RECURRENT GLIOBLASTOMA MANAGEMENT USING STEREOTACTIC RADIOSURGERY AND SYSTEMIC TREATMENT

Oleksandr Glavatskyi
MD, Professor
Department of Adjuvant Treatment of CNS Tumors[1]
oleksandr.glavatskyi@gmail.com

Oksana Zemskova
PhD
Department radioneurosurgery[1]
oxzemskova@gmail.com
[1]*State Institution "Institute of Neurosurgery named after acad. A. P. Romodanov of NAMS of Ukraine"*
32 Platona Mayborody str., Kyiv, Ukraine, 04050

Abstract: Glioblastoma multiforme (GBM) is the most common primary malignant tumor of the central nervous system in adults. Dismal survival rates and poor prognosis for recurrent GBM patients still remains a challenging problem. Despite aggressive initial treatment, above 100 % GBM patients have development of recurrent diseases. Management of GBM recurrence is still debatable. The multimodality approaches using combination of stereotactic radiosurgery (SRS), cytostatic agents (Temozolomide (TMZ)) and antiangiogenic therapy (bevacizumab (BEV)) are often beneficial for such patients and may achieve survival improving.

Aim of research: to assess the efficacy and toxicity of combination therapy approach using stereotactic radiosurgery (SRS) and systemic treatment (chemotherapy and antiangiogenic therapy) in glioblastoma multiforme recurrence treatment.

Materials and methods: at the State Institution "Institute of Neurosurgery named after acad. A.P. Romodanov of NAMS of Ukraine" (Kyiv, Ukraine) 21 patients (pts) with GBM recurrence were treated (8 females and 11 men; median age at time of diagnosis 52.4 (29.7–69.3) from January 2014 till December 2017. The initial surgical treatment as gross total tumor resection was performed in 12 pts (57.1 %), subtotal resection – 5 pts (23.9 %), biopsy – 4 pts (19 %). 12 pts (57.1 %) were MGMT methylated and 9 pts (42.9 %) were MGMT unmethylated. In all cases adjuvant radiation therapy (60 Gy in 30 fractions) were used, 12 pts of them (57.1 %) – in combination with TMZ followed by 6–12 courses of chemotherapy (TMZ) according Stupp protocol. Recurrent disease was treated by SRS followed by TMZ + BEV. SRS was performed by means of "Trilogy" LINAC ("Varian", USA) with a median dose and fractions of 19.2 Gy (range, 12.0–36.0) in 1 to 5 fractions.

Results: median survival after initial diagnosis was 18.3 months, and 1- and 2-year survival rates of 85.7 % (18 from 21 pts) and 38.1 % (8 from 21 pts) respectively. The median survival from the time of recurrence treatment was 8.3 months. The 6- and 12-months overall survival from SRS were 95.2 % (20 from 21 pts) and 23.8 % (5 from 21 pts), respectively. Adverse radiation effects were noted in 6 (28.6 %) pts and were controlled with corticosteroids. Adverse events grade 1-2 related to the systemic therapy included hematological complications, fatigue, hypertension and proteinuria were observed in 23.8 % (5 from 21 pts) without the occurrence of grade 3 events.

Conclusion: recurrent GBM management using combination of SRS, chemotherapy and antiangiogenic therapy is a promising multimodal treatment approach providing survival improving whereas appropriate toxicity ratio. Further studies of combined treatment of GBM relapse are needed.

Keywords: glioblastoma multiforme recurrence, multimodality approaches, radiosurgery, temozolomide, bevacizumab, toxicity.

