ORIGINAL ARTICLE

Determining the optimum tumor control probability model in radiotherapy of glioblastoma multiforme using magnetic resonance imaging data pre- and post- radiation therapy

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Background: Glioblastoma multiforme (GBM) is the most common and malignant brain tumor. The current standard of care is surgery followed by radiation therapy (RT). Radiotherapy treatment plan evaluation relies on radiobiological models for accurate estimation of tumor control probability (TCP). This study aimed to assess the impact of obtained magnetic resonance imaging (MRI) data before and 12 weeks after RT to achieve the optimum TCP model to improve dose prescriptions in radiation therapy of GBM. **Materials and Methods::** In this quasi-experimental study, MR images and its relevant data from 30 patients consisting of 9 females and 21 males (mean age of 46.3 ± 15.8 years) diagnosed with GBM, whose referred for radiotherapy were selected. The data of age, gender, tumor size, volume, and signal intensity using analysis of MRI data pre- and postradiotherapy were used for calculating TCP. TCP was calculated from three common radiobiological models including Poisson, linear quadratic, and equivalent uniform dose. The impact of some radiobiological parameters on final TCP in all patients planned with three-dimensional conformal radiation therapy was obtained. **Results:** A statistically significant difference was found among TCP in Poisson model compared to the other two models ($P < 0.001$). Changes in tumor volume and size after treatment were statistically significant ($P < 0.05$). Different combinations of radiobiological parameters (α/β and SF_2 in all models) observed were meaningful ($P < 0.05$). **Conclusion:** The results showed that among TCP radiobiological models, the optimum is the Poisson. The results also identified the importance of TCP radiobiological models in order to improve radiotherapy dose prescriptions.

Key words: Cancer, glioblastoma multiforme, magnetic resonance imaging, radiation therapy, radiobiological models

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INTRODUCTION

Glioblastoma multiforme (GBM) can originate from the central nervous system and no metastases have been noticed, but it is wildly expanded to parenchyma around the brain. The most common treatment for GBM was established as surgery with maximum safe resection followed by concurrent chemotherapy and conformal radiation therapy.[1]

Magnetic resonance imaging (MRI) is the best standard method for diagnosing GBM, which is widely utilized in the classification of patients.[2] MRI techniques include T_1-weighted imaging (T_1W), T_1 contrast-enhancing (T_1CE), T_2-weighted imaging (T_2W), and fluid-attenuated inversion recovery (FLAIR) sequences. Furthermore, advanced imaging techniques can provide more information about the size and position of tumors.[2]

Radiation therapy (RT) has a significant effect on the treatment of brain tumors. The goal of RT is to find

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the best treatment plan for high local tumor control with minimal side effects. The main goal of RT is to deliver 95% of prescribed dose to maximum volume of the tumor and safety of organ at risk.[3] Mathematical models have been expanded to quantify the biological effects of radiation and predict treatment outcome known as concepts tumor control probability (TCP) and normal tissue complication probability (NTCP).[4] TCP modeling plays an important role in assessing the impact of RT treatment strategies.[5] Three of the most common TCP radiobiological models are Poisson, equivalent uniform dose (EUD), and linear quadratic (LQ). Using mentioned radiobiological models, TCP was calculated for three-dimensional conformal radiation therapy (3DCRT), and the relative impact of the radiobiological parameters for patients treated with radiation was also evaluated. Then, treatment planning was modified by using the results of TCP radiobiological models and MRI.

Since there is no published results in conventional MRI to distinguish between true progression and pseudoprogression, the Response Assessment in Neuro-Oncology (RANO) criteria are used for high-grade glioma to define progressive disease according to the radiographic changes.[6]

Many research studies have examined almost similar data from different perspective studies and reported different conclusions.[4,7,8] For instance, Majós *et al*. have looked at MR images after surgery and shortly pre- and 6–12 weeks post-RT.[7] They found that performing MRI before RT has positive impacts on the management of patients with GBM by reducing the ratio of pseudoprogression assessments and providing additional predictive information. In another study, Ahmad *et al*.[4] examined the impact of radiobiological parameters on TCP for prostate cancer. They have observed that (surviving fraction) SF_2 is the dominant predictor to radiation response. Consequently, other researchers assessed the impact of radiation dose escalation from 59.6 to 90 Gy on TCP and NTCP in 10 patients planned with 3DCRT, but they have calculated only TCP using radiobiological models of EUD and LQ.[8]

