BIOLOGICAL DOSE EVALUATION OF RADIOTHERAPY BY EQUIVALENT DOSE IN 2Gy FRACTIONS (EQD2) IN RECURRENT GLIOBLASTOMA

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Received December 9, 2021

Abstract

The standard treatment for glioblastoma is surgery followed by radiation therapy (RT) and temozolomide (TMZ) chemotherapy. A total dose of 60 Gy given in 2 Gy fractions (fr) with concurrent and adjuvant TMZ has been recommended; however, local recurrences are frequent and the prognosis remains very poor. In this study, the equivalent dose in 2Gy fr (EQD2) at the recurrent site of glioblastoma was assessed to evaluate the biological effect of RT on glioblastoma considering that α / β ratios might vary from 1 to 10 Gy.

Recurrences were found in gross tumor volume (GTV) areas in all 11 patients, and 8 of them also showed recurrence in clinical target volume (CTV). Differences in EQD2 according to α / β ratios were relatively small in high-dose areas around 60 Gy; however, low-dose areas often showed significant differences of EQD2 according to the α / β ratios. In patients that received 60 Gy in 2 Gy fr, EQD2 was less than the original physical dose and became smaller as the α / β ratio became smaller. The comparison of the dose distribution of EQD2 and dose volume histogram (DVH) of EQD2 between α / β ratios 1 and 10 suggested that little difference was found in relatively high-dose areas but a significant difference was found in low-dose areas. In contrast, if the fraction size was larger than 2 Gy, EQD2 was greater than the original physical dose and it became larger as the α / β ratio became smaller.

In conclusion, this study showed that the standard RT 60 Gy in 2 Gy fr is insufficient for glioblastoma, and it suggested that biological effects might differ significantly according to each fraction size of radiation and α / β ratio of the linear quadratic (LQ) model.

Key Words: Glioblastoma, Recurrence, Radiotherapy, EQD2

Background

Glioblastoma is the most common primary malignant brain tumor, and the present standard treatment is surgery followed by radiation therapy (RT) and temozolomide (TMZ) chemothera-

py. A total dose of 60 Gy in 2 Gy fractions (fr) given over 6 weeks with concurrent and adjuvant TMZ has been recommended for this type of tumor[1,2]. However, local recurrences are frequent even after the standard chemoradiotherapy, and the prognosis of the patients remains very poor. The median survival time (MST) is less than 2 years, and the 2-year survival rate is 35% or less according to many clinical trials[3,4].

The target volume for radiation treatment planning (RTP) is usually defined by pre- and post-operative magnetic resonance imaging (MRI); post-contrast T1 and FLAIR/T2 sequences are used to define gross tumor volume (GTV) and clinical target volume (CTV)[2]. In post-operative RT, 60 Gy in 2 Gy fr is delivered not to the whole brain but to the extensive local field containing GTV and CTV considering the adverse effect on normal brain tissue. Furthermore, the actual irradiated dose in the target is not always homogenous even though precise RTP for intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) is performed routinely. Thus, it is necessary to evaluate the biologically equivalent dose delivered in 2 Gy fr in order to estimate the radiation effect on the target volume more precisely.

The linear quadratic (LQ) model, the biologically effective dose (BED), and the equivalent dose in 2Gy fr (EQD2) based on the LQ models shown below have often been used for comparison of radiation effects with different treatment planning or fractionation schedules[5]. The α / β ratio, the ratio of the parameters α and β in the LQ model, is used to quantify the fractionation sensitivity of tumor and normal tissues. The ratio of tumors is usually assumed to be higher than that of late responding normal tissue, but it is not constant and may vary according to the tumor type[6].

LQ model, BED, and EQD2:

$E = n(\alpha d + \beta d^2) = \alpha (nd)(1 + d/(\alpha / \beta)) = \alpha$ (total dose)(relative effectiveness)

BED = (total dose)(relative effectiveness) $= E/\alpha = nd(1 + d/(\alpha / \beta))$

$EQD2 = nd(d + \alpha / \beta)/(2 + \alpha / \beta)$

(E: biological effect, BED: biologically effective dose, EQD2: equivalent dose in 2Gy fraction, n: number of fractionations, d: single fraction dose, α / β : α / β ratio)

The present study examined the simple physical dose and biologically equivalent dose estimated by EQD2 calculation in the recurrent site of glioblastoma to evaluate the biological effect of RT on the glioblastoma precisely.