1. Introduction

Glioblastoma multoforme (GBM) is the most frequent and aggressive primary malignant brain tumor in adults, with a median overall survival (OS) between 10 and 20 months [1]. The vast majority of patients with GBM experience recurrent disease, with a median time to recurrence of 7 months [2]. Surgery, temozolomide (TMZ), and fractionated radiotherapy are standards of care for newly diagnosed GBM [3]. However, the approach for GBM recurrence is considerably more heterogenous [4]. Options include repeated surgery, chemotherapy, bevacizumab (BEV), experimental agents, or re-irradiation. Numerous re-irradiation strategies exist, including conventional fractionated external beam radiotherapy (EBRT), fractionated stereotactic radiotherapy, hypo-fractionated stereotactic radiotherapy, high dose rate (HDR) brachytherapy, high dose rate (HDR) brachytherapy, low dose rate (LDR) brachytherapy, or stereotactic radiosurgery (SRS). Despite numerous options, median survival post-recurrence remains poor at 9–20 months [5]. The poor prognosis can be attributed to unique treatment limitations, which include the infiltrative nature of tumor cells, failure of anti-glioma drugs to cross the blood–brain barrier, tumor heterogeneity and the highly metastatic and angiogenic nature of the tumor making cells resistant to chemotherapy. Combination therapy approach is being developed against glioblastoma with new innovative combination drug regimens being tested in preclinical and clinical trials [6]. Despite the higher risk of distant brain lesions or subependymal spread, almost all patients develop tumor recurrence within or adjacent to the primary tumor bed [7]. Even though gliomas are infiltrative with ill-defined margins, SRS has been reported to be an effective treatment modality [8–11].

The aim of our study to assess the efficacy and toxicity of combination therapy approach using SRS and systemic treatment (chemotherapy (TMZ) and antiangiogenic therapy (BEV)) in recurrent GBM treatment.

2. Methods

We retrospectively reviewed 21 patients (pts) who were treated for GBM recurrence at the State Institution "Institute of Neurosurgery named after acad. A.P. Romodanov of NAMS of Ukraine" (Kiyv, Ukraine) from January 2014 till March 2018. This study was approved by local Ethics Committee. We included 8 females and 11 men with pathologically confirmed GBM who received comprehensive initial treatment and combination of SRS and systemic treatment for GBM recurrence. Median age at time of diagnosis was 52.4 (29.7–69.3) years. The initial surgical treatment as gross total tumor resection was performed in 12 pts (57.1 %), subtotal resection – 5 pts (23.8 %), biopsy – 4 pts (19 %). Tumor MGMT promoter methylation was seen in 12 pts (57.1 %). In all cases adjuvant radiation therapy (60 Gy in 30 fractions) was used, 12 pts of them (57.1 %) – in combination with concurrent TMZ followed by 6-12 courses of TMZ according R. Stupp protocol [3]. Patient's demographic and clinical data were collected in **Table 1**.

Recurrent disease was treated by combination of SRS followed by systemic treatment (chemotherapy (TMZ) + antiangiogenic therapy (BEV)). SRS was performed by means of "Trilogy" LINAC ("Varian", USA) with a median dose and fractions of 19.2 Gy (range, 12.0 –36.0) in 1 to 5 fractions. Four pts (19 %) received 12 Gy in single fraction, 5 pts (23.8 %) received 14 Gy in single fraction, 5 pts (23.8 %) received 24 Gy in 3 fractions, 7 pts (33.3 %) received 25 Gy in 5 fractions, treating 5 days/week. SRS was given combining IMRT and MLC Dynamic Arc dose delivery techniques. This approach provides maximal homogeneous dose distribution in target volume whereas minimal radiation exposure of normal tissue and organs at risk (chiasma, brainstem, ect.). Further combined dose delivery technique allows to reduce time of treatment procedures to 10-15 minutes per fraction. Due to the infiltrative characteristics of GBM we added safety margin

(5–10 mm) around the contrast-enhancing target. The median Planning Target Volume (PTV) was 13.5 cm^3 (range: 3.9–40.7 cm^3). Seventeen (81 %) targets were located at the edge of the previous tumor resection cavity or at the area of previous biopsy.

Systemic treatment was applied after SRS (intravenous BEV 10–12 mg/kg once in 3 weeks up to 6 times; TMZ 150–200 mg/m^2 PO for 5 days, then 23-treatment free days until progression).

Table 1
Patient's characteristic: demographic and clinical data.