All previous relevant studies have evaluated image parameters such as signal intensity, tumor dimensions, and size just pre- and posttreatment for high-grade glioma in the region of interest (ROI), but none of them have investigated the association of these changes with TCP in order to introduce the appropriate radiobiological models. For this reason, this study aimed to assess the impact of obtained MRI data before and 12 weeks after RT to achieve the optimum TCP model to improve dose prescriptions in radiation therapy of GBM.

METHODS

Study design and participants

In this quasi-experimental study, 30 patients consisting of 9 females and 21 males (mean age of 46.3 ± 15.8 years) having Grade IV glioma GBM according to the World Health Organization (WHO)[6] were included. Patients with fear of the indoor or intolerance MRI and insufficient information were excluded from the study. Pre- and postoperative MRI studies were carried out on all studied patients. The study was approved by the university ethical committee (ethical code no. IR.MUI.MED.REC.1399.167).

Referred patients to Seyed-Al-Shohada Hospital, Isfahan, Iran, were scanned with a 1.5 T MR scanner (Siemens Healthcare, Erlangen, Germany) using commercially quadrature head coils before RT and after surgical resection.[9] Approximately 12 weeks after RT complication, MRI process was performed again with similar protocols. Performing MRI 3 months after RT reduces the chance of pseudoprogression and determines tumor residual by evaluating surgical site.[6] The standard protocol consists of sequences of axial T_1W and T_2W images, fast spin echo-axial (FLAIR) images, and coronal T_1W images. Contrast agent of gadolinium-diethylenetriaminepentaacetic acid was IV injected at standard dose (0.1 mmol/kg) and T_1W images were repeated.[10]

3DCRT was performed with Varian treatment planning system (TPS). All patients underwent computed tomography (CT) with bed similar to treatment bed before RT. CT and MR images of patients were used as input data in TPS. The prescription dose of 60 Gy was delivered during 30 fractions with a range of 1.8–2.0 Gy each session.[11]

Gross tumor volume (GTV) is specified with regard to T_1 contrast enhancement region with a 20–30 mm extra margin, and clinical target volume is obtained by adding a 1.5–2 cm margin to GTV.[12]

To evaluate the response of radiobiological models, cumulative dose–volume histogram (DVH) of calculated treatment plans was extracted from the TPS. Software package (BIOPLAN) was used to calculate TCP. DVH was given as software input data. The MATLAB (The MathWorks Inc., Natick, USA) codes were utilized in all of the models to calculate the TCP.

Three radiobiological models for tumor control are considered: EUD, Poisson, and LQ.

The equivalent uniform dose model

In EUD, if two different distributions doses have the same effect, the number of their clonogenic cells be equal and TCP is calculated by the following formula:[8]

$$TCP = \frac{1}{1+(\frac{TCD50}{EUD})^{4\gamma 50}} \quad (1)$$

$$EUD = [\sum_{i=1}(Vi.Di^{a})]^{a} \quad (2)$$

Where the tumor control dose (TCD_{50}) is the tumor dose for controlling 50% of the tumors when the tumor is homogeneously irradiated and γ50 is the normalized dose–response gradient at the dose of 50 Gy; in the second formula, *vi* is the fractional organ volume receiving a dose *Di* and *a* is a tissue-specific parameter that describes the volume effect.

The Poisson model

To predict the random killing of clonogenic cells (the Poisson standard model) by radiation, TCP is calculated using the following equation:[13]

$$P(D_i) = exp[exp[e\gamma - \frac{Di}{D50}(e\gamma - ln(ln2))]] \quad (3)$$

Where D_{50} is the dose at which 50% of tumors are controlled. The number of clonogenic cells is predicted by exp(eγ) and where γ is called γ-value (normalized dose–response gradient) and may be defined as the percentage point change in response for a 1% change in dose.

