Original article

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Stages of stereotactic radiosurgery in the treatment of recurrent glioblastomas

Andriy B. Gryazov, Oksana V. Zemskova, Andriy A. Gryazov

Department of Radioneurosurgery, Romodanov Neurosurgery Institute, Kyiv, Ukraine

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Address for correspondence*:*
Andriy B. Gryazov, Department of Radioneurosurgery, Romodanov Neurosurgery Institute, 32 Platona Maiborody st., Kyiv, 04050, Ukraine, e-mail: grandoc61@gmail.com

Objective: to evaluate the effectiveness of stereotactic radiosurgery as a therapy method taking into account overall survival in patients with recurrent glioblastoma at all stages of treatment.

Materials and methods. A sample of patients (66 ailments) who were treated in 2016-2021 with a molecularly confirmed diagnosis of wild-type glioblastoma was analyzed. Only patients, who, were treated in several stages and as a rule, underwent stereotaxic radiosurgery (SRS), or SRS alone after a biopsy, or SRS in case of relapse, after surgery and radiotherapy, or SRS for subsequent relapses were selected. When evaluating the results, the following were taken into account: 1) age at the diagnosis, 2) volume of surgical resection, 3) use of radiation therapy, 4) use of adjuvant chemotherapy after SRS and response evluation criteria in solid tumors. Overall survival (OS) was assessed after diagnosis and at the time of SRS.

Results. Patients received SRS at an average 10 months after initial diagnosis. Median duration of follow-up was 8 months after SRS and 12 months after diagnosis, median OS for all patients was nine months (1 to 42 months) after SRS and 20 months (4 to 64 months) respectively. The median survival after SRS was 9 months ($p=0.008$; $\chi^2=7.008$). The median OS for younger patients (<50 years) was 32.5 months, for elderly patients (>50 years) was 14.8 months ($p=0.04$; $\chi^2=3.870$). The median overall survival rate was 32.2 months in patients who received SRS 10 months after the diagnosis was made, and 16 months in those who received SRS earlier than 10 months ($p=0.004$, $\chi^2=8.145$). Radiosurgical doses ≥15 Gy were correlated with a mean survival rate of nine months and seven months in patients treated at doses <15 Gy ($p=0.01$; $\chi^2=6.756$). In patients who received adjuvant therapy with bevacizumab and/or chemotherapy after SRS, the median OS was 12 months, in patients who did not receive additional therapy after SRS, it was 7 months ($p=0.04$, $\chi^2=4.19$).

Conclusions. Stereotactic radiosurgery promotes the effectiveness of glioblastoma treatment due to the possibility of carrying out this method at various stages of treatment. The overall survival of our patients depended on the period of SRS after diagnosis, patient age, radiation dose, and adjuvant chemotherapy.

Keywords: *recurrent glioblastoma; stereotactic radiosurgery; radiation therapy; neurosurgery; chemotherapy*

Introduction

Glioblastoma (GBM) is the most common and dangerous primary malignant neoplasm of the central nervous system [1]. Due to its aggressive and infiltrative nature and complexity of the pathophysiology, GBM is one of the most difficult tumors to treat [2]. This tumor almost always recurs, with a progression-free survival (PFS) usually of <9 months and a survival of 12 to 16 months regardless of combined treatment strategies (aggressive surgical resection, chemotherapy, and radiotherapy). Only few patients survive 2.5 years and less than 5% – survive 5 years following diagnosis [4,5].

Methods of treatment for tumor recurrence include surgery, radiosurgery, targeted and immunotherapy. Recurrence is associated with almost universal mortality. Median survival after recurrence ranges from 9 to 20 months [6–8], depending on the treatment strategy.

Due to the lack of standard guidelines for the treatment of recurrent glioblastoma, there are different approaches to therapy. Bevacizumab (BEV), a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), and temozolomide introduced into standard therapy, although did not increase overall survival (OS), but did improve PFS [7,9]. Resection of recurrent GBM is an alternative, but surgery alone is

insufficient for control due to the infiltrative nature of the disease. In addition, GBM often spreads to other areas of the patient's brain, exacerbating the initial neurological or physiological status, limiting surgical approach [10], but potential cumulative toxicity and risk of radiation necrosis limit the regular use of radiation therapy [11].

Stereotactic radiosurgery (SRS) has been studied for more than 20 years as a treatment method for recurrent GBM. Only one prospective, randomized trial has been published that examined the effect of SRS, given in addition to conventional remote radiotherapy, on survival in patients with newly diagnosed GBM. The authors found no benefit for patients when SRS was administered as a booster therapy compared to standard radiation and carmustine (BCNU) [12]. The evidence regarding SRS in tumor recurrence does not provide a reason to make SRS a standard practice [6,13–16]. Stereotactic radiosurgery appears to be an attractive alternative due to minimal invasiveness in case of focal recurrences. In addition, submillimetre precision of SRS and steep dose gradient are considered to be useful in case of recurrence, since high dose radiation has previously been used and some non-invasive alternatives (tumor treatment fields (TTF)) are not widely available.

Objective: to evaluate the effectiveness of stereotactic radiosurgery as a therapy method taking into account overall survival in patients with recurrent glioblastoma at all stages of treatment.

Materials and methods

Study participants

The results of treatment of patients who received SRS for GBM in the period from 2016 to 2021 at the Institute of Neurosurgery named after Acad. A.P. Romodanov, Ukraine were analyzed.

