Ukrainian Scientific Medical Youth Journal
Issue 1 (128), 2022
ISSN 1996-353X
ISSN 2311-6951

UDC: 616.831-006.04-085.849.11-036.8
https://doi.org/10.32345/USMYJ.1(128).2022.57-73

Received: December 25, 2021
Accepted: February 18, 2022

Survival after stereotactic radiosurgery of recurrent glioblastomas in patients with radical resection of primary tumor

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Abstract: *glioblastoma (GBM) is an aggressive tumor with high rate of recurrence and estimated survival of 15-18 months after diagnosis. Factors associated with longer survival of GBM patients are age < 50 years, high performance status and radical resection of the primary tumor. The optimal treatment for recurrence/ progression of GBM has not yet been determined and remains a challenging issue. Stereotactic radiosurgery (SRS) is considered today as a therapeutic option for effective treatment of recurrent malignant gliomas. The aim of this retrospective study was to analyze the survival after SRS of the recurrent GBM in a cohort of 59 patients, which had a radical resection of the primary tumor. The cohort consisted of 59 patients (28 / 47.5% of women and 31 / 52.5% of men); the average age was 51 years (interval 24 - 81). SRS was performed by means of linear accelerator "Trilogy" (USA) (6 MeV) from 2014 to 2020 at the State Institution "Romodanov Neurosurgery Institute". In all cases, the diagnosis of grade 4 GBM according to the WHO classification was confirmed after neurosurgical procedures of the primary tumor. All 59 patients underwent the maximal safe removal of the primary tumor: in the vast majority of cases (54 / 91.5%) - in the perifocal area; in 5 / 8.5% of cases - subtotal. In all 59 cases, patients received adjuvant radiation therapy (total dose 60 Gy in 30 fractions); in 33 / 55.9% of cases radiotherapy was combined with concomitant alkylating chemotherapy (CHT) (Temozolomide 75 mg / m^2). In 31 / 52.5% of patients, maintenance alkylating CHT was continued (Temozolomide 150-200 mg / m^2). In most cases (51 / 86.4%) recurrent GBM (RGBM) was diagnosed by clinical and radiological signs; in 8 / 13.6% of patients - after repeated surgery. Overall survival (OS), recurrence/progression free survival (RFS) and survival after recurrence (SAR) represented the end-points of the study. The effect of the following quantitative and categorical factors (covariates) on the survival was studied: sex, age, performance status, combination of adjuvant RT with alkylating chemotherapy, neurosurgical procedures of RGBM, type of GBM recurrence, total dose of irradiation (BED_{11}) and SRS dose (BED_{11}), number of SRS fractions, volume of target in SRS, duration of RFS. The effect of RFS was studied in three independent groups: group I – RFS < 10 months; group II – RFS from 10 to 20 months; group III – RFS > 20 months. The survival was analyzed by Kaplan-Meier (KM) method. Log-rank test was used for analysis of the survival according to the binary predictors. The effect*

ISSN 1996-353X
ISSN 2311-6951

of several categorical factors on survival was analyzed by Pearson Chi-square test. The effect of the quantitative covariates on survival was studied by regression analysis in Cox proportional risk model. Hazard ratio was calculated with 95 % confidential intervals (CI). The analysis revealed the following. Median OS following SRS RGBM was 26.3 months (95 % CI 17 – 45.5), median RFS was 12.9 months (95 % CI 8.4 – 25.6), median SAR – 9.8 months (95 % CI 6.7 – 24.4). Two-year OS in our study was 56 %. 6-month survival after SRS –77 %; one-year survival after SRS – 39 %, and two-year survival after SRS – 28 %. The significant impact of performance status (p = 0.00159), duration of recurrence-free period (p = 0.02711) and surgical resection of RGBM (p = 0.009391) on the OS was demonstrated. The best OS was shown for the patients with Karnofsky score 90, recurrence occurring after more than 20 months and previous surgical resection of RGBM. The effects of other factors on OS were not demonstrated. Such factors as age, sex, performance status, adjuvant RT with concomitant alkylating CHT, surgical resection of RGBM, type of recurrence, number of SRS fractions, BED_{II} in SRS RGBM, BED_{II} for overall courses of irradiation, SRS target volume demonstrated no effect on SAR. SRS is non-invasive method for RGBM treatment that allows for improving the survival without significant radiation toxicity. Primary biological properties of the tumor seem to be of priority in determining the survival of RGBM patients. Although irradiation of GBM is advantageous regarding the improvement of the survival, one could also speculate that re-irradiation of the recurrent malignant glioma triggers some changes in its biology neutralizing the potential effect of the survival factors that had predictive value before re-irradiation.

Key words: neoplasms, malignant glioma, glioblastoma, neurosurgical procedures, recurrence, radiosurgery, survival.

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults l that is characterized by the negative prognosis, high rate of recurrence and mortality (Wen et al., 2019, Simińska et al., 2021). GBM ranks third by the prevalence among all tumors of central nervous system (CNS) and first among malignant tumors of CNS. GBM is the most aggressive of all brain tumors. In majority of cases, patients die within 15-18 months after diagnosis. Five-year survival of GBM patients is not more than 6.8 % (Ostrom et al., 2021). Among the factors associated with better survival of GBM patients are the age below 50, better performance status, and radical resection of tumor. O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation is considered as more favorable prognostic molecular feature (Wick et al., 2018). Mutation of *IDH* gene (isocitrate dehydrogenase) and 1p19q codeletion were considered as the significant prognostic factor in the former WHO classifications of CNS tumors. Nevertheless, in WHO classification 2016, these features are considered as the characteristic signs of the specified subtypes of gliomas. Therefore, these markers could not be of prognostic value within the framework of each specified subtype (Weller et al., 2021).

It should be recognized that the association between the extent of tumor resection and treatment outcome in GBM patients is still a point of discussion. It is believed the prevention of the surgically acquired neurological deficits that worsen the quality of life of the patient and increase the risk of the additional postoperative complication is more important than the extent of resection per se. Moreover, the surgical intervention is not sufficient for the treatment of the diffuse gliomas, which require complex therapy (Gulati et al., 2011, Kommers et al., 2021, Sacko et al., 2021). Nevertheless, less extent of resection and larger volume of residual tumor tissue represent the negative prognostic factors for gliomas of different subtypes whichever are their grades (Grabowski et al., 2014, Brown et al., 2016, Molinaro et al., 2020). There are no data from corresponding randomized controlled clinical trials since the design of the trial to resolve this problem encounters the utmost difficulties (Weller et al., 2021). At the same time, one should take note of the local recurrence pattern (usually within 2 cm from the area covered by the primary tumor) that is typical for GBM (Rapp et al., 2017). Such local recurrence within 2 cm from the resection cavity is believed as inevitable taking into account extremely high

ISSN 1996-353X
ISSN 2311-6951

level of recurrence (Brandes et al., 2009, Dörner et al., 2013). The optimal approach for treating recurrence or progression of high-grade glioma is still debatable and remains a difficult problem for multidisciplinary teems of neurooncologists. Stereotactic radiosurgery (SRS) as the high-tech precision treatment is considered as the therapeutic option for effective management of the recurrent malignant gliomas (Bräutigam et al., 2019, Lovo et al., 2021). Due to up-to-date improved techniques of radiotherapy, novel visualization techniques, and increasing radiobiological knowledge of brain tissues, the repeated irradiation became possible for this complicated category of patients. The decision is taken on an individual basis taking into account the nature of the recurrence, the previous treatment, the performance status as well as the preferences of the patient and the expected quality of life (García-Cabezas et al., 2021). Several aspects of reirradiation of GBM patients are awaiting their decision, in particular, criteria for selecting of the most favorable candidates for such a treatment and accounting for the factors that affect positively the survival. The present study deals with the analysis of the survival after radiosurgery of recurrent GBM (RGBM) in patients with radical resection of primary tumor. The factors affecting survival in this category of patients is also analyzed.

