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PHYSICS CONTRIBUTION

AN ESTIMATION OF RADIOBIOLOGIC PARAMETERS FROM CLINICAL OUTCOMES FOR RADIATION TREATMENT PLANNING OF BRAIN TUMOR

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Purpose: To estimate a plausible set of radiobiologic parameters such as α, α/β values, from clinical outcomes for biologically based radiation treatment planning of brain tumors.
Methods and Materials: Linear-quadratic (LQ) formalism and the concept of equivalent uniform dose were used to analyze a series of published clinical data for malignant gliomas involving different forms of radiation therapy.
Results: A plausible set of LQ parameters was obtained for gliomas: $\alpha = 0.06 \pm 0.05$ Gy^{-1}, $\alpha/\beta = 10.0 \pm 15.1$ Gy, the tumor cell doubling time $T_d = 50 \pm 30$ days, with the repair half-time of 0.5 h. The present estimated biologic parameters can reasonably predict the effectiveness of most of the recently reported clinical results employing either single or combined radiation therapy modalities. Different LQ parameters between Grade 3 and Grade 4 astrocytomas were found, implying the radiosensitivity for different grade tumors may be different. Smaller α, β from *in vivo* was observed, indicating lower radiosensitivity occurred *in vivo* as compared with *in vitro*.
Conclusions: A plausible set of radiobiologic parameters for gliomas was estimated based on clinical data. These parameters can reasonably predict most of the clinical results. They may be used to design new treatment fractionation schemes and to evaluate and optimize treatment plans.

Malignant gliomas, Glioblastoma multiforme, Linear-quadratic model, Equivalent uniform dose.

INTRODUCTION

The recent surge in popularity of intensity-modulated radiotherapy, especially biologic/functional image guided intensity-modulated radiotherapy, has significantly increased the need for reliable dose–response relationships. It is generally believed that these relationships should and will play an increasingly more important role in designing, optimizing, and evaluating radiation treatment plans. A great deal of effort is being spent on developing quantitative models to predict the likely biologic radiation response of tumor and normal tissues. Among these models, the linear-quadratic (LQ) model is widely used in evaluating treatment plans and in designing new treatment strategies. Because the LQ model uses a minimum number of radiobiologic parameters, its predictions are sensitive to its parameters (e.g., α/β ratio). The selection of proper LQ parameters becomes important in the success of using this model and has been challenging particularly in the clinical setting.

Glioblastoma multiforme (GBM), representing approximately 80% of all malignant gliomas (MG), is the most common intracranial primary malignancy (1–6). Although aggressive treatments, including the maximum macroscopic resection, chemotherapy, followed by external beam radiation therapy (EBRT) were undertaken, the median survival remains poor. The 1-year median survival rate is only approximately 50% (1–3); the median survival time of 8–12 months is generally quoted (1, 4). The pattern of failure is primarily local recurrence due in part to inadequate therapeutic doses limited by the tolerance of normal tissues (3, 7, 8). Walker *et al.* (9), representing the Brain Tumor Study Group, demonstrated a clear-cut dose–response relationship for EBRT in conventional dose range (50–60 Gy). On the other hand, Salazar *et al.* (10, 11) explored the radiation doses beyond conventional levels, and found that there was no evidence of improved long-term survival despite the increase in dose as high as 80 Gy. In several randomized trials (7, 12), further dose escalations (>80 Gy) with external beam have resulted in no benefit in prolonging the total survival. Recently, multiple studies employing new treatment techniques with dose escalations have shown significant improvement in the survival rates for patients with primary GBM (4, 8, 13–16).

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Despite several decades of work, treatment outcomes for MG are generally poor. The present clinical radiation treatment dose for MG, using single or multimodality radiation therapy (RT), is largely based on the Brain Tumor Study Group findings as well as other empirical experience. Clearly, more effective radiation treatments that aim to increase tumor cell killing and, in the meantime, to minimize the damage to normal tissues are needed. The purpose of this work is to estimate a plausible set of radiobiologic parameters that may be used to compare different radiation treatment plans in terms of their biologic effectiveness or to design new treatment strategies for malignant gliomas. A series of published clinical data will be analyzed to derive a plausible set of radiobiologic parameters, such as α, α/β ratio (radiosensitive parameters in LQ model), with consideration of tumor repopulation and sublethal damage repair. Other radiobiologic parameters, e.g., potential doubling time, will be also extracted from this analysis. The biologic equivalent dose (BED), the equivalent uniform dose (EUD), and the tumor control probability (TCP) will be calculated using the presently derived parameter set for a series of published clinical studies. The comparison between the calculations and clinical results will be used to test the applicability and predictability of the derived radiobiologic parameters.

METHODS AND MATERIALS

Radiobiologic models

Linear-quadratic formalism is the most prevalent model to predict the radiation killing of cells. According to Dale (17, 18), the LQ model with repopulation reads as (19, 20):

$$S = e^{-E} \tag{1}$$

and

$$E = \alpha D + \beta G D^2 - \gamma T \tag{2}$$

where S is the cell surviving fraction, α and β characterize intrinsic radiosensitivity, G is the dose protraction factor; γ is the effective tumor-cell repopulation rate: $\gamma = \ln 2/T_d$, and T_d is the potential doubling time. D is the total dose delivered within the effective treatment time T. The quantity E is the biologically effective yield of lethal damage per cell corrected for repopulation effects. The α/β ratio measures the relative importance of the linear and quadratic terms in the LQ model. The dose protraction factor G accounts for both dose rate and sublethal damage repair. In this analysis, the repair half-time for sublethal damage repair, T_γ, was assumed to be 0.5 h based on a previous study (21). The detailed calculations for the dose protraction factor G for the irradiation techniques involved in this study are included in the Appendix.

Biologically effective dose (BED) is the concept commonly used to compare different treatment modalities or fractionation schedules (19):

$$\mathrm{BED} = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\gamma(T - T_k)}{\alpha} \tag{3}$$

The overall treatment time (T) for EBRT can be approximately calculated as the number of treatment fractions multiplied by 1.4 (5 fractions per week). T_k is the time at which repopulation begins after treatment. We assume $T_K = 0$ in this study, because the available clinical data are not sufficient to analyze this effect.

The tumor control probability (TCP) with clonogen proliferation is calculated from the cell surviving fraction S using the Poisson hypothesis (22):

$$\mathrm{TCP} = e^{-k \cdot S} \tag{4}$$

where k is the cell number of tumor clonogens. S is the cell surviving fraction shown in Eqs. (1) and (2).