Informed and voluntary written consent to participate in the study was obtained from all patients.

The study was approved by by the Committee on Ethics and Bioethics of the Institute of Neurosurgery named after Acad. A. P. Romodanov, Ukraine (Minutes №2 dated 15.04. 2019).

Inclusion criteria:

1. Verified diagnosis of GBM.
2. Method of treatment - SRS.

Characteristics of the group

Stereotactic radiosurgery of GBM was performed in 66 patients aged 30 to 86 years (mean age - 60 years). Among the patients, men predominated (40). The tumor size was from 1.8 to 6.4 cm, the volume - from 6 to 30 cm^3 (average volume - 12 cm^3) ***(Table 1).***

Study design

Tumors were irradiated in 5 directions according to the Dyn Arc technique and in 8–12 directions according to the IMRT technique, depending on the beamlets parameters. The most commonly used technique was Dyn Arc+ IMRT.

In the case of single-fraction SRS, the average dose was 15 Gy, in the case of hypofractionated SRS, the total radiation dose was from 40 to 60 Gy (median - 30 Gy), administered in 3-5 fractions depending on the size of the tumor. Dose per fraction was from 4 to 8 Gy. The maximum number of fractions depended on the size and localization of the tumor.

Table 1. Characteristics of the patient group (n=66)

Indicator Value	Value
Male	40 (60,6%)
Female	26 (39,3%)
Age, years:	
minimum	30
maximum	80
Extent of surgery:	
Total resection	26 (42,4%)
Limited resection	30 (45,4%)
biopsy	8 (12,1%)
Radiation therapy after surgery	66 (100%)
Temozolomide	26 (39,3%)
Temozolomide + BEV	10 (15,1%)
Time between diagnosis, recurrence and SRS, months*	10 (1–64)
BED dose for one fraction when multiple fractions were delivered using α/β 10, Gy*	15 (10–40)
Tumor volume, sm^{3*}	12 (6–30)

Notes: BED – biological effective dose; BEV - bevacizumab. * – Arithmetic mean, minimum and maximum values are given.

This article contains some figures that are displayed in color online but in black and white in the print edition

The tumor was contoured by combining magnetic resonance images, which were transmitted to the planning station and superimposed on computer tomography scans of the patient in a thermoplastic mask. Macroscopic tumor volume was determined at the Brain LAB planning station. Irradiation volume was calculated from the gross tumor volume (GTV) + 5 mm of intact surrounding tissue. The planning target volume (PTV) was limited by the 90% isodose curve.

Statistical analysis

Median OS was estimated using Kaplan-Meier survival analysis. The patient's age, gender, radiosurgical dose, tumor volume, and the use of adjuvant chemotherapy were taken into account. The results of comparisons were considered statistically significant when the value of margin of error probability (p) was <0.05.

Results and discussion

Patients received SRS at an average in 10 months (from 1 to 64 months) after diagnosis. The median follow-up was 8 months after SRS and 12 months after diagnosis.

Single lesions were treated in 50 (75.7%) patients, the rest had multiple lesions. Due to tumor recurrence, 10 (15.1%) patients received a second SRS session. Only 4 (6.0%) patients underwent SRS.

The average period between the first and second treatment was 5 months (from 1 to 40 months). The median prescribed dose was 15 Gy (10 to 40 Gy).

Median OS for all patients was 9 months (1 to 42 months, p=0.008, χ^2=7.008) after SRS and 20 months (4 to 64 months) after diagnosis. Median OS for younger patients (<50 years) was 32.5 months, for elderly ones (≥50 years) was 14.8 months (p=0.04, χ^2=3.870) ***(Fig. 1).***

Median OS was 32.2 months in patients who received SRS 10 months after diagnosis, those who received SRS earlier than 10 months had a median OS of 16 months (p=0.004, χ^2=8.145) **(Fig. 2).**

Radiosurgical doses >15 Gy were correlated with mean survival of 9 months, doses <15 Gy were correlated with mean survival of 7 months (p=0.01, χ^2=6.756) **(Fig. 3)**.

Patients who received adjuvant bevacizumab (BEV) and/or chemotherapy after SRS had a median survival of 12 months compared to 7 months in patients who did not receive any additional therapy after SRS (p=0.04, χ^2=4 ,19) **(Fig. 4)**.

It was established that the tumor volume did not affect the median OS (p=0.494, p=0.08 and p=0.622, respectively).

The prognosis for GBM, despite multimodal treatment methods (surgery, radiation therapy, and