Aim

Analysis of survival after SRS of RGBM in cohort of patients with radical resection of primary tumor.

Methods

The data of the prospective study performed at the State Institution "Romodanov Neurosurgery Institute, National Academy of Medical Sciences of Ukraine" have been presented. The study included 59 patients with RGBM treated with SRS using linear accelerator "Trilogy" (USA) (6 MeV) in 2014-2020. The study was approved by the Committee on Ethics and Bioethics of the Institute (Meeting Minutes No. 3 of June 6, 2016).

Inclusion criteria:

- males and females aged above 18 years;
- voluntary informed written consent to participate in the study, willingness and ability to comply with the procedures of the study and the follow-up;
- anticipated survival time of more than 3 months;
- pathohistologically confirmed diagnosis of GBM;
- pathohistologically confirmed recurrence/progression of GBM or clinical-and-radiological features of recurrence/progression of GBM;
- > 3 de novo multicentric recurrent tumors;
- Karnofsky performance status (KI) ≥ 70; performance status according to ECOG (Eastern Cooperative Oncology Group) scale ≤ 0–2.

The distribution of the patients under study according to the major characteristics is given in Table 1.

Table 1. Major characteristics of patients

Characteristics	Number of patients (total number n=59)	%
Sex		
males	31	52.5
females	28	47.5
Age (years)		
mean	51	
range	24 – 81	
Localization of primary tumor		
lobar	54	91.5
median extension	5	8.5
multicentric growth	0	0
MGMT status		
methylated promoter of *MGMT* gene	3	5.1
non-methylated promoter of *MGMT* gene	6	10.2
no data	50	84.7
IDH 1 status		
IDH1 - wild type	9	15.3
no data	50	84.7
Adjuvant radiotherapy (RT) (60 Gy, 30 fractions) + concomitant chemotherapy (CHT) (Temozolomide 75 mg/m^2 7 days a week during RT course)	33	55.9
Adjuvant RT (60 Gy, 30 fractions) without concomitant CHT	26	44.1

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Volume of primary tumor resection		
total	54	91.5
subtotal	5	8.5
Adjuvant CHT (Temozolomide 150-200 mg/m^2)		
yes	31	52.5
no	28	47.5
Type of GBM recurrence		
local growth	41	69.5
multifocal growth	11	18.6
de novo solitary tumor	7	11.9
Performance status (KI) prior to SRS		
90	11	18.6
80	22	37.3
70	26	44.1
Surgical resection of RGBM		
yes	8	13.6
no	51	86.4
Number of SRS fractions		
1	40	67.8
3	6	10.2
4	6	10.2
5	7	11.8
PTV (cm^3) in SRS		
median	13.99	
95 % confidence interval (CI)	11.6 – 17.2	
p	< 0.0001	
BED_{11} in SRS of RGBM (Gy)		
median	39.3	
95 % CI	39.3 – 43.3	
p	0.0217	
Overall BED_{11} for all courses (Gy)		
median	110.2	
95 % CI	108.0–114.2	
p	0.0483	
Prescription dose (PD) in SRS of RGBM (Gy)		
median	14.0	
95 % CI	12 – 16	
p	0.0001	
Total boost dose (TBD) in SRS of RGBM (Gy)		
median	18.0	
95 % CI	16 – 18.5	
p	< 0.0001	

According to the requirements of the State Standard of Ukraine, Shapiro-Wilk test was used for testing normality of data distribution. The following data were shown to be normally distributed: the age in the general group of observation ($p = 0.0785$); biologically effective dose (BED_{11}) – both overall BED_{11} and BED_{11} in SRS of the recurrent tumor in female patients ($p = 0.8020$ and $p = 0.1373$, respectively); the age and BED_{11} in SRS of the recurrence in male patients ($p = 0.3752$ and $p = 0.8355$, respectively). When the data were not normally distributed, the parameters of a central tendency (median with 95 % confidential intervals (CI): min-max) were used.

The group under study comprised 28 (47.5 %) females and 31 (52.5 %) males. The mean age was 51 years (range 24-81). The mean age of male patients was 52.7 years (29-81). The median age of female patients was 54.4 (95 % CI 38.5–56.0; $p = 0.0088$).

The diagnosis of GBM grade 4 according to WHO classification was verified following the surgical treatment of the primary tumor.

The maximal safe resection of the primary tumor was performed in radical extent. In most cases (54/91.5 %), the "total" resection along the perifocal area was provided; in 5 (8.5 %) cases, the resection was subtotal.

It should be noted that molecular genetic assessment of *MGMT* status and *IDH1* mutation of the primary tumor was performed only in few cases (9/15.3 %). This could be explained by the fact that the majority of patients included into the study have been under treatment before the molecular genetic tests were implemented following the revision of WHO classification of CNS tumors in 2016 (Louis et al., 2016).

In all cases, the neurosurgical procedure of the primary tumor was followed by the adjuvant radiotherapy (TBD 60 Gy, 30 fractions). In 33 cases, radiotherapy was combined with the concomitant alkylating CHT (Temozolomide 75 mg/m^2). In 31 (52.5 %) cases, CHT with Temozolomide (150-200 mg/m^2) continued after the completion of adjuvant CHT.

In most cases (51/86.4 %), the persistence of the disease was confirmed by the complex of clinical and radiological features being indicative of the local recurrence or extended GBM growth. RGBM was visualized as the focus of pathological accumulation of paramagnetic in brain MRI

ISSN 1996-353X
ISSN 2311-6951

with intravenous paramagnetic contrast within the area of the resection of the primary tumor (local recurrence/continuous GBM growth) or de novo solitary focus or several foci of multicenter growth without pseudoprogression features according to RANO (Response Assessment in Neuro-Oncology) criteria (Wen et al., 2010). When possible, the conventional diagnostic procedures were supplemented with perfusion techniques (MRI or CT) taking into account their advantages in differential diagnosis between RGBM and pseudoprogression.

In 8 (13.6 %) cases, the recurrent/continuous tumor growth was diagnosed based on pathomorphological findings following the secondary surgical intervention (5 cases of subtotal resection and 3 cases of partial resection).

In all cases, when the persistence of the disease was suspected, the final decision was taken by the multidisciplinary neuro-oncological group consisted of neurosurgeon, medical oncologist, radiation oncologist and radiologist.

