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Extreme hypofractionated radiosurgery in recurrent inoperable High-Grade Ultra-Large gliomas

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► ***Original article***

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ABSTRACT

***Background*:** To elucidate the efficacy and toxicity of brain re-radiotherapy for recurrent large inoperable gliomas using radiosurgery. ***Materials and Methods*:** Between 2014 and 2018, extreme hypofractionated radiosurgery was performed using Accuray's Cyberknife® system on 14 lesions (12 patients) grade 4 recurrence lesions of 6 patients with anaplastic astrocytoma and 6 patients with glioblastoma who had previously undergone surgery and cranial radiotherapy and had a local-regional recurrence. Six patients (8 lesions) were given a biologic effective dose (BED10) of 48 Gy and lower, and six patients were given a BED_{10} of 59.5 Gy and higher. The Response Assessment in Neuro-Oncology Criteria (RANO) were used for tumor response, and the Common Terminology for Adverse Events (CTCAE) was used for adverse effect assessment. The primary endpoint was determined as overall survival, and first treatment and salvage treatment time. ***Results*:** The median age of the patients was 43 years, and the median Karnofsky Performance Status (KPS) was 70. The median time from the first radiotherapy to death was 34 months. The median time from the previous radiotherapy was 29.5 months (R:17-40). The median survival was 10 months for those with recurrence before 29.5 months and 11 months for those with recurrence after 29.5 months. The median total tumor volume was 29.224 mL (~30 mL). One grade 4 toxicity was observed. ***Conclusion*:** Radiosurgery can be used effectively as salvage therapy in ultra-large inoperable gliomas.

INTRODUCTION

High-grade gliomas (HGG) are the most common primary brain tumors. They account for about 75% of all brain tumors [1]. HGGs are life-threatening and often cause death. The median overall survival is under 15 months and almost all patients develop a recurrence [2]. Today, almost all HGGs relapse, thus salvage treatments become very important. Recurrence usually develops in the previous location or just around it [3, 4]. The median survival in recurrent HGGs is 6 months [5]. It has tumor repopulation and rapid doubling time (3-39.5 days) [6] Therefore, extreme hypofractionated radiotherapy (RT) may be a good alternative in terms of both technical and radiobiologic advantages. Extreme hypofractionated RT is a treatment used in the form of ≤5 fractions. It is also called fractionated stereotactic surgery and is considered less toxic than radiosurgery given in a relatively single fraction [7].

Treatment of recurrent brain tumors should first involve the resection of the local tumor if possible [8]. For patients who are unsuitable for surgery, clinical studies can be tried, or palliative care, systemic chemotherapy, alternating electric field therapy, and RT, which has provided a promising development in recent years, can be used. Although there is currently no consensus on recurrent glioma treatment [9], patients with high Karnofsky Performance Status (KPS) who do not have an eloquent localization, small volume, and who can undergo complete resection are referred for surgery by our tumor board.

RT, which used to be used as a last resort in the past, started to become more popular after it was observed that it had an advantage in 10-11–month follow-up related to survival after recurrence [10]. However, at this point, the patient's age and performance status, diffuse-natured tumors, and the time passing after the first treatment in terms of the risk for radionecrosis become important.

Re-irradiation should be mostly preferred for small tumors [11], and low-dose radiosurgery [12] in cases in which a time of at least 6 months to 1 year has passed after the first RT. However, there is still no standard dosage schedule. Also related to this, in a single-arm prospective study, Bevacizumab was given as 30 Gy in 5 fractions, and this regimen was shown to be safe and well-tolerated and contributed

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to a lifetime with disease control [13]. The most important study on this subject is that of Fogh *et al*. published in JCO. In young patients with small-volume tumors (<15 mL), survival contribution of 35 Gy and overdoses in 10 fractions was shown in patients who relapsed later than 6 months [14].

Regarding re-irradiation, the RTOG 1205 phase 2 study was started to investigate the effect of bevacizumab treatment in addition to 35 Gy radiotherapy in 10 fractions [15]. Nevertheless, the efficiency and advantages of brain re-irradiation using stereotactic radiosurgery (SRS) for recurrent glioma remain unclear. In this single-institution retrospective study, the objective was to evaluate the impact of 14 cases of brain re-irradiation using SRS on the overall survival (OS) outcomes in patients with recurrent gliomas.