The dose inhomogeneities are considered by using the concept of equivalent uniform dose (EUD), which is defined as the dose that, if distributed uniformly, will lead to the same biologic effect as the actual nonuniform dose distribution (23). The EUD is commonly used to compare and optimize various treatment schemes and can be calculated by (20, 24):

$$\mathrm{EUD} = \frac{-\log(S)}{\alpha + \beta \mathrm{d} - 1.4\gamma/d} \tag{5}$$

where d is the mean value of the dose fraction. In this study, the conventional dose fraction 2 Gy ($d = 2$ Gy) was used to calculate the numerical value of EUD. In the presence of dose inhomogeneity, the overall surviving fraction S was calculated by

$$S = \sum_i v_i S(D_i) \tag{6}$$

where V_i is the fractional volume of dose bin D_i in the dose–volume histograms (DVH). The representative DVHs for brachytherapy and EBRT, as shown in Fig. 1, were used in the calcula-

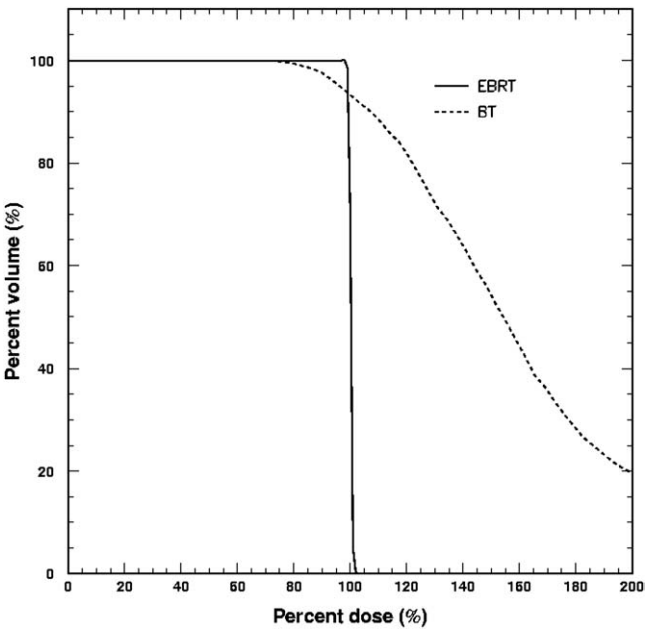

Fig. 1. Representative dose–volume histograms for external beam radiotherapy (EBRT, solid line) and brachytherapy (BT, dashed line).

Table 1. List of the patient characteristics and treatment modalities for studies analyzed in this work

Reference	No. of patients	Median age	Karnofsky Performance Status	Median survival (mo)	Reoperation rate (%)	Survival rate at 1 year (%)
EBRT alone series						
Walker *et al.* (9)	621	56	—	4–10	—	20–40
Salazar *et al.* (10, 11)	243	47	—	10–21	—	20–50
EBRT + SRS series						
Mehta *et al.* (1)	31	57	70	10	—	38
Loeffler *et al.* (16)	37	51	85	26 (GBM)	40	90
Shrieve *et al.* (33)	78	51	90	20	50	88.5
Buatti *et al.* (34)	11	42	90	17	67	81
EBRT + LDR series						
Wen *et al.* (4)	56	50	90	18	64	83
Sneed *et al.* (8)	159	52	90	18	51	85
Prados *et al.* (15)	56	47	90–100 (64%)* 70–80 (21%)*	21	46	87
Loeffler *et al.* (26)	41	51	85	26	40	87
EBRT + HDR series						
Chang *et al.* (30)	28	50	≥90 (46%)* <90 (54%)*	20	54	89
Hyperfractionated series						
Curran *et al.* (38)	167	53	80–100 (70%)*	11.7†	—	47
	137	53	80–100 (70%)*	10.8‡	—	46
Werner-Wasik *et al.* (37)	747	52	80–100 (70%)*	11.8 (MG) 10.6 (GBM)	— —	

Abbreviations: EBRT = external beam radiation therapy; GBM = glioblastoma multiforme; HDR = high-dose-rate; LDR = low-dose-rate; MG = malignant gliomas; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery.

* The percentage of patients belongs to the selected Karnofsky Performance Status range.

†,‡ RTOG 8302 accelerated hyperfractionated radiation therapy doses of 48 Gy and 54.4 Gy treatment arms.

tion. The density of clonogens throughout the tumor was presumed as constant.

Clinical data

Clinical studies analyzed to derive the radiobiologic parameters. The Brain Tumor Study Group (9) reported the results from a randomized trial on the dose–effect relationship of radiotherapy in the treatment of MG. A total of 621 patients with 86% GBM, 9.9% malignant astrocytomas, and 4.1% mixed MG were included in the trial. These patients underwent surgery followed by EBRT with total doses of 1–45 Gy, 50 Gy, 55 Gy, or 60 Gy. The dose was delivered in 1.71–2.0 Gy per fraction with 5 fractions per week. The median survival time increased from 18 weeks (no irradiation) to 42 weeks with a median dose of 60 Gy. Patients who had received a dose of <45 Gy radiation were not included in the analysis because they were not comparable with other subgroups who received higher doses. Survival curves of all patients were reported by Walker *et al.* (9), demonstrating strong dose dependence.

Salazar *et al.* (10, 11) reported their results based on 253 patients with histologically confirmed supratentorial malignant gliomas. Among these patients, 107 had Grade 3 astrocytoma and 146 had Grade 4 astrocytoma. The patients at each grade were divided into three groups depending on the total median dose delivered to the tumor, e.g., 50, 60, and 75 Gy. All the patients were treated with EBRT, with 5 weekly fractions of 1.5–2.0 Gy. The minimum follow-up time was 12 months. Given the histologic grade (Grade 3 or Grade 4), the results demonstrated the striking differences in median survival: for Grade 4 tumors, the median survival times of the very high dose group (75–80 Gy), the median high dose group (50–65 Gy), and the conventional dose group (50–55 Gy) were 56, 42, and 30 weeks respectively; whereas, for patients with Grade 3 were 204, 82, and 43 weeks respectively.

Clinical studies analyzed to validate the parameters. A series of published clinical studies are analyzed to validate the biologic parameters derived based on the above two sets of data (9, 10). These studies involved the combination of EBRT with low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy, or stereotactic radiosurgery (SRS). Table 1 shows the patient and treatment characteristics for these studies. It has been reported by several groups that a dose of 50–60 Gy delivered with LDR brachytherapy in addition to the standard EBRT reduces tumor recurrence and prolongs patient survival to 18–27 months (4, 13, 15, 25, 26). Wen *et al.* (4) used an I^{125} temporary implant to deliver a dose of 50 Gy in addition to the EBRT. The median survival of their patients undergoing brachytherapy was significantly prolonged, reaching 18 months, as compared with 11 months for the control group. Sneed *et al.* (27) reported a median survival time of 17.7 months from a randomized trial using combined brachytherapy and EBRT.

In contrast to many studies of LDR brachytherapy with favorable results, only a few HDR brachytherapy studies were reported (28–30). Koot *et al.* (31) found no difference in median survival between using I^{125} LDR and Ir^{192} HDR brachytherapy. In their study, a total of 120 patients with newly diagnosed MG received an EBRT with median dose of 60 Gy with or without HDR brachytherapy. The HDR dose of 30 Gy was given in 10 fractions in 5 days. The toxicity for the brachytherapy was acceptable, and median survival was prolonged to 19.5 months, compared with 12.5 months for those patients without the HDR brachytherapy.

