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Feasibility of Salvage Re-irradiation With Stereotactic Radiotherapy for Recurrent Glioma Using CyberKnife

KANA ADACHI[1], KAZUHIKO HAYASHI[2,3], NAOKI KAGAWA[4], MANABU KINOSHITA[4], IORI SUMIDA[2], YUICHI AKINO[2], HIROYA SHIOMI[2], KEISUKE TAMARI[2], OSAMU SUZUKI[2], RYUICHI HIRAYAMA[4], NORIYUKI KIJIMA[4], FUMIAKI ISOHASHI[2], YUJI SEO[2], KEISUKE OTANI[2], HARUHIKO KISHIMA[4] and KAZUHIKO OGAWA[2]

[1]*Department of Radiation Oncology, Toyonaka Municipal Hospital, Toyonaka, Japan;*
[2]*Department of Radiation Oncology, Osaka University Graduate School of Medicine, Suita, Japan;*
[3]*Osaka Heavy Ion Therapy Center, Osaka, Japan;*
[4]*Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Japan*

Abstract. *Aim: To evaluate the toxicity and efficacy of re-irradiation with salvage stereotactic radiotherapy (SRT) for recurrent glioma using CyberKnife. Patients and Methods: This study retrospectively investigated 35 patients with 48 recurrent grade 2-4 gliomas who received SRT between 1998 and 2011. Six patients (17.1%) had grade 2 gliomas, nine (25.7%) had grade 3 gliomas, and 20 (57.1%) had glioblastomas; all initially underwent surgery and conventional radiotherapy. The median initial and subsequent radiotherapy doses were 60 and 26 Gy, respectively. Results: After a median follow-up period of 9.0 months, the only toxicity of grade 2 or more was radiation-induced brain necrosis in four patients (11.4%). The median overall and progression-free survival periods following re-irradiation were 9.0 and 3.0 months, respectively. Univariate analysis revealed that performance status at salvage re-irradiation was a significant predictor of progression-free survival. Conclusion: Salvage re-irradiation using CyberKnife is feasible, with an acceptable toxicity profile, for patients with recurrent glioma.*

Gliomas are relatively rare tumours, their annual incidence is approximately seven patients per 100,000 population (1). They are classified by cell type and grade according to the World Health Organization (WHO) classification of CNS tumours (2). Eighty-five percent of all diagnosed gliomas are high-grade (1), and their treatment strategies depend on the tumour's grade, location, and histological type. The standard initial treatment for high-grade glioma includes maximal surgical resection and postoperative chemoradiotherapy. However, intracranial recurrence frequently occurs despite multimodality treatments, with most recurrences occurring locally (typically within 2 cm of the primary lesion) (3).

A standard treatment regimen for gliomas that recur has yet to be established; treatment options are re-resection, chemotherapy (including with temozolomide or bevacizumab), and salvage radiotherapy (4). Patients with recurrent gliomas who are under 70 years of age, have tumour volumes <50 cm^3, and have preoperative Karnofsky performance status scores >80% are generally considered candidates for repeat resection (4); however, this treatment is often limited because of the infiltrative nature of gliomas. Alternatively, focal lesion recurrences may be treatable with salvage radiotherapy; however, patients who previously received intracranial radiotherapy at doses >40 Gy are at a high risk of radiation-induced toxicity, especially brain radionecrosis, upon re-irradiation.

To date, many retrospective studies have found that stereotactic surgery (SRS) and stereotactic radiotherapy (SRT) employed *via* various methods are well-tolerated and effective (5-12). However, most of these studies were performed using a linear accelerator (Linac) or Gamma Knife (Elekta AB, Stockholm, Sweden). CyberKnife (Accuray Inc., Sunnyvale, CA, USA) combines computer-controlled robotics with real-time imaging guidance to provide high conformality without resorting to aggressive target fixation, thereby offering an attractive SRS or SRT option (13, 14). To our knowledge, only a few studies of re-irradiation for recurrent gliomas using CyberKnife have been published (11, 12, 14, 15). Therefore, we performed this

Correspondence to: Kazuhiko Hayashi, Kazuhiko Ogawa, Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan. Tel: +81 668793482, Fax: +81 668793489, e-mail: k.hayashi@osaka-himak.or.jp

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study to retrospectively evaluate the toxicity and efficacy of salvage re-irradiation with SRT for recurrent gliomas using CyberKnife.

