Efficacy of Gamma Knife Radiosurgery for Recurrent Gliomas

Ying Sun
General Hospital of Northern Theater Command
Zhenning Tao
General Hospital of Northern Theater Command
Haibo Zhang
General Hospital of Northern Theater Command
Ying Yan (yanyingdoctor@sina.com)
General Hospital of Northern Theater Command

Research Article

Keywords: Recurrent Gliomas, Gamma knife radiosurgery, Prognosis

Posted Date: May 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1614892/v1

Abstract

Objective: To investigate the efficacy and safety of gamma knife radiosurgery (GKRS) for recurrent gliomas.

Methods: We retrospectively analyzed 88 patients who underwent GKRS in our department from 2009 to 2020, including 56 cases of high-grade glioma (HGG) and 32 cases of low-grade glioma (LGG). The median target volume was 17.8 cm^3 (1.6–124.1), the median maximum dose was 25 Gy (13.5–42 Gy), and the median marginal dose was 13.0 Gy (7.5–24.5 Gy). The Kaplan–Meier method was used to calculate the overall survival (OS) and progression free survival (PFS), and log rank test was used to analyze the multivariate prognosis of the Cox proportional-hazards model. Adverse reactions were evaluated according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE).

Results: The median follow-up time was 79.5 months. The median OS and PFS were 12.5 months and 5.0 months for all patients. The median OS and PFS were 10.0 months and 4.5 months for HGG, respectively. The median OS and PFS were 27.0 months and 12.0 months for LGG, respectively. Multivariate analysis showed that Karnofsky performance status (KPS), pathological grade and the times of GKRS significantly affected OS and PFS. Stratified analysis showed that recurrence time interval (15 months) significantly affected OS and PFS for LGG. KPS significantly affected OS and PFS for HGG, and tumor volume (25 cm^3) significantly affected PFS for HGG. No serious adverse events were noted post-GKRS.

Conclusions: Gamma knife radiosurgery as a salvage treatment for recurrent gliomas was safe and effective with tolerable adverse reactions.

Background

Gliomas are the most common primary brain tumors, and their treatment remains one of the most challenging issues in neurooncology. Gliomas are highly invasive and recurrence is very common. However, the approach for recurrence is considerably more heterogeneous [1]. There is no unified standard treatment for recurrent glioma. Options include repeat surgery [2, 3], chemotherapy (e.g., temozolomide [4–6]), bevacizumab [7, 8], reirradiation [9], electric field therapy, targeted therapy, etc. Reoperation is possible in a subgroup of patients. However, it is limited by the risk of substantial morbidity due to the infiltrative nature of the disease [10]. Reirradiation can be applied for the treatment of recurrent tumors, nevertheless, it is limited by the high doses of radiotherapy applied after primary diagnosis and the tumor volume at the time of recurrence. Systemic chemotherapy can be applied using regimens such as carmustine, temozolomide (TMZ), or PCV (prednisone, carmustine, vincristine), but commonly offers only minimal long-term benefit [11–13]. In recent years, gamma knife radiosurgery (GKRS) has become increasingly more popular as a salvage treatment modality for patients diagnosed with recurrent gliomas because of its short treatment cycle, small economic burden, and low adverse

reactions. However, there is no consensus recommendation. We sought to contribute by analyzing our treatment experience over 10 years.

Methods

Patient selection and Baseline Clinical Characteristics

We retrospectively reviewed 88 patients who underwent GKRS for recurrent gliomas at our center between September 2009 and July 2020. We gathered the clinical characteristics of patients including demographics (sex, age), pre-GKRS treatment specifics (initial surgical time, multiple craniotomies, surgery-to-GKRS interval, adjuvant treatment after initial surgery, KPS scale), and GKRS treatment parameters (number of targets, volume of targets, maximum dose, marginal dose, whether multiple GKRS, concurrent/adjuvant chemotherapy) through clinical notes, radiology reports, demographic data, and telephone follow-up. For patients with multiple targets treated in the same GKRS session, we focused on parameters from the volumetric of total lesions. We focused on patients' first GKRS session. The general status of the patients was assessed according to the KPS scale [14]. Pre- and post-GKRS clinical characteristics are summarized in Table 1.

Gamma knife radiosurgical procedure

According to the magnetic resonance imaging (MRI) data before treatment, patients are fitted with a stereotactic head frame under local anesthesia. They underwent 1.5T MRI examination with intravenous gadolinium contrast after then. The 1.5T MRI machine produced by GE company was used to obtain the positioning image, which was transmitted to the gamma treatment planning system through a special network. Stereotactic radiosurgery and dose planning were then performed in consultation with a neurosurgeon, radiation-oncologist, and medical physicist. The target was defined as the contrast enhancing lesion on the T1 weighted axial images that were obtained with a slice thickness of 3.0 mm (**Fig.1**). Target delineation was limited to the target enhancing lesion only for progressive LGG and HGG as confirmed by the ASTRO guidelines [15]. The median marginal dose was 13.0 Gy (7.5–24.5 Gy), and the isodose covering 40%–60% of the target. The median maximum dose was 25 Gy (13.5–42 Gy). We showed the relationship of the treatment volume compared with its marginal dose (**Fig.2a**) and estimated maximal dose (**Fig.2b**) in **Fig.2**. The lesions which were larger than 3.5 cm in diameter or located in important functional areas (such as the brain stem) were treated twice after several weeks.

