with such simplistic biological dose is intrinsically limited and must be complemented in practice by clinical experience and biology experiment.

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References

- Barendsen, G. (1982). Dose fractionation, dose rate and iso-effect relationships for normal tissue responses, *International Journal of Radiation Oncology Biology Physics* **8**(11): 1981–1997.
[http://dx.doi.org/10.1016/0360-3016\(82\)90459-X](http://dx.doi.org/10.1016/0360-3016(82)90459-X)
- Carabe-Fernandez, A., Dale, R. G. and Jones, B. (2007). The incorporation of the concept of minimum RBE (RBE min) into the linear-quadratic model and the potential for improved radiobiological analysis of high-LET treatments, *International Journal of Radiation Biology* **83**(1): 27–39.
<http://dx.doi.org/10.1080/09553000601087176>
- Castro, J. R. (1993). Heavy ion therapy: Bevalac epoch, in U. Amaldi and B. Larsson (eds), *Hadrontherapy in Oncology: Proceedings of the First International Symposium on Hadrontherapy, Como, Italy, 18-21 October 1993*, International Congress Series 1077, Elsevier Science, Amsterdam, pp. 208–216.
<http://www.osti.gov/scitech/servlets/purl/10150868>
- Combs, S. E. and Debus, J. (2013). Treatment with heavy charged particles: Systematic review of clinical data and current clinical (comparative) trials, *Acta Oncologica* **52**(7): 1272–1286.
<http://dx.doi.org/10.3109/0284186x.2013.818254>
- Dale, R. (1989). Time-dependent tumour repopulation factors in linear-quadratic equations — implications for treatment strategies, *Radiotherapy and Oncology* **15**(4): 371–381.
[http://dx.doi.org/10.1016/0167-8140\(89\)90084-4](http://dx.doi.org/10.1016/0167-8140(89)90084-4)
- Dale, R. G. and Jones, B. (1999). The assessment of RBE effects using the concept of biologically effective dose, *International Journal of Radiation Oncology Biology Physics* **43**(3): 639–645.
[http://dx.doi.org/10.1016/s0360-3016\(98\)00364-2](http://dx.doi.org/10.1016/s0360-3016(98)00364-2)
- Douglas, B. G. and Fowler, J. F. (1976). The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation, *Radiation Research* **66**(2): 401.
<http://dx.doi.org/10.2307/3574407>
- Fowler, J. F. (1989). The linear-quadratic formula and progress in fractionated radiotherapy, *The British Journal of Radiology* **62**(740): 679–694.
<http://dx.doi.org/10.1259/0007-1285-62-740-679>
- Friedrich, T., Scholz, U., Elsässer, T., Durante, M. and Scholz, M. (2012). Systematic analysis of RBE and related quantities using a database of cell survival experiments with ion beam irradiation,

- Journal of Radiation Research* **54**(3): 494–514.
<http://dx.doi.org/10.1093/jrr/rrs114>
- Fukahori, M., Matsufuji, N., Himukai, T., Kanematsu, N., Mizuno, H., Fukumura, A., Tsuji, H. and Kamada, T. (2016). Estimation of late rectal normal tissue complication probability parameters in carbon ion therapy for prostate cancer, *Radiotherapy and Oncology* **118**(1): 136–140.
<http://dx.doi.org/10.1016/j.radonc.2015.11.023>
- Furukawa, T., Inaniwa, T., Sato, S., Shirai, T., Takei, Y., Takeshita, E., Mizushima, K., Iwata, Y., Himukai, T., Mori, S., Fukuda, S., Minohara, S., Takada, E., Murakami, T. and Noda, K. (2010). Performance of the NIRS fast scanning system for heavy-ion radiotherapy, *Medical Physics* **37**(11): 5672.
<http://dx.doi.org/10.1118/1.3501313>
- Furusawa, Y., Fukutsu, K., Aoki, M., Itsukaichi, H., Eguchi-Kasai, K., Ohara, H., Yatagai, F., Kanai, T. and Ando, K. (2000). Inactivation of aerobic and hypoxic cells from three different cell lines by accelerated 3 He-, 12 C- and 20 Ne-ion beams, *Radiation Research* **154**(5): 485–496.
[http://dx.doi.org/10.1667/0033-7587\(2000\)154\[0485:ioaahc\]2.0.co;2](http://dx.doi.org/10.1667/0033-7587(2000)154[0485:ioaahc]2.0.co;2)
- Hawkins, R. B. (1994). A statistical theory of cell killing by radiation of varying linear energy transfer, *Radiation Research* **140**(3): 366.
<http://dx.doi.org/10.2307/3579114>
- Inaniwa, T., Furukawa, T., Kase, Y., Matsufuji, N., Toshito, T., Matsumoto, Y., Furusawa, Y. and Noda, K. (2010). Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model, *Physics in Medicine and Biology* **55**(22): 6721–6737.
<http://dx.doi.org/10.1088/0031-9155/55/22/008>
- Inaniwa, T., Kanematsu, N., Matsufuji, N., Kanai, T., Shirai, T., Noda, K., Tsuji, H., Kamada, T. and Tsujii, H. (2015). Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan, *Physics in Medicine and Biology* **60**(8): 3271–3286.
<http://dx.doi.org/10.1088/0031-9155/60/8/3271>
- Inaniwa, T., Suzuki, M., Furukawa, T., Kase, Y., Kanematsu, N., Shirai, T. and Hawkins, R. B. (2013). Effects of dose-delivery time structure on biological effectiveness for therapeutic carbon-ion beams evaluated with microdosimetric kinetic model, *Radiation Research* **180**(1): 44–59.
<http://dx.doi.org/10.1667/rr3178.1>
- Jones, B. (2010). The apparent increase in the β -parameter of the linear quadratic model with increased linear energy transfer during fast neutron irradiation, *The British Journal of Radiology* **83**(989): 433–436.
<http://dx.doi.org/10.1259/bjr/68792966>
- Jones, B., Carabe-Fernandez, A. and Dale, R. G. (2006). Calculation of high-LET radiotherapy dose required for compensation of overall treatment time extensions, *The British Journal of Radiology* **79**(939): 254–257.
<http://dx.doi.org/10.1259/bjr/49977661>
- Kamada, T., Tsujii, H., Blakely, E. A., Debus, J., Neve, W. D., Durante, M., Jäkel, O., Mayer, R., Orecchia, R., Pötter, R., Vatnitsky, S. and Chu, W. T. (2015). Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience, *Lancet Oncology* **16**(2): e93–e100.
[http://dx.doi.org/10.1016/s1470-2045\(14\)70412-7](http://dx.doi.org/10.1016/s1470-2045(14)70412-7)
- Kanai, T., Matsufuji, N., Miyamoto, T., Mizoe, J., Kamada, T., Tsuji, H., Kato, H., Baba, M. and Tsujii, H. (2006). Examination of GyE system for HIMAC carbon therapy, *International Journal of Radiation Oncology Biology Physics* **64**(2): 650–656.
<http://dx.doi.org/10.1016/j.ijrobp.2005.09.043>
- Kanematsu, N., Endo, M., Futami, Y., Kanai, T., Asakura, H., Oka, H. and Yusa, K. (2002). Treatment planning for the layer-stacking irradiation system for three-dimensional conformal heavy-ion radiotherapy, *Medical Physics* **29**(12): 2823–2829.
<http://dx.doi.org/10.1118/1.1521938>