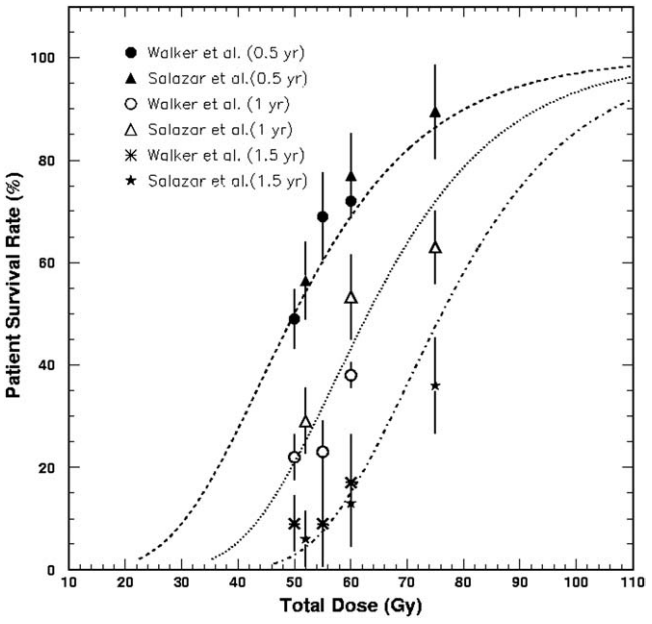

Fig. 2. Dose–response curves for malignant gliomas at 0.5, 1.0, and 1.5 years. The patient survival rates given by Walker *et al.* (9) and Salazar *et al.* (10, 11) are considered. The lines represent the fitting to the data points for the survival rates given at 0.5, 1.0, and 1.5 years, respectively. The fitting yields: $\alpha = 0.06 \pm 0.05$ Gy^{-1} and $\alpha/\beta = 10.0 \pm 15.1$ Gy. The error bars represent statistical uncertainty.

Chang *et al.* (30) reported another study with 28 GBM patients treated by the HDR brachytherapy in addition to the standard EBRT. The HDR doses ranged between 18 and 30 Gy (median, 30 Gy) delivered over 10 fractions in 5 days. For patients treated with the HDR, the 1- and 2-year survival rates were 89% and 42%, respectively, vs. 61% and 28% for those without HDR treatment.

Stereotactic radiosurgery has become popular in recent years because it is capable of delivering a high dose to the target in a very precise manner. SRS is commonly used for small tumors with diameters less than 4 cm (32); whereas, the brachytherapy may be used for larger tumor sizes. Loeffler *et al.* (16) conducted a study with 37 MG patients (23 of them had GBM) who, after surgery, were treated by EBRT and SRS. For SRS, the median dose was in the range of 12–15 Gy. With a median follow-up of 19 months, 24% of the patients died. This median survival of 27 months for GBM was similar to that for brachytherapy (26). Shrieve *et al.* (33) demonstrated their experience in 78 patients. The median survival for all patients was 19.9 months, and the 12-month and 24-month survival rates were 88.5% and 35.9% respectively. Similar studies demonstrating the benefits of SRS were reported by many others (7, 32, 34).

Although interstitial brachytherapy or SRS seem promising to improve the survival rate for gliomas, a majority of patients with gliomas do not qualify for brachytherapy or radiosurgery because of the sizes of their tumors (35, 36). For those patients, EBRT remains the most effective and tolerable regimen. Hyperfractionated radiation therapy and accelerated hyperfractionated radiation therapy may potentially allow for delivery of a higher total dose without increasing normal tissue late effects. The Radiation Therapy Oncology Group (RTOG) conducted a randomized study (RTOG-8302) from 1983 to 1989 (37); they included 786 patients with supratentorial gliomas. All patients received partial brain irradiation, using 1.6 Gy twice daily to a total dose of 48 or 54.4 Gy (accelerated hyperfractionated radiation therapy), or 1.2 Gy twice daily (hyperfractionated radiation therapy) to 64.8 Gy or even higher dose. The survival outcome for all patients in this RTOG trial at 12 months was approximately 46% (38).

The fitting method

In our study, the least chi-square (chi-square) method is found to be convenient to fit the clinical data sets (9–11). The fitting parameters, as shown in Eqs. 1, 2, and 4, are: α, β, the clonogenic number K, the effective tumor-cell repopulation rate characterized by γT ($\gamma = \ln 2/T_d$). All parameters are independent variables. The basic idea of this fitting method is that the best-fit curve for a given data set has the minimal sum of the squares of the offsets (the least chi-square error). The sum of the squares of the offsets is defined as:

$$\chi^2 = \sum_{j=1}^{n} \frac{\left[S'(D_j,\ \tau) - S(D_j,\ \tau)\right]^2}{\sigma^2(D_j)} \tag{7}$$

where $S(D_j, \tau)$ is the j-th clinically observed survival rate given by Walker *et al.* and Salazar *et al.* (9–11) at the time τ after the treatment; $\sigma^2(D_j)$ is the corresponding statistical error for the j-th data point; $S'(D_j, \tau)$ is the model-predicted survival rate for the given dose D_j at time τ after the treatment and can be calculated by the following empirical equation:

$$S'(D_j,\ \tau) = e^{-k \cdot e^{-(\alpha D + \beta G D^2 - \gamma T)} \cdot e^{\alpha \tau}} \tag{8}$$

Here, we assume that the survival rate depends exponentially on elapse time. The parameter a is to be found during the fitting.

RESULTS

Radiobiologic parameters

The parameter fitting for survival rate at 0.5, 1.0, and 1.5 years vs. the dose delivered by EBRT with conventional fractionation is plotted in Fig. 2. Data points reported by Walker *et al.* (9) and by Salazar *et al.* (10, 11) were employed in the fitting. The standard 1.8 Gy per fraction was assumed for both studies. The lines represent the fitting to the data points for the survival rates given at 0.5, 1.0, and 1.5 years, respectively. The fitting yields: $\alpha = 0.06 \pm 0.05$ Gy^{-1} and $\alpha/\beta = 10.0 \pm 15.1$ Gy for MG. These results are also presented along with other data in Table 2. The parameter a was found to be equal to 1.63 based on the fitting. The error bars represent statistical uncertainty.

Table 2. The presently estimated α and α/β values (*in vivo*) compared with the previously reported *in vitro* data

	In vivo (this analysis) (95% CI)	*In vitro* (39–41)
Malignant gliomas	$\alpha = 0.06 \pm 0.05$ Gy^{-1} $\alpha/\beta = 10.0 \pm 15.1$ Gy	
Grade 3	$\alpha = 0.11 \pm 0.10$ Gy^{-1} $\alpha/\beta = 5.8 \pm 11.8$ Gy	$\alpha = 0.20 \pm 0.02$ Gy^{-1} $\alpha/\beta = 5.6 \pm 0.7$ Gy
Grade 4	$\alpha = 0.04 \pm 0.06$ Gy^{-1} $\alpha/\beta = 5.6 \pm 9.4$ Gy	$\alpha = 0.30 \pm 0.07$ Gy^{-1} $\alpha/\beta = 6.7 \pm 2.2$ Gy