Our study, unlike other studies, investigates treatments adminstered to control inoperable, large-volume, eloquent localized recurrent tumors with new radiosurgery techniques, which were previously feared due to toxicity. For tumors with this volume, local control and OS were desired. The patient group in our study had tumors that recurred only as high grade and were at least grade 3 at the beginning. In this study, the effectiveness, safety, and toxicity of new radiosurgical techniques were evaluated.

Although there has been an explosion in publications on glioblastoma reirradiation in recent years, it has yet to be accepted as a standard treatment method. Many more recent meta-analyses, together with our study and others, are urgently needed.

MATERIALS AND METHODS

Patient eligibility

Between January 2014 and June 2018, radiosurgery was performed using a Cyberknife® (Accuray Incorporated, Sunnyvale, CA, USA) on 14 grade 4 recurrence lesions (12 patients, two patients had 2 lesions) of six patients with anaplastic astrocytoma and six patients with glioblastoma, who had previously undergone surgery and cranial radiotherapy and had local-regional recurrence. The mean age of the women was 36 years (R: 32-42). The mean age of the men was 44 years. (R:32-52). Given that the median volumes we administer in radiosurgery are quite large, we preferred not to treat our patients using Linac-based treatment devices, but with the Cyberknife®, which can apply real tracking and therefore offers the advantage of treatment without internal target volume (ITV) margins.

All patients were surgically inoperable as evaluated by our hospital's tumor boards. All of the patients had previously received RT to the same treatment area. The median KPS was 70 (range, 60-80). The median dose of the previous RT of the patients was 30×200 cGy (interquartile range (IQR): 58-60Gy). All patients were given the first treatment simultaneously with temozolomide 75 mg/m^2 and then 150-200 mg/m^2, a total of six cycles of therapy. The first recurrences occurred in a time longer than 24 months in six patients and in a time shorter than 24 months in six patients. Of the patients who had recurrence in a time longer than 24 months and were being treated, three had anaplastic astrocytoma and three had glioblastoma.

Radiotherapy specifications

Our preparation, planning, and treatment protocol for radiosurgery treatment were administered to our patients. In this protocol, the 6-MV CyberKnifeR radiosurgery system (Accuracy Inc., Sunnyvale, CA, USA), which effectively compensates for intrafraction motion with a 6-D skull tracking system, is used in all second series cranial RT applications because it provides patient compliance and comfort, does not require a rigid frame, can enable real-time tracking with 0.1-millimeter sensitivity, offers the possibility of applying fractional treatment when necessary, has almost no penumbra, does not require ITV margin, and provides dosimetric success in lesions below the size of 4 cm as non-coplanar.

In all patients, immobilization was provided using a custom thermoplastic mask. The simulations of the patients were contoured using 1 mm computed tomography (CT) and 1 mm T1-weighted Brava magnetic resonance imaging (MRI) sequences under these conditions. The ITV margin was not given because the organ motion was below 1 mm. The planning target volume (PTV) margin was determined as 0-2 mm. PTV was not given a margin in large lesions and critical organ conditions. PTV margins were not used. Inverse planning was performed using the MultiPlan Treatment Planning System (Accuray) software. During treatment, bony landmarks were used to define the location of the tumor with X-ray cameras, real-time images were taken and instant follow-up and corrections were made.

Follow-up and primary and secondary endpoints

Our patients were followed up via MRI at 2-4-month intervals in our clinic or by the clinics that had referred them [16]. However, when clinical progression was considered, MRI was performed without waiting. MRI used to evaluate possible adverse effects such as progression and radionecrosis. The RANO criteria were considered while evaluating all patients [17]. Adverse effects were evaluated using the Common Terminology Criteria for Adverse Advents) CTCAE (version 5.0) [18]. The primary endpoint was determined as of OS, and first treatment and salvage treatment time, and the

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secondary endpoint as disease-free survival (DFS). All of our patients died, except for one patient. The maximum follow-up has been reached for this study.

Statistical design

The IBM® Statistical Package for the Social Sciences (SPSS® Statistics, SPSS Inc., Chicago, IL), version 23 was used for all statistical analyses. All-time related events (failure or death) were calculated from the date of the first stereotactic radiotherapy (SRT) to the date of death or censoring at last clinical follow-up, and analyzed using Kaplan-Meier methods [19, 20]. Survival significance was considered at $p < 0.05$ and all significance levels were two-sided.