- Kellerer, A. M. and Rossi, H. H. (1972). The theory of dual radiation action, *Current Topics in Radiation Research Quarterly* **8**(3): 85–158.
- Lam, G. K. Y. (1987). The survival response of a biological system to mixed radiations, *Radiation Research* **110**(2): 232.
<http://dx.doi.org/10.2307/3576901>
- Matsufuji, N., Kanai, T., Kanematsu, N., Miyamoto, T., Baba, M., Kamada, T., Kato, H., Yamada, S., Ietsu Mizoe, J. and Tsujii, H. (2007). Specification of carbon ion dose at the national institute of radiological sciences (NIRS), *Journal of Radiation Research* **48**(Suppl.A): A81–A86.
<http://dx.doi.org/10.1269/jrr.48.A81>
- Munro, T. R. and Gilbert, C. W. (1961). The relation between tumour lethal doses and the radiosensitivity of tumour cells, *The British Journal of Radiology* **34**(400): 246–251.
<http://dx.doi.org/10.1259/0007-1285-34-400-246>
- Nomiya, T., Tsuji, H., Maruyama, K., Toyama, S., Suzuki, H., Akakura, K., Shimazaki, J., Nemoto, K., Kamada, T. and Tsujii, H. (2014). Phase I/II trial of definitive carbon ion radiotherapy for prostate cancer: evaluation of shortening of treatment period to 3 weeks, *British Journal of Cancer* **110**(10): 2389–2395.
<http://dx.doi.org/10.1038/bjc.2014.191>
- Suzuki, M., Kase, Y., Yamaguchi, H., Kanai, T. and Ando, K. (2000). Relative biological effectiveness for cell-killing effect on various human cell lines irradiated with heavy-ion medical accelerator in chiba (HIMAC) carbon-ion beams, *International Journal of Radiation Oncology Biology Physics* **48**(1): 241–250.
[http://dx.doi.org/10.1016/S0360-3016\(00\)00568-X](http://dx.doi.org/10.1016/S0360-3016(00)00568-X)
- Takahashi, W., Nakajima, M., Yamamoto, N., Tsuji, H., Kamada, T. and Tsujii, H. (2014). Carbon ion radiotherapy in a hypofractionation regimen for stage I non-small-cell lung cancer, *Journal of Radiation Research* **55**(suppl 1): i26–i27.
<http://dx.doi.org/10.1093/jrr/rrt216>
- Yoshida, Y., Ando, K., Ando, K., Murata, K., Yoshimoto, Y., Musha, A., Kubo, N., Kawamura, H., Koike, S., Uzawa, A., Takahashi, T., Ohno, T. and Nakano, T. (2015). Evaluation of therapeutic gain for fractionated carbon-ion radiotherapy using the tumor growth delay and crypt survival assays, *Radiotherapy and Oncology* **117**(2): 351–357.
<http://dx.doi.org/10.1016/j.radonc.2015.09.027>
- Zaider, M. and Rossi, H. H. (1980). The synergistic effects of different radiations, *Radiation Research* **83**(3): 732.
<http://dx.doi.org/10.2307/3575352>