Table 1

Baseline Clinical Characteristics of all Patients pre- or post-GKRS [%]

Patient characteristics	Number of patients (%)	Patient characteristics	Number of patients (%)
Sex		Number of targets	
Female	45(51)	Single	51(58)
Male	43(49)	Multiple	37(42)
Histopathology		Total volume of target	
LGG(WHO I & II)	32(36)	≥18 cm^3	41(47)
HGG(WHO &)	56(64)	<18 cm^3	47(53)
Adjuvant treatment after initial surgery		Maximum dose ≥25 Gy	46(52)
Chemoradiotherapy	36(41)	<25 Gy	42(48)
EBRT only	23(26)	Marginal dose	
TMZ only	5(6)	≥13 Gy	48(55)
GKRS only	9(10)	<13 Gy	40(45)
None	15(17)	Multiple GKRS	
Age at GKRS procedure		Yes	29(33)
≥50 years	46(52)	No	59(67)
<50 years	42(48)	Adjuvant medication after GKRS	
Recurrence time interval			
≥15 months	45(51)	TMZ	
<15 months	43(49)	Yes	28(32)
Reoperation		No	60(68)
Yes	23(26)	Bevacizumab	
No	65(74)	Yes	9(10)
KPS scale		No	79(90)
≥80	38(43)		
<80	50(57)		

Abbreviations: PTV (planning target area), Recurrence time: Duration between first surgery and first GK procedure; Recurrence time interval: Time interval between date of initial surgery and date of initial GKRS.

Drug treatment after GKRS

The patients were given mannitol injection 125 mL BID, and dexamethasone injection 10 mL once daily intravenously to reduce and prevent the occurrence of brain edema. Twenty-eight patients received TMZ periodic chemotherapy (150-200 mg/m^2) after gamma knife treatment, 1-5 days, 28 days as a cycle, and 9 patients received dose density scheme (75-100 mg/m^2), 1-21 days, 28 days as a cycle, or 100-150 mg/m^2, 1-7 days, 14 days as a cycle. One patient was treated with PCV; this was not analyzed because of the statistical insignificance of the small number. Nine patients were treated with bevacizumab 7.5 mg/kg every 3 weeks; 5 cases were treated with bevacizumab combined with TMZ.

Statistical analysis

The overall survival (OS) was the time from the beginning of gamma knife treatment to death or the last follow-up time, and progression free survival (PFS) was the time from GKRS to local tumor progression or the last follow-up. The follow-up time was defined as the time from GKRS to death or the last follow-up time. Treatment-related toxicities were scored using the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).

Data are presented as median with the range. The Pearson correlation coefficient was obtained through linear regression analysis. Survival analysis was done by the log rank test on Kaplan–Meier survival estimates. Multivariate prognostic analysis was performed using the Cox proportional-hazards model. Statistics were calculated with SPSS 23.0 software; values with $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

We analyzed the characteristics of 88 patients(table2), the median age was 50.5 (17-80) years. The 88 patients include 56 patients with HGG (WHO &) and 32 patients with LGG (WHO I & II). All patients had histologically confirmed gliomas. Eighty-six patients had undergone at least one operation before GKRS, and 2 patients' diagnosis of glioma by histopathologic biopsy (both HGG). Fourteen patients (4 cases of LGG and 10 cases of HGG) did not follow-up the specific time of disease progression after gamma knife treatment, but there was a specific time of death. Seventy-three patients had received adjuvant treatment after first surgery, including chemoradiotherapy (41%), EBRT (26%), TMZ (6%), GKRS (10%), and another 15 patients had without any medical treatment. Twenty-nine patients had received multiple GKRS after the recurrence. Univariate analysis demonstrated that prognostic factors associated with OS (**Fig.3**) and PFS (**Fig.4**) were primary pathological grade, recurrence time, reoperation, KPS, pathological grade after

recurrence and multiple gamma knife treatment; central dose and peripheral dose were correlated with PFS.

Table 2

Univariate analysis of OS and PFS in all patients pre- and post-GKRS

characteristics	Number of patients (%)	Median PFS (95% CI) *P*-value	Median OS (95% CI) *P*-value
Sex		0.861	0.864
Female	45(51)	4.5(1.7–7.4)	10.0(0.0–22.0)
Male	43(49)	5.0(4.3–5.7)	12.5(8.0–17.0)
Histopathology		0.008	0.001
WHO I & II	32(36)	12.0(3.9–20.1)	27.0(0.0–56.0)
WHO □ & □	56(64)	4.5(3.0–6.0)	10.0(4.9–15.1)
Adjuvant treatment after first surgery		0.877	0.446
Chemoradiotherapy	36(41)	4.0(1.5–6.5)	7.5(5.9–9.1)
EBRT	23(26)	6.0(0.8–11.1)	14.3(4.6–24.0)
TMZ	5(6)	5.5(4.4–6.6)	18.0(11.6–24.4)
GKRS	9(10)	8.0(0.0–18.2)	33.5(17.4–50.0)
None	15(17)	4.0(1.4–6.6)	12.5(4.4–20.6)
Age at GKRS procedure		0.939	0.915
≥50 years	46(52)	5.0(3.5–6.5)	17.0(3.6–30.4)
<50 years	42(48)	4.5(2.1–7.0)	10.3(7.3–13.3)
Recurrence time interval		0.014	0.001
≥15 months	45(51)	6.0(0.9–11.1)	24.0(2.2–45.8)
<15 months	43(49)	4.5(3.0–6.0)	10.0(4.7–15.3)
Reoperation		0.005	0.003
Yes	23(26)	15.3(0.0–51.4)	39.0(0.0–97.1)
No	65(74)	4.5(3.7–5.3)	11.0(7.0–15.0)
KPS		0.046	0.013
≥80	38(43)	7.5(4.9–10.1)	28.0(7.3–48.7)
<80	50(57)	4.0(2.6–5.4)	9.0(6.5–11.5)
Number of targets		0.097	0.479
Single	51(58)	6.0(4.7–7.3)	12.5(3.3–21.7)
Multiple	37(42)	4.0(2.8–5.1)	10.3(4.4–16.2)

