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Cyberknife re-irradiation for recurrent glioblastoma multiforme

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Abstract

Objective: Treatment of patients with recurrent glioblastoma multiforme (GBM) is challenging. Treatment alternatives include re-operation, chemotherapy and re-irridation. Stereotactic radiosurgery with cyberknife is a good therapeutic approach to deliver high-dose radiation to a definite target volume with minimizing re-irradiation to nearby healthy tissues. This study, evaluated the efficacy of cyberknife treatment in 24 patients with recurrent GBM.

Methods: Total 24 patients with recurrent GBM who received cyberknife treatment in any line of recurrence between the 2011, 2015 were included in this study. A median dose of 30 Gy was applied to each patient.

Results: Median survival was 10.3 months after cyberknife treatment and 23 months after diagnosis. Patients younger than 60 years (4.8 vs 14.2 month; p:0.05) and patients with primary total tumor excision (9.3 vs 4.9 month; p:0.05) had longer overall survival than other patients in univariate analysis but not in multivariate analysis. In this patient population, any other variables predicting longer overall survival could not be found. Treatment was well-tolerated and no severe toxicities observed.

Conclusion: Although limitations exist, our study demonstrates that SRS in terms of cyberknife for recurrent GBM is feasible and well tolerated by patients with low toxicity.

Key words: Sterotactic radiotherapy, glioma, cyberknife, recurrent, GBM

Introduction

Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor of adults with a median overall survival of around a year (1). Primary treatment modalities consist of maximal safe surgical resection and radiochemotherapy with temozolamide followed by temozolamide chemotherapy (2). Despite multimodality treatment, almost all patients experience recurrence and prognosis remains dismal for these patients (3).

The treatment of recurrent patients is challenging because of, high rates of morbidity and toxicity of treatment in this setting. Second surgery, can be performed in a subset of patients, but it may cause a high risk of neurologic sequele, because of the infiltrative behavior of the tumor (4). Bevacizumab plus irinotecan combination chemotherapy, demonstrated significant antitumor activity in recurrent GBM with a 6 month progression free survival, which resulted with its approval by the US Food and Drug Administration (5-7).

However, treatment options for recurrent patients remain limited and optimal treatment schedules should be established.

Another effective treatment option for recurrent GBM is re-irradiation, which can be achieved with stereotactic radiosurgery (SRS) in the form of cyberknife treatment. Stereotactic radiosurgery is a good therapeutic option to deliver high-dose radiation to a definite target volume with minimizing re-irradiation to nearby healthy tissues (8). The risk of radionecrosis is the primary limitation of this treatment.

This study evaluated the efficacy and tolerability of cyberknife treatment in patients with recurrent GBM. We aimed to define a group of patients who would most benefit from cyberknife treatment.

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Material and Methods

Patients

Patients with GBM who received cyberknife re-irridation as a part of recurrence treatment in any line included in to the study. A total of 24 GBM patients identified from 2011-2015 at our instution. Primary therapy of the included patients after diagnosis mostly consisted of total surgical excision, radiotherapy at a dose of 60 Gy with temozolamide and sequential adjuvant temozolamide chemotherapy. Patients were followed with clinical assessment and magnetic resonance imaging (MRI) scans with diffusion, perfusion and spectroscopic sequences which were performed 6–8 weeks after treatment and at 2-month intervals thereafter. No patient was lost from follow up.

Radiation treatment planning

Treatment planning was performed with Accuray system. The cyberknife include a linear accelerator attached on a robotic arm with six degrees of freedom. It delivers 6 MV photons. All patients undergoing irradiation were immobilized with custom-made thermal plastic masks.

Treatment planning MRI and computed tomography (CT) images were obtained at the same day and fused. All patients had thin cut (1–1.5 mm) axial T1, post-contrast T1 and T2/FLAIR MRI. The gross tumor volume (GTV) was determined on MRI using the gadolinium enhanced T1 weighted sequence. Surrounding edema was not contained in the treatment volume. GTV was the planning target volume the with minimum margin (0–2 mm per the treating physician). Critical normal structures, such as optic nerves, chiasm, and brainstem were also contoured.

Concomittant chemotherapy was not applied. All patients received 1 mg/kg prednisolone therapy during the week of treatment and then decreased doses over a month.