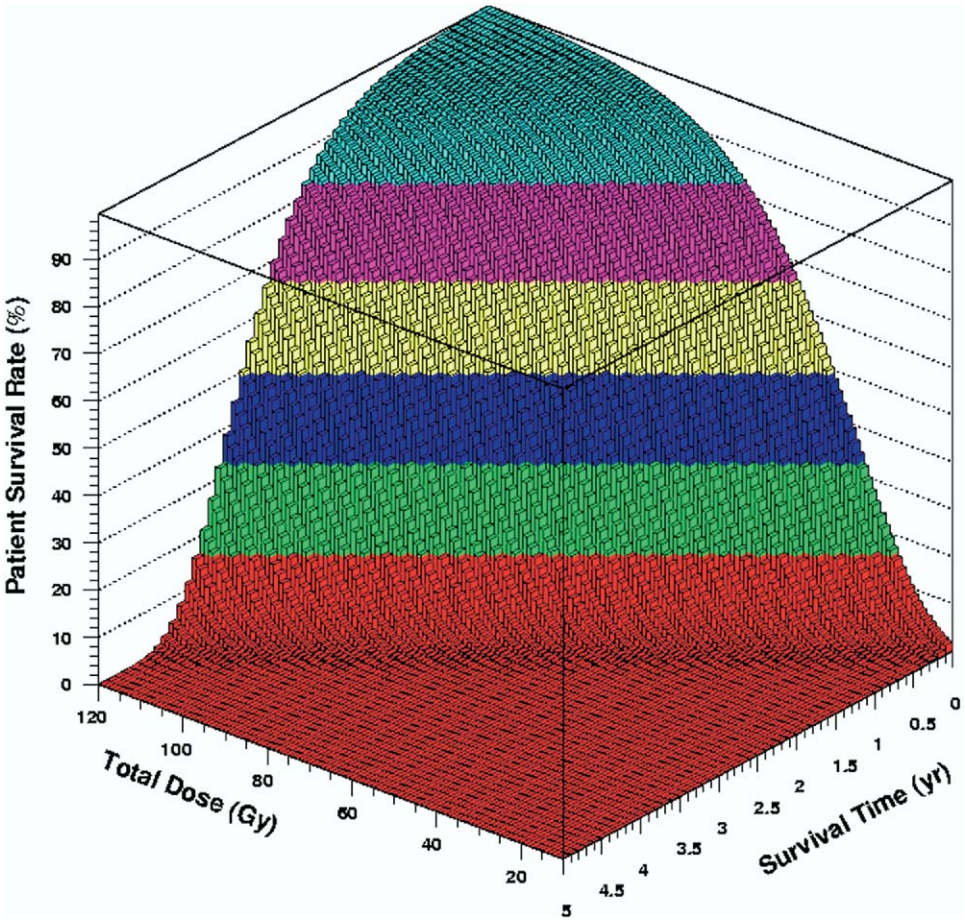

Fig. 3. Patient survival rate as a function of radiation dose and survival time for malignant gliomas. The data are predicted based on the parameters estimated in this work: $\alpha = 0.06 \pm 0.05$ Gy^{-1}, $\alpha/\beta = 10.0 \pm 15.1$ Gy, the tumor cell doubling time $T_d = 50 \pm 30$ days, with a repair half-time of 0.5 h.

Using the parameters derived from the above fitting (Fig. 2), we have calculated the relationship between radiation dose, survival time, and survival rate, which is presented in Fig. 3. The prediction in Fig. 3 indicates that, for a survival rate of 70% at 2 years, the radiation dose should be 100 Gy, or, for a total dose of 80 Gy, the survival rate at 1 year would be 78%.

Figure 4 shows a comparison between the prediction of the present α and α/β values (solid line) with the calculations using the parameters suggested by others for GBM based on *in vitro* measurements: the dashed line is for $\alpha = 0.24$ Gy^{-1}, $\alpha/\beta = 8.3$ Gy (38); and the dotted line is for $\alpha = 0.31$ Gy^{-1} and $\alpha/\beta = 5.2$ Gy (39). The 1-year clinical data points from the studies by Walker *et al.* (9) and by Salazar *et al.* (10, 11) were included in Fig. 4. Clearly, the higher α values (higher radiosensitivity) from *in vitro* data fail to explain the clinical data (9–11), indicating that the MG, of which 86% were GBM, is more radioresistant *in vivo*.

Salazar *et al.* (10, 11) reported the separate data for Grade 3 and 4 malignant astrocytomas. These data allow us to explore the difference in radiosensitivity, as characterized by α and α/β, for different grades of astrocytomas. Employing the same fitting method and considering the fixed tumor doubling time of 50 days as revealed from this analysis, the data of Salazar *et al.* were fitted and the results are shown in Fig. 5. These data are compared with those from *in vitro* results in Table 2. *In vitro* results reported previously (39–41) are also included in Table 2 for comparison. It is seen that the α/β ratios for Grade 3 between the *in vitro* and the *in vivo* results (present study) are very similar, while the α values are comparable within the uncertainties. The difference in these α values is not statistically significant. For the data with Grade 4, the *in vivo* α value is smaller than that from the *in vitro* studies, implying that a lower radiosensitivity is observed for *in vivo* as compared with that for *in vitro*. It is also clear that, as indicated by a smaller α value, Grade 4 is more radioresistant than Grade 3 *in vivo*.

Potential doubling time (T_d)

We have estimated the potential doubling time (T_d) on the basis of the study by Walker *et al.* (9) and Salazar *et al.* (10, 11). Assuming an average fraction size of 1.8 Gy, we obtained $T_d = 50 \pm 30$ days from the data fitting. This value is consistent with that reported previously (42–44). Because of the limited number of clinical data points, the potential

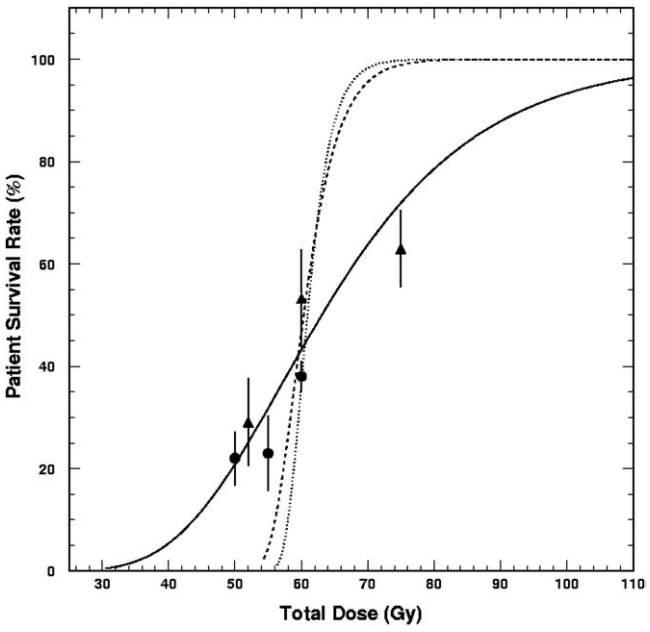

Fig. 4. A comparison between the prediction of the present α and α/β values (solid line) with the calculations using the parameters suggested by others for glioblastoma multiforme based on *in vitro* measurements: the dashed line is for $\alpha = 0.24$ Gy^{-1}, $\alpha/\beta = 8.3$ Gy (41); and the dotted line is for $\alpha = 0.31$ Gy^{-1} and $\alpha/\beta = 5.2$ Gy (40). The 1-year clinical data points from the studies by Walker *et al.* (9) and Salazar *et al.* (10, 11) are included.

doubling time was assumed to be the same for different histologies of MG (such as GBM and astrocytoma) and different grades of astrocytomas (such as Grade 3 and 4).

An attempt was made to evaluate the influence of considering the potential doubling time as a distribution, rather than a single value. A random number generator was used to create a log-normal distribution associated with a mean T_d value to be determined. This distribution was used in the subsequent data fitting. This process resulted in a shorter mean T_d of 32.2 days, which, however, is within the range of the T_d value (50 $\pm$ 30 days) obtained based on the single T_d assumption. In addition, a larger uncertainty was found to be associated with the result based on the log-normal distribution.