Total volume of target		0.728	0.611
≥18 cm^3	41(47)	5.0(3.7–6.3)	10.5(4.0–17.0)
<18 cm^3	47(53)	5.0(3.4–6.6)	13.2(3.2–23.2)
Maximum dose		0.042	0.145
≥25 Gy	46(52)	6.0(3.0–9.0)	18.0(7.6–28.4)
<25 Gy	42(48)	4.0(2.8–5.2)	10.0(6.0–14.3)
Marginal dose		0.040	0.079
≥13 Gy	48(55)	6.0(3.5–8.5)	21.0(11.7–30.3)
<13 Gy	40(45)	3.5(2.1–4.9)	9.0(6.2–11.8)
Multiple GKRS		0.036	0.022
Yes	29(33)	12.0(3.2–20.8)	22.0(9.4–34.6)
No	59(67)	4.0(2.9–5.6)	9.0(6.6–11.4)
TMZ used post-GKRS		0.754	0.603
Yes	28(32)	4.5(2.7–6.3)	11.0(2.9–19.1)
No	60(68)	5.0(3.5–6.5)	12.5(7.2–17.8)
bevacizumab used post-GKRS		0.674	0.880
Yes	9(10)	6.0(0.9–11.1)	17.0(5.7–28.3)
No	79(90)	5.0(3.7–6.3)	12.5(7.7–17.3)

Abbreviations: LGG (low-grade glioma), HGG (high-grade glioma), WHO (World Health Organization), EBRT (External beam radiotherapy), TMZ (Temozolomide), GKRS (gamma knife radiosurgery), KPS (Karnofsky performance status).

Survival and subgroup analysis

Survival analysis and prognostic factors by PFS and OS was shown in Table 2, Kaplan–Meier survival curves are shown in **Fig.5**. The median follow-up time was 79.5 months (95% CI: 60.6–98.4). By the end of the study, 65 patients died during the follow-up period. The median OS and PFS for all patients were 12.5 months (95% CI: 7.8–17.1) and 5.0 months (95% CI, 3.8–6.2), respectively. The median OS and the median PFS was 10.0 months (95% CI: 4.9–15.1) and 4.5 months (3.0–6.0) for HGG, respectively. The median OS and the median PFS was 27.0 months (95% CI: 0.0–56.0) and 12.0 months (95% CI: 3.9–20.1) for LGG, respectively.

On multivariate analysis, KPS≥80, pathological grade and multiple GKRS significantly affected OS (*P* =0.005, *P* =0.001, *P* =0.032, respectively) and PFS (*P* =0.038, *P* =0.012, *P* =0.021, respectively) (Table 3).

Stratified analysis showed that recurrence time interval (≥ 15 months) was an independent influencing factor of OS and PFS for LGG (*P* < 0.001, *P* =0.029) (Table 4). KPS≥80 and tumor volume (≥25 cm^3) were the influencing factors of OS for HGG (*P*=0.001, *P* =0.033). Tumor volume (≥25 cm3) was an independent influencing factor of PFS for HGG (*P* =0.037) (Table 5).

Table 3

Cox proportional-hazards multivariate models of PFS and OS in all patients

Parameters	OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
KPS	2.109(1.248–3.564)	0.005	1.700(1.030–2.803)	0.038
Pathological grade	0.363(0.201–0.655)	0.001	0.489(0.281–0.853)	0.012
GKRS times	1.757(1.049–2.925)	0.032	1.858(1.100–3.138)	0.021

Table 4

Cox proportional-hazards multivariate models of PFS and OS in LGG patients

Parameters	OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
KPS	0.977(0.388–2.461)	0.960	0.948(0.385–2.332)	0.907
GKRS times	0.964(0.374–2.486)	0.939	1.043(0.412–2.584)	0.982
Recurrence time(15 m)	0.081(0.020–0.327)	<0.001	0.320(0.116–0.889)	0.029

Table 5

Cox proportional-hazards multivariate models of PFS and OS of HGG patients

Parameters	OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
KPS	0.275(0.128–0.590)	0.001	1.647(0.899–3.019)	0.107
Tumor volume (25 cm^3)	1.990(1.058–3.743)	0.033	0.508(0.269–0.959)	0.037

Adverse reactions:

Seventy-four patients (84%) had no adverse reactions, 9 patients (10.2%) had mild headache (grade I–II), and 4 patients (4.5%) had mild dizziness, which were relieved after symptomatic treatment with mannitol and hormone. Nausea occurred in 3 patients (3.4%), and nausea accompanied with vomiting in 1 (1.1%), which was relieved after antiemetic and brain dehydration treatment. Two patients with fatigue and weakness were relieved after rest. One patient had mild lethargy, which was relieved after three days. No serious adverse reactions occurred. The specific adverse reactions are shown in Table 6.