Materials & Methods

Study group:

Between July 2017 and November 2019, 18 consecutive patients with histologically confirmed glioblastoma were treated with radiation in our institute. Diagnostic evaluation MRI and follow-up MRI were performed before and after the treatment (operation and post-operative RT). Each patient was evaluated at the Brain Tumor Board review to determine the treatment policy and the diagnosis of recurrence.

Overall survival (OS) was estimated with the Kaplan-Meier method, compared using the log-

rank test, and modelled by the Cox proportional hazards method to determine the prognosis for this group. Statistical significance was assessed at $p<0.05$. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of the R interface that is designed to add statistical functions frequently used in biostatistics.

Radiotherapy treatment planning and RT:

The radiotherapy treatment planning (RTP) system Eclipse (Varian Medical Systems, Palo Alto, CA U.S.A.) was used for the precise RTP for VMAT. All patients were treated with 10-MV X-ray of the linear accelerator TrueBeam STx or TrueBeam (Varian). VMAT is a novel radiation technique that delivers a highly conformal radiation dose to the target volume using multiple intensity-modulated arcs. Positioning verification was accomplished using an ExacTrac IGRT couch (BrainLAB, Munich, Germany) and on-board cone beam computed tomography.

The total dose of RT was 60 Gy in 2 Gy fractions (fr) in principle, but 40.05 Gy in 2.67 Gy fr was also used for some elderly patients[7,8].

Target volumes in RTP for glioblastoma were defined using pre- and post-operative MRI using post-contrast T1 weighted images (WI) and T2WI/FLAIR images as follows: GTV was defined as pre- and post-operative contrast-enhanced (CE) lesions and post-operative cavities on MRI. CTV was defined as fields containing 1.5–2-cm margins from the area showing high intensity on T2WI/FLAIR images on MRI. Planning target volume (PTV) was defined as fields containing 0.5-cm margins from CTV in consideration of set-up errors. Most patients received 60 Gy in 2 Gy fr in total: the initial PTV (PTV-I) covering CTV received 40–50 Gy in 2Gy fr, and the boost PTV (PTV-B; GTV plus margins or high-intensity area on T2WI/FLAIR images) received 10–20 Gy in 2 Gy fr considering the adverse effects on organs at risk (OARs; eyes, optic nerve, brain stem, etc.).

Physical dose and EQD2 evaluation:

The physical dose received in the recurrent sites was evaluated by dose distributions and dose volume histogram (DVH) using the RTP system Eclipse. EQD2 in the recurrent sites was estimated using Eclipse and Velocity software (Varian). Assuming α / β ratios of 1, 2, 3, 5, 7, and 10, Gy EQD2 values were EQD2(1), EQD2(2), EQD2(3), EQD2(5), EQD2(7), and EQD2(10) Gy, respectively. EQD2 values of recurrent sites in each of the following were calculated and plotted: the whole recurrent site (Whole), GTV, CTV, and out of CTV (Extra). Furthermore, differences in EQD2, dose distribution, and DVH according to α / β ratios (1–10) were evaluated.

Results

Patient follow-up and survival:

MRIs and survival of the 18 patients were reviewed. Three patients were lost to follow-up, and further analysis was performed on the other 15 patients.

The median patient age was 69 years old (range; 55–91) at the initiation of the treatment.

Three patients were alive and 12 had died at the last follow-up (November 2021), with a median follow-up time of 15.8 months (range; 7.7–41.2 months). The MST was also 15.8 months (range; 7.7–41.2 months). Recurrence was not yet shown in four patients. Recurrence was found in the other 11 patients; one of them lived for 41.2 months with the disease, and 10 had died. The MST of the patients with recurrence was 15.4 months (range; 7.7–41.3 months) (Table 1). OS curves are shown in Figure 1. No significant difference was shown between the two groups (p = 0.111).