According to the recurrence pattern, the patients with local growth of tumor (within the area of the primary tumor) were predominant (41/69.5 %). The progression of multicenter type (11/18.6 %) or de novo appearance of solitary tumor focus (7/11.9 %) was less prevalent. Suggesting that the shared features exist in de novo appearance of solitary tumor focus and GBM progression of multicenter type, we could consider these two patterns as the phases of the single process of the multifocal tumor growth. On this assumption, we thought it appropriate to combine the patients with these two patterns of progression into a single group for the purposes of the statistical analysis of the results.

SRS was performed provided that the performance status of the patient was not less than 70 points according to KI or ≤ 0-2 according to ECOG scale. In almost half of the patients under study (26/44.1 %), KI was 70.

Linear accelerator “Trilogy” (USA) (6 MeV) was used for SRS treatment. The target volume of irradiation was delineated by fusion MRI and CT images. The gross tumor volume (GTV) was defined as the visible lesion on MRI contrast-enhanced images. The additional field for CTV (Clinical Tumor Volume) was not added but for PTV (Planning Tumor Volume) the “safety margin” up to 5.0 mm was added (Bräutigam et al., 2019). In cases of previous surgical resection of RGBM, the irradiation target comprised the surgical cavity and the adjacent cerebral tissue. The borderlines for irradiation target were delineated in the way allowing to reduce maximally the contact between the irradiation area and the brain critical structures (visual tracts, optic nerves, chiasm, brainstem, hippocampus). The dose regime was defined on an individual basis taking into account the volume of the irradiated target, its localization regarding the proximity to the brain critical structures, BED_{11} for the first course of irradiation; time elapsed since the first irradiation. The permissible dose loading onto the critical structures of the brain was calculated according to the estimated normal tissue complication probability (NTCP) (Marks et al., 2010).

The parameters of irradiation and dose fractionation in SRS of RGBM are given in Table 1.

SRS was performed without concomitant systemic therapy.

As accompanying therapy (by clinical indications – symptomatic cerebral edema, epileptic attacks, etc.), corticosteroids with oral inhibitors of proton pump, anticonvulsants, and osmotic diuretics were used.

Overall survival (OS), recurrence-free (progression-free) survival (RFS) and survival after recurrence (SAR) represented the end-points of the study. OS was calculated in months as the time from the date of the surgical resection of the primary tumor to the date of death (event) or the date of the last observation (censured observation). The rates of 3-, 6-, 12-, 18-, 24-month survival were also assessed.

RFS was calculated as the time from the date of the surgical resection of the primary tumor to the date of SRS RGBM. SAR was calculated as the time from the date of SRS to the date of death (event) or the date of the last observation (censured observation).

The effect of the following quantitative and categorical factors (covariates) on the survival was studied: sex, age, performance status (KI), combination of adjuvant RT with alkylating CHT, surgical resection of RGBM, type of GBM recurrence, overall dose for the total courses of

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ISSN 2311-6951

irradiation (BED_{11}) and SRS dose (PD, TBD, BED_{11}), number of SRS fractions, volume of target in SRS, duration of RFS.

The effect of RFS was studied in three independent groups of patients: group I – RFS < 10 months; group II – RFS from 10 to 20 months; group III – RFS > 20 months.

The survival was analyzed by Kaplan-Meier (KM) method.

Log-rank test (for comparing survival curved for different groups under study) was used for analysis of the survival according to the binary predictors. The effect of several categorical factors on survival was analyzed by Pearson Chi-square test

The effect of the quantitative covariates on survival was studied by regression analysis in Cox proportional risks model. Hazard ratio (HR) was calculated with 95 % CI.

The statistical significance was proved by comparing p values obtained with the critical acceptance/rejection level for statistical hypotheses α = 5 %. STATISTICA 64 ver.10.0.1011.0 StatSoft Inc was used for the statistical processing of the data.

Results

1. Survival study

At the time of the survival analysis, 42 (71.19 %) of 59 patients died.

OS median in the cohort under study was 26.3 months (95 % CI 17 – 45.5), RFS median – 12.9 months (95 % CI 8.4 – 25.6), SAR median – 9.8 months (95 % CI 6.7 – 24.4).

12-month OS was 93 % (95 % CI 86 – 100), 18-month OS – 68 % (95 % CI 56 – 80), 24-month OS – 55 % (95 % CI 42 – 68).

6-month RFS was 84 % (95 % CI 74 – 93), 12-month RFS – 52 % (95 % CI 38 – 66); 18-month RFS – 52 % (95 % CI 38 – 66); 24-month RFS – 26 % (95 % CI 12 – 39).

For SAR, 3-month survival was 89 % (95 % CI 82 – 97), 6-month survival – 77 % (95 % CS 67 – 88), 12-month survival – 39 % (95 % CI 26 – 53), 18-month survival – 34 % (95 % CI 21 – 48), 24-month survival – 28 % (95 % CI 14 – 41).

The analysis of survival demonstrates the most patients (77 %) survive not less than 6 months following SRS RGBM, while more than half of patients (56 %) survive 24 months following the surgical resection of the primary tumor.

Survival data in the cohort under study are presented in Fig. 1-3.

2. Analysis of survival predictors

The design of the study envisaged to analyze OS and SAR depending on several quantitative and categorical factors: sex, age, performance status (KI), combination of adjuvant RT with alkylating CHT, surgical resection of RGBM, type of GBM recurrence, overall dose load for the total courses of itradiation (BED_{11}) and in SRS (BED_{11}; PD; TBD), number of SRS fractions, volume of target in SRS, duration of RFS.

These factors were considered as such that could affect potentially the survival parameters in RGBM patients. This fact encouraged us to perform the corresponding analysis.

2.1. Analysis of survival according to binary predictors

OS and SAR were analyzed according to the following predictors:

- Combination of adjuvant RT with alkylating CHT (Temozolomide 75 mg/m2): groups “Adjuvant RT + concomitant CHT” vs “Adjuvant RT without concomitant CHT”;
- Type of GBM recurrence: groups “Local recurrence” vs “De novo solitary tumor + multifocal growth”;
- Number of SRS fractions: groups “one fraction” vs “more than one fraction”;
- Sex: groups “males” vs “females”;
- BED11 in SRS RGBM: groups “≥ 40.0 Gy” vs “< 40.0 Gy”;
- BED11 for overall courses of irradiation: groups “≥ 110.0 Gy” vs “< 110.0 Gy”;
- Surgical resection of RGBM: groups “Surgical resection of RGBM” vs “Without surgical resection of RGBM”
- Age: groups “< 45 years” vs “≥ 45 years”.

The results of the statistical analysis are given in Table 2.