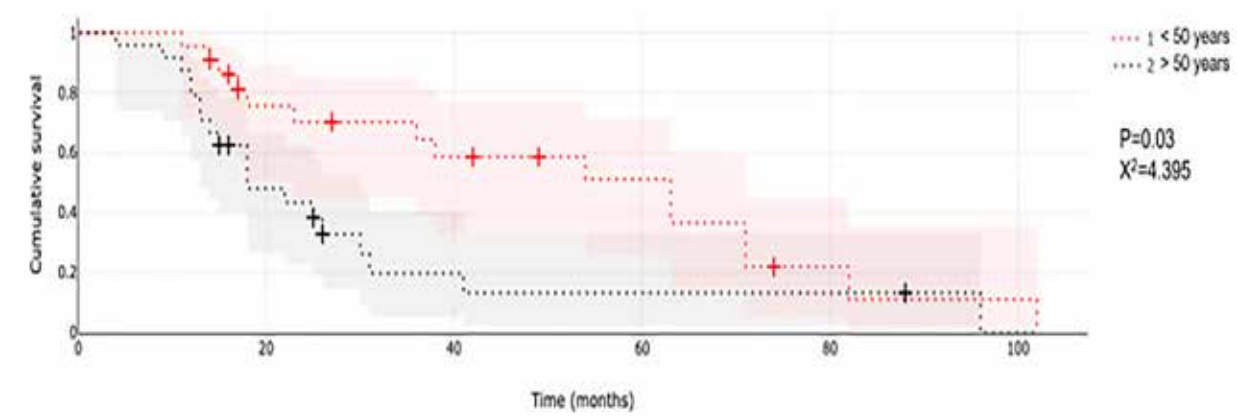

Fig. 1. Comparison of mean survival in age groups

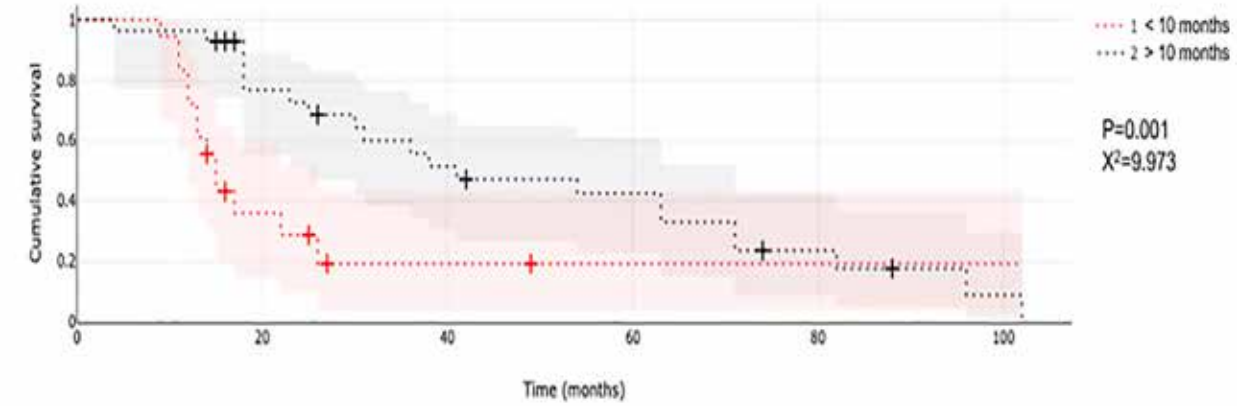

Fig. 2. Comparison of overall survival of patients who received stereotactic radiosurgery within 10 months after diagnosis or later

chemotherapy), remains unfavorable. The disease is characterized by aggressive local invasion. Recurrences in most cases occur proximal to the original focus of the tumor. Therefore, approaches such as surgery, SRS alone ***(Figures 5 and 6)***, or SRS with additional treatment options have been explored. Various survival rates were obtained. Independent predictors of survival in patients with GBM who received SRS were evaluated to determine their effect on median OS, in particular dose, duration of SRS after diagnosis and age.

Median OS was longer in patients treated earlier, although the difference was not statistically significant (35.3 and 29.5 months, p=0.415). The OS of patients who received SRS with concomitant chemotherapy and those who received SRS alone was compared ***(Figures 7 and 8).***

Some studies that have evaluated outcomes of patients receiving BEV in combination with SRS and compared them with patients receiving SRS alone, it was found that the first group had higher PFS and OS (median PFS was 5.2 and 2.1 months, median OS was 11.2 and 2.1 months) [16,17]. In the case of adjuvant therapy with bevacizumab during re-irradiation for recurrent GBM in 25 patients, median PFS was 7.3 months, median OS was 12.4 months [17]. A dose-escalation study of single-fraction radiosurgery for GBM recurrence in the course of BEV therapy demonstrated that BEV treatment 10–14 days before SRS was associated with a decrease in mean lesion volume from 4.7 to 2.86 cm^3 (p=0.103). The median PFS and OS were 7.5 and 12 months, respectively [2].

In our study, the median OS was 12 months in patients who received mainly adjuvant SRS therapy with BEV and less often temozolomide, and 7 months in those who did not receive any adjuvant therapy (p=0.04).

Bevacizumab as an anti-VEGF has been shown to reduce interstitial fluid pressure and tumor vascular normalization network. It also reduces edema and prevents radionecrosis after SRS [18–21]. The combination of SRS with BEV has a double effect on endothelial cells: SRS is cytotoxic for vascular cells, high irradiation doses cause microvascular endothelial apoptosis, and BEV increases endothelial cells sensitivity to high irradiation doses [22]. In addition, high doses of SRS have an ablative effect on vascular endothelial cells, which exceeds that of radiation therapy [23].