Table 6

Adverse events after GKRS

Adverse reactions	Number of LGG patients (%)	Average duration	Number of HGG patients (%)	Average duration
none	28(87.5)	-	46(82.1)	-
Headache (grade Ⅰ)	2(6.3)	2d	4(7.1)	3d
Headache (grade Ⅱ)	1(3.1)	3d	2(3.6)	5d
Dizziness (grade Ⅱ)	1(3.1)	1d	3(5.4)	2d
Nausea and vomiting	1(3.1)	2d	2(3.6)	2d
Fatigue (grade Ⅱ)	0(0)	-	2(3.6)	3d
Somnolence (grade Ⅱ)	0(0)	-	1(1.8)	3d

Discussion

LGG are more suitable for reoperation because of their poor radiosensitivity. However, some patients are more suitable for GKRS because of the special location and small size of tumor recurrence. HGG is highly

invasive and tends to recur. The survival time of patients with recurrent glioblastoma is limited [16,17,18]. The risk of the adverse events of reoperation or radiotherapy may be increased, and they tend to accept GKRS. Larson Da [19] and other authors found that the factors influencing the survival time of all grades of glioma after radiotherapy were young age, high KPS index, small tumor size, and single lesion. However, young age and single lesion had no significant relationship with PFS and OS in our study, but the high KPS index were significantly improved PFS and OS in patients, especially KPS score greater than 80. During our follow-up, it was found that the main factors affecting KPS index were postoperative status, including whether there was neurological dysfunction, limb movement disorder, epilepsy, fatigue, etc. Further stratified analysis showed that KPS index were the influencing factors of OS in patients with HGG. KPS was an independent influencing factor of PFS in patients with HGG.

Stupp [20] and other authors found that the median survival time of HGG was only 14.6 months. The recurrence of glioma is usually local, and the recurrence site is usually within 2 cm of the primary lesion [21]. In 80% to 86% of patients with recurrent disease, recurrent lesions occurred within the irradiation volume and within 2 years of initial diagnosis [22]. The results of our study are similar to those of the above research. The present study showed that Recurrence time interval significantly affected OS and PFS. Further stratified analysis showed that a recurrence time interval longer than 15 months can significantly prolong the OS and PFS for patients with LGG patients. Brandon [23] and other authors have shown that for a recurrence time interval longer than 20 months in patients with recurrent HGG, OS would be prolonged if GKRS is chosen, especially for young patients with a small recurrence focus and long recurrence interval.

We also report target dose (maximum dose and marginal dose) had a significant association with PFS. Scoccianti s et al. [24] found that it was suitable to choose stereotactic radiosurgery (12–15 Gy/F) when the target volume is smaller than 12.5 mL for patients with recurrent gliomas, and the median OS was 7.5–16 months and the median PFS was 4.6–7.0 months. Several studies have shown that GKRS may be more suitable for patients with small, focal, or nodular recurrent gliomas [25,26,27,28]. One study found that for patients with target volume small than 14 cm^3, the OS after SRS was significantly better [28]. GKRS treatment for large lesions may increase the incidence of side-effects. Our study showed that the median target volume of all patients was 17.8 cm^3, and the multivariate analysis showed that it will prolong the PFS and OS if the total target volume is smaller than 25cm^3 in HGG patients. For patients with large single lesions, we would make the GKRS fractional irradiation, which not only increases the cumulative dose of tumor, but also reduces the dose to normal tissues, and reduces the incidence of side-effects. In the present study, univariate and multivariate analysis showed that repeated GKRS significantly prolonged the OS and PFS of the whole group of patients and improved the quality of life of patients. As a salvage treatment, GKRS was safe and effective.

Patients with recurrent gliomas have often already received radiotherapy. Before GKRS treatment, the optic chiasma, optic nerve, brainstem, and normal brain tissue may have reached the maximum tolerance. External beam radiotherapy is usually limited and dose is not too large for recurrent gliomas. The present study showed that the maximum dose and marginal dose of the target area are the

prognostic factors of PFS. Therefore, the PFS of these patients is directly affected by whether or not the target dose is enough. In the present study, 84% of patients with recurrent gliomas had no adverse reactions and grade □-□severe adverse reactions. Therefore, compared with conventional radiotherapy, gamma knife therapy for recurrent glioma can increase the target dose and minimizing the risk of side-effects.

Although stereotactic radiosurgery (SRS) is a feasible treatment, systemic therapy should not be ignored. Some studies have shown that patients with recurrent glioblastoma (GBM) receiving bevacizumab after gamma knife GKRS treatment have a median survival time of 18 months [29]. The one-year survival rate after SRS is 73%, and the grade 3 toxicity is lower (9%). Compared with the patients without bevacizumab, they have higher survival benefits (12 vs. 18 months). Gutin PH et al. found that adding bevacizumab also increased OS in a hypofractionated stereotactic regimen [30]. However, there were some studies reported that it rarely been significantly associated with improved OS in multivariable models [31]. We also did not find it had a significant correlation with the PFS and OS, and it may be due to the long follow-up period in this study, and the number of patients treated with bevacizumab was small. Next, we will collect more cases to prove the application of bevacizumab after GKRS may a valuable adjuvant treatment.

Limitations of the study

This is a single-center retrospective study with a relatively small number of patients and therefore subjected to biases (selection bias and treatment bias) and limitations. This study is limited due to its retrospective nature and limited population size. The reported radiation-related toxicities may be underreported due to difficulty of capturing these data in the retrospective setting.