Clonogenic cells

The number of clonogens is one of the parameters that can be determined by the fitting. However, the number of tumor cells at the initial diagnosis is difficult to estimate because, for the MG cases, almost all patients underwent surgery before RT. The surgery can vary from biopsy, subtotal resection, to total gross resection, resulting in very different numbers of clonogen cells left within the RT target region. There is no detailed information reported by Walker *et al.* (9) and Salazar *et al.* (10, 11) about the extension of the surgery. The number of clonogenic cells should be small because of the maximum macroscopic resection, but it can be considerably different due to the variation in surgery. In this work, the clonogenic number was found to be 6 for MGs based on the fitting.

Validation with clinical data

To validate the newly derived biologic parameters based on the clinical data of Walker *et al.* (9) and Salazar *et al.* (10, 11), a series of additional clinical studies involving different RT modalities were analyzed. Both BED and EUD values were calculated and used to measure the biologic effectiveness. These clinical studies, along with their EUD and BED values, are tabulated in Table 3. The physical doses of different RT modalities/fractionations were converted to EUDs using Eqs. 5 and 6. The numerical values of EUD are expressed as the EBRT dose in 2.0 Gy fractions.

Unlike BED, EUD includes the impacts of dose inhomogeneities and volumetric effects. It is well known that the dose distributions for EBRT are quite different from those for brachytherapy. In addition, DVHs may be different for different patients. Because no actual dose distributions/DVHs were reported in all the published studies considered in this work, we selected representative DVHs of EBRT and brachytherapy (Fig. 1) to consider the dose inhomogeneities. As expected, the EUD values are fairly close to the prescription dose for EBRT (Table 3). For brachytherapy, differences between EUDs and prescribed doses are significant owing to the inherent dose inhomogeneity and are dependent on the DVH used. As for linac-based SRS, the same DVH for EBRT was assumed, although the DVH for SRS can be different from that for EBRT. It is expected that this difference may not significantly influence the present result. Because the prescription for SRS is normally not at

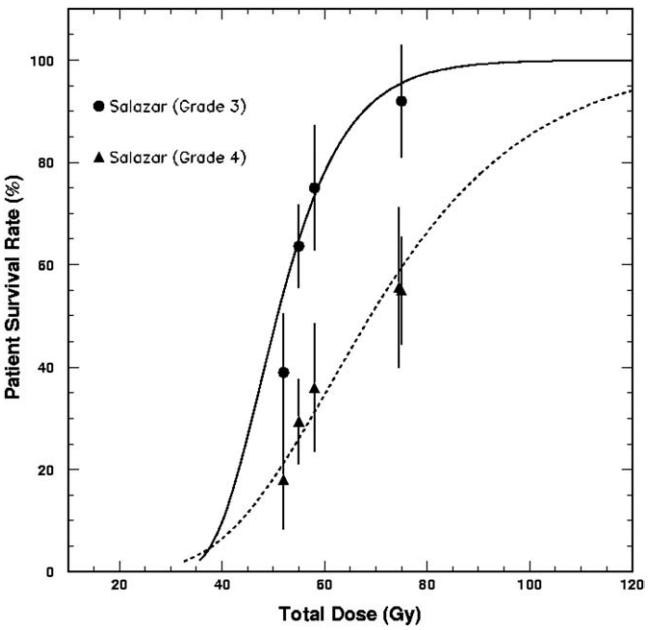

Fig. 5. Fitting of different grades of astrocytomas using the data of Salazar *et al.* (10, 11). For Grade 3 astrocytoma, our fitting yields: $\alpha = 0.11 \pm 0.10$ Gy^{-1} and $\alpha/\beta = 5.8 \pm 11.8$ Gy; whereas, for Grade 4 astrocytoma, $\alpha = 0.04 \pm 0.06$ Gy^{-1} and $\alpha/\beta = 5.6 \pm 9.4$ Gy.

Table 3. The calculated EUDs and BEDs for EBRT, EBRT combined with brachytherapy or linac-based SRS, and hyperfractionation

Modalities (Refs.)	EBRT dose (Gy)	Boost dose (Gy)	EUD^1 (Gy)	EUD^2 (Gy)	BED^1 (Gy)	BED^2 (Gy)
EBRT alone (4, 9, 10, 30)						
	50.0 (1.7–2.0/fr)	0	51	51	51	60
	52.0 (1.8–2.0/fr)	0	53	53	53	62
	55.0 (1.8–2./0fr)	0	56	56	56	66
	60.0 (1.8–2.0/fr)	0	61	61	61	73
	75.0 (1.8–2.0/fr)	0	76	76	76	90
EBRT + SRS (7, 16, 33, 34)						
	59.4 (1.8–2.0/fr)	13.5 (95%)	95	97	91	106
	60.0 (1.8–2.0/fr)	12.0 (85%)	95	97	91	107
	60.0 (1.5/fr, 2/day)	12.5 (80%)	96	98	97	111
EBRT + LDR (I-125) (4, 8, 15)						
	59.4	50	86	91	112	124
	59.5	51	86	92	113	126
	60.0	55	90	95	117	130
EBRT + HDR (Ir-192) (30)						
	60.0	30 (3.0/fr)	98	98	97	113
Hyperfractionation (38)						
	48.0 (1.6/fr, 2/day)	0	50	47	51	56
	54.4 (1.6/fr, 2/day)	0	56	53	58	64
	64.8 (1.2/fr, 2/day)	0	63	61	64	72
	72.0 (1.2/fr, 2/day)	0	70	67	71	80
	76.8 (1.2/fr, 2/day)	0	74	72	76	85

Abbreviations: BED = biologic equivalent dose; EBRT = external beam radiotherapy; EUD = equivalent uniform dose; HDR = high-dose-rate; LDR = low-dose-rate; LQ = linear-quadratic; SRS = stereotactic radiosurgery.

Two different sets of LQ parameters were used in the calculation. All EUD values were normalized to 2.0 Gy fraction.

The LQ parameters used in the calculations of EUD and BED are as follow:

EUD^1, BED^1: $\alpha = 0.06\ Gy^{-1}$, $\alpha/\beta = 10.0$ Gy, $T_d = 50$ days, $T_r = 0.5$ h, as derived from this analysis;

EUD^2, BED^2: $\alpha = 0.24\ Gy^{-1}$, $\alpha/\beta = 8.3$ Gy, $T_d = 50$ days, $T_r = 0.5$ h, as suggested from *in vitro* data.

100% isodose line, different normalizations, ranging from 60% to 100% isodose lines (median, 80%), were considered according to the corresponding prescriptions in the selected studies (1, 7, 32–34).