Patients and Methods

This study was approved by the Institutional Review Board of Osaka University Hospital (No. 18512). Research was conducted in accordance with the Helsinki Declaration. Re-irradiation was defined as treatment in which the initial and post-recurrence radiotherapy planning target volumes (PTVs) overlapped.

Patients. A retrospective survey was carried out of all patients who were treated with salvage re-irradiation using CyberKnife for recurrent glioma after initial treatment at Osaka University Hospital. Thirty-five patients with 48 lesions who were treated between 1998 and 2011 were applicable. All patients were initially treated with surgery and conventional radiotherapy. The median dose of initial irradiation was 60 Gy (range=40-80 Gy). Recurrent gliomas were diagnosed by the presentation of new or increasingly contrast-enhanced lesions on magnetic resonance imaging (MRI). Gliomas were graded according to the WHO classification of CNS tumours at the initial surgery (2).

CyberKnife treatment planning and delivery. Patients were immobilized with a custom thermoplastic head mask system and underwent a contrast-enhanced computed tomographic (CT) simulation in the treatment position with 1.0 mm slices; they also underwent brain MRIs to which the simulated CTs were fused. The gross tumour volume (GTV) was defined as the contrast enhancing CT-detectable lesion(s) and T1-weighted MRI images. The PTV was defined as the GTV plus a 1 mm margin to account for positioning errors. All treatment planning was performed using the CyberKnife Planning System (On Target-TPS; Accuray Inc., Sunnyvale, CA, USA). An inverse planning method with a non-isocentric technique was used. Total doses were prescribed to the isodose line that covered 90% of the PTV. The prescribed doses for re-irradiation were 9-30 Gy in 1 fraction for 29 lesions, 24-36 Gy in 3 fractions for 11 lesions, and 20-35 Gy in 5 fractions for eight lesions. The median doses of re-irradiation per fraction were 27 Gy for 1 fraction, 30 Gy for 3 fractions, and 25 Gy for 5 fractions. The most commonly prescribed dose was 30 Gy in 1 fraction (eight lesions), followed by 27 Gy in 1 fraction (seven lesions), 25 Gy in 5 fractions (five lesions), and 24 Gy in 1 fraction (five lesions). Total dose and fractionation were determined in consideration of the tumour size, dose of previous irradiation, proximity of organs-at-risk, and the patient's condition. All treatments were delivered with 6 MV photons utilizing CyberKnife (G2) between 1998 and 2003 and CyberKnife II (G3) between 2004 and 2011.

Follow-up. After treatment, follow-up MRIs were performed every 3 months in the absence of any neurological deterioration. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0) (16); we collected information on toxicities of grade 2 or more. The patients' performance statuses were scored according to the Eastern Cooperative Oncology Group criteria.

Statistical analyses. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method. PFS was defined as the interval between the date of commencing re-irradiation and that of disease progression at any site, death from any cause, or the last follow-up. OS was defined as the interval between commencing re-irradiation and either death from any cause or the last follow-up date.

Univariate analyses of factors that predict PFS and OS were performed using the log-rank test. The patients were divided into subgroups according to the median values of age, interval between initial irradiation and re-irradiation, re-irradiation dose, and the PTV at re-irradiation. A two-tailed value of $p<0.05$ was considered statistically significant. All statistical analyses were conducted using the JMP statistical software (version 14.0; SAS Institute Inc., Cary, NC, USA).

Table I. *Patient and tumour characteristics (N=35).*

Factor	Value
Gender, N (%)	
Male	24 (68.6)
Female	11 (31.4)
Age at initial irradiation	
Median, years (range)	57 (11-78)
Glioma grades (WHO classification), N (%)	
2	6 (17.1)
3	9 (25.7)
4	20 (57.1)
Initial irradiation dose (Gy [RBE])	
Median (range)	60 (40-80)
Interval between initial irradiation and re-irradiation, months	
Median (range)	11 (1-126)
Site of failure at salvage re-irradiation, N (%)	
In-field	32 (91.4)
Marginal	2 (5.7)
Out of field	1 (2.9)
Age at salvage re-irradiation (years)	
Median (range)	58 (12-79)
ECOG PS at salvage re-irradiation, N (%)	
0	10 (28.6)
1	13 (37.1)
2	3 (8.6)
3	7 (20.0)
4	2 (5.7)
Follow-up from salvage re-irradiation, months	
Median (range)	9 (2-109)
Salvage surgery before salvage re-irradiation	
Yes	3 (8.6)
No	32 (91.4)
Chemotherapy at salvage treatment	
Interferon-based	20 (57.1)
Temozolomide-based	6 (17.1)
Other	5 (14.3)
Re-irradiation dose [Gy (RBE)]	
Median (range)	26 (9-36)
PTV at salvage re-irradiation, (ml)	
Median (range)	4.2 (0.2-49.6)