Conclusion

GKRS as a salvage treatment for recurrent glioma is safe and effective., GKRS can significantly prolong the OS and PFS of patients, improve their quality of life, prolong the survival period for patients, especially for the patients with small recurrent lesions, short interval, high KPS and who received multiple GKRS treatments.

Abbreviations

GKRS: Gamma knife radiosurgery; HGG: Ligh-grade glioma; LGG: Low-grade glioma; Gy: Gray; OS: Overall survival; PFS: Progression free survival; CTCAE: Common terminology criteria for adverse events; KPS: Karnofsky performance status; TMZ: Temozolomide; PCV: Prednisone, carmustine, vincristine; CI: Confidence interval; MRI: Magnetic resonance imaging; ASTRO: American society for radiation oncology; SRS: Stereotactic radiosurgery; GBM: Glioblastoma.

Declarations

Ethics approval and consent to participate

This study passed the medical ethics review of Branch of Medical Ethics Committee of General Hospital of Northern Theater Command [NO. Y (2020) 089], and as it was a retrospective study, the requirement for informed consent was waived.

Consent for publication

The study contained no individual person's data and individual consent for this retrospective analysis was waived.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was funded by Major Science and Technology Project of Liaoning Province in 2019 (2019JH/10300007)

Authors' contributions

Ying Sun, Zhenning Tao, Haibo Zhang and Ying Yan all contributed to study concept, design, and/or acquisition of data. Ying Sun, Zhenning Tao completed the data collection and contributed to the data analysis. Ying Sun was responsible for drafting the manuscript. Ying Yan and Haibo Zhang contributed to revising and giving final approval to the manuscript. All authors agreed to be accountable for all aspects of the work including accuracy and integrity. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

Authors' information

Department of Radiation Oncology, General Hospital of Northern Theater Command, Shenyang, 110016, China.

References

1. Niyazi M, Siefert A, Schwarz SB, et al. Therapeutic options for recurrent malignant glioma. Radiother Oncol. 2011;98(1):1-14. https://doi.org/10.1016/j.radonc.2010.11.006
2. Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012;117(6):1032-1038. https://doi.org/10.3171/2012.9.JNS12504
3. Park CK, Kim JH, Nam DH, et al. A practical scoring system to determine whether to proceed with surgical resection in recurrent glioblastoma. Neuro Oncol. 2013;15(8):1096-1101. https://doi.org/10.1093/neuonc/not069
4. Abacioglu U, Caglar HB, Yumuk PF, Akgun Z, Atasoy BM, Sengoz M. Efficacy of protracted dose-dense temozolomide in patients with recurrent high-grade glioma. J Neurooncol. 2011;103(3):585-593. https://doi.org/10.1007/s11060-010-0423-2
5. Conti A, Pontoriero A, Arpa D, et al. Efficacy and toxicity of CyberKnife re- irradiation and “dose dense” temozolomide for recurrent gliomas. Acta Neurochir (Wien). 2012;154(2):203-209. https://doi.org/10.1007/s11060-010-0423-2
6. Omuro A, Chan TA, Abrey LE, et al. Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma. Neuro Oncol. 2013;15 (2):242-250. https://doi.org/10.1093/neuonc/nos295
7. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009 Feb 10;27(5):740-745. https://doi.org/10.1200/JCO.2008.16.3055
8. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733-4740. https://doi.org/10.1200/JCO.2008.19.8721
9. Combs SE, Debus J, Schulz-Ertner D. Radiotherapeutic alternatives for previously irradiated recurrent gliomas. BMC Cancer. 2007 Aug 30;7:167. https://doi.org/10.1186/1471-2407-7-167
10. Harsh GR, Levin VA, Gutin PH, Seager M, Silver P, Wilson CB. Reoperation for recurrent glioblastoma and anaplastic astrocytoma. Neurosurgery. 1987 Nov;21(5):615-621. https://doi.org/10.1227/00006123-198711000-00002
11. Brandes AA, Fiorentino MV. The role of chemotherapy in recurrent malignant gliomas: an overview. Cancer Invest. 1996;14(6):551-559. https://doi.org/10.3109/07357909609076900
12. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-Brain Tumor Treatment Group. Lancet. 1995 Apr 22;345(8956):1008-1012. https://doi.org/10.1016/s0140-6736(95)90755-6
13. Rajan B, Ross G, Lim CC, et al. Survival in patients with recurrent glioma as a measure of treatment efficacy: prognostic factors following nitrosourea chemotherapy. Eur J Cancer. 1994;30A(12):1809-1815. https://doi.org/10.1016/0959-8049(94)00248-4

14. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Macleod CM, ed. Evaluation of Chemotherapeutic Agents. New York, Columbia University Press, 1949, 199-205.
15. Alvin R Cabrera, John P Kirkpatrick, John B Fiveash, et al. Radiation therapy for glioblastoma: Executive summary of an American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. Pract Radiat Oncol, Jul-Aug 2016;6(4):217-225. https://doi.org/10.1016/j.prro.2016.03.007
16. Tithi Biswas1, Paul Okunieff, Michael C Schell, et al. Stereotactic radiosurgery for glioblastoma: retrospective analysis. Radiat Oncol 2009 Mar 17;4:11. https://doi.org/10.1186/1748-717X-4-11
17. Kathleen R Lamborn, W K Alfred Yung, Susan M Chang, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol Actions Search in PubMed Search in NLM Catalog Add to Search. 2008 Apr;10(2):162-170. https://doi.org/10.1215/15228517-2007-062
18. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Pra-dos MD, Levin VA, Yung WK (1999) Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clini-cal trials. J Clin Oncol Actions Search in PubMed Search in NLM Catalog Add to Search . 1999 Aug;17(8):2572-2578. https://doi.org/10.1200/JCO.1999.17.8.2572
19. Larson DA, Gutin PH, McDermott M, et al. (1996). Gamma knife for glioma: selection factors and survival. Int J Radiat Oncol Biol Phys. 1996 Dec 1;36(5):1045-1053. https://doi.org/10.1016/s0360-3016(96)00427-0
20. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987-996. https://doi.org/10.1056/NEJMoa043330
21. De Bonis P, Anile C, Pompucci A, et al. The influence of surgery on recurrence pattern of glioblastoma. Clin Neurol Neurosurg. 2013 Jan;115(1):37-43. https://doi.org/10.1016/j.clineuro.2012.04.005
22. Hess CF, Schaaf JC, Kortmann RD, Schabet M, Bamberg M. Malignant glioma: patterns of failure following individually tailored limited volume irradiation. Radiother Oncol Actions Search in PubMed Search in NLM Catalog Add to Search. 1994 Feb;30(2):146-149.https://doi.org/10.1016/0167-8140(94)90044-2
23. Brandon S Imber, Ishan Kanungo, Steve Braunstein, et al. Indications and Efficacy of Gamma Knife Stereotactic Radiosurgery for Recurrent Glioblastoma: 2 Decades of Institutional Experience. Neurosurgery,2017 Jan 1;80(1):129-139. https://doi.org/10.1227/NEU.0000000000001344
24. Scoccianti S, Francolini G, Carta GA, et al. Re-irradiation as salvage treatment in recurrent glioblastoma: A comprehensive literature review to provide practical answers to frequently asked questions. Crit Rev Oncol Hematol. 2018 Jun;126:80-91. https://doi.org/10.1016/j.critrevonc.2018.03.024
25. Mahajan A, McCutcheon IE, Suki D, et al. Case-control study of stereotactic radiosurgery for recurrent glioblastoma multiforme. J Neurosurg. 2005;103(2): 210-217.

https://doi.org/10.3171/jns.2005.103.2.0210
26. Kong DS, Lee JI, Park K, Kim JH, Lim DH, Nam DH. Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. Cancer. 2008 May 1;112(9):2046-2051. https://doi.org/10.1002/cncr.23402
27. Elliott RE, Parker EC, Rush SC, et al. Efficacy of Gamma Knife radiosurgery for small-volume recurrent malignant gliomas after initial radical resection. World Neurosurg. 2011;76(1-2):128-140; discussion 61-62. https://doi.org/10.1016/j.wneu.2010.12.053
28. Niranjan A, Kano H, Iyer A, Kondziolka D, Flickinger JC, Lunsford LD. Role of adjuvant or salvage radiosurgery in the management of unresected residual or progressive glioblastoma multiforme in the pre-bevacizumab era. J Neurosurg. 2015 Apr;122(4):757-765. https://doi.org/10.3171/2014.11.JNS13295
29. Park KJ, Kano H, Iyer A, Liu X, Niranjan A, Flickinger JC, et al. Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: A case-control study. J Neurooncol, 2012 Apr;107(2):323-333. https://doi.org/10.1007/s11060-011-0744-9
30. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2009 Sep 1;75(1):156-163. https://doi.org/10.1016/j.ijrobp.2008.10.043
31. Brandon S Imber, Ishan Kanungo, Steve Braunstein, Indications and Efficacy of Gamma Knife Stereotactic Radiosurgery for Recurrent Glioblastoma: 2 Decades of Institutional Experience. Neurosurgery Actions Search in PubMed Search in NLM Catalog Add to Search. 2017 Jan 1;80(1):129-139. https://doi.org/10.1227/NEU.0000000000001344

Figures

Figure 1

The target delineation(a) and the isodose covering of the target(b).

Figure 2

Distribution of marginal dose (a) and maximum dose (b) by treatment volume.