The linear-quadratic model

The concept of survival cells in the irradiated tissue with a total radiation dose of $D = n \times d$ (which *n* is the number of fractions and *d* is the dose per fraction) based on LQ model is presented as the following formula:[14]

$$TCP = e^{-N(SF_2)^{\frac{D}{D_{ref}} \times \frac{\frac{\alpha}{\beta}+\frac{D}{n}}{\frac{\alpha}{\beta}+D_{ref}}}} \quad (4)$$

Radiobiological parameters for GBM included radiosensitivity (a): 0.12 Gy^{-1}, repair capability (b): 0.015 Gy^{-2}, α/β ratio: 8, repopulation doubling time (T_d): 15.4 days, the number of clonogeneses (N): 1×10^4, kick-off time (T_K): 27, D_{ref}: 2 Gy, and TCD_{50} which was chosen from similar Published work[15]: 47.2 and used in the present study to determine TCP. The slope of the dose–response curve is calculated by the following formula:

$$\gamma 50 = -0.25\ln(2).TCD50.\ln(SF2) \quad (5)$$

Magnetic resonance imaging data acquisition

MR image ROI was manually drawn by the Oncologist around the tumor to separate nonenhancing lesion, contrast-enhancing lesion, necrotic lesion, and normal white matter. The feasibility of tumor volume, area, and size (two perpendicular diameters and signal intensity measurement were evaluated using the routine clinic software (Digimizer and 3D-Doctor) for image processing data of each patient were investigated. The volume was calculated using 3D-Doctor software and TPS feasibility. Furthermore, two perpendicular diameters, area and signal intensity, were obtained using Digimizer software. According to the RANO criteria, shrinkage more than 50% in tumor size is considered for partial response, and 25% increase in the sum of enhancing target lesions means progressive disease, but the rest of the patients were not included in these two groups.[16] The images were interpreted by expert oncologists and radiologists.

Statistical analysis

Data were analyzed using IBM SPSS (IBM Crop. 2019. IBM SPSS Statistics for Windows, version 26.0. NY, EUA). For quantitative data, the descriptive statistics were calculated for each category. It was presented as the range of observations (the lowest observation [minimum] minus the largest one [maximum]), the median value (Md), the interquartile range (IQR = the 3rd quartile minus the 1st quartile), the average value (mean), the standard deviation, and 95% confidence interval for the mean parameters. Initially, the Shapiro–Wilk test was used to test normality in each group. Despite the data violated the normality test, according to the central limit theorem, the parametric tests were used to compare the differences in the mean values between groups. Since the sphericity test was violated for all the tests, a repeated measures ANOVA with a Greenhouse–Geisser correction was conducted to compare the mean between more than two dependent groups, followed by the Bonferroni test, as the *post hoc* tests. For dependent groups (pre- and postobservations), the paired samples *t*-test was utilized. Finally, the Spearman correlation was run for investigating the monotonic relationship between two continuous nonnormal variables. A level of 5% was considered to be significant in all the analyses.

RESULTS

From 30 studied patients (9 females and 21 males, mean age of 46.28 ± 15.8 years), after RT, 4 patients had progressive diseases, 5 patients showed partial response, and the rest of them showed stable conditions to treatment. These observations were based on the RANO criteria.[17] Figure 1 indicates that there existed no statistically significant differences in tumor volume, area, size, and the signal intensity of the tumor, before and after RT ($P > 0.05$). On the other hand, for each patient, the TCP values were calculated from three models (Poisson, EUD, and LQ models). Descriptive statistics of computed TCPs from Poisson model (based on three values of α/β) and EUD and LQ models (based on different values of SF_2) are presented in Table 1. In addition, in Figure 2, the repeated measures ANOVA with a Greenhouse–Geisser correction determined that mean TCPs in Poisson model differed statistically significantly between minimum, middle, and maximum groups ($F_{(1.1,31.9)} = 134.31$, $P < 0.001$, effect size = 0.82). The same results were observed for the EUD model ($F_{(1.3,36.2)} = 108.49$,