Table 1. Summary of recurrent cases

Case No.	Age (Y)	Sex	Survival (M)	Alive/Dead	Total dose/fr	PTV-I	PTV-B1	PTV-B2	Fraction size
1	73	M	7.7	dead	60 Gy/30fr	40 Gy	10 Gy	10 Gy	2 Gy
2	69	F	11.9	dead	60 Gy/30fr	40 Gy	10 Gy	10 Gy	2 Gy
3	72	F	15.8	dead	60 Gy/30fr	40 Gy	20 Gy		2 Gy
4	57	M	17.7	dead	60 Gy/30fr	40 Gy	10 Gy	10 Gy	2 Gy
5	66	F	27.4	dead	60 Gy/30fr	40 Gy	20 Gy		2 Gy
6	78	M	9.6	dead	40.05 Gy/15fr	32.04 Gy	8.01 Gy		2.67 Gy
7	66	F	41.3	alive	60 Gy/30fr	46 Gy	14 Gy		2 Gy
8	63	M	11.7	dead	60 Gy/30fr	40 Gy	20 Gy		2 Gy
9	65	M	15.4	dead	60 Gy/30fr	40 Gy	20 Gy		2 Gy
10	74	F	12.2	dead	60 Gy/30fr	50 Gy	10 Gy		2 Gy
11	55	M	16.5	dead	60 Gy/30fr	40 Gy	14 Gy	6 Gy	2 Gy

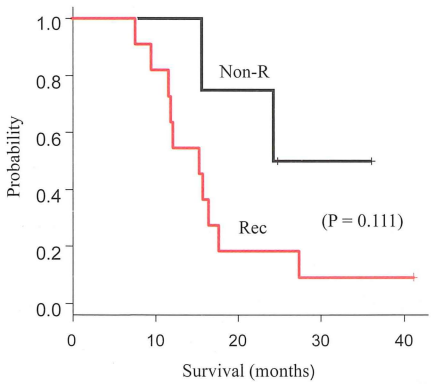

Fig.1. OS curves. Rec: patients with recurrence. Non-R: patients without recurrence.

RTP and RT:

Twelve patients were treated with 60 Gy in 2 Gy fr, and three were treated with 40.05 Gy in 2.67 Gy fr. In the 11 patients with recurrence, 10 received 60 Gy in 2 Gy fr, and eight of them received 40 Gy for PTV-I and 20 Gy for PTV-B. One patient with recurrence received 40.05 Gy in 2.67 Gy fr (Table 1.)

Physical dose and EQD2 of recurrent sites:

Recurrences were found in GTV areas in all 11 patients, and eight of them also showed recurrence in CTV. Furthermore, recurrences were found in the CTV in three patients.

Ten patients with recurrence were irradiated with 60 Gy according to the RTP. The actual mean dose (Dmean) of the recurrence within the GTV was 59.7 +/- 0.6 Gy (mean +/- SD), and that within the CTV was 50.5 +/- 6.3 Gy (mean +/- SD).

In the 11 cases, the EQD2 values estimated by Eclipse and Velocity assuming α / β ratios of 1, 2, 3, 5, 7, and 10 Gy were EQD2(1), EQD2(2), EQD2(3), EQD2(5), EQD2(7), and EQD2(10) Gy, respectively. These are shown in Figures 2a–k (cases No. 1–11). EQD2 values of recurrent sites in each of the following were calculated and plotted: the whole recurrent site (Whole), GTV, CTV, and outside of CTV (Extra).

Differences in EQD2, dose distribution, and DVH according to α / β ratios were relatively small in 10 cases (Figures 2a–e and g–k, Figures 3a, b, and Figures 4a, b). In particular, high-dose areas in GTV around 60 Gy showed little difference; however, relatively low-dose areas in GTV, CTV, and Extra often showed significant differences of EQD2 according to α / β ratios, especially in cases No. 5, 8, and 9 (Figures 2e, 2f, 2h, and 2i).

In the 10 cases that received 60 Gy in 2 Gy fractions, EQD2 was less than the original physical dose and became smaller as the α / β ratio became smaller: EQD2(1) < EQD2(2) < EQD2(3) < EQD2(5) < EQD2(7) < EQD2(10) < Original physical dose (Figures 2a–e and g–k).