Statistical analysis

Overall survival (OS) after cyberknife treatment was described as the duration between initial cyberknife treatment and death or the last follow-up for surviving patients. Kaplan-Meier curves were used to evaluate the OS. Log-rank test was used for univariate analyses and cox regression hazard modelling was used for multivariate analyses. Age (≤ 51 years and >51 years), gender (female and male), cyberknife fraction (≤5 and >5), cyberknife dose (30 Gy≤ and >30 Gy), tumor size (≤35mm and >35mm), tumor side (left and right), tumor location (frontal and the others), primary surgical procedure (subtotal and total), gross tumor volume (≤10.9 cm3 and >10.9 cm3) were included in univariate analysis. Although tumor location, age and surgical procedure were suitable for multivariate analysis, gender was also included in multivariate analysis since it might have confounding effect. Distributions of continuous variables were controlled with Shapiro-Wilk (SW) test and Histogram. Descriptive statistics were presented as frequency (percentage) for categorical variables and as mean (± standard deviation) for normally distributed continuous variables or median (minimum – maximum) for not normally distributed continuous variables. Statistical analysis was performed with Statistical Package for Social Sciences for MacOS version 24.0 (SPSS Inc; Chicago, IL, USA). Type-1 error (α) was accepted as 0.05.

Results

Patient population and primary treatment parameters

A total of 24 patients who had disease relapse or progression and received cyberknife re-irridation in any line of recurrence treatment included in this study. Pathology was glioblastome multiforme for all patients. Patient characteristics are shown in Table 1. There were 15(62.5%) males and 9(32.5) females. The most common tumor localization was temporal lobe (45.8%). Median age of patients was 51. Primary surgical intervention was total excision for 13(54.2%) patients, subtotal excision for 9(37.5%) patients and biopsy for 2(8.4%) patients. All but three patients had chemoradiotherapy after first operation. Applied total dose of primary radiotherapy was 60 Gy per 2 fractions for all patients. Three patients received radiotherapy without temozolamide because of thrombocytopenia, liver toxicity and patient refuse, concurrently and after radiotherapy.

SRS treatment characteristics

Cyberknife re-irridation treatment was given to 20 patients (83.4%) as the first line treatment, 2(8.3%) patients for second line treatment and 2 (8.3%) patients for the third line treatment after recurrence is confirmed. Median GTV was 10.92 cm3 (2.70-60.84). Lesions were re-irridated with either a median dose of 18Gy in one fraction with a median GTV of 10.98 cm3 (five lesions), 18 Gy in three fractions with an median GTV of 8.03 cm3 (five lesions), and 30 Gy in five fractions with a median GTV of 16.72 cm3 (14 lesions). 3 patients had received cyberknife treatment after reoperation.

Survival

Two patients were alive at the time of survival analysis. All patients died as a result of disease progression. Median survival was 10.3 months after re-irridation with cyberknife and 23 months after diagnosis. Median overall survival from the diagnosis and median overall survival after cyberknife is represented in Figure 1 and Figure 2; respectively.

In univariate analysis; patients younger than 50 years had significantly longer overall survival compared with older patients (4.8 vs 14.2 month; p :0.05). Patients with total resection as primary treatment had also longer OS when compared with subtotal resection (9.3 vs 4.9 month; p :0.05).

There was no correlation between survival and fraction (<5 vs >5 fraction), total dose (<30 vs>30 Gy), tumor diameter (<35 vs >35 mm), tumor side (right or left) and primary operation (subtotal or total) type. Univariate analysis of prognostic factors was shown in Table 2.

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Multivariate analysis

Multivariate analysis was performed to investigate whether different variables influenced OS from cyberknife treatment in the study group. These included age at recurrence, localization of recurrence, and primary surgical procedure. None of these variables, demonstrated a statistically significant association with OS. Multivariate analysis of prognostic factors was shown in Table 3.

Toxicity

We did not observe any clinically significant acute toxicity and all patients were able to take the prescribed cyberknife radiation dose without interruption. No patient required hospitalization or surgery for early acute or delayed toxicity.

Table 1: Patient demographic characteristics

		N:24(%)
Gender	Female	9 (37.5)
	Male	15 (62.5)
Primary operation type	Total	13 (54.2)
	Subtotal	9 (37.5)
	Biopsy	2 (8.4)
First line treatment	Chemoradiotherapy	21 (87.5)
	Radiotherapy	3 (12.5)
Side	Left	12 (50)
	Right	12 (50)
Location of recurrence	Temporal	11 (45.8)
	Frontal	8 (33.4)
	Other	9 (20.8)
Age at cyberknife	<50	9 (37.5)
	>50	15 (62.5)
Recurrence treatment	Re-irridation	24 (100)
	Re-resection	3 (12.5)
	Bevacizumab	10 (41.6)
	Temozolamid	3 (12.5)
	Carmustine	1 (4.1)
Mean dose	18 Gy	10 (41.7)
	30 Gy	14 (58.3)
Dose per fraction	6	20 (83.3)
	18	4 (16.7)