The analysis has not revealed the statistically significant effects on survival (OS or SAR) of the following factors: combination of adjuvant RT with alkylating CHT, type of GBM recurrence (“Local recurrence” vs “De novo solitary tumor + multifocal growth)”, number of SRS fractions (“one fraction” vs “more than one fraction”), sex, age (“< 45 years” vs “≥ 45 years”), BED11 in SRS RGBM (“≥ 40.0 Gy” vs “< 40.0

ISSN 1996-353X
ISSN 2311-6951

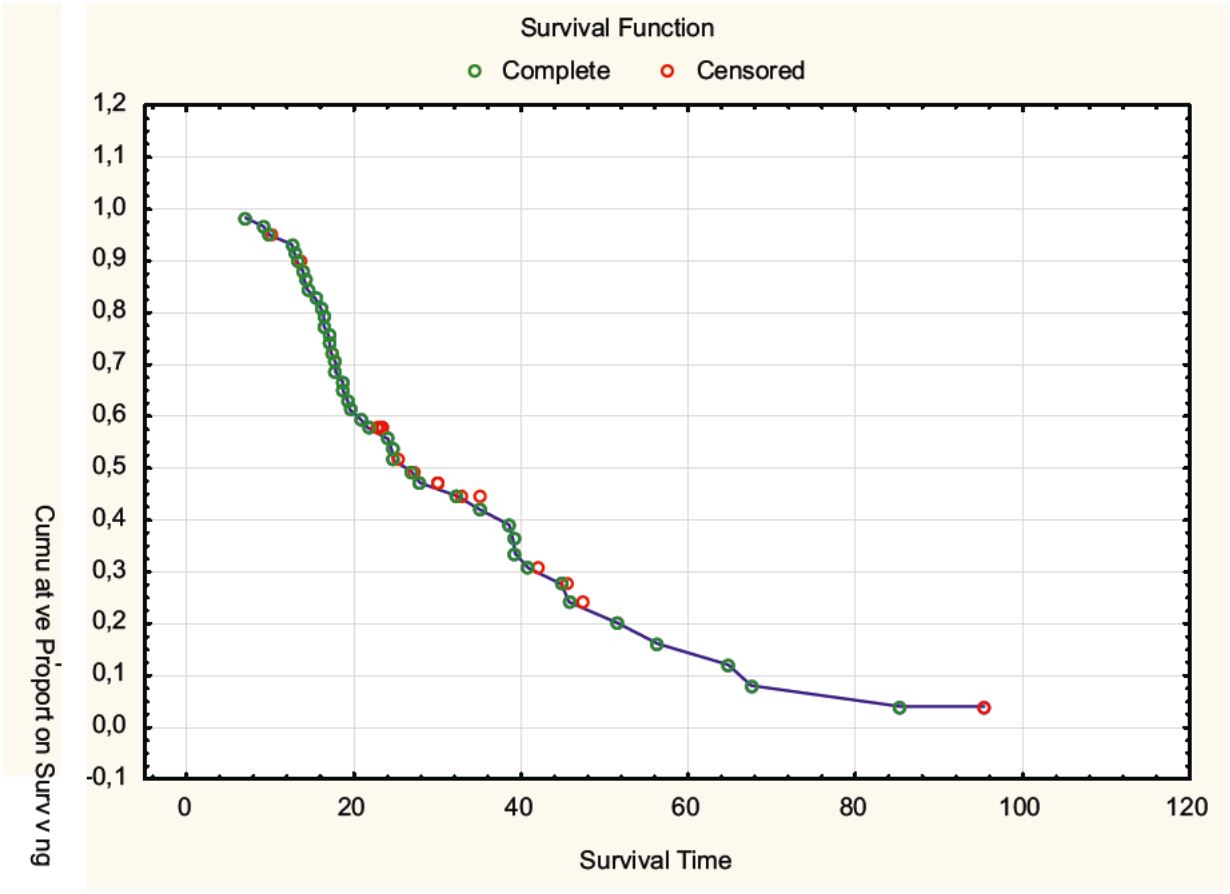

Fig. 1. Kaplan-Meier curve of OS (in months) for retrospective analysis of 59 RGBM patients

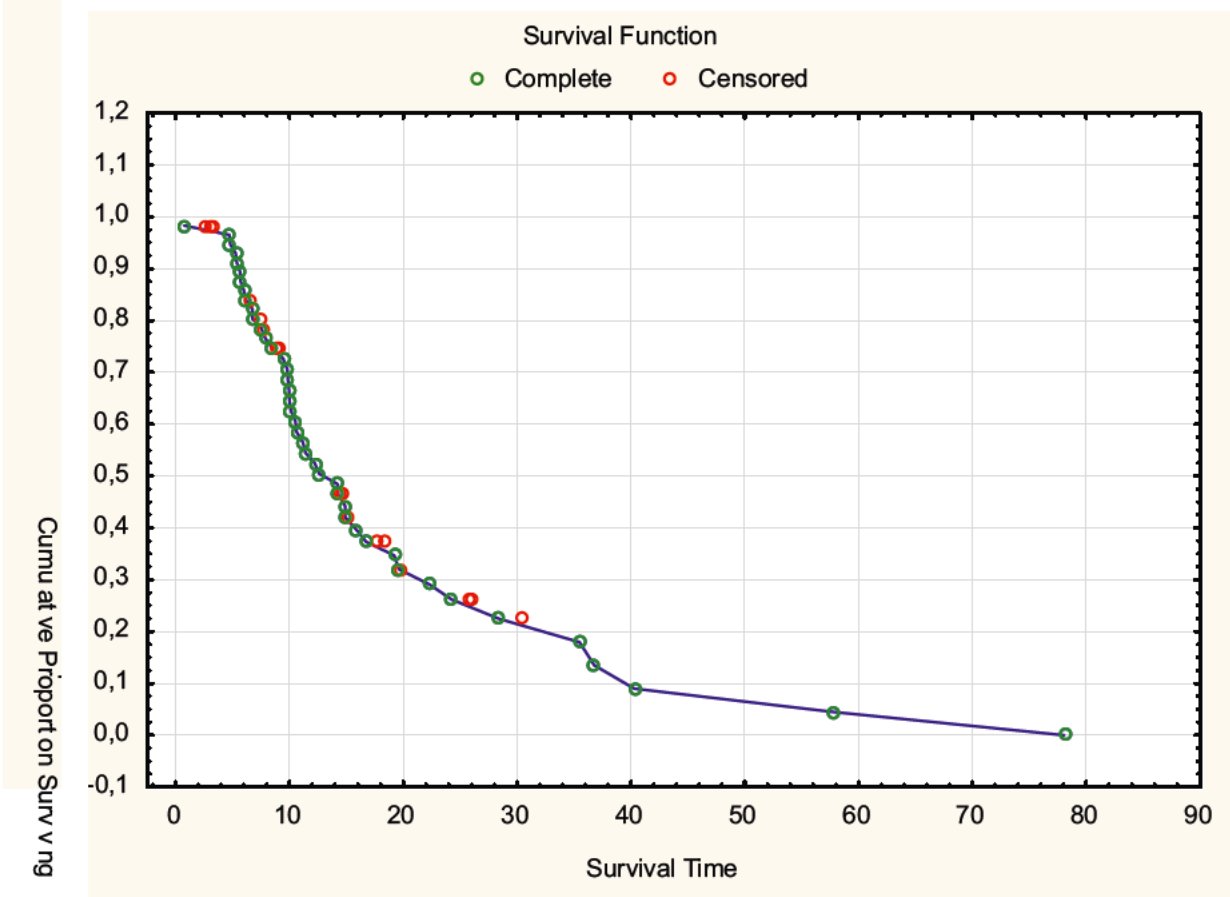

Fig. 2. Kaplan-Meier curve of RFS (in months) for retrospective analysis of 59 RGBM patients