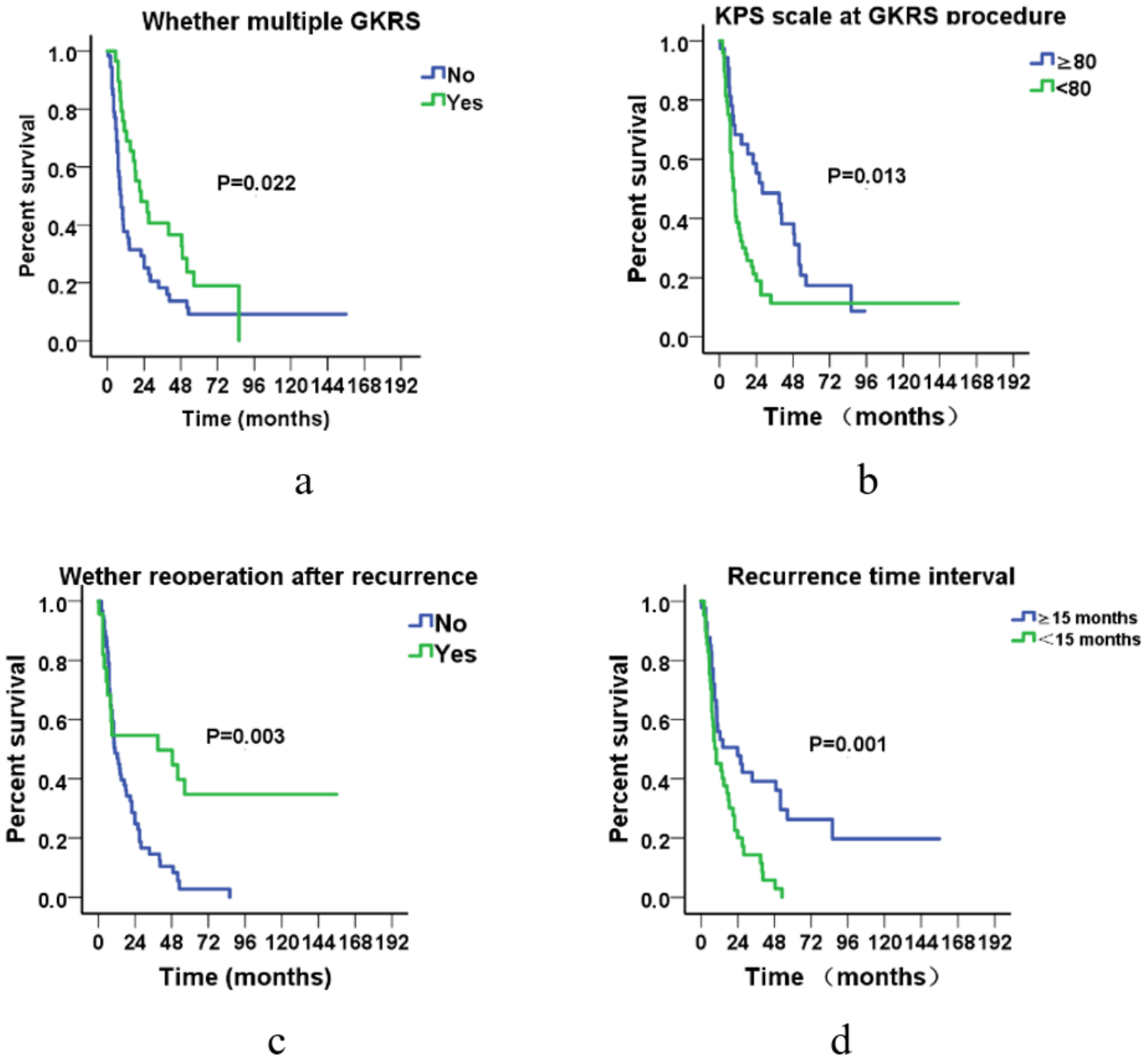

Figure 3

Kaplan-Meier OS after GKRS with various subgroups, including (a) KPS scale at GKRS procedure, (b) whether multiple GKRS, (c) whether reoperation after recurrence, and (d) Recurrence time interval.