Number of patients	N=21
Male	11/52 %
Female	8/38 %
Age at time of diagnosis (years):	
Median	52.4
Range	29.7–69.3
Initial surgical treatment:	
Gross total tumor resection	12/57.1 %
Subtotal resection	5/23.8 %
Biopsy	4/19 %
Histopathologic diagnosis Glioblastoma multiforme	21/100 %
MGMT Promoter Methylation Status:	
MGMT unmethylated	9/42.9 %
MGMT methylated	12/57.1 %
Adjuvant radiation therapy	21/100 %
Adjuvant chemotherapy	12/57.1 %

3. Results

Retrospective analysis of outcomes revealed median survival after initial diagnosis of 18.3 months, and 1- and 2-year survival rates of 85.7 % (18 from 21 pts) and 38.1 % (8 from 21 pts) respectively.

The median survival from the time of recurrence was 8.3 months.

The 6- and 12-months overall survival from SRS were 95.2 % (20 from 21 pts) and 23.8 % (5 from 21 pts), respectively.

Adverse radiation effects were noted in 6 (28.6 %) pts and were controlled with corticosteroids.

Adverse events grade 1–2 related to the systemic therapy included hematological complications, fatigue, hypertension and proteinuria were observed in 23.8 % (5 from 21 pts) without the occurrence of grade 3 events.

Survival and adverse events are represented in **Table 2.**

Table 2
Survival and adverse events

Parameter	Score
Median survival after initial diagnosis	18.3 months
1-year survival	85.7 % (18 from 21 pts)
2-year survival	38.1 % (8 from 21 pts)
Median survival from the time of recurrence	8.3 months
6-months overall survival from SRS	95.2 % (20 from 21 pts)
12-months overall survival from SRS	23.8 % (5 from 21 pts)
Adverse radiation effects	28.6 % (6 from 21 pts)
Adverse events grade 1–2 related to the systemic therapy	23.8 % (5 from 21 pts)

6. Discussion

GBM is an aggressive fatal disease with dismal median overall survival of 10 to 20 months. Even despite multimodality therapy and favorable pathologic features the vast majority of patients will recur in 6–8 months [10, 12]. Recurrence leads to progressive neurocognitive impairment and death in 3 to 9 months regardless re-operation [13, 14]. Current options for recurrence therapy are as follows: surgery, systemic therapy and re-irradiation. Combination therapy is an option for recurrence GBM recently being tested by some investigators [15, 16]. Our experience is consistent with latter and shows increase in survival rates with appropriate toxicity compared to other approaches as described in the current literature. We report a median survival from the time of recurrence 8.3 months and the 6- and 12-months overall survival from recurrence 95.2 % (20 from 21 pts) and 23.8 % (5 from 21 pts), respectively. The weak points of our study are an absence of direct comparison with the control group, low number of patients included and lack of tumor molecular data.

Recurrent GBM management using combination of SRS, chemotherapy and antiangiogenic therapy is a promising multimodal treatment approach providing survival improving whereas appropriate toxicity ratio. Further studies of combined treatment of GBM relapse are needed.

References

1. Touat, M., Idbaih, A., Sanson, M., Ligon, K. L. (2017). Glioblastoma targeted therapy: updated approaches from recent biological insights. Annals of Oncology, 28 (7), 1457–1472. doi: https://doi.org/10.1093/annonc/mdx106
2. Wen, P. Y., DeAngelis, L. M. (2007). Chemotherapy for low-grade gliomas: Emerging consensus on its benefits. Neurology, 68 (21), 1762–1763. doi: https://doi.org/10.1212/01.wnl.0000266866.13748.a9
3. Stupp, R., Mason, W. P., van den Bent, M. J., Weller, M., Fisher, B., Taphoorn, M. J. B. et. al. (2005). Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine, 352 (10), 987–996. doi: https://doi.org/10.1056/nejmoa043330
4. Niyazi, M., Siefert, A., Schwarz, S. B., Ganswindt, U., Kreth, F.-W., Tonn, J.-C., Belka, C. (2011). Therapeutic options for recurrent malignant glioma. Radiotherapy and Oncology, 98 (1), 1–14. doi: https://doi.org/10.1016/j.radonc.2010.11.006
5. Imber, B. S., Kanungo, I., Braunstein, S., Barani, I. J., Fogh, S. E., Nakamura, J. L. et. al. (2016). Indications and Efficacy of Gamma Knife Stereotactic Radiosurgery for Recurrent Glioblastoma: 2 Decades of Institutional Experience. Neurosurgery, 80 (1), 129–139. doi: https://doi.org/10.1227/neu.0000000000001344
6. Ghosh, D., Nandi, S., Bhattacharjee, S. (2018). Combination therapy to checkmate Glioblastoma: clinical challenges and advances. Clinical and Translational Medicine, 7 (1). doi: https://doi.org/10.1186/s40169-018-0211-8