The time between surgery and SRS/recurrence was considered to be an independent factor associated with OS. A strong relationship between the time between surgery and SRS and OS after SRS was established. Patients with a longer interval (>20.2 months) had better survival (median OS – 15.1 months, p=0.001)

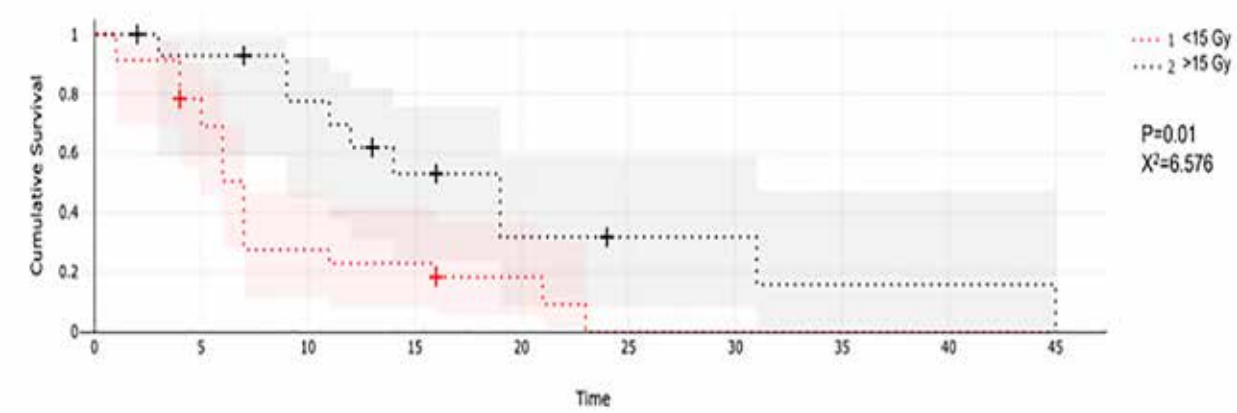

Fig. 3. Comparison of overall survival of patients after single radiosurgery

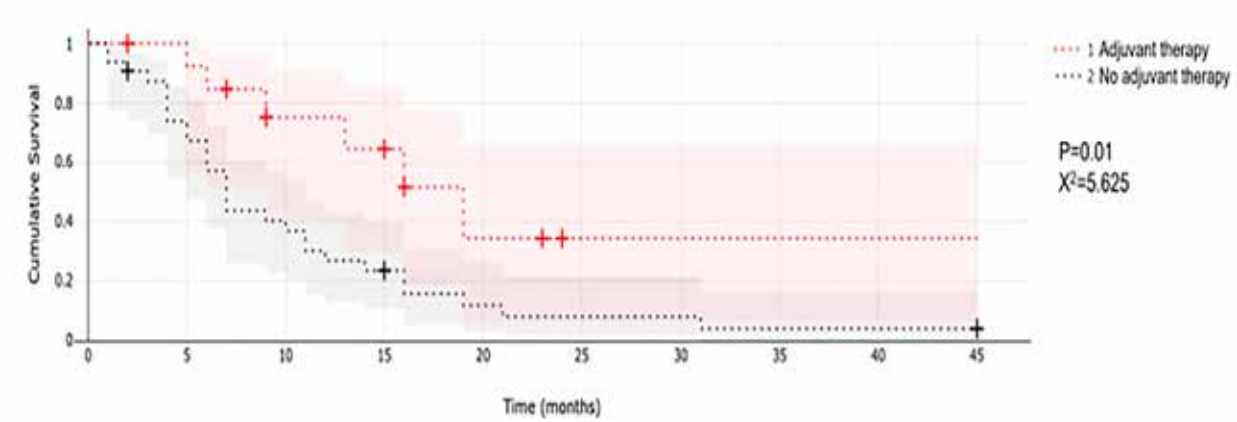

Fig. 4. Comparison of median survival after stereotactic radiosurgery in patients who received and did not receive adjuvant therapy

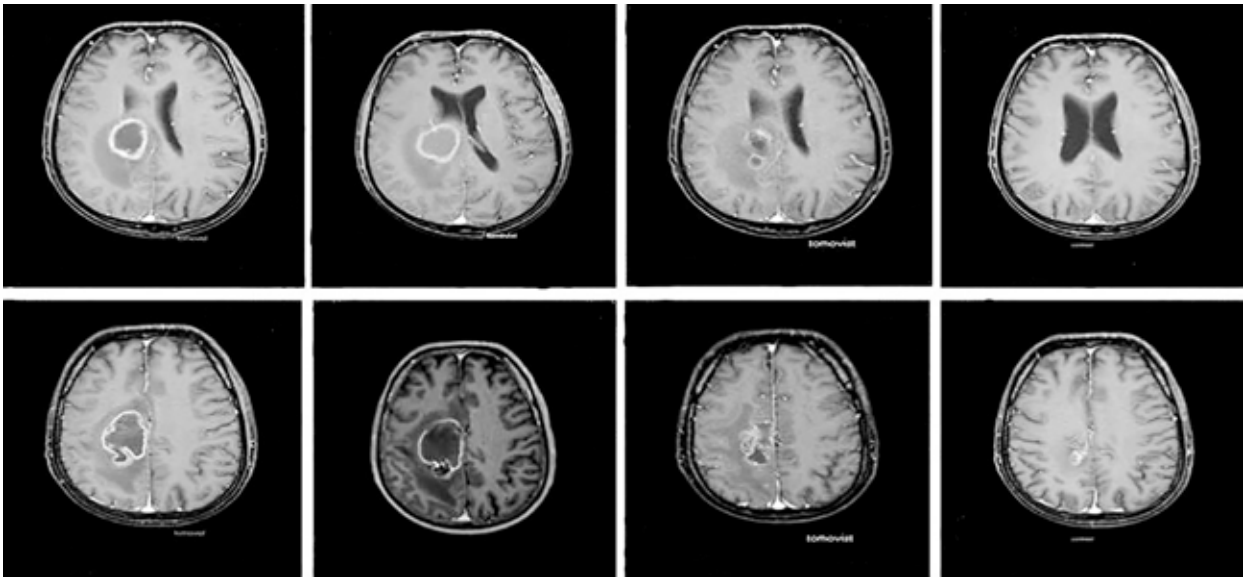

Fig. 5. A 55-year-old patient. According to biopsy data, glioblastoma was detected. Single fraction SRS was performed. Magnetic resonance therapy before SRS (A) and after SRS: after 1 week (B), 3 weeks (C) and 4 weeks (D). Radiomodification with Trikasaid (metronidazole). Subsequently, 10 sessions of chemotherapy (temozolamide) were performed. Complete response to treatment. Tumor growth control was achieved. Relapse-free period is 37 months