$P < 0.001$, effect size = 0.79) and LQ model ($F_{(1.0,29.0)} = 550.04$, $P < 0.001$, effect size = 0.95). Moreover, *post hoc* tests using the Bonferroni correction revealed that in Poisson model, in the maximum group ($\alpha/\beta = 10.8$), the TCPs (15.07 ± 5.20) were significantly more than the minimum (11.24 ± 3.95) and maximum (11.36 ± 4.28) groups ($P < 0.01$). Therefore, increase in α parameter, followed by increase in tumor sensitivity and decrease in β-coefficient, increases the α/β ratio, and according to the findings, TCP was almost increasing [Figure 2a]. However, in EUD and LQ models, the computed TCPs in the maximum group ($SF_2 = 0.7$) were statistically less than the other groups ($P < 0.001$). As well, the differences in TCPs between EUD and LQ models were investigated by independent samples *t*-test, individually for $SF_2 = 0.3$, 0.4, 0.5, 0.6, and 0.7 Gy. The results in Figure 3a show that the obtained TCPs from EUD and LQ models were not significantly different, except for $SF_2 = 0.7$ Gy ($P < 0.001$). Moreover, the computed TCP values in the middle groups were compared among the three models via ANOVA. The results are presented in Figure 3b. As expected, in the middle groups, the mean value of computed TCP from the Poisson model (11.36 ± 4.28) was significantly less than the TCPs from the EUD (96.91 ± 10.64) and LQ models (99.99 ± 0.01) ($P < 0.001$). Finally, the Spearman rank-order correlation was run to determine the relationship between computed TCPs in three models [Table 2]. From the results, the computed TCP values from the Poisson and EUD models were positively correlated ($\rho = 0.37$, $P < 0.05$). It can be concluded that increasing one leads to increasing the other and vice versa. However, no monotonic correlation was found in TCP values between Poisson and LQ models ($\rho = 0.20$, $P > 0.05$), and the same results were observed for TCP values between EUD and LQ models ($r = 029$, $P > 0.05$). On the other side, Table 3 shows the descriptive statistics of EUD values in three experimental groups. From the one-way repeated measures ANOVA results, there existed no statistically significant differences in EUD values between low, medium, and high groups ($F_{(1.0,29.4)} = 2.65$, $P > 0.05$, effect size = 0.08).

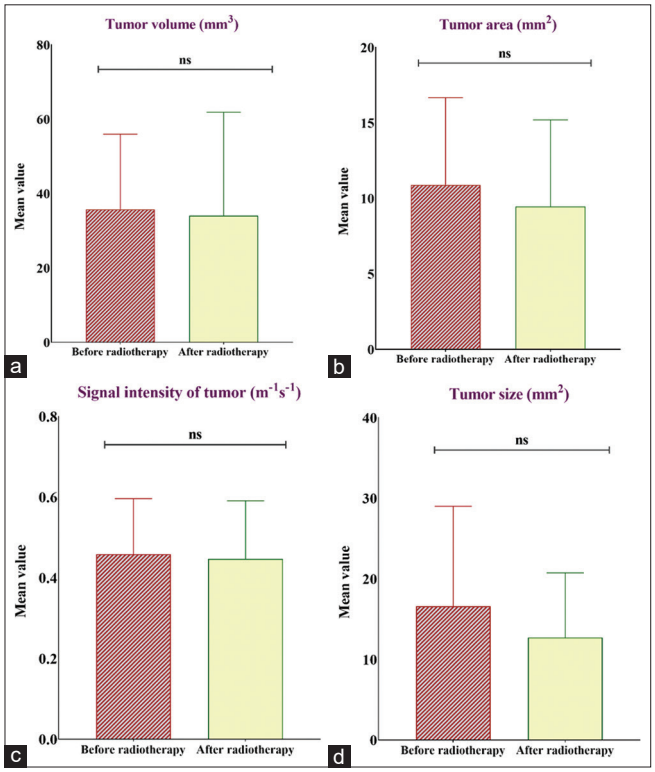

Figure 1: The mean ± standard deviation of (a) tumor volume, (b) tumor area, (c) the signal intensity of tumor, and (d) tumor size (calculated by multiplying two diameters perpendicular to each other). Using paired samples *t*-test, NS = Not significant and *n* = 30