ISSN 1996-353X
ISSN 2311-6951

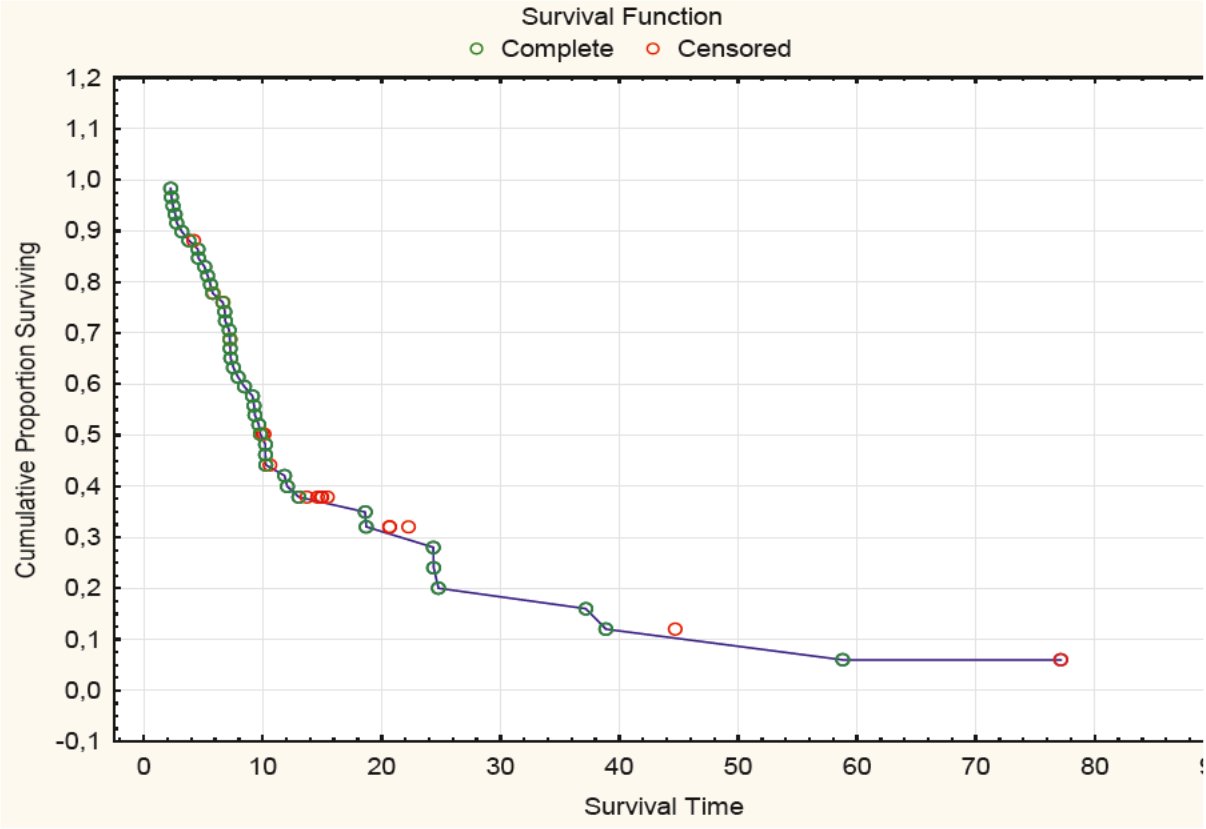

Fig. 3. Kaplan-Meier curve of SAR (in months) for retrospective analysis of 59 RGBM patients

Gy"), BED11 for overall courses of irradiation ("≥ 110.0 Gy" vs "< 110.0 Gy").

The significance of the predictive value of the sex as to OS (p = 0.05627) is borderline as to the acceptance or rejection of null hypothesis. It is probable that the increased number of observations could result in statistically significant difference in OS between males and females (p ≤ 0.05). Therefore, this question requires further analysis with increased number of patients that should contribute to the increased statistical power.

We have shown the statistically significant difference in OS between groups "Surgical resection of RGBM" and "Without surgical resection of RGBM" (p = 0.02711) with better outcome in patients to whom the surgical resection of RGBM has been performed. Nevertheless, no difference in SAR between these groups has been demonstrated (p = 0.36582). Further studies are required to resolve this inconsistency. Since surgical resection of RGBM affects positively on OS, the same effect could be supposed also for SAR with increasing number of patients included into further study.

2.2. Analysis of the effects of categorical factors on survival

According to the design of the study, we have analyzed the effects of categorical factors (performance status, type of GBM recurrence, age group and RFS) on the survival.

We have not demonstrated the predictive value of the type of GBM recurrence as to OS when OS of patients with local recurrence, de novo solitary tumor and multifocal type progression was compared (Chi-square = 1.750949; df = 2; p = 0.41667). Moreover, the type of recurrence was not predictive for survival after SRS (Chi-square = 3.579759; df = 2; p = 0.16700).

The comparison of survival in groups stratified according to their age (group I – < 45 years; group II – 45–59 years; group III – ≥ 60 years) has not demonstrated statistically significant difference both for OS (Chi-square = 1.822209; df = 2; p = 0.40209) and for survival after SRS (Chi-square = 2.296786; df = 2; p = 0.31716).

In contrast, the significant effect of performance status (KI) on OS has been shown (Chi-square = 12.88648; df = 2; p = 0.00159).

ISSN 1996-353X
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Table 2. Analysis of the predictive value of studied factors on OS and SAR