RESULTS

The median age of the patients was 43 (IQR: 35-46) years, and the median KPS was 70 (range, 60-80). The median dose that was administered was 30 (range, 16-35) Gy. The median fraction was 5 (1-10). Seven (58.7%) patients who received adjuvant chemotherapy lived a median 9.4 months, and five patients who did not receive chemotherapy lived a median 12.8 months. The characteristics of the patients are presented in table 1. All patients who were treated died. The median survival was 10 months (95% CI: 5.756% to 14.244%). OS was 83.3% in the third month, 66.6% in the sixth month, and 50% in the first year figure 1. The median follow-up was 6 (range, 1-24) months. The median BED_{10} was 48-59.5 Gy (patients 6 and 7), the median BED_2 was 157.5-300 Gy. The median time elapsed from the previous radiotherapy was 29.5 (range, 17-40) months. Six patients (8 lesions) were given a BED_{10} of 48 Gy and below, and six patients were given a BED_{10} of 59.5Gy and above. The median survival for both dose groups was 10 months figure 2. The median total tumor volume was 29.224 (~30 mL) (range, 14.846-53.340) mL. The patients with recurrence volume over the median volume lived for a median of 11 (mean: 12.3) months and those with recurrence volumes below the median lived for 10 (mean: 17.1) months (figure 3). The median survival was 10 months for those with recurrence before 29.5 months and 11 months for those with recurrence after 29.5 months figure 4. All patients were considered inoperable by the tumor board after recurrence. At the initial diagnosis, six patients had grade 3, and six had grade 4 tumors. The final histopathologic tumor grade was determined as grade 4 in all patients. Before relapse as grade 4, patients with first histopathologic grade 3 had a median time of 11 months, and patients with grade 4 had a median of 10 months figure 5.

Local control was not achieved in three patients 1 month after follow-up. Thus, the rate of local control (partial response and stable disease) was 75% in the first month. In addition to three patients at the beginning whose local control could not be provided, three patients also died of local recurrence. Thus, the total local failure became 50% in six months. The PFS rate was 50%, because no regional recurrence developed in the 6 months in addition to local failure. The other two patients died in the third month of local progression. Thus, a total of eight patients died of progression. Four patients died of regional recurrence.

Table 1. Patient, tumor, and treatment characteristics.

	Brain CA (n=12)
Sex M/F	8/4
Age (median (IQR))	43 (35-46)
SRS time, month (median (IQR))	29.5 (17.25-38.75)
BED2 (median (IQR))	120-300 Gy (6-7th patients)
BED10 (median (IQR))	48-59.5 Gy (6-7th patients)
Total tumor volume (median (IQR))	29224 mL (14846-53340)
First radiotherapy dose (Gy) 60Gy 54Gy 46Gy	 9 (75.0) 2 (16.7) 1 (8.3)
Additional CT (n (%))	7 (58.3)
KPS (median)	70 (60-80)

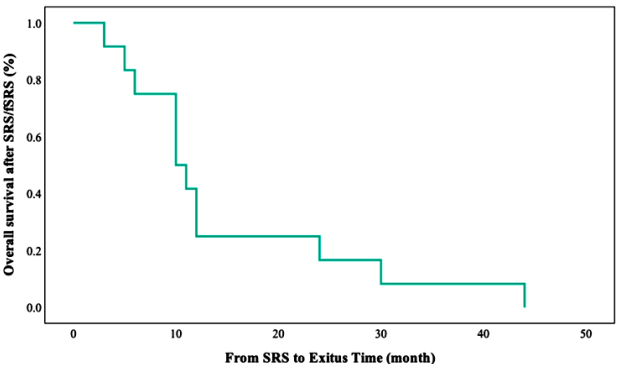


Figure 2. Dose-Survival Relationship (Time=months).

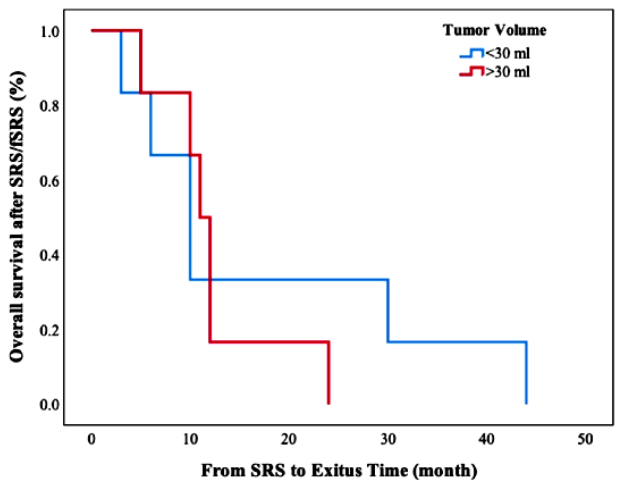


Figure 3. Volume-Survival Relationship (Time=months).