DISCUSSION

Despite technical advances for patient treatment with GBM, nearly all patients die due to local progression of the tumor; however, improvement in local tumor control is considered to play an important role in patient management. Clinical outcome data have shown that four patterns including complete response, partial response, stable disease, and progression were defined for tumor growth that satisfactorily correlated with patient survival.[9,15] In this study, with

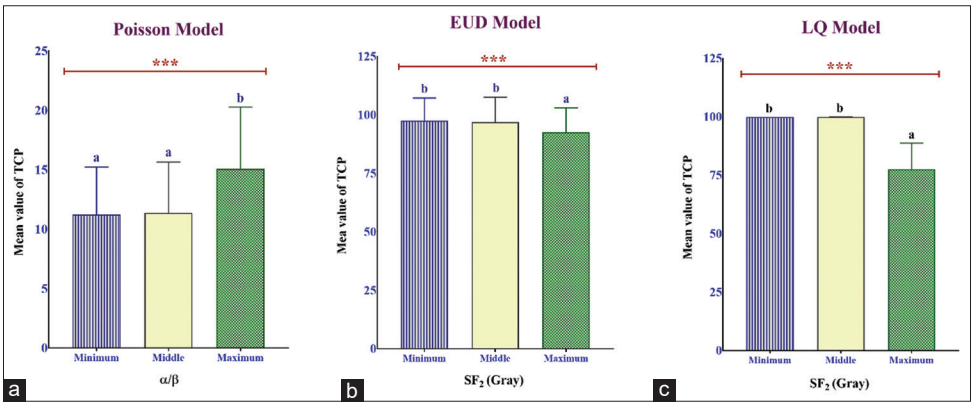

Figure 2: The mean value of TCP (±standard deviation) among minimum, middle, and maximum groups individually for (a) Poisson model, (b) EUD model, and (c) LQ model. Using one-way repeated measures ANOVA with a Greenhouse–Geisser correction, followed by Bonferroni test. In each type of model, the groups with a similar English letter are not statistically significantly different from each other, ***$P < 0.001$, and $n = 30$. EUD = Equivalent uniform dose, TCP = Tumor control probability; LQ = Linear quadratic

Table 1: Descriptive statistics of tumor control probability values in three models (Poisson, equivalent uniform dose, and linear quadratic)

	n	R (maximum-minimum)	Median (IQR)	Mean±SD	95% CI of mean
Poisson model					
Minimum (α/β=5)	30	18.00 (23.20-5.20)	11.10 (3.88)	11.24±3.98	9.76-12.73
Middle (α/β=8)	30	19.60 (24.90-5.30)	11.90 (−4.50)	11.36±4.28	9.76-12.96
Maximum (α/β=10.8)	30	24.60 (31.40-6.80)	15.0 (5.07)	15.07±5.20	13.12-17.01
EUD model					
Minimum (SF_2=0.3)	30	47.62 (100.00-52.38)	99.99 (0.00)	97.58±9.65	93.97-101.18
SF_2=0.4	30	48.17 (99.99-51.82)	99.96 (0.03)	97.35±10.18	93.55-101.15
Middle (SF_2=0.5)	30	48.59 (99.95-51.36)	99.7 (0.17)	96.91±10.64	92.94-100.88
SF_2=0.6	30	48.66 (99.67-51.01)	98.7 (0.48)	95.80±10.84	91.75-99.85
Maximum (SF_2=0.7)	30	47.67 (98.16-50.70)	95.26 (1.16)	92.54±10.49	88.62-96.46
LQ model					
Minimum (SF_2=0.3)	30	0 (100.00-100.00)	100 (0.00)	100.00±0.00	100.00-100.00
SF_2=0.4	30	0 (100.00-100.00)	100 (0.00)	100.00±0.00	100.00-100.00
Middle (SF_2=0.5)	30	0.03 (100.00-99.97)	100 (0.00)	99.99±0.01	99.99-100.00
SF_2=0.6	30	2.79 (99.99-97.20)	99.8 (0.11)	99.91±0.54	99.41-99.69
Maximum (SF_2=0.7)	30	20.1 (93.30-73.20)	83.45 (4.80)	81.77±11.17	77.60-85.94