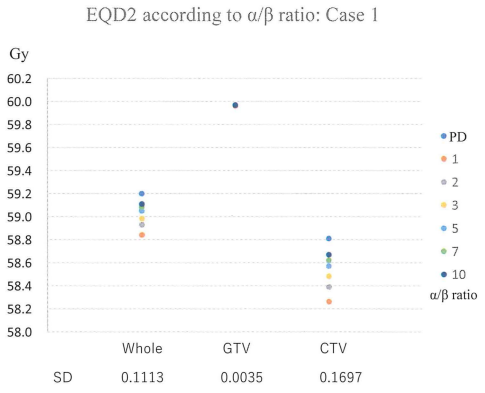

Fig.2. EQD2 according to α / β ratio of cases No. 1–11 (a–k). PD: physical dose.
Fig.2a.

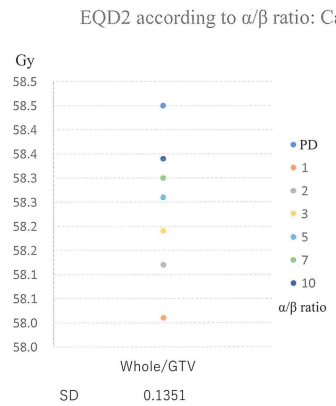

Fig.2b.

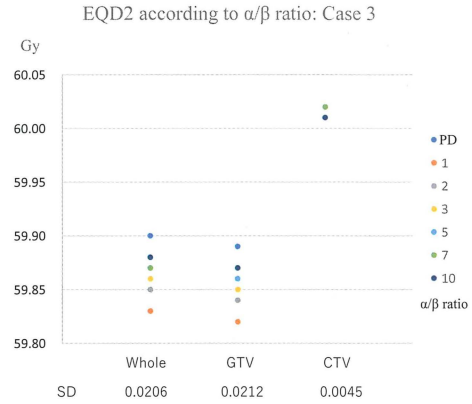

Fig.2c.

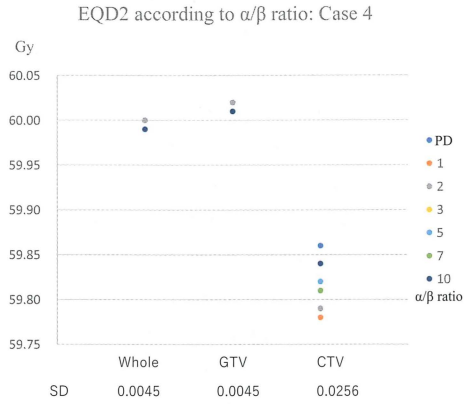

Fig.2d.

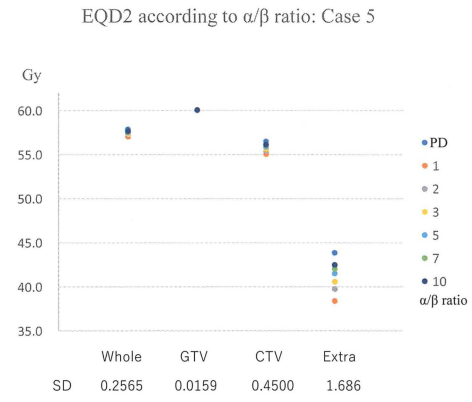

Fig.2e.

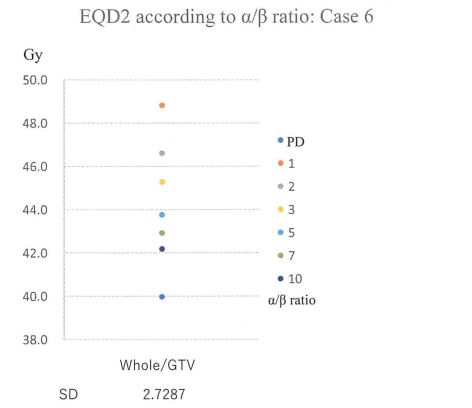

Fig.2f.

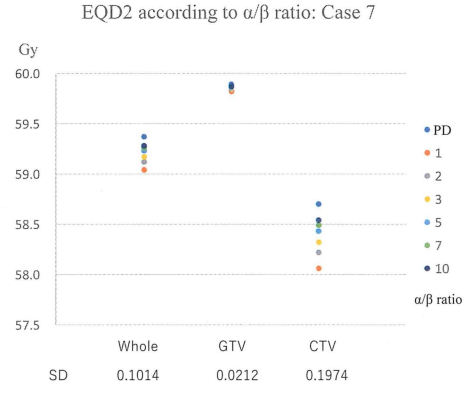

Fig.2g.