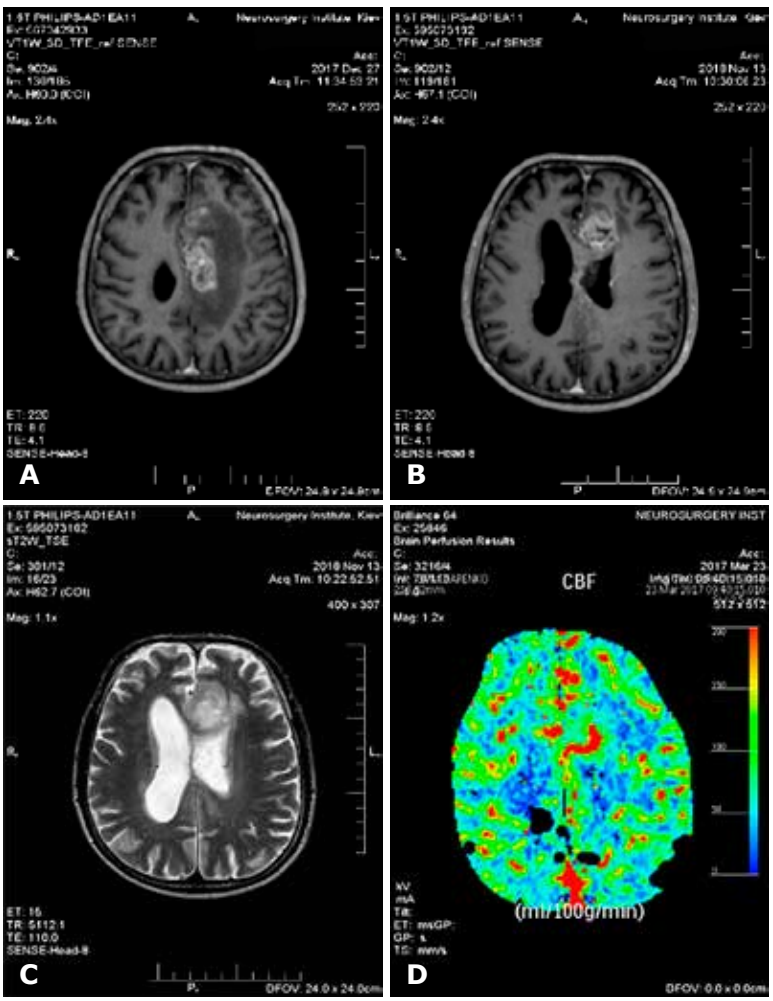

Fig. 6. The same patient. Magnetic resonance therapy: A and B – T1-weighted images; C – T2-weighted images; D - computed tomography, perfusion. Three years after radiosurgery and chemotherapy with temozolamide, a large size multifocal glioblastoma growth is observed on the opposite side. Hypofractionated repeat SRS was performed

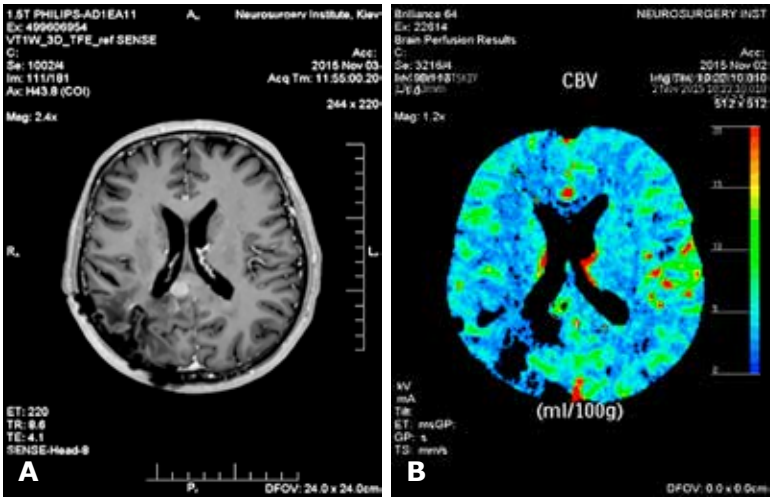

Fig. 7. The patient is 51 years old. Condition after glioblastoma removal and SRS. Local recurrence after 18 months: A – magnetic resonance therapy, T1-weighted image with contrast; B - computed tomography, perfusion (image of blood flow volume). The focus of glioblastoma recurrence. Single fraction SRS with concomitant chemotherapy was performed (on the site of recurrence with a volume of 2.2 cm3 – 18 Gy)