To examine the sensitivity of calculated BED and EUD values to LQ parameters, we have compared the calculations using two sets of parameters in Table 3: (*1*) $\alpha = 0.06\ Gy^{-1}$, $\alpha/\beta = 10.0$ Gy, $T_d = 50$ days, $T_\gamma = 0.5$ h, as derived from this analysis; and (*2*) $\alpha = 0.24\ Gy^{-1}$, $\alpha/\beta = 8.3$ Gy (39), $T_d = 50$ days, $T_\gamma = 0.5$ h, as suggested from *in vitro* data (39). It is seen that the EUD is less sensitive to the biologic parameters as compared with BED, implying the EUD is more informative than BED in evaluating and comparing RT treatment plans as also suggested by others (22). Figure 6 shows the calculated EUD and BED using four different radiobiologic parameter sets: (a) $\alpha = 0.06$

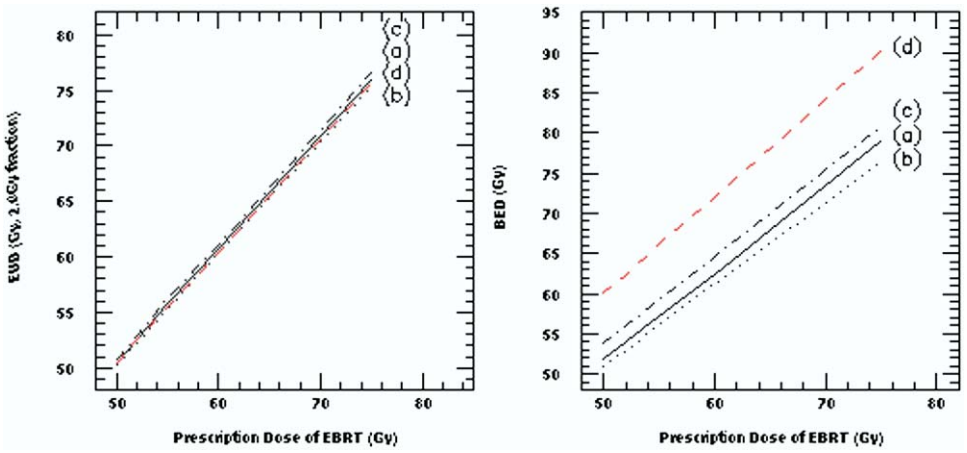

Fig. 6. The calculated equivalent uniform dose (EUD) and biologic equivalent dose (BED) values using four different radiobiologic parameter sets: (a) $\alpha = 0.06\ Gy^{-1}$ and $\alpha/\beta = 10.0$ Gy estimated from this analysis; (b) and (c): the present α value ± 68.3% (±1 σ) variation [i.e., (b): $\alpha = 0.06 + 0.03 = 0.09\ Gy^{-1}$ and $\alpha/\beta = 15.0$ Gy, and (c): $\alpha = 0.06 - 0.03 = 0.03\ Gy^{-1}$ and $\alpha/\beta = 5.0$ Gy]; and (d): $\alpha = 0.24\ Gy^{-1}$, $\alpha/\beta = 8.3$ Gy as suggested from *in vitro* data (38).

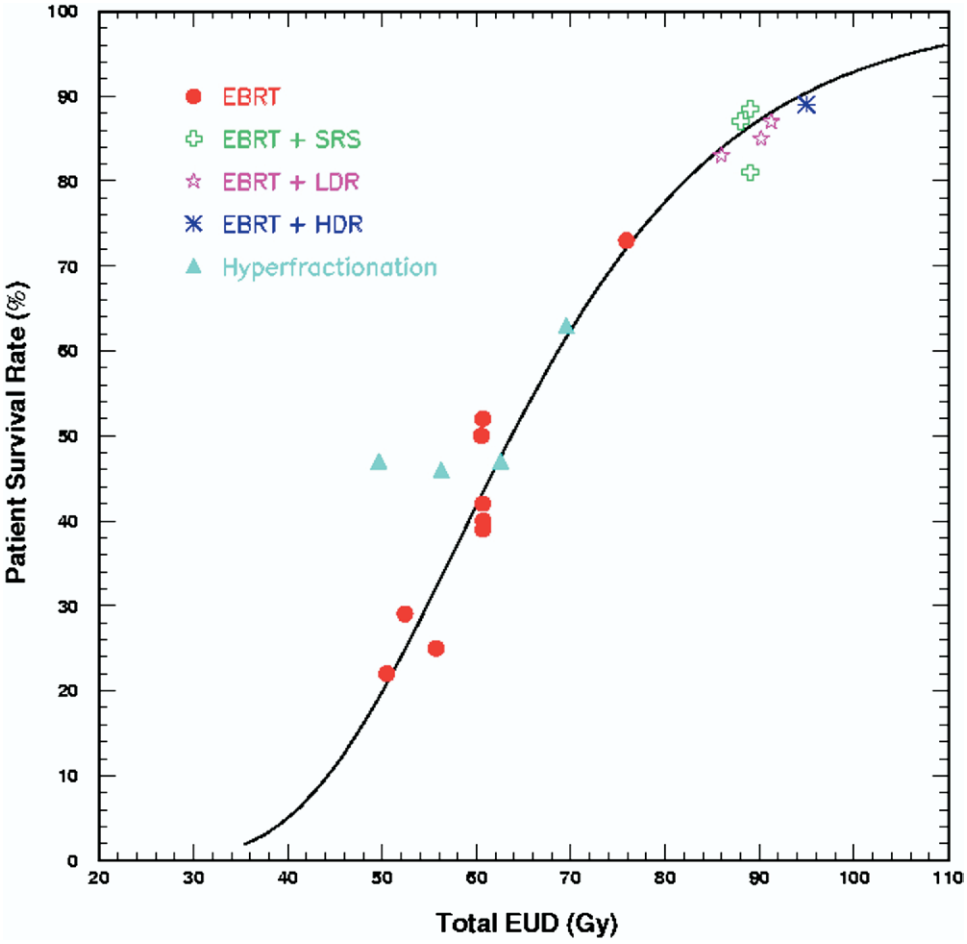

Fig. 7. The calculated equivalent uniform doses (EUDs) of single or combined radiation therapy modalities vs. patient survival rates reported by a series of clinical studies. These clinical studies include external beam radiation therapy (EBRT) only (4, 9, 10, 30), external beam radiation therapy combined with low-dose-rate (LDR) (4, 8, 15) or high-dose-rate (HDR) (30) brachytherapy, or stereotactic radiosurgery (SRS) (7, 16, 33, 34), and hyperfractionation (38). The solid line is the prediction with the linear-quadratic parameters estimated presently.

Gy^{-1} and $\alpha/\beta = 10.0$ Gy estimated from this analysis; (b) and (c): the present α value $\pm$ 68.3% ($\pm 1\ \sigma$) variation [i.e., (b): $\alpha = 0.06 + 0.03 = 0.09\ Gy^{-1}$ and $\alpha/\beta = 15.0$ Gy, and (c): $\alpha = 0.06 - 0.03 = 0.03\ Gy^{-1}$ and $\alpha/\beta = 5.0$ Gy]; and (d): $\alpha = 0.24\ Gy^{-1}$, $\alpha/\beta = 8.3$ Gy as suggested from *in vitro* data (39).

Figure 7 shows the 1-year survival rates vs. EUDs for a series of clinical studies. These clinical studies include EBRT only (4, 9, 10, 30), EBRT combined with LDR (4, 8, 15) or HDR (30) brachytherapy or SRS (7, 16, 33, 34), and hyperfractionation (38). The solid curve was calculated using the parameters derived presently (e.g., $\alpha = 0.06\ Gy^{-1}$, $\alpha/\beta = 10.0$ Gy, $T_d = 50 \pm 30$ days, $T_\gamma = 0.5$ h). Figure 7 indicates that the presently derived LQ parameters can reasonably predict these published clinical outcomes involving different RT modalities. To further verify this, we performed a new fitting based on the clinical data included in Fig. 7 with the use of EUD. The α and α/β values from this new fitting were found to be within their uncertainty ranges as presented in Table 2. This provides a reasonable validation for the parameter set derived.