Factor	Calculation data		
Combination of adjuvant RT with alkylating CHT: groups "Adjuvant RT + concomitant CHT" vs "Adjuvant RT without concomitant CHT"	OS	Log-Rank Test WW = -1.052; Sum = 39.078; Var = 9.7979; Test statistic = -0.336057	p = 0.73683
	SAR	Log-Rank Test WW = -2.843; Sum = 39.42; Var = 9.8842; Test statistic = - 0.904326	p = 0.36582
Type of GBM recurrence: groups "Local recurrence" vs "De novo solitary tumor + multifocal growth"	OS	Log-Rank Test WW = -2.564; Sum = 39.078; Var = 8.4276; Test statistic = -0.883379	p = 0.37703
	SAR	Log-Rank Test WW = -3.401; Sum = 39.421; Var = 8.5018; Test statistic = -1.16627	p = 0.24350
Number of SRS fractions: groups "one fraction" vs "more than one fraction"	OS	Log-Rank Test WW = 1.1857; Sum = 39.078; Var = 8.6788; Test statistic = 0.4024739	p = 0.68734
	SAR	Log-Rank Test WW = -0.8917; Sum = 39.421; Var = 8.7552; Test statistic = -0.301355	p = 0.76314
Sex: groups "males" vs "females"	OS	Log-Rank Test WW = 6.0101 Sum = 39.078; Var = 9.9121; Test statistic = 1.908977	p = 0.05627
	SAR	Log-Rank Test WW = 4.2980; Sum = 39.421; Var = 9.9994; Test statistic = 1.359195	p = 0.17408
BED11 in SRS RGBM: groups "≥ 40.0 Gy" vs "< 40.0 Gy"	OS	Log-Rank Test WW =0.28047. Sum = 39.078. Var = 9.9350; Test statistic = 0.0889822	p = 0.92910
	SAR	Log-Rank Test WW = 2.4034; Sum = 39.421; Var = 10.022; Test statistic = 0.7591867	p = 0.48381
BED11 for overall courses of irradiation: groups "≥ 110.0 Gy" vs "< 110.0 Gy"	OS	Log-Rank Test WW = -2.165; Sum = 39.078; Var = 9.5924; Test statistic = -0.698928	p = 0.48460
	SAR	Log-Rank Test WW = 2.1781; Sum = 39.421; Var = 9.6768; Test statistic = 0.7001883	p = 0.48381
Surgical resection of RGBM: groups "Surgical resection of RGBM" vs "Without surgical resection of RGBM"	OS	Log-Rank Test): WW = 4.7700; Sum = 39.078; Var = 4.6592; Test statistic = 2.209868	p = 0.02711
	SAR	Log-Rank Test WW = -2.843; Sum = 39.421; Var = 9.8842; Test statistic = -0.904326	p = 0.36582
Age: groups "< 45 years" vs "≥ 45 years"	OS	Log-Rank Test WW = 3.8279 Sum = 39.078 Var = 9.2955; Test statistic = 1.255516	p = 0.20929
	SAR	Log-Rank Test WW = 2.5193; Sum = 39.421; Var = 9.3773; Test statistic = 0.8227000	p = 0.41068

Significant difference in OS was also demonstrated when OS was compared in three groups of patients stratified according to RFS, namely, RFS < 10 months; 10–20 months; > 20 months (Chi-square = 1.750949; df = 2; p = 0.00066). The median of OS in patients with KI = 70 was 17.1 months, KI = 80 – 26.6 months, KI = 90 – 39.1 months.

At the same time, neither the duration of recurrence-free period, nor performance status affected SAR (Chi-square = 1.468320; df = 2; p = 0.47992 and Chi-square = 1.203675; df = 2; p = 0.54781, respectively). The corresponding KM curves were practically the same.

The results of the analysis are presented in Fig. 4-7.

ISSN 1996-353X
ISSN 2311-6951

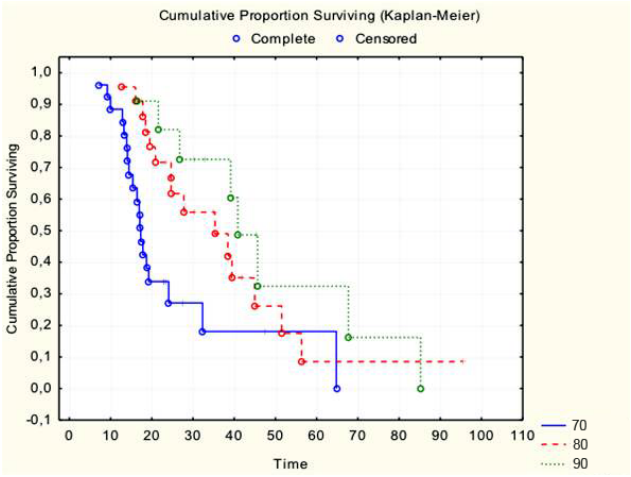

Fig. 4. Kaplan-Meier curves of OS (in months) for retrospective analysis of the cohort of 59 RGBM patients depending on Karnofsky performance status

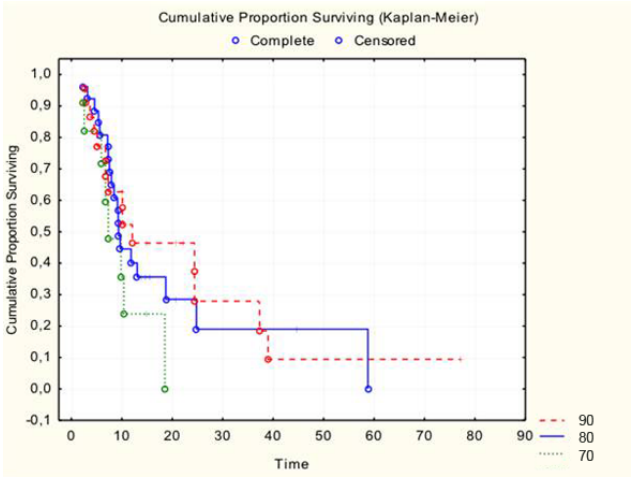

Fig. 5. Kaplan-Meier curves of SAR (in months) for retrospective analysis of the cohort of 59 RGBM patients depending on Karnofsky performance status

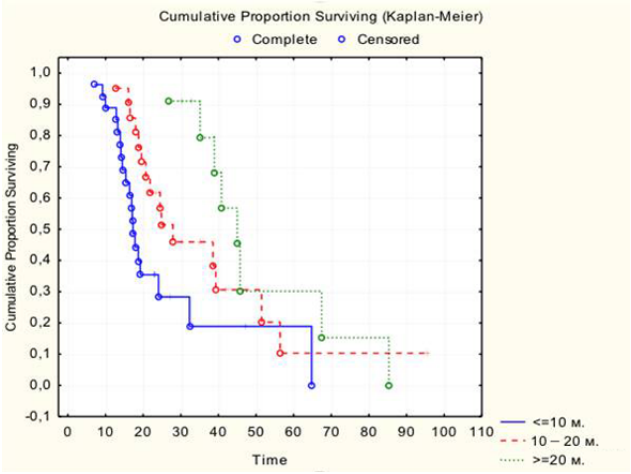

Fig.6. Kaplan-Meier curves of OS (in months) for retrospective analysis of the cohort of 59 RGBM patients depending on the time to recurrence with stratification in three groups: RFS < 10 months; 10–20 months; > 20 months

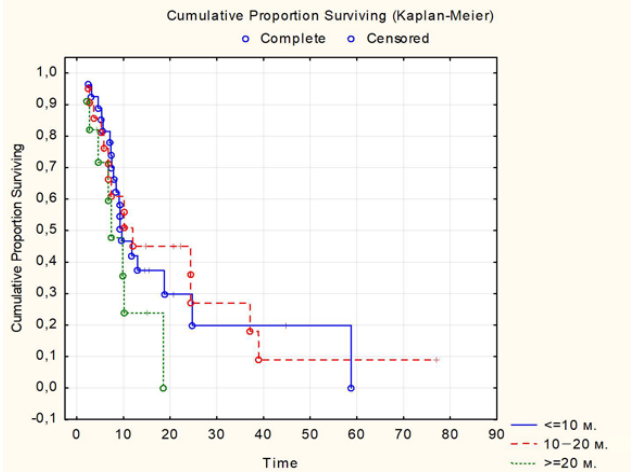

Fig. 7. Kaplan-Meier curves of SAR (in months) for retrospective analysis of the cohort of 59 RGBM patients depending on the time to recurrence with stratification in three groups: RFS < 10 months; 10–20 months; > 20 months

2.3. Analysis of the effects of quantitative covariates on survival

The Cox proportional risk model was used for analyzing the effect of quantitative covariates on the survival. According to the design of the study, we have analyzed the effects of the following covariates: age, duration of recurrence-free period, number of SRS fractions, SRS RGBM dose (PD, TBD, BED_{11}), BED_{11} for overall courses of irradiation, SRS target volume. The results of the corresponding statistical calculations are given in Tables 2 and 3.