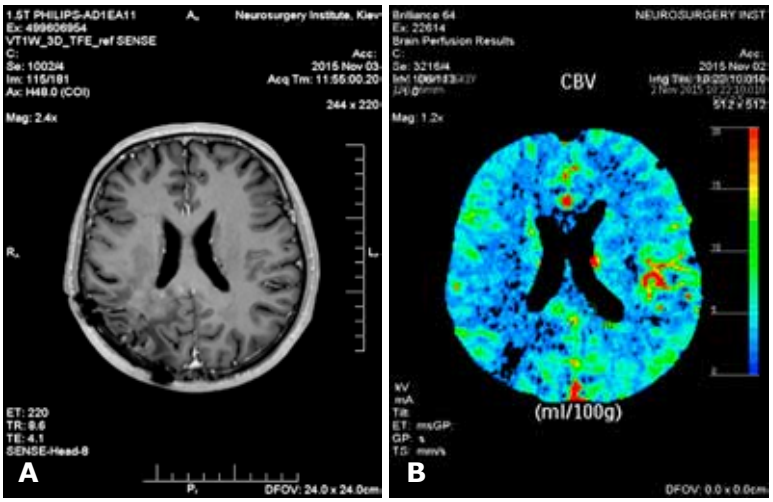

Fig. 8. The same patient. The condition 6 months after SRS of glioblastoma recurrence: A – magnetic resonance therapy. The focus is not visualized in a T1-weighted image with contrast; B - computed tomography. Blood flow volume and blood flow velocity are low (hypoperfusion). The recurrence-free period is 11 months

compared to those who underwent SRS 15–20 months after surgery (median OS – 8.3 months) [6]. In this series, it was also found that a longer period (>10 months) between the diagnosis and SRS was correlated with a longer OS ***(Fig. 9)***.

Median survival was 36.2 months in patients who received SRS 10 months after diagnosis, and 15.0 months in those who received SRS within 10 months after diagnosis (p=0.004). The length of time between diagnosis and SRS did not affect the median OS after SRS (p=0.364). Other authors report that the length of time from initial diagnosis to SRS was not correlated with OS to SRS [16]. We agree with B.S. Imber et al. [6] that in patients with a longer period to recurrence, tumor progression occurs more slowly, and consequently, the course of the disease is somewhat slower. In contrast, patients treated for recurrence earlier than 10 months may have a more aggressive tumor and tumor recurrence with rapid growth. No differences in demographic characteristics, type of microsurgical resection, or method of radiation therapy explain the following results.

Glioblastoma is more commonly diagnosed between the ages of 55 and 85. In the United States, the average age of onset is 64 years. Age of patients with GBM and comorbidities may predict survival and the likelihood that patients will receive and endure aggressive treatment. Some authors report age as an important prognostic variable. Thus, younger patients (<60 years old) at the time of diagnosis had a higher survival rate [24].

In other studies, it was reported that in patients younger than 50 years by the time of radiosurgery, the OS after SRS improved [6,16]. Median OS for younger patients (<50 years) was 37.1 months, for elderly patients (≥50 years) was 18.6 months (p=0.04).

Although the age of patients did not significantly affect the median survival after SRS, the 6-month difference in this indicator in our study is a good result, given prognosis of the disease. Our data are consistent with literature data [25–29].

Despite survival rates after diagnosis or SRS, most authors have found that younger age correlates with improved survival. Younger patients may tolerate procedures better and presumably have a better prognosis.

The patient's general condition may be a better predictor of tolerability and survival than age at diagnosis [9], which can also be considered in younger populations. In our patients, there was no significant relationship with the Karnofsky index in the case of SRS (p=0.165).

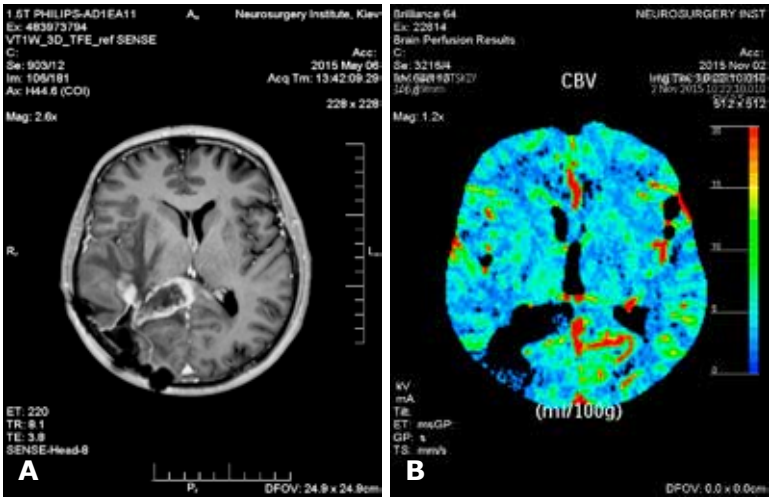

Fig. 9. Magnetic resonance therapy 7 months after a course of hypofractionated SRS (5 fractions of 8 Gy) for tumor recurrence 10.5 months after SRS (A, is shown by arrows). Multispiral computed tomography: hypoperfusion (B). Chemotherapy: temozolamide + avastin. The patient's condition is satisfactory. Overall survival is 26 months

The dose and number of radiation fractions and prescribing concomitant therapy are chosen taking into account the molecular status of the tumor, the patient's general condition, tumor volume, preliminary radiation doses.