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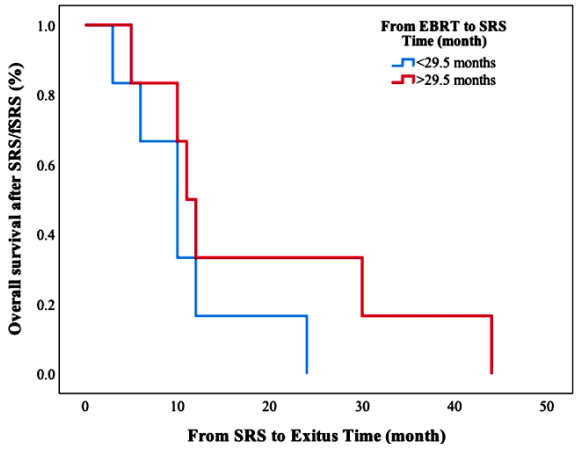


Figure 4. From first EBRT (External beam radiation therapy) to SRS –Survival Relationship (Time=months).

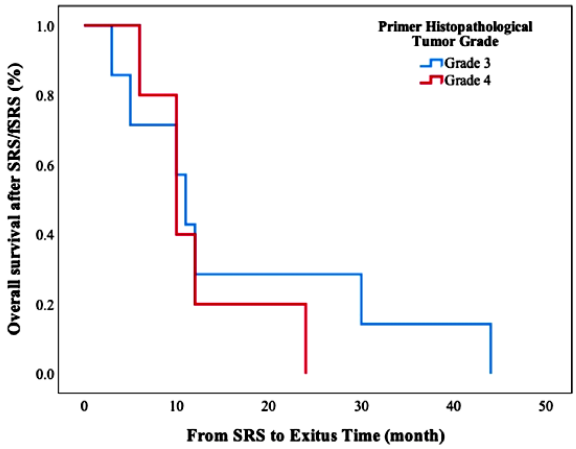


Figure 5. Primary Histopathologic Tumor Grade-Survival Relationship.

Toxicity

Headache and fatigue were seen in two patients with large treatment volume, and nausea and vomiting were observed in one patient at grade 1 level. However, all responded to corticosteroids. Premedication was not given.

After 45 days, two patients with primary glioblastoma recurrence with response to steroids were accepted as progressed because our patients who had clinical and MRI (decrease in T2 FLAIR hyperintensity) findings could not have MRI perfusion and MRI spectrography at that time. However, the steroid doses of these patients were later reduced, and they lived relatively longer than the other patients.

Although we used very high doses for the second series in our patients, only one (8.3%) patient developed grade 4 radionecrosis. Two (16.6%) patients developed leptomeningeal metastasis.

DISCUSSION

Almost all HGGs recur, and patients die of local-regional recurrence. Treatment of recurrent brain tumors is primarily considered successful if the local tumor can be resected [8, 21]. However, 25% of patients with glioblastoma are eligible for re-surgery [22]. The best results are obtained with surgery [23]. Nevertheless, it should not be forgotten that surgery is performed on the patients with the smallest tumors, who are in an operable condition. There is no prospective study comparing radiosurgery and surgery and such a study cannot be performed due to its nature [21]. In patients for whom surgery cannot be performed, palliative care, chemotherapy, alternating field therapy and radiosurgery with radiobiologic advantages can be used [14, 24, 25]. RT, which was used as a last resort in the past, started to become more popular after it was observed that it had an advantage related to survival after recurrence in 10-11–month follow-ups [10, 26, 27].

The 10-month median survival we obtained in our study is consistent with the literature [27, 28]. The statistical analysis of our study differs from other studies in terms of reaching the maximum follow-up because it was performed after the loss of all our patients.

After 45 days, two (16.6%) patients with primary glioblastoma recurrence with response to steroids were accepted to be progressed because our patients who had clinical and MRI (decrease in T2 FLAIR hyperintensity) findings could not have MRI perfusion and MRI spectrography at that time. However, the steroid dosages of these patients were later reduced, and they lived relatively longer than other patients. In the later evaluation of these patients, it was decided that they had pseudo progression because there were reports in the literature that such patients live longer [17, 27]. It is seen in 10% of patients receiving only radiotherapy [29]. Although rates of pseudoprogression seem to be slightly higher in our study, this may be due to the low number of cases, as well as impaired capillary permeability and damage caused by radiosurgery.