RBE: Relative biological effectiveness; WHO: World Health Organization; ECOG PS: Eastern Cooperative Oncology Group performance status; PTV: planning target volume.

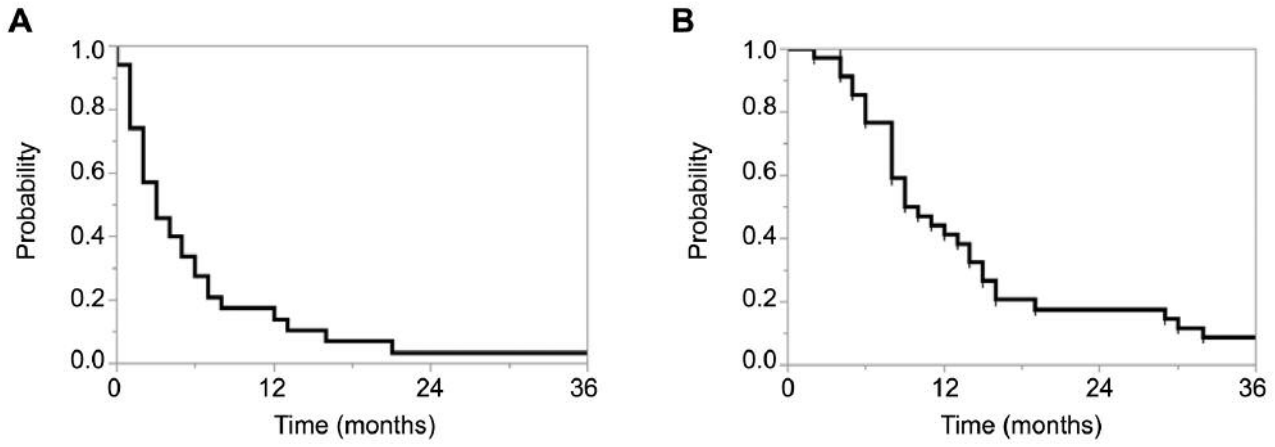

Figure 1. *Kaplan–Meier curves of progression-free (A) and overall (B) survival in patients with recurrent glioma following salvage re-irradiation using CyberKnife.*

Results

Patient characteristics. The patient characteristics are summarized in Table I. In terms of glioma grade, 17.1%, 25.7%, and 57.1% had grades 2, 3, and 4 (glioblastoma), respectively. Moreover, 28.6%, 37.1%, 8.6%, 20.0%, and 5.7% of the patients had performance status scores of 0, 1, 2, 3, and 4, respectively, at the time of salvage re-irradiation. Patients routinely received concomitant temozolomide from 2006 onwards.

Toxicities. During the follow-up period, 4 patients (11.4%) developed grade ≥2 radiation-induced brain necrosis [2 patients (5.7%) with grade 3 and 1 patient each (2.9%) with grade 2 and 4, respectively]. There were no other toxicities of grades ≥2 among the patients.

The patient who developed grade 4 brain necrosis had been re-irradiated for two recurrent lesions using CyberKnife after conventional radiotherapy (66 Gy) for glioblastoma surrounding the right lateral ventricle. Brain necrosis with serous cyst formation occurred, and the cyst was resected 3 months later.

Local control and survival. All patients completed planned treatment without interruption. During the follow-up period, 32 patients (91.4%) died of gliomas, two (5.7%) survived, and one (2.9%) was lost to follow-up. Twenty-nine patients (82.9%) experienced local recurrences. The 1-year OS and PFS rates were 41.3% [95% confidence interval (CI)=26.2-58.2%] and 13.9% (95% CI=5.5-30.9%), respectively (Figure 1). The median OS and PFS following re-irradiation were 9.0 months (95% CI=6-16 months) and 3.0 months (95% CI=1-6 months), respectively. When categorized by grade, the median OS was 12.0, 8.0, and 9.5 months for those with grade 2 gliomas, grade 3 gliomas, and glioblastomas, respectively.