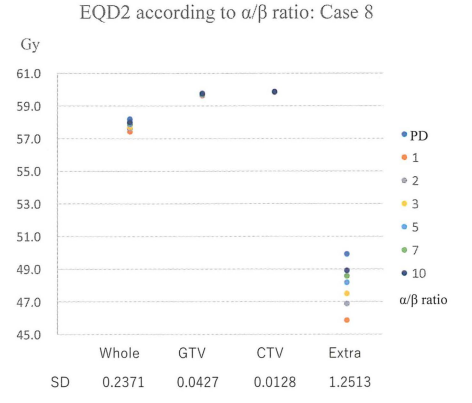

Fig.2h.

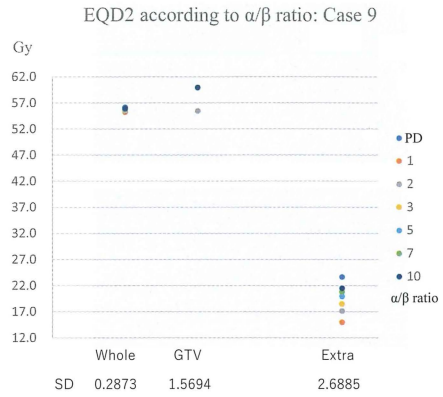

Fig.2i.

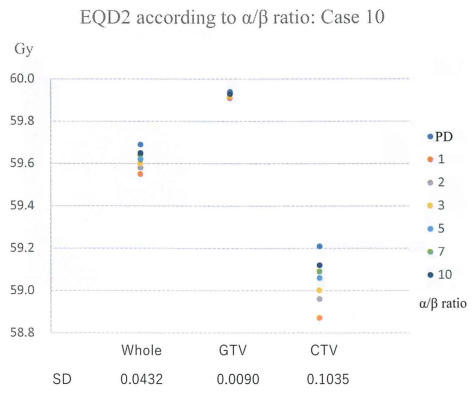

Fig.2j.

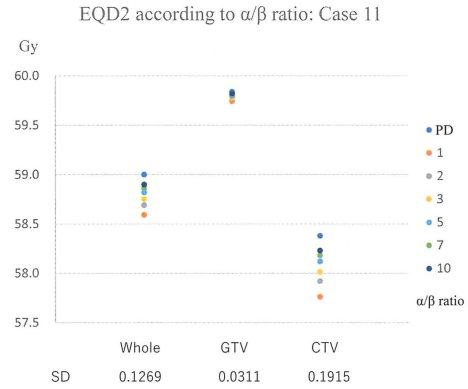

Fig.2k.

The comparison of the dose distribution of EQD2 between α / β ratios 1 and 10 in case No. 5 demonstrates that high-dose areas show little differences (red and orange lines) but low-dose areas show significant differences (blue and green lines) (Figures 3a, b). Similarly, the comparison of DVH demonstrates that high-dose areas show little differences between α / β ratios 1 (solid lines) and 10 (dotted lines) in cases No. 5 and No. 8 (Figures 4a, b), but low-dose areas show significant differences in CTV (pink) between α / β ratios 1 (solid lines) and 10 (dotted lines) (Figure 4a).

On the contrary, in case No. 6, which received 40.05 Gy in 2.67 fr, EQD2 was much greater than 40.05 Gy and it became larger as the α / β ratio became smaller: EQD2(1) > EQD2(2) > EQD2(3) > EQD2(5) > EQD2(7) > EQD2(10) > Original physical dose (Figure 2f).

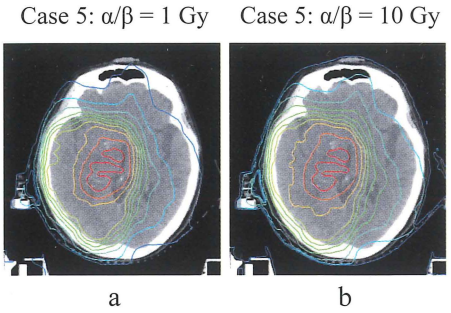

Fig.3a, b. Comparison of dose distribution of EQD2 between α / β ratios 1 (a) and 10 (b) in case No. 5.