The relation between survival and small volumes has been revealed in the literature [30, 31]. In our study, patients with a recurrence volume above the median tumor volume of 30 mL lived for a median of 11 (mean: 12.33) months and those with a recurrence volume below the median tumor volume lived for a median 10 (mean: 17.1) months. Although it was clinically significant, it was not statistically significant because our case number was low. Radiosurgery is recommended to be avoided because of fear of radionecrosis in tumors with a volume greater than 25 mL [12], but in our study, although the median volume was 30 mL, severe radionecrosis was not detected, except for one patient. Therefore, these patients should be treated without fear. As can be seen in our study, all these patients had a median survival rate of 10 months, which is similar to that of smaller-volume tumors in the literature.

Hasan *et al.* found the time from the first radiotherapy until recurrence as over 16 months,

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which was significant. This time was found as 29.5 months in our study [32]. However, statistical significance could not be achieved due to the small number of patients.

Seven of our patients received temozolomide (TMZ) treatment until progression after the treatment. However, despite the advantage in survival as stated in the literature, in our study, patients receiving post radiosurgery TMZ had a similar prognosis [13, 15, 33]. Seven (58.7%) patients who received adjuvant TMZ lived for a median of 9.4 months, and five patients who did not receive chemotherapy lived for a median of 12.8 months. However, because the number of patients was low, statistical significance could not be obtained.

Publications are indicating that local control rates increase without any adverse effects at doses above 30 Gy / 5-6 frx depending on the radiosurgery dose [33, 34]. However, because the number of patients was low, no statistical significance was found for increase in survival as the dose increased. Although those with small volume tumors and those who received doses over BED_{10} 48 Gy (our upper initial dose was 59.5 Gy) had apparent superiority in median times over those with late recurrences and those who did not receive chemotherapy, p-values were not significant because the number of patients was low.

Although we administered very high doses for the second series in our patients, only one patient developed grade 4 radionecrosis. Radionecrosis usually occurs at 18-24 months after RT, characterized by intense edema. However, this period can be shortened up to 3 months or it can be extended up to 30 years. After RT, the probability of developing radionecrosis increases depending on the total treatment dose, the fraction dose size, and the increase in the treatment volume [35]. Under the cumulative dose of 110 Gy, redionecrosis has not been observed if more than 6 months have passed between both RTs. Radionecrosis development has not been shown to affect total survival [36]. Blonigen et al. showed that the risk of radionecrosis was higher when V10 was >10.5 cm^3 and V12 was >7.9 cm^3 [37]. Although our patients were given relatively high doses and large volumes for the second series, the low rate of radionecrosis may be related to the short survival time. In addition, we may have seen less radionecrosis because of the technique we used. Our PTV margins are close to zero because we use the Cyberknife® in our patients, with which we also use real tracking, and this may have given us a volume advantage when considered in three dimensions. We think that our rate of radionecrosis was low because our median survival was around 10 months and radionecrosis generally appears after 18 months.

Hughes *et al.*'s phase I dose-escalation study in patients with tumor volumes ≤20 mL were associated with a higher likelihood of response in recurrent gliomas [38]. In the literature, large tumor volume creates concerns because the control rate will be lower and its toxicity will be high, and such tumors are left untreated [39, 40]. Unlike other studies, the tumors in our patient group were large, tumors of a median size of 30 mL were administered median BED_{10} of 48-59.5 Gy which quite high doses for reirradiation of large volume tumours. However, a reasonable survival and acceptable toxicity profile was observed. Therefore, these types of inoperable, large volume, and eloquent localized patients should not be left untreated and should be evaluated for treatment with radiosurgical methods.

CONCLUSION

Today, with the development of radiosurgery techniques, it is possible to reach high dosages in limited areas. In the group, even in inoperable disease, radiosurgery had very low toxicity as a salvage treatment. As a result of the developments in radiotherapy, it can be used effectively as a salvage therapy in gliomas, which are deadly tumors.

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***Author contributions*:** Designed and supervised the study T.B. Concept: T.B.; resources: T.B.İ.H, F.A, Y.B, F.A.; materials: T: B,B. D.Y, S.TD, G.C.; data Collection and/or processing: T:B., Ç.N, M.N.G, ; analysis and/or interpretation: T:B, M.E.G, C.Y.; literature search: T:B, A.A.Y.; writing manuscript: T: B.C.Y.; critical review: T:B, Ç.N.; other: T:B.

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