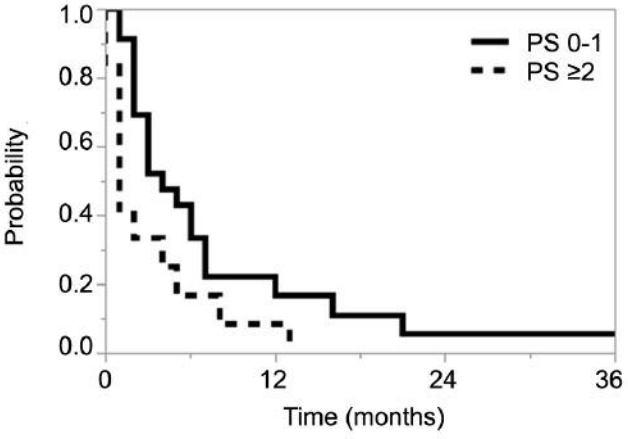

Figure 2. *Kaplan–Meier curves of progression-free survival according to performance status (PS) at the time of salvage re-irradiation of patients with recurrent glioma.*

Prognostic factors. Univariate analyses were performed to identify potential prognostic factors for PFS and OS among the different subgroups. Our results revealed that performance status at salvage re-irradiation was a significant predictor of PFS (p=0.034) (Table II). Kaplan–Meier PFS plots according to the patient performance status at salvage re-irradiation are shown in Figure 2. The 1-year PFS rate of patients with performance status scores of 0-1 at the time of re-irradiation was 16.7%, whereas that of patients with scores of 2-4 was 8.3%. No significant associations were observed in univariate analysis for OS.

Table II. *Univariate analysis of progression-free (PFS) survival and overall survival (OS).*

Factor	N	1-Year PFS rate (%)	*p*-Value	1-Year OS rate (%)	*p*-Value
Gender					
Male	24	9.1	0.410	36.4	0.545
Female	11	16.2		43.7	
Age at salvage re-irradiation					
≥57 Years	18	13.0	0.706	41.3	0.150
<57 Years	17	14.7		41.2	
Grading of the gliomas due to WHO classification					
2	6	0	0.305	60	0.297
3	9	16.7		33.3	
4	20	15.0		40.0	
PS score at salvage re-irradiation					
0-1	23	16.7	0.034	41.0	0.211
≥2	12	8.3		41.7	
Interval between initial irradiation and re-irradiation					
<11 Months	17	6.7	0.438	37.7	0.359
≥11 Months	18	20.8		44.4	
Site of failure at salvage re-irradiation					
Marginal	2	0	0.161	50.0	0.697
In-field	32	10.3		38.8	
Out-of-field	1	100		100	
Salvage re-irradiation dose					
≥26 Gy	17	19.6	0.114	56.5	0.628
<26 Gy	18	8.3		27.8	
PTV at salvage re-irradiation					
≥4.2 ml	23	15.7	0.951	34.8	0.127
<4.2 ml	12	11.1		55.0	
Temozolomide					
Yes	6	16.7	0.722	33.3	0.787
No	29	12.9		43.0	

N: Number of patients; WHO: World Health Organization; PS: performance status; PTV: planning target volume.

Discussion

Salvage radiotherapy *via* SRT using Linac or Gamma Knife has already been shown to be a reasonable treatment option for patients with gliomas who experience recurrences in the form of focal lesions following surgery and conventional radiotherapy (5-12). However, few studies to date have investigated the use of re-irradiation with CyberKnife for recurrent glioma (11, 12, 14, 15). Our findings demonstrated that re-irradiation with CyberKnife achieves moderate survival benefits with acceptable toxicity, and that performance status upon salvage re-irradiation is a significant predictor of PFS. Therefore, salvage re-irradiation using CyberKnife may be a viable option for patients with recurrent glioma, especially for those with good performance status scores.