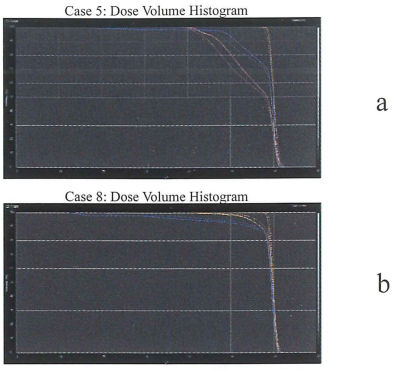

Fig.4a, b. Comparison of DVH of EQD2 between α / β ratios 1 (solid lines) and 10 (dotted lines) in cases No. 5 (a) and No. 8 (b).

Discussion

The present standard treatment for glioblastoma is surgery followed by RT 60 Gy in 2 Gy fr and TMZ chemotherapy for patients 70 years old or younger with good performance status[2]. However, local recurrences are frequent and the prognosis remains very poor[1-4]. In this study, local recurrence within GTV was found in every case with recurrence, although the appropriate standard irradiation was performed according to the RTP for VMAT. Additionally, recurrence in CTV was often found, but there is no clinical indication to use more than 60 Gy for this type of tumor[2,9,10]. These results might suggest the limitation of modern RT for glioblastoma.

Hypofractionated RT using a fraction size larger than 2 Gy is often used for elderly patients[2,7,8,11]. However, hypofractionated fractionation is not always as effective as the standard schedule of 60 Gy in 2 Gy fr, and short-course hypofractionation for 1 to 3 weeks should be used for poorly performing or elderly patients[2,11].

The RT dose of 60 Gy in 2 Gy fr by VMAT delivered to the extensive local field containing GTV and CTV is very common, but not every irradiated dose distribution in the target is homogenously 60 Gy in 2 Gy fr. The Dmean of the recurrence within the GTV was approximately 60 Gy, but that within the CTV was less than 60 Gy (50.5 +/- 6.3 Gy).

If the fraction size is not 2 Gy, biological effects on tumors and normal tissues may differ from those in 2 Gy fr even if the total dose is identical. Thus, we must evaluate the biologically equivalent dose, such as BED or EQD2 based on the LQ model, to estimate the radiation effect more precisely.

The EQD2 has often been used for comparison of the radiation effects of different treatment planning or fractionation schedules[5]. The α / β ratio of tumors in the LQ model is usually assumed to be higher than that of late responding normal tissue[5,6], but the ratio is not always constant and may vary according to the tumor type, dose range, concomitant chemotherapy, surrounding environment, and other factors[6,12,13,14].

In the 10 recurrent glioblastomas treated with 60 Gy in 2 Gy fr, recurrence was found in each GTV, although approximately 60 Gy was actually radiated to the GTV as the standard treat-

ment. Additionally, recurrence was often found in CTV irradiated with 60 Gy or less, and the Dmean of the recurrence within the CTV was 50.5 +/- 6.3 Gy. If the total dose is less than 60 Gy, the fraction size is not always 2 Gy and is usually less than 2 Gy. The biologically equivalent dose estimated by EQD2 calculation in the recurrent site of glioblastoma was studied to evaluate the biological effect of RT on glioblastoma considering the possibility that α / β ratios might vary from 1 to 10 Gy.

Differences in EQD2 according to α / β ratios were relatively small in high-dose areas around 60 Gy; however, low-dose areas often showed significant differences in EQD2 according to the α / β ratio. In patients that received 60 Gy in 2 Gy fractions, EQD2 was equal to or less than the original physical dose and became smaller as the α / β ratio became smaller.

The comparison of the dose distribution of EQD2 and DVH of EQD2 between α / β ratios 1 and 10 suggested that relatively high-dose areas in 2 Gy fr therapy show little differences but low-dose areas show significant differences. On the contrary, when the fraction size was more than 2 Gy, EQD2 was much larger than the standard dose and the EQD2 became larger as the α / β ratio became smaller.

In conclusion, this study showed that the standard RT 60 Gy in 2 Gy fr is insufficient for glioblastoma, and it suggested that biological effects might differ significantly according to the fraction size of radiation and the α / β ratio of the LQ model.

Ethical statement

This study was approved by Nara Medical University Ethics Committee.

Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

Acknowledgements

We thank the members of Departments of Radiation Oncology, Radiology, and Neurosurgery, Nara Medical University for their help in this research.

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