Table 2: Univariate Analysis of Prognostic Factors for Survival After Cyberknife Re-irridation

Clinical characteristics	Mean survival	p value
Age ≤51 vs >51	4.8 vs 14.2	0.05
Gender (female vs male)	6.5 vs 10.7	0.51
Cyber fraction <5	9.3 vs 8.5	0.58
Cyber dose <30 or >30	9.3 vs 8.5	0.58
Tumor size <35mm or>35 mm	9.4 vs 8.4	0.90
Tumor side (right vs left)	11.5 vs 7.0	0.96
Frontal vs other location	16.8 vs 6.3	0.08
Total vs subtotal resection	9.3 vs 4.9	0.05
Gross tumor volume (≤10.9 cm3 and >10.9 cm3	8.5 vs 11.5	0.86

Table 3: Multivariate analysis of prognostic factors for survival after cyberknife re-irridation

Variable	Comparison	Hazard ratio	95% CI	p
Age	≤51 >51 years	0.859	0.272-2.719	0.797
Gender	Male Female	1.574	0.563-4.401	0.388
Localization	Others Frontal	1.836	0.551-6.116	0.322
Surgery	Total Subtotal	2.465	0.876-6.938	0.087

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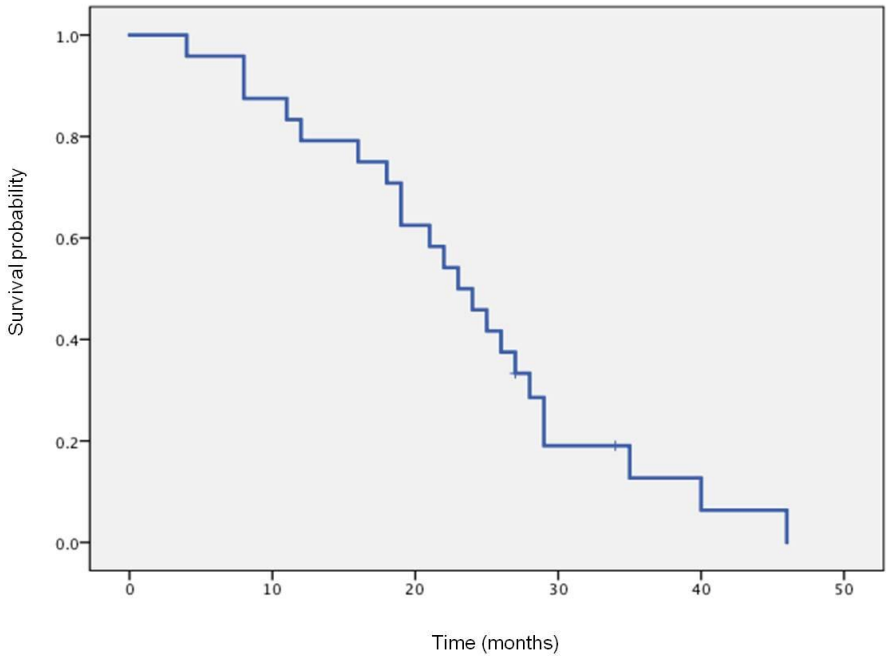

Figure 1: Kaplan–Meier overall survival curve showing OS from the time of initial diagnosis (time in month). A total of 20 patients were included in the survival analysis. Two patients were alive at the time of analysis. Median survival was 23 months from the initial diagnosis.