Radiation-induced brain necrosis is generally considered a major toxicity risk after re-irradiation for recurrent glioma. Notably, however, there were no other toxicities of grade 2 or more among our patients. Several studies of SRS or SRT using Linac or Gamma Knife for recurrent gliomas revealed that grade 2 or more and grade 4 radiation-induced brain necrosis occurred in 6.4-29% and 3.8-5.5% of their treated patients, respectively (5, 8, 17-20). Pinzi *et al*. reported that seven out of their 128 patients with high-grade gliomas who underwent re-irradiation using CyberKnife experienced radiation-induced necrosis, three of whom required surgical intervention; however, they did not report the grades of necrosis (12). Conti *et al*. reported that one (4.3%) of their 23 patients with recurrent glioblastoma multiforme who underwent CyberKnife SRS experienced radiation-induced necrosis that required surgery (11). Levy *et al*. investigated survival rates for 13 patients who underwent CyberKnife reirradiation for recurrent glioma following chemoradiotherapy, and reported that three (23%) developed radionecrosis without revealing their grades (15). In our present study, four (11.4%) and one (2.9%) of our patients who were re-irradiated with CyberKnife for recurrent glioma developed grade 2 or more and grade 4 radiation-induced brain necrosis, respectively. These toxicity rates are similar to those reported in patients who underwent Linac or Gamma Knife treatment.

Although several studies of patients with recurrent glioma who were treated with SRS or SRT re-irradiation have been

performed using Linac or Gamma Knife, the median OS of these patients following re-irradiation was 5.3-13.5 months (5, 7-10, 17-21). Relatively fewer studies have investigated the use of re-irradiation with CyberKnife for recurrent glioma; these revealed a median post-re-irradiation OS of 7.0-14.0 months. (11, 12, 14, 15). The median OS among our patients following re-irradiation was 9.0 months. Such findings indicate that the survival benefits following re-irradiation with CyberKnife are comparable to those following Linac or Gamma Knife treatment.

With respect to prognostic factors, studies that investigated patients with recurrent glioma re-irradiated using SRT or SRS (12, 14, 22) found that the tumour histology at initial surgery, age, time between initial radiotherapy and re-irradiation, other therapies after re-irradiation, and extent of surgical interventions were predictors of overall survival. Our results showed that performance status at salvage re-irradiation is a previously unreported significant predictor of PFS, although no significant predictors of OS were identified. Our finding is similar to that by Carson *et al*., who found that the Karnofsky performance status was a significant predictor of survival in patients with recurrent glioma who were treated with chemotherapy (23).

Our study had several limitations. Firstly, it was a single-centre retrospective analysis using observational data. Secondly, the median follow-up period after re-irradiation was short (9.0 months) because patients with recurrent glioma have poor prognoses; consequently, our results might have underestimated the toxicity of re-irradiation with CyberKnife. Thirdly, as the sample size was small, it is premature to generalize our findings, especially in terms of prognostic factors. Finally, we included a wide variety of doses and fractionation schemes that may have influenced the treatment outcome; as such, additional prospective studies are warranted.

In conclusion, salvage re-irradiation using CyberKnife appears to be a feasible treatment option with an acceptable toxicity profile for patients with recurrent glioma, especially those with a good performance status.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

Kana Adachi: Study design, treatment of the patients, data assembly, statistical analyses and interpretation, writing of the article, revision of the article, and approval of the final article. Kazuhiko Hayashi: Study design, data assembly, statistical analyses and interpretation, writing of the article, revision of the article, and approval of the final article. Naoki Kagawa: Study design, treatment of the patients, data assembly, and approval of the final article. Manabu Kinoshita: Study design, treatment of the patients, data assembly, and approval of the final article. Iori Sumida: Study design, data interpretation, and approval of the final article. Yuichi Akino: Data interpretation, revision of the article, and approval of the final article. Hiroya Shiomi: Study design, treatment of the patients, and approval of the final article. Keisuke Tamari: Study design, data interpretation, writing of the article, and approval of the final article. Osamu Suzuki: Study design, data interpretation, writing of the article, and approval of the final article. Ryuichi Hirayama: Data interpretation, and approval of the final article. Noriyuki Kijima: Data interpretation, and approval of the final article. Fumiaki Isohashi: Data interpretation, and approval of the final article. Yuji Seo: Data interpretation, and approval of the final article. Keisuke Otani: Study design, data assembly, statistical analyses and interpretation, and approval of the final article. Haruhiko Kishima: Study design, data interpretation, revision of the article, and approval of the final article. Kazuhiko Ogawa: Study design, data interpretation, revision of the article, and approval of the final article.

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