Only RFS demonstrated the significant impact on OS in the cohort under study (HR 0.97; 95 % CI 0.94 – 0.99, p = 0.009391). For other covariates, no statistically significant effect on survival risks has been demonstrated.

Radiotoxicity following SRS

All patients tolerated well SRS. No cases of severe radiotoxicity grade > 2 according to CTC (Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0) (Freites-Martinez et al., 2021) was registered.

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Table 2. Calculation of the effects of covariates on OS according to Cox model

Covariate	Parameter estimate	Standard error	Chi-square	P value	95% Lower CL	95% Upper CL	Hazard Ratio	95% Hazard Ratio Lower CL	95% Hazard Ratio Upper CL
Number of SRS fractions	-0.050451	0.098225	0.263808	0.607516	-0.242969	0.142067	0.950801	0.784296	1.152654
PD in SRS	0.010829	0.034250	0.099974	0.751861	-0.056299	0.077958	1.010888	0.945256	1.081078
TBD in SRS	-0.017769	0.022070	0.648220	0.420750	-0.061026	0.025488	0.982388	0.940799	1.025815
BED11 in SRS	-0.011558	0.015677	0.543588	0.460950	-0.042284	0.019168	0.988508	0.958597	1.019353
BED11 for overall courses of irradiation	-0.019626	0.011443	2.941724	0.086319	-0.042054	0.002801	0.980565	0.958818	1.002805
Target volume in SRS	-0.002754	0.005062	0.296042	0.586374	-0.012674	0.007166	0.997250	0.987406	1.007192
Age	0.017077	0.011941	2.045281	0.152679	-0.006327	0.040481	1.017224	0.993693	1.041312
RFS	-0.034411	0.013248	6.746824	0.009391	-0.060376	-0.008446	0.966175	0.941410	0.991590

Table 3. Calculation of the effects of covariates on SAR according to Cox model

Covariate	Parameter estimate	Standard error	Chi-square	P value	95% Lower CL	95% Upper CL	Hazard Ratio	95% Hazard Ratio Lower CL	95% Hazard Ratio Upper CL
PD in SRS	-0.005437	0.035300	0.023719	0.877601	-0.074623	0.063750	0.994578	0.928093	1.065826
TBD in SRS	0.020451	0.025647	0.635867	0.425211	-0.029816	0.070718	1.020662	0.970625	1.073278
BED11 in SRS	0.016601	0.018504	0.804939	0.369621	-0.019665	0.052868	1.016740	0.980527	1.054290
BED11 for overall courses of irradiation	0.006133	0.011817	0.269379	0.603749	-0.017027	0.029294	1.006152	0.983117	1.029727
Target volume in SRS	-0.001070	0.005015	0.045538	0.831017	-0.010900	0.008760	0.998930	0.989159	1.008798
Age	0.011677	0.011660	1.002857	0.316620	-0.011177	0.034531	1.011745	0.988885	1.035134
RFS	0.013943	0.010955	1.620053	0.203084	-0.007527	0.035414	1.014041	0.992501	1.036048

ISSN 1996-353X
ISSN 2311-6951

Discussion

RGBM prognosis is the most desperate in neuro-oncology. Meanwhile, there is still no consensus as to the standards of treatment of such patients. One of the reasons is the absence of the highly effective therapies with the acceptable toxicity profile. When the strategy of treatment is elaborated, such factors as the previous therapy, age of patient, performance status, status of the methylation of the promoter of *MGMT* gene, and the feature of the progression of the disease are conventionally considered (Weller et al., 2021). Nevertheless, certain evidence in favor of the usefulness of the repeated irradiation in RGBM currently exists. SRS RGBM as the repeated irradiation following the first RT course is deemed as one of the most promising method for treatment of such patients allowing for improving their survival. Nevertheless, the randomized clinical trials are required for elucidating the optimal treatment strategy (García-Cabezas et al., 2021).

SRS as the technique for RGBM treatment has been known for more than two decades. Firstly, SRS is promising due to its noninvasiveness. Moreover, SRS allows delivering a dose with high submillimeter precision providing for the high dose gradient at the border between the irradiated target and the adjacent tissues with minimal neurotoxicity. This is of peculiar importance since these patients have already received high radiation dose during the first course of RT. After all, other non-invasive alternatives are not available. As to such non-invasive technique as low intensity alternating electric fields (Tumor-treating fields, TTF), this method is not highly available (Lovo et al., 2021).

In 1995, one of the first studies devoted to the use of SRS for RGBM treatment analyzed the outcome of SRS treatment in 35 patients with recurrent malignant glioma (26 GB multiforme and 9 anaplastic gliomas; mean volume of irradiated target 28 cm^3) (Hall et al., 1995). OS in this cohort was 21 months with survival after SRS – 8 months. Young age of the patient represented the predictive factor of better survival in both univariate and multivariate analysis. Improved survival was associated with better performance status (KI) in univariate analysis. Nevertheless, such factors as histological type of tumor, target volume or dose did not affect survival. Radiation necrosis rate was 14 % and the number of the surgeries due to symptomatic necrosis was lower than after brachitherapy.

In the study by German authors (Combs et al., 2005), survival rate after SRS RGBM was somehow higher. In a group of 32 patients with RGBM, median of OS was 22 months and median of survival after SRS – 10 months (the median follow-up time was 13 months). The survival rate at one year was 90 %, and 49 % and 26 % at 2 and 3 years. 6-month and 12-month survival following SRS was 72 % and 28 %, respectively. The median of progression-free survival following SRS was 7 months. The profile of SRS toxicity was acceptable. No severe cases of acute radiation toxicity (grade >2) or severe long-term toxicities including radionecrosis were observed.

It should be emphasized that both studies above were published before the large-scale implementation of Stupp protocol of alkylating CHT with Temozolomide into neurooncological practice (Stupp et al., 2005). The use of Temozolomide in concomitant and adjuvant regimens allows increasing two-year OS in GBM patients to 26.5 % as compared to 10.4 % for postoperative RT as single treatment modality. Nevertheless, if one checks these data against those obtained with SRS in RBGM, a credit should be given to the contribution of the improved radiation technologies into the increasing survival of such patients.

In this context, the study by Ohgaki et al., 2004 that presented results of the population study of the GBM patients' survival in Zurich canton is worthwhile noticing. Among 715 patients treated in 1980-1994, one-year survival amounted to 17.7 % while two-year survival – only 3.3 %.