DISCUSSION

In this work, we have analyzed a series of clinical studies to estimate radiobiologic parameters for brain tumor. Using the least chi-square fitting technique, we have obtained a plausible set of LQ parameters for malignant gliomas: $\alpha = 0.06 \pm 0.05\ Gy^{-1}$, $\alpha/\beta = 10.0 \pm 15.1$ Gy, the tumor cell doubling time of $T_d = 50 \pm 30$ days, and the repair half-time of 0.5 h. Using this set of parameters, we have calculated the biologic effectiveness as measured by EUD for a series of clinical studies employing different radiotherapy modalities. The calculations agreed reasonably with the clinical findings, which validates the parameter set derived presently.

The derived α and α/β values indicate that MG is radioresistant as known from clinical practice. In addition, the difference of the LQ parameters observed between the Grade

3 and 4 astrocytomas ($\alpha = 0.11 \pm 0.10$ Gy^{-1}, $\alpha/\beta = 5.8 \pm 11.8$ Gy for Grade 3, and $\alpha = 0.04 \pm 0.06$ Gy^{-1}, $\alpha/\beta = 5.6 \pm 9.4$ Gy for Grade 4) implies that the radiosensitivities for different grades of MGs could be different. For Grade 3 astrocytomas, our values of α and α/β are smaller but comparable to those published based on *in vitro* data (39, 40); whereas, for Grade 4 astrocytomas, the α and α/β values estimated presently on the basis of clinical data are significantly smaller than those from *in vitro* measurements, indicating lower radiosensitivity occurred *in vivo* as compared with *in vitro* for high-grade astrocytomas.

The radiation treatment outcomes for MG remain poor, despite many decades of efforts made and very aggressive treatment schemes applied. New treatment strategies that can improve local tumor control while sparing normal tissue are required. The presently derived radiobiologic parameters may be useful in the design of these new strategies. In particular, they may be used to evaluate and compare treatment plans using single or combined RT radiation modalities, to calculate new fractionation schemes, and to design biologically conformed treatment dose distribution based on biologic images.

However, it should be pointed out that the estimation was carried out with certain assumptions in biologic models. For example, a repair half-time of 0.5 h was assumed in the analysis; it has been argued (45) that a biexponential repair mode with short and long repair times might provide a better fitting. Because the number of data points available for the fitting is limited, we were unable to consider the biexponential repair model in the present work. Instead, as a first-order approximation, we examined the exponential part of the model and studied how the change of repair half-time would affect the α/β derived. It was found that, for a selected data set, the corresponding α/β ratio varies from 9.8 to 10.1 Gy when the repair half-time changes from 0.25 to 1.0 h. This variation on α/β ratio is within the uncertainty estimated based on the assumption of 0.5 h repair half-time.

Because of the limited number of available clinical data, the uncertainties for the derived parameters are relatively large: $\alpha = 0.06 \pm 0.05$ Gy^{-1}, $\alpha/\beta = 10.0 \pm 15.1$ Gy. It is known that prognostic factors, such as patient age, histology, Karnofsky Performance Status, RTOG classes, extent of surgery, and radiation dose, can influence patient survival rate. To minimize this influence, we have carefully selected clinical studies with similar patient selection criteria (as shown in Table 1). Nevertheless, more prospective clinical studies are required to verify the present finding. Caution needs to be exercised when using the parameters for clinical purposes.

REFERENCES

1. Mehta MP, Masciopinto J, Rozental J, *et al.* Stereotactic radiosurgery for glioblastoma multiforme: Report of a prospective study evaluating prognostic factors and analyzing long-term survival advantage. *Int J Oncol Biol Phys* 1994;30: 541–549.
2. Leibei SA, Scott CB, Loeffler JS. Contemporary approaches to the treatment of malignant gliomas with radiation therapy. *Semin Oncol* 1994;21:198–219.
3. Curran WJ, Scott CB, Horton J, *et al.* Recursive partitioning analysis in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 1993;85:704–710.
4. Wen PY, Alexander E, Black PM, *et al.* Long term results of stereotactic brachytherapy used in the initial treatment of malignant glioblastoma. *Cancer* 1994;73:3029–3036.
5. Surawicz TS, Davis F, Freels S, *et al.* Brain tumor survival: Results from the National Cancer Data Base. *J Neurooncol* 1998;40:151–160.
6. Wallner KE, Galicich JH, Krol G, *et al.* Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys* 1989;16:1405–1409.
7. Sarkaria JN, Mehta MP, Loeffler JS, *et al.* Radiosurgery in the initial management of malignant gliomas: Survival comparison with the RTOG recursive partitioning analysis. *Int J Radiat Oncol Biol Phys* 1995;32:931–941.
8. Sneed PK, Prados MD, McDermott MW, *et al.* Large effect of age on the survival of patient with glioblastoma treated with radiotherapy and brachytherapy boost. *Neurosurg* 1995;36: 898–904.
9. Walker MD, Strike TA, Sheline GE. An analysis of dose effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys* 1979;5:1725–1731.
10. Salazar OM, Rubin P, Feldstein ML, *et al.* High dose radiation therapy in the treatment of malignant gliomas: Final report. *Int J Radiat Oncol Biol Phys* 1979;5:1733–1740.
11. Salazar OM, Rubin P, McDonald JV, *et al.* High dose radiation therapy in the treatment of glioblastoma multiforme: A preliminary report. *Int J Radiat Oncol Biol Phys* 1976;1:717–727.
12. Deutsch M, Green SB, Strike TA, *et al.* Results of a randomized trial comparing BCNU plus radiotherapy, streptozotocin plus radiotherapy, and BCNU following misonidazole plus radiotherapy in the postoperative treatment of malignant glioma. *Int J Radiat Oncol Biol Phys* 1989;16:1389–1396.
13. Gutin PH, Prados MD, Phillips TL, *et al.* External irradiation followed by an interstitial high activity iodine-125 implant 'boost' in the initial treatment of malignant gliomas: NCOG study 6G82-2. *Int J Radiat Oncol Biol Phys* 1991;2:601–606.
14. Masciopinto JE, Levin AB, Mehta MP, Rhode BS. Stereotactic radiosurgery for glioblastoma: A final report of 31 patients. *J Neurosurg* 1995;82:530–535.
15. Prados MD, Gutin PH, Phillips TL, *et al.* Interstitial brachytherapy for newly diagnosed patients with malignant gliomas: The UCSF experience. *Int J Radiat Oncol Biol Phys* 1992;24: 593–597.
16. Loeffler JS, Alexander E, Shea WM, *et al.* Radiosurgery as part of the initial management of patients with malignant gliomas. *J Clin Oncol* 1992;10:1379–1385.
17. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515–528.
18. Dale RG. Radiobiological assessment of permanent implants using tumor repopulation factors in linear-quadratic model. *Br J Radiol* 1989;62:241–244.
19. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679–694.
20. Li XA, Wang JZ, Stewart RD, *et al.* Dose escalation in