Example

Diagnosis: Intracerebral tumor of the left occipital region (glioblastoma) IDH-wildtype, MGMT. Condition after surgical removal of the tumor and radiotherapy. Local recurrence. Pathohistological and immunohistochemical conclusion № 13SP114926: glioblastoma WHO Gr IV, ICD-O 9440/3), IDH-wildtype.

Initiation of irradiation. Concomitant chemotherapy: temozolomide N20 140 mg per os. Irradiation target is the recurrence zone and perifocal tissue in the occipital area on the left PTV=Tumor + 5 mm. Irradiation method IMRT + Dyn Arc MLC. The number of irradiation fractions – 5. Irradiation target volume – V PTV=42.710 cm3, V Tumor=29.002 cm^3, single dose – 8 Gy, total dose for 99.5% of irradiation target volume – 40.0 Gy, maximum dose – 34.47 Gy $BED_{(11)}$ =38 Gy. Ionizing radiation dose to critical brain structures is within tolerance limits.

A meta-analysis showed that an average of 16 Gy was the most commonly administered dose [10]. Other authors also report that the use of marginal radiation dose >15 Gy is an important prognostic factor for patient survival [13]. In another report, the same authors found that the median OS for patients who received marginal doses of 15 Gy was 12 months, and for those who received <15 Gy, it was 8.2 months [24]. In patients who received doses >15 Gy, the median survival was 9 months, in individuals who received doses <15 Gy (p=0.01), it was 7 months, which is consistent with the literature.

Tumor volume in our series did not affect the median OS after SRS (p=0.494, p=0.08, and p=0.622, respectively). Other authors showed that the treatment volume was not strongly correlated with survival or disease progression [6,16]. Several studies have shown that tumor volume is an important prognostic factor, and a number of thresholds have been proposed as a surrogate for survival prognosis, suggesting that small tumors are more suitable for SRS [13,15,29]. A study involving 297 patients found that smaller tumors (<14 cm^3) were associated with better OS [13].

Conclusions

Stereotactic radiosurgery is a method of glioblastoma management that can be used at different stages of therapy and is particularly effective in the treatment of recurrent glioblastoma, when the stages of surgery and radiation therapy have been completed and only radiosurgery and adjuvant chemotherapy methods remain.

Overall survival in our observations depended on the period of stereotactic radiosurgery, patient age, radiation dose, and concomitant adjuvant chemotherapy. The results obtained are consistent with the literature data.

Additional multicenter studies should be conducted to provide definitive recommendations for stereotaxic radiosurgery.

Information disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The written informed consent was obtained from each patient.

Funding

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References

1. Shah JL, Li G, Shaffer JL, Azoulay MI, Gibbs IC, Nagpal S, Soltys SG. Stereotactic Radiosurgery and Hypofractionated Radiotherapy for Glioblastoma. Neurosurgery. 2018 Jan 1;82(1):24-34. doi: 10.1093/neuros/nyx115
2. Abbassy M, Missios S, Barnett GH, Brewer C, Peereboom DM, Ahluwalia M, Neyman G, Chao ST, Suh JH, Vogelbaum MA. Phase I Trial of Radiosurgery Dose Escalation Plus Bevacizumab in Patients With Recurrent/Progressive Glioblastoma. Neurosurgery. 2018 Sep 1;83(3):385-392. doi: 10.1093/neuros/nyx369

3. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987-96. doi: 10.1056/NEJMoa043330
4. Tamimi AF, Juweid M. Epidemiology and Outcome of Glioblastoma. In: De Vleeschouwer S, editor. Glioblastoma [Internet]. Brisbane (AU): Codon Publications; 2017 Sep 27. Chapter 8. doi: 10.15586/codon.glioblastoma.2017.ch8
5. Bunevicius A, Sheehan JP. Radiosurgery for Glioblastoma. Neurosurg Clin N Am. 2021 Jan;32(1):117-128. doi: 10.1016/j.nec.2020.08.007
6. Imber BS, Kanungo I, Braunstein S, Barani IJ, Fogh SE, Nakamura JL, Berger MS, Chang EF, Molinaro AM, Cabrera JR, McDermott MW, Sneed PK, Aghi MK. Indications and Efficacy of Gamma Knife Stereotactic Radiosurgery for Recurrent Glioblastoma: 2 Decades of Institutional Experience. Neurosurgery. 2017 Jan 1;80(1):129-139. doi: 10.1227/NEU.0000000000001344
7. Fernandes C, Costa A, Osório L, Lago RC, Linhares P, Carvalho B, Caeiro C. Current Standards of Care in Glioblastoma Therapy. In: De Vleeschouwer S, editor. Glioblastoma [Internet]. Brisbane (AU): Codon Publications; 2017 Sep 27. Chapter 11. doi: 10.15586/codon.glioblastoma.2017.ch11
8. Regev O, Merkin V, Blumenthal DT, Melamed I, Kaisman-Elbaz T. Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis. Neurooncol Pract. 2021 Apr 20;8(4):426-440. doi: 10.1093/nop/npab026
9. Braun K, Ahluwalia MS. Treatment of Glioblastoma in Older Adults. Curr Oncol Rep. 2017 Oct 26;19(12):81. doi: 10.1007/s11912-017-0644-z
10. Fetcko K, Lukas RV, Watson GA, Zhang L, Dey M. Survival and complications of stereotactic radiosurgery: A systematic review of stereotactic radiosurgery for newly diagnosed and recurrent high-grade gliomas. Medicine (Baltimore). 2017 Oct;96(43):e8293. doi: 10.1097/MD.0000000000008293
11. Guan Y, Xiong J, Pan M, Shi W, Li J, Zhu H, Gong X, Li C, Mei G, Liu X, Pan L, Dai J, Wang Y, Wang E, Wang X. Safety and efficacy of Hypofractionated stereotactic radiosurgery for high-grade Gliomas at first recurrence: a single-center experience. BMC Cancer. 2021 Feb 5;21(1):123. doi: 10.1186/s12885-021-07856-y
12. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, Schultz CJ, Sause W, Okunieff P, Buckner J, Zamorano L, Mehta MP, Curran WJ Jr. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys. 2004 Nov 1;60(3):853-60. doi: 10.1016/j.ijrobp.2004.04.011
13. Niranjan A, Monaco EA III, Kano H, Flickinger JC, Lunsford LD. Stereotactic Radiosurgery in the Multimodality Management of Residual or Recurrent Glioblastoma Multiforme. Prog Neurol Surg. 2018;31:48-61. doi: 10.1159/000466998
14. Guseynova K, Liscak R, Simonova G, Novotny J Jr. Gamma knife radiosurgery for local recurrence of glioblastoma. Neuro Endocrinol Lett. 2018 Oct;39(4):281-287.
15. 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):2046-51. doi: 10.1002/cncr.23402
16. Cuneo KC, Vredenburgh JJ, Sampson JH, Reardon DA, Desjardins A, Peters KB, Friedman HS, Willett CG, Kirkpatrick JP. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):2018-24. doi: 10.1016/j.ijrobp.2010.12.074
17. Gutin PH, Iwamoto FM, Beal K, Mohile NA, Karimi S, Hou BL, Lymberis S, Yamada Y, Chang J, Abrey LE. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2009 Sep 1;75(1):156-63. doi: 10.1016/j.ijrobp.2008.10.043
18. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000 Sep 14;407(6801):249-57. doi: 10.1038/35025220
19. Winkler F, Kozin SV, Tong RT, Chae SS, Booth MF, Garkavtsev I, Xu L, Hicklin DJ, Fukumura D, di Tomaso E, Munn LL, Jain RK. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. Cancer Cell. 2004 Dec;6(6):553-63. doi: 10.1016/j.ccr.2004.10.011
20. Gonzalez J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacizumab on radiation necrosis of the brain. Int J Radiat Oncol Biol Phys. 2007 Feb 1;67(2):323-6. doi: 10.1016/j.ijrobp.2006.10.010
21. Gerstner ER, Duda DG, di Tomaso E, Ryg PA, Loeffler JS, Sorensen AG, Ivy P, Jain RK, Batchelor TT. VEGF inhibitors in the treatment of cerebral edema in patients with brain cancer. Nat Rev Clin Oncol. 2009 Apr;6(4):229-36. doi: 10.1038/nrclinonc.2009.14
22. Cabrera AR, Cuneo KC, Vredenburgh JJ, Sampson JH, Kirkpatrick JP. Stereotactic radiosurgery and bevacizumab for recurrent glioblastoma multiforme. J Natl Compr Canc Netw. 2012 Jun 1;10(6):695-9. doi: 10.6004/jnccn.2012.0072
23. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol. 2008 Oct;18(4):240-3. doi: 10.1016/j.semradonc.2008.04.005
24. 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):757-65. doi: 10.3171/2014.11.JNS13295
25. Skeie BS, Enger PØ, Brøgger J, Ganz JC, Thorsen F, Heggdal JI, Pedersen PH. γ knife surgery versus reoperation for recurrent glioblastoma multiforme. World Neurosurg. 2012 Dec;78(6):658-69. doi: 10.1016/j.wneu.2012.03.024
26. Koga T, Maruyama K, Tanaka M, Ino Y, Saito N, Nakagawa K, Shibahara J, Todo T. Extended field stereotactic radiosurgery for recurrent glioblastoma. Cancer. 2012 Sep 1;118(17):4193-200. doi: 10.1002/cncr.27372
27. Cabrera AR, Cuneo KC, Desjardins A, Sampson JH, McSherry F, Herndon JE 2nd, Peters KB, Allen K, Hoang JK, Chang Z, Craciunescu O, Vredenburgh JJ, Friedman HS, Kirkpatrick JP. Concurrent stereotactic radiosurgery and bevacizumab in recurrent malignant gliomas: a prospective trial. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):873-9. doi: 10.1016/j.ijrobp.2013.04.029
28. Martínez-Carrillo M, Tovar-Martín I, Zurita-Herrera M, Del Moral-Ávila R, Guerrero-Tejada R, Saura-Rojas E, Osorio-Ceballos JL, Arrebola-Moreno JP, Expósito-Hernández J. Salvage radiosurgery for selected patients with recurrent malignant gliomas. Biomed Res Int. 2014;2014:657953. doi: 10.1155/2014/657953
29. Elliott RE, Parker EC, Rush SC, Kalhorn SP, Moshel YA, Narayana A, Donahue B, Golfinos JG. Efficacy of gamma knife radiosurgery for small-volume recurrent malignant gliomas after initial radical resection. World Neurosurg. 2011 Jul-Aug;76(1-2):128-40; discussion 61-2. doi: 10.1016/j.wneu.2010.12.053