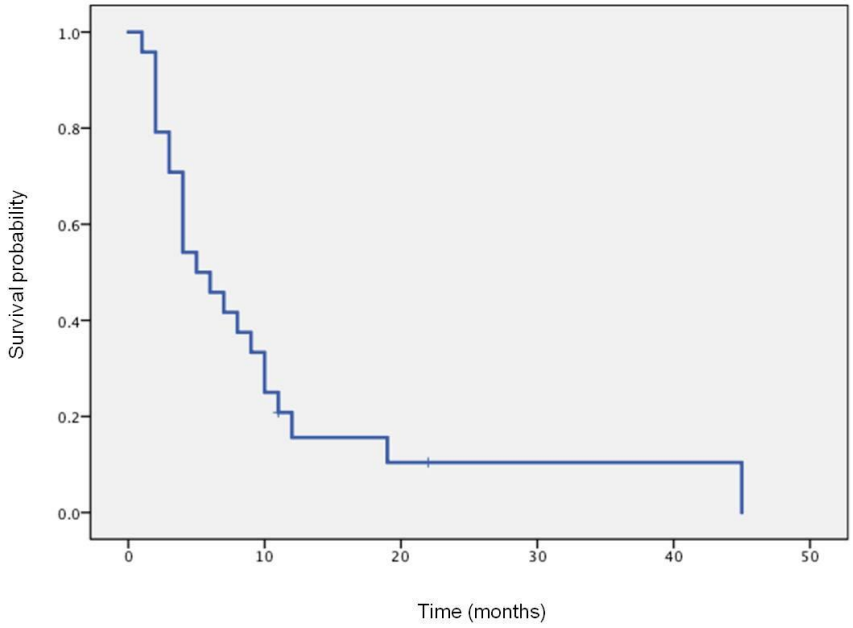

Figure 2: Kaplan–Meier overall survival curve showing OS from the initiation of cyberknife re-irridation (time in month). Median survival was 10.3 months after re-irridation with cyberknife

Discussion

Sterotactic radiosurgery (SRS), is a safe and effective treatment option for the patients with recurrent glioblastoma multiforme. It can be preffered in treating previously irradiated tumors, as it allows deliver the therapeutic dose to tumor area, while minimizing normal tissue toxicity (9). We evaluated sterotactic radiosurgery outcomes of recurrent GBM patients treated in our instution. We observed 10.3 months overall survival after cyberknife treatment. We could not find any prognostic factors for overall survival.

Median survival times of around 11 months for patients with high grade glioma who were treated with fractionated stereotactic radiotherapy has been reported in the literature (10-12). Sutera et al reported salvage SRS results for 55 high-grade glioma patients (13). Overall survival was 23.9 months and survival from SRS was 10.25 months, which is comparable to our results of 10.3 months.

However; overall survival was 23 months which is longer than many historical controls. We could not find any prognostic factors associated with overall survival after sterotactic radiotherapy. Sutera et al evaluated 55 high grade and 21 low grade patients treated with salvage SRS. They did not find any prognostic factors associated with inferior survival on univariate analysis for high grade glioma patients. Also, Combs et al could not find any statistical difference in survival in terms of gender, Karnofsky performance score, presence of neurological symptoms, age or type of primary surgical intervention or size of the lesion (<49 ml vs. >49 ml). Longer overall survival, for our patient cohort may be related with the selection criteria of patients for cyberknife. First, most of the patients received cyberknife treatment after recurrence as first line treatment, so overall survival after SRS might be relatively long; but overall survival in this group of patients was also longer. Second, cyberknife treatment is more effective in low volume tumors, so tumor volumes of the patient cohort are lower which have better prognosis. Third, most of the patients received bevacizumab therapy which was known to reduce radiotherapy related edema and radiation necrosis.

Glioblastoma multiforme recurrences, mostly develop within or in close proximity of the primary tumor site, which require tolerable and effective recurrence treatment (14). There are a number of radiotherapeutic approaches for recurrent gliomas. Conventional external-beam radiotherapy is often associated with only small benefit for the patients, with mostly unacceptable toxicity and total dose is limited by normal tissue tolerance (15). Cyberknife reduces this concern with minimal tissue exposure.

Our patients have not received any chemotherapy or immunotherapy during cyberknife treatment. The role of chemotherapy combined with SRS for recurrent glioma patients are unclear and prospective trials are needed. Stereotactic reirradiation in combination with temozolomide or bevacizumab reported to yield longer overall survival compared with radiation treatment alone (16). Minniti et al evaluated the efficacy of hypofractionated stereotactic radiotherapy (HSRT) combinationed with fotemustine or bevacizumab in patients with recurrent malignant glioma as salvage treatment. They reported longer overall survival after HSRT with bevacizumab than fotemustine combination (11 vs 8.3 months). The treatment was well tolerated (17).

In our study, patients younger than 50 years had longer overall survival than patients older than 50 years after SRS in univariate analysis, but not in multivariate analysis. Age is reported to be a prognostic factor in some studies however some studies did not find an association between young age and better prognosis. Fogh et al reported that younger age was associated with better overall survival (18) . Conversely, Veninga et al did not find overall survival difference between patients under 40 years and others (19).

This study has limitations, in terms of; the small sample size and retrospective nature of the cohort. Additionally treatment modalities before and after SRS are heterogenous as a result of physician choice and experience. Radiation toxicity was difficult to evaluate because of limited reporting and unclear documentation. Although limitations exist, our study demonstrates that salvage SRS for recurrent GBM is feasible and well tolerated by patients with observed low toxicity

In conclusion, this study demonstrated the efficacy and tolerability of salvage SRS for recurrent glioma and contributed new data to the growing body of research. A group of patient benefit from first line cyberknife treatment after recurrence. Prospective randomized trials are necesseray to identify these patients.