permanent brachytherapy for prostate cancer: Dosimetric and biological considerations. *Phys Med Biol* 2003;48:2753–2765.
21. Brenner DJ, Hall EJ. Conditions for the equivalence of continuous to pulsed low dose rate brachytherapy. *Int J Radiat Oncol Biol Phys* 1991;20:181–190.
22. Webb S, Nahum AE. A model for calculating tumor control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density. *Phys Med Biol* 1993;38:653–666.
23. Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. *Med Phys* 1997;24:103–110.
24. Wang JZ, Li XA. Evaluation of external beam radiotherapy and brachytherapy for localized prostate cancer using equivalent uniform dose. *Med Phys* 2003;30:34–40.
25. Gutin PH, Leibel SA, Wara WM, *et al.* Recurrent malignant gliomas: Survival following interstitial brachytherapy with high activity iodine-125 sources. *J Neurosurg* 1987;67:864–873.
26. Loeffler JS, Alexander EA III, Shea WM, *et al.* Results of stereotactic brachytherapy used in the initial management of patients with glioblastoma. *J Nat Cancer Inst* 1990;82:1918–1921.
27. Sneed PK, Stauffer PR, McDermott MW, *et al.* Survival benefit of hyperthermia in a prospective randomized trail of brachytherapy boost +/− hyperthermia for glioblastoma multiforme. *Int J Radiat Oncol Biol Phys* 1998;40:287–295.
28. Garcia DM, Zamorano L, Mundinger F. High dose rate brachytherapy in the treatment of malignant gliomas. In: Nag S, editor. High dose rate brachytherapy: A textbook. New York: Future Publishing Company; 1991. p. 215–235.
29. Johannesen TB, Watne K, Lote K, *et al.* Intracavity fractionated balloon brachytherapy in glioblastoma. *Acta Neurochir* 1999;141:127–133.
30. Chang CN, Chen WC, Wei KC, *et al.* High-dose-rate stereotactic brachytherapy for patients with newly diagnosed glioblastoma multiforme. *J Neuro-Oncology* 2003;61:45–55.
31. Koot RW, Maarouf M, Hulshof MC, *et al.* Brachytherapy: Results of two different therapy strategies for patients with primary glioblastoma multiforme. *Cancer* 2000;88:2796–2802.
32. Shrieve DC, Alexander E, Wen PY, *et al.* Comparison of stereotactic radiosurgery and brachytherapy in the treatment of recurrent glioblastoma multiforme. *Neurosurg* 1995;36:275–284.
33. Shrieve DC, Alexander E, Black PM, *et al.* Treatment of patients with primary glioblastoma multiforme with standard postoperative radiotherapy and radiosurgical boost: Prognostic factors and long-term outcome. *J Neurosurg* 1999;90:72–77.
34. Buatti JM, Friedman WA, Bova FJ, *et al.* Linac radiosurgery for high-grade gliomas: The University of Florida experience. *Int J Radiat Oncol Biol Phys* 1995;32:205–210.
35. Scharfen CO, Sneed PK, Wara WM, *et al.* High activity iodine-125 interstitial implant for gliomas. *Int J Radiat Oncol Biol Phys* 1992;24:583–591.
36. Curran WJ, Scott CB, Weinstein AS, *et al.* Survival comparison of radiosurgery-eligible and ineligible malignant glioma patients treated with hyperfractionated radiation therapy and carmustine: A report of RTOG 83-02. *J Clin Oncol* 1993;11:857–862.
37. Werner-Wasik M, Scott CB, Nelson DF, *et al.* Final report of a phase I/II trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas. *Cancer* 1996;77:1535–1543.
38. Curran WJ, Scott CB, Nelson JS, *et al.* A randomized trial of accelerated hyperfractionated radiation therapy and bis-chloroethyl nitrosourea for malignant glioma: A preliminary report of Radiation Therapy Oncology Group 83-02. *Cancer* 1992;70:2909–2917.
39. Malaise EP, Fertil B, Deschavanne PJ, Chavaudra N, Brock WA. Initial slope of radiation survival curves is characteristic of the origin of primary and established cultures of human tumor cells and fibroblasts. *Rad Res* 1986;111:319–333.
40. Wigg DR. Applied radiobiology and bioeffect planning. Madison, WI: Med Phys. 2001; p. 247.
41. Schultz CJ, Geard CR. Radioresponse of human astrocytic tumors across grade as a function of acute and chronic irradiation. *Int J Radiat Oncol Biol Phys* 1990;19:1397–1403.
42. Tsuboi K, Yoshii Y, Nakagawa K, Maki Y. Regrowth patterns of supratentorial gliomas: Estimation from computed tomographic scans. *Neurosurgery* 1986;19:946–951.
43. Alvord EC. Is necrosis helpful in the grading of gliomas? Editorial opinion. *J Neuropath Exp Neur* 1992;51:127–132.
44. Tracqui P, Cruywagen GC, Woodward DE, *et al.* A mathematical model of glioma growth: Effect of chemotherapy on spatio-temporal growth. *Cell Prolif* 1995;28:17–31.
45. Fowler JF. Repair between dose fractions: A simpler method of analyzing and reporting apparently biexponential repair. *Radiat Res* 2002;158:141–151.
46. Sachs RK, Hahnfeld P, Brenner DJ. The link between low-LET dose-response and the underlying kinetic of damage production/repair misrepair. *Int J Radiat Biol* 1997;72:351–374.

APPENDIX: GENERALIZED LEA-CATCHESIDE DOSE PROTRACTION FACTOR (*G*)

The general Lea-Catcheside dose protraction factor G is given by (46)

$$G = \frac{2}{D^2}\int_{-\infty}^{\infty} D(t)dt \int_{-\infty}^{t} e^{-\mu(t-t')}D(t')dt' \qquad \text{(A1)}$$

Here, $D(t)$ is the dose rate function at time t, μ is the repair rate of tumor cells ($\mu = ln2/T_\gamma$, T_γ is the characteristic repair half-time of cells with sublethal damage), and D is the total dose.

For conventional external beam radiation therapy (EBRT), i.e., 2 Gy per fraction, the dose-delivery time (several minutes) is much shorter than the time for tumor cell repair, leading to $G = 1$ for entire EBRT and $G = 1/n$ for each fraction (17, 18, 24), where n is the number of dose fractions.

For high-dose-rate (HDR) brachytherapy, the dose-delivering time T_f of each fraction may be long and may be comparable to the repair half-time. As an approximation, each HDR fraction is assumed presently to be delivered within 15 min with a constant dose rate; therefore $D = nd$, and G can be written as (17, 20)

$$G = \frac{2}{n\mu T_f}\left[1 - \frac{1}{\mu T_f}\left(1 - e^{-\mu T_f}\right)\right] \qquad \text{(A2)}$$

In this analysis, $T_\gamma \approx 0.5$ h was used (21). Because typical HDR consists of very few fractions delivered in few days, the repopulation of tumor clonogens should have little impact on cell killing. In this work, the treatment time of HDR is handled in a similar way as that for EBRT.

For low-dose-rate (LDR) brachytherapy, the dose delivered within the treatment time T is given by (17, 18, 24)

$$D = \frac{R_0}{\lambda}\left(1 - e^{-\lambda T}\right) \tag{A3}$$

and the dose protraction factor G is given by (17, 18)

$$G = \frac{2R_0^2}{D^2(\mu - \lambda)}\left[\frac{1}{2\lambda}\left(1 - e^{-2\lambda T}\right) - \frac{1}{\mu + \lambda}\left(1 - e^{-(\mu-\lambda)T}\right)\right] \tag{A4}$$

The treatment time T can be calculated by (24)

$$T \approx -\frac{1}{\lambda}\ln\left(\frac{\gamma}{\alpha R_0}\right) \tag{A5}$$

R_0 is the initial dose rate; D_0 is the prescribed dose, $D_0 = R_0/\lambda$, λ is the decay constant for the implanted isotopes ($\lambda = \ln 2/T_s$, and T_s is the half-time of the isotope, i.e., T_s is equal to 60.2 days for I-125, and 17 days for Pd-103 implants).