7. Kong, D.-S., Lee, J.-I., Park, K., Kim, J. H., Lim, D.-H., Nam, D.-H. (2008). Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. Cancer, 112 (9), 2046–2051. doi: https://doi.org/10.1002/cncr.23402
8. Bokstein, F., Blumenthal, D. T., Corn, B. W., Gez, E., Matceyevsky, D., Shtraus, N. et. al. (2015). Stereotactic radiosurgery (SRS) in high-grade glioma: judicious selection of small target volumes improves results. Journal of Neuro-Oncology, 126 (3), 551–557. doi: https://doi.org/10.1007/s11060-015-1997-5
9. Cheon, Y.-J., Jung, T.-Y., Jung, S., Kim, I.-Y., Moon, K.-S., Lim, S.-H. (2018). Efficacy of Gamma Knife Radiosurgery for Recurrent High-Grade Gliomas with Limited Tumor Volume. Journal of Korean Neurosurgical Society, 61 (4), 516–524. doi: https://doi.org/10.3340/jkns.2017.0259
10. Dodoo, E., Huffmann, B., Peredo, I., Grinaker, H., Sinclair, G., Machinis, T. et. al. (2014). Increased Survival Using Delayed Gamma Knife Radiosurgery for Recurrent High-Grade Glioma: A Feasibility Study. World Neurosurgery, 82 (5), e623–e632. doi: https://doi.org/10.1016/j.wneu.2014.06.011
11. Sheehan, J. P., Lee, C.-C. (2014). Stereotactic Radiosurgery for Recurrent High-Grade Gliomas. World Neurosurgery, 82 (5), e593–e595. doi: https://doi.org/10.1016/j.wneu.2014.06.042
12. Barker, F. G., Chang, S. M., Gutin, P. H., Malec, M. K., McDermott, M. W., Prados, M. D., Wilson, C. B. (1998). Survival and Functional Status after Resection of Recurrent Glioblastoma Multiforme. Neurosurgery, 42 (4), 709–719. doi: https://doi.org/10.1097/00006123-199804000-00013
13. Dirks, P., Bernstein, M., Muller, P. J., Tucker, W. S. (1993). The value of reoperation for recurrent glioblastoma. Canadian Journal of Surgery, 36 (3), 271–275.
14. Young, B., Oldfield, E. H., Markesbery, W. R., Haack, D., Tibbs, P. A., McCombs, P. et. al. (1981). Reoperation for glioblastoma. Journal of Neurosurgery, 55 (6), 917–921. doi: https://doi.org/10.3171/jns.1981.55.6.0917
15. Heron, D., Holt, D., Bernard, M., Quan, K., Clump, D., Engh, J., Burton, S. (2016). Salvage stereotactic radiosurgery for recurrent glioblastoma multiforme with prior radiation therapy. Journal of Cancer Research and Therapeutics, 12 (4), 1243. doi: https://doi.org/10.4103/0973-1482.199537
16. Park, K.-J., Kano, H., Iyer, A., Liu, X., Niranjan, A., Flickinger, J. C. et. al. (2011). Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: a case–control study. Journal of Neuro-Oncology, 107 (2), 323–333. doi: https://doi.org/10.1007/s11060-011-0744-9