R=Range (=the maximum observation - the minimum observation); IQR=Interquartile range (=the 3rd quartile minus the 1st quartile); Mean=Arithmetic mean; SD=Standard deviation; CI=Confidence interval; EUD=Equivalent uniform dose; SF=Surviving fraction; LQ=Linear-quadratic

Table 2: The Spearman correlation in tumor control probability values between Poisson, equivalent uniform dose, and linear-quadratic models in the middle groups

Sample 1	Sample 2	*n*	*P*	*P*
Poisson (α/β=8)	EUD (SF_2=0.5)	30	0.37	0.044*
Poisson (α/β=8)	LQ (SF_2=0.5)	30	0.20	0.279
EUD (SF_2=0.5)	LQ (SF_2=0.5)	30	0.29	0.120

*Significant at the level of 5%. EUD=Equivalent uniform dose; SF=Surviving fraction; LQ=Linear quadratic

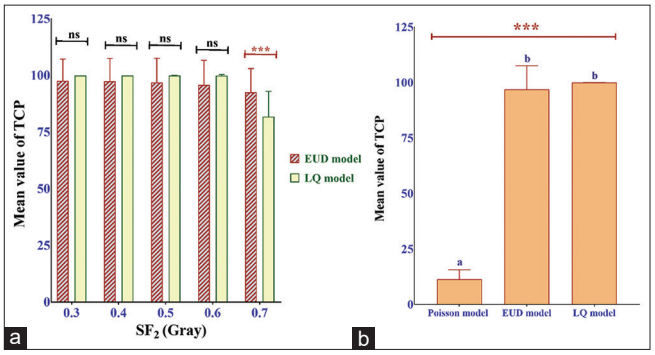

Figure 3: The mean value of computed TCP (±standard deviation). (a) Comparison of TCPs between EUD and LQ models, individually for different values of SF_2 (0.3, 0.4, 0.5, 0.6, and 0.7 Gray), using paired samples *t*-test. (b) Comparison of TCPs in the middle group (Poisson model: α/β =8, and EUD and LQ models: SF_2 = 0.5) among the three models. Using one-way repeated measures ANOVA with a Greenhouse–Geisser correction, followed by Bonferroni test; The groups with a similar English letter are not statistically significantly different from each other. NS = Not significant, ***P < 0.001, and n = 30. EUD = Equivalent uniform dose; TCP = Tumor control probability; LQ = Linear quadratic

RANO criteria, tumor progression after radiation therapy was found in 4 out of 30 studied patients, most of whom died in <15 months. Partial response was indicated in five patients, and in the remaining 21 patients, stable condition was seen. Treatment response, measured by changes in GTV observed on T_1W MR images, can be predicted and quantified based on relationship between model parameters and various measures of the external RT response.

The results demonstrated that volume, area, and two perpendicular diameters significantly reduced after treatment (P < 0.05), but signal intensity remained unchanged [Figure 1]. From point of comparison view among TCP in three studied models, the mean TCP over the patient in EUD was 88% more than Poisson and 3% more than LQ. In addition, in Poisson, it was 88.5% less than the other two models.

As shown in Table 1, a statistical significance in TCP values between three investigated models (P < 00.1) was obtained. TCP in Poisson was observed statistically less than EUD and LQ. Moreover, TCP values were compared between EUD and LQ for different values of SF_2 (0.3–0.7) using Mann–Whitney test. The result showed that TCP values in EUD are statistically less than that of LQ for SF_2 (0.3–0.6), but in SF_2=0.7, TCP values in LQ are more than EUD (P < 0.01). Furthermore, TCP in LQ for SF_2 (0.3-0.5) shows almost the same value.

In this model, TCP value corresponds to α/β of 5–10.8. Assuming tumor clones with varying SF_2 from 0.3 to 0.7 were used. In EUD, it was found that the mean TCP decreases with increasing SF_2 (P < 0.001) [Figure 2]. If SF_2 is constant, TCP in EUD model increases with increasing α/β ratio, but it is not very impressive. As LQ shown in Figure 2, TCP was evaluated with respect to SF_2 changes, which decreased with increasing SF_2. By comparing TCP in EUD and LQ for different SF_2 values, it is found that TCP in EUD for SF_2 (0.3–0.6) was lower than LQ, but in SF_2=0.7, the LQ was lower than that in EUD.