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Ethical issues: All Authors declare, Originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Yersal O. Clinical outcome of patients with glioblastoma multiforme: Single center experience. Journal of Oncological Sciences 2017; 3:123-126.

2. Stupp R, Mason WP, van den Bent MJ, et al. European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups, National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987

3. Shi W, Blomain ES, Siglin J, Palmer JJ, Dan T, Wang Y, Werner-Wasik M, Glass J, Kim L, Bar Ad V, Bhamidipati D, Evans JJ, Judy K, Farrell CJ, Andrews DW. Salvage fractionated stereotactic re-irradiation (FSRT) for patients with recurrent high grade gliomas progressed after bevacizumab treatment. J Neurooncol. 2017 Dec 12. (Epub ahead of print)

4. Salvage fractionated stereotactic re-irradiation (FSRT) for patients with recurrent high grade gliomas progressed after bevacizumab treatment.

5. Shawn L. Hervey-Jumper, Mitchel S. Berger; Reoperation for Recurrent High-Grade Glioma: A Current Perspective of the Literature, Neurosurgery, 2014,75: 491–499.

6. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE et al (2009) Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27:4733–4740

7. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA et al (2007) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25:4722–4729

8. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Dowell JM, Reardon DA, Quinn JA et al (2007) Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13:1253–1259

9. Lévy S, Chapet S, Scher N, Debbi K, Ruffier A, Bernadou G, Pointreau Y, Calais G. Reirradiation of gliomas under stereotactic conditions: Prognostic factors for survival without relapse or side effects, a retrospective study at Tours regional university hospital (France). Cancer Radiother. 2017 Dec;21(8) 759-765.

10. Dong Y, Fu C, Guan H et al. Re-irradiation alternatives for recurrent high-grade glioma. Oncology Lett. 12(4), 2261–2270 (2016).

11. Cho KH, Hall WA, Gerbi BJ, Higgins PD, McGuire WA, Clark HBC: Single dose versus fractionated stereotactic radiotherapy for recurrent high-grade gliomas. Int J Radiat Oncol Biol Phys 45(5): 1133–1141, 1999

12. Laing RW, Warrington AP, Graham J, Britton J, Hines F and Brada M. Efficacy and toxicity of fractionated stereotactic radiotherapy in the treatment of recurrent gliomas (phase I/II study). Radiotherapy Oncol 27: 22–29, 1993

13. Holt DE, Bernard ME, Quan K et al.Salvage sterotactic radiosurgery for recurrent glioblastoma multiforme with prior radiation therapy. J. Cancer Res. Ther. 12(4), 1243–1248 (2016).

14. Sutera PA, Bernard ME, Gill BS, Quan K, Engh JA, Burton SA, Heron DE. Salvage stereotactic radiosurgery for recurrent gliomas with prior radiation therapy.Future Oncol. 2017 Dec;13(29):2681-2690.

15. Sneed PK, Gutin PH, Larson DA, Malec MK, Phillips TL, Prados MD, Scharfen CO, Weaver KA, Wara WM: Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. Int J Radiat Oncol Biol Phys 29: 719– 727, 1994.

16. Nieder C, Andratschke NH, Grosu AL. Re-irradiation for recurrent primary brain tumors. Anticancer Res. 36(10), 4985–4995 (2016).

17. Hasan S, Chen E, Lanciano R, et al. Salvage Fractionated Stereotactic Radiotherapy with or without Chemotherapy and Immunotherapy for Recurrent Glioblastoma Multiforme: A Single Institution Experience. Frontiers in Oncology. 2015;5:106. doi:10.3389/fonc.2015.00106.

18. Minniti G, Agolli L, Falco T, Scaringi C, Lanzetta G, Caporello P et al (2015) Hypofractionated stereotactic radiotherapy in combination with bevacizumab or fotemustine for patients with progressive malignant gliomas. J Neurooncol 122:559–566

19. Fogh SE, Andrews DW, Glass J, et al. Hypofractionated Stereotactic Radiation Therapy: An Effective Therapy for Recurrent High-Grade Gliomas. Journal of Clinical Oncology. 2010;28(18):3048-3053. doi:10.1200/JCO.2009.25.6941.

20. Veninga T, Langendijk HA, Slotman BJ, Rutten EH, van der Kogel AJ, Prick MJ, Keyser A, van der Maazen RW. Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. Radiotherapy and Oncology , Volume 59 , Issue 2 , 127 – 137