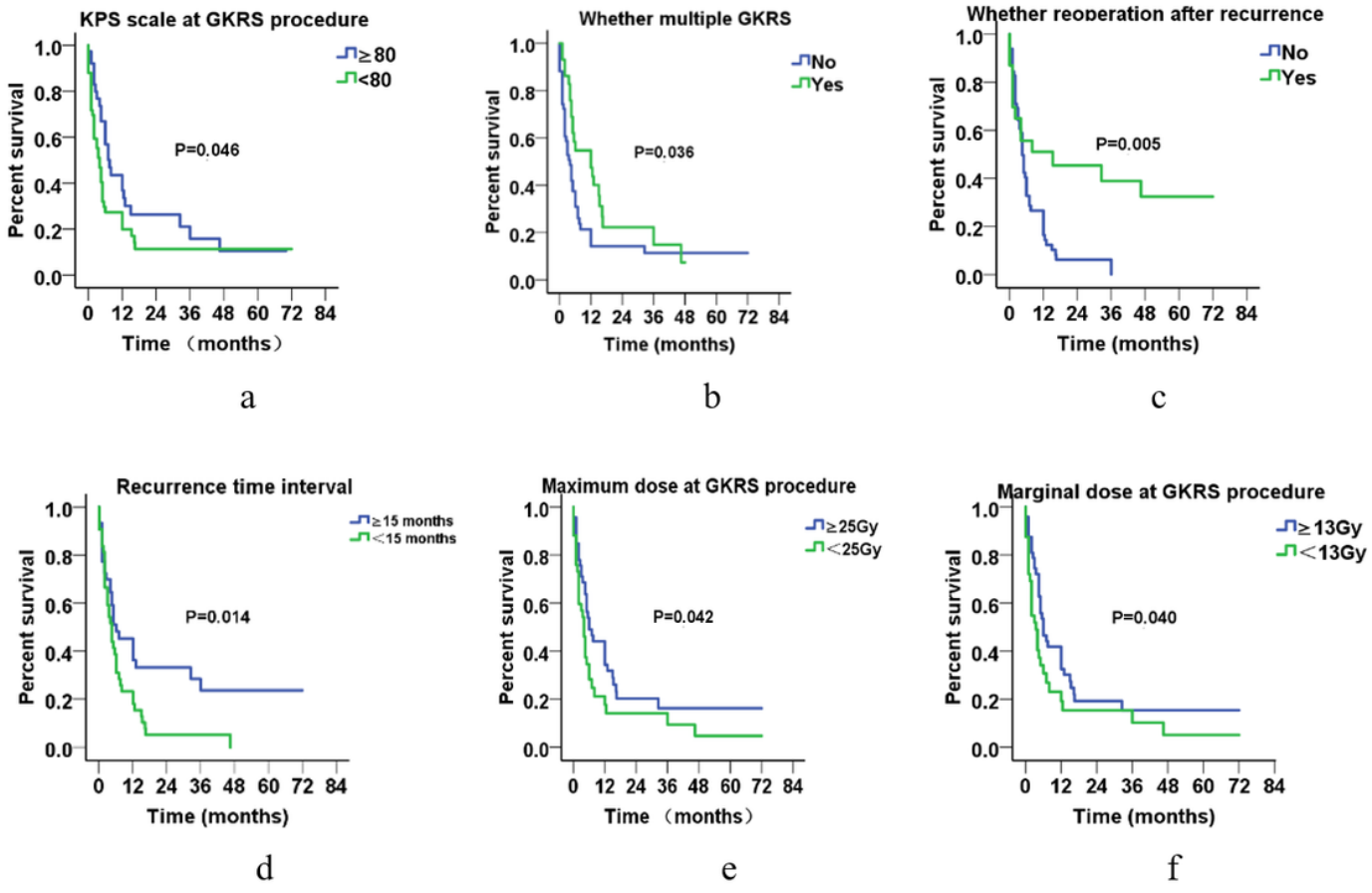

Figure 4

Kaplan-Meier PFS after GKRS with various subgroups, including (a) KPS scale at GKRS procedure, (b) whether multiple GKRS, (c) whether reoperation after recurrence, (d) Recurrence time interval，(e) Maximum dose at GKRS procedure，and (f) Marginal dose at GKRS procedure

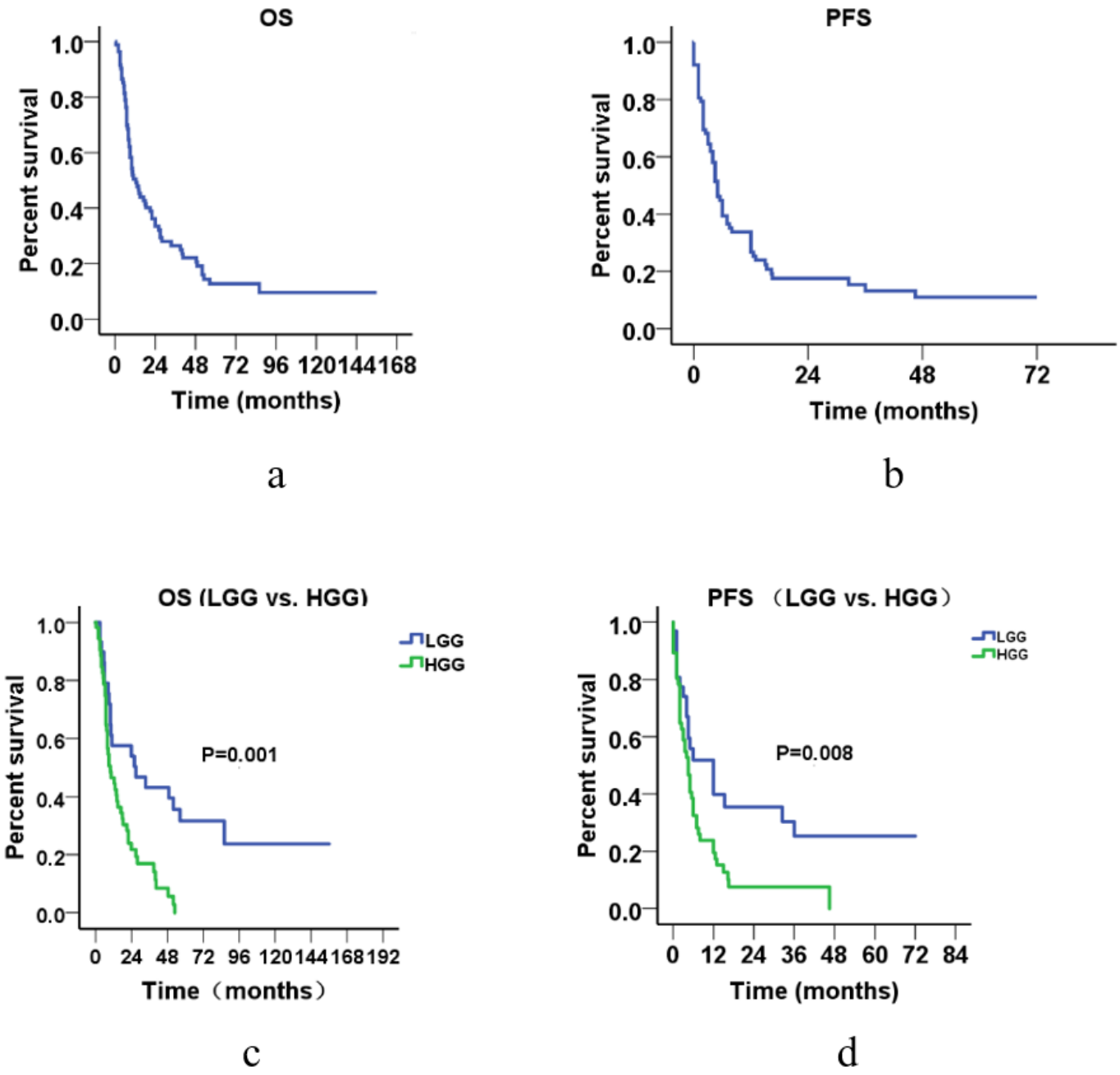

Figure 5

Kaplan-Meier survival after GKRS for (a) OS of all patients, (b) PFS of all patients, (c) Comparison of OS of LGG and HGG, (d) Comparison of PFS of LGG and HGG.