Table 3: Descriptive statistics of equivalent uniform dose values in three experimental studied groups

	n	R (maximum-minimum)	Median (IQR)	Mean±SD	95% CI of mean	*P*†
Low (α/β=5)	30	22.23 (68.45-46.22)	61.63 (1.91)	61.33±3.35	60.08-62.58	0.114
Medium (α/β=8)	30	19.21 (66.52-47.31)	63.20 (1.58)	60.55±3.72	59.16-61.94	
High (α/β=10.8)	30	19.71 (67.55-47.84)	61.16 (1.60)	60.57±3.66	59.20-61.94	

†Using one-way repeated measures ANOVA with a Greenhouse-Geisser correction. R=Range (=the maximum observation-the minimum observation); IQR=Interquartile range (=the 3rd quartile - the 1st quartile); Mean=Arithmetic mean; SD=Standard deviation; CI=Confidence interval

The Spearman correlation analysis revealed a fair positive partial correlation between TCP values in Poisson and EUD (r = 0.37, P < 0.05), but the relation between LQ with Poisson and EUD (α/β =8 and SF_2 = 0.5) showed no statistically significant difference.

EUD expresses cell survival with SF_2 at dose of 2 Gy, which indicates the dose required to produce a specific effect on tissue and depends on the type of tumor, but it is independent of SF_2, γ50 and TCD_{50}. Thus, by changing (α) and α/β ratio, the EUD reduces whereas these changes are not statistically significant [Table 2]. Hence, the effect of α/β on EUD was much greater when compared with SF_2.

In studies performed on mathematical models with the aim of estimating radiobiological parameters,[14] no specific value was observed for TCP, but according to their low survival probability, it is expected to be 30%. Figure 3 shows that TCP in LQ and EUD was more than 90%, which is in conflict with the probability of low survival. Therefore, these two models cannot be considered suitable indicators for calculating TCP. In Poisson model, the average TCP was 11.36 on average, which is lower than the threshold introduced in the literature.[7,8,14] The reasons for TCP reduction here consist of lack of dose coverage in PTV. Therefore, the low TCP value corresponding to the mentioned clinical data and low survival rate of the patients, which is proportional to low TCP value, confirming the Poisson model as an appropriate model.

Previous studies[7,8] focused on patients who had undergone surgical resection to compare their MRI. However, the present study included all patients for MRI pre- and post- treatment to adapt with radiobiological models. The differences between previous observations[8] and the present study may arise from calculated TCP with the Poisson model to adapt with MRI outcome data. Treatment response is still a serious problem, and Rowe *et al*.'s study showed that MR images are not enough alone to recognize true progression in patients with GBM.[6]

The survival of patients with glioma depends on ability to respond to treatment. Although previous studies have indicated that MR images pre- and post- radiotherapy may be an important factor in predicting survival for gliomas, the present study is the first to collect the data from pre- and post- treatment and their radiobiological models analyses.

Some limitations of this study are distribution of the set of patients into three possibilities of tumor growth (progressive disease, partial response, and stable) examination, which produced low numbers of patients in some groups and also lack of control study group.

CONCLUSION

This study offers a combination of clinical observations and mathematical modeling to test the hypothesis that there is a relationship between image changes and TCP. The radiobiological parameter implications in the final TCP calculation were also illustrated. Therefore, improvement of mathematical models based on clinical results might be useful. The findings of this work showed that among the studied TCP radiobiological models using MRI data before and 12 weeks after RT of GBM, the optimum is the Poisson model. The importance of using radiobiological models to improve dose prescriptions in radiation therapy of GBM was another outcome. In the clinics, this study may be used to delineate radiation field and help to evaluate treatment response. Further studies could provide additional information about the clinical performance by working on diffusion- and perfusion-weighted MR images and their findings in relation to the TCP radiobiological models.

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Conflicts of interest

There are no conflicts of interest.

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