Niranjan et al., 2018 analyzed 297 histologically confirmed RGBM cases treated by Gamma knife in Pittsburgh, USA. Retrospective analysis demonstrated OS median of 18 months and one-year and two-year survival – 72.5 % and 29.5 %, respectively. The survival median after SRS was 9 months. Among significant predictors were target volume < 14 cm3, dose ≥ 15 Gy and age of patients < 60 years. The side reactions were observed in 23 % of cases. In most cases, they were controlled by corticosteroids.

Along with several clinical reports on the repeated irradiation treatment of RGBM, including SRS, there are some publications on contain-

ISSN 1996-353X
ISSN 2311-6951

ing meta-analyses of the current experience in the field. In recent study, the database comprising 2095 RGBM patients who were subjected to the re-irradiation in 1998-2018 due to GBM recurrence/progression was analyzed (Kazmi et al., 2019). Meta-analysis demonstrated that 6-month survival following irradiation was 73 % and 12-month survival – 36 %. Irradiation with ≤5 fractions was associated with higher 6-month progression-free survival (47 % vs 26 %, P = 0.005) that is in favor of radiosurgical treatment approaches in RGBM. In general, the toxicity of re-irradiation was acceptable, although the data presented ion different studies varied. Therefore, according to meta-analysis data, re-irradiation of RGBM provides for the acceptable control of the disease and acceptable survival levels.

Our data on survival following SRS RGBM are quite comparable to that of other authors. Namely, OS median was 26.3 months (95 % CI 17 – 45.5), RFS median was 12.9 months (95 % CI 8.4 – 25.6), SAR median – 9.8 months (95% CI 6.7 – 24.4). Two-year survival of patients in our study was 56 % (95 % CI 42 – 68); one-year survival – 39 % (95 % CI 26 – 53). These data are similar to those presented in both clinical reports and meta-analyses. Our analysis of the survival predictors deserves special attention. We have demonstrated that only surgical resection of RGBM, performance status before SRS and duration of recurrence-free period are predictors of better OS. No factors under study affected SAR that was rather unexpected. Such results are somehow related to the results presented by Combs et al., 2005, who did not find the association between any of studied factors (age, performance status, extent of respectability of primary tumor, duration of recurrence-free period, class according to RPA classification, PTV volume) and survival values.

It is logical to assume that both our data and the findings presented by other teams are in favor of the concept claiming the priority of the primary biological properties of the tumors in defining the survival of GBM patients independently of treatment modalities. Although irradiation of GBM is advantageous regarding the improvement of the survival, one could also suppose that re-irradiation of the recurrent malignant glioma triggers some changes in its biological properties offsetting the potential effects on survival exerted by several factors that had predictive survival value before re-irradiation.

To sum up, both our own data and the data by other authors demonstrate the suitability of SRS in the treatment of RGBM. This therapeutic modality could be considered as the appreciable factor of the current progress in RGBM treatment. Nevertheless, the optimization of the approaches in RGBM treatment remains the urgent problem in neuro-oncology inciting to further studies in the field.

Conclusions

1. OS median following SRS RGBM was 26.3 months (95 % CI 17 – 45.5), RFS median was 12.9 months (95 % CI 8.4 – 25.6), SAR median – 9.8 months (95 % CI 6.7 – 24.4).
2. Two-year OS in our study was 56 %. 6-month survival after SRS –77 %; one-year survival after SRS – 39 %, and two-year survival after SRS – 28 %.
3. The significant effect of performance status (p = 0.00159), duration of recurrence-free period (p = 0.02711) and surgical resection of RGBM (p = 0.009391) on the OS was demonstrated. The best OS was shown for the patients with KI 90, recurrence occurring after more than 20 months and previous surgical resection of RGBM. The effects of other factors on OS were not demonstrated.
4. No significant impact on SAR of such factors as age, sex, KI, combination of the adjuvant RT with alkylating CTH, surgical resection of RGBM, type of recurrence, number of SRS fractions, BED_{11} in SRS RGBM, BED_{11} for overall courses of irradiation, SRS target volume was demonstrated.
5. Radiosurgery is non-invasive method for RGBM treatment that allows for improving the survival without significant radiation toxicity. Primary biological properties of the tumor seem to be of priority in determining the survival of RGBM patients.
6. Although irradiation of GBM is advantageous regarding the improvement of the survival, one could also suppose that re-irradiation of the recurrent malignant glioma triggers some changes in its biological properties offsetting the potential effects on survival exerted by several factors that had predictive survival value before re-irradiation.

ISSN 1996-353X
ISSN 2311-6951

Funding

Financing by the State Budget of Ukraine.

Conflict of interest

Authors claim the absence of the conflict of interests that could potentially be harmful to objectivity of the study.

Consent to publication

All authors have read and approved the final version of the manuscript. All authors have agreed to publish this manuscript.

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Ukrainian Scientific Medical Youth Journal
Issue 1 (128), 2022
ISSN 1996-353X
ISSN 2311-6951

Виживаність після радіохірургічного лікування рецидивних гліобластом у хворих із радикальною резекцією первинної пухлини

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Анотація: гліобластома (ГБ) – це агресивна пухлина, що характеризується високим рівнем рецидивування та призводить до смерті більшості хворих через 15–18 місяців після встановлення діагнозу. Факторами, що асоціюються з більш тривалою виживаністю хворих на ГБ, є вік до 50 років, кращий функціональний статус та радикальна резекція первинної пухлини. Оптимальне лікування при рецидиві або прогресуванні ГБ до цього часу не визначено та залишається складною проблемою. Стереотаксична радіохірургія (СРХ) є методом прецизійного високотехнологічного опромінення, що розглядається сьогодні як терапевтична опція ефективного впливу на рецидивні злоякісні гліоми. Метою даного ретроспективного дослідження був аналіз виживаності після СРХ рецидивної ГБ в когорті 59 хворих, яким було проведено радикальну резекцію первинної пухлини. Досліджувана когорта складалась з 59 хворих (28 / 47,5% жінок та 31 / 52,5% чоловіків); середній вік в загальній групі склав 51 рік (інтервал 24 – 81). СРХ проводилось на лінійному прискорювачі «Trilogy» (США) (6 MeV) в період з 2014 р. по 2020 р. в Державній установі «Інститут нейрохірургії ім. акад. А.П. Ромоданова НАМН України». В усіх випадках діагноз ГБ 4 ступеню за класифікацією ВООЗ був підтверджений патоморфологічно після резекції первинної пухлини. Всім 59 хворим було проведено максимальне безпечне видалення первинної пухлини в радикальному об'ємі: в переважній кількості спостережень (54 / 91,5%) – по перифокальній зоні; в 5 / 8,5% випадках – субтотально. В усіх 59 випадках хворим було проведено ад'ювантне променеве лікування після видалення первинної пухлини (сумарна вогнищева доза (СВД) 60 Гр, 30 фракцій), яке в 33 випадках було поєднане з алкілюючою ХТ (темозоломід 75 мг/м^2). У 31 / 52,5 % хворого після завершення конкомітантної ХТ продовжилось ХТ лікування (темозоломід 150-200 мг/ м^2). У більшості спостережень (51 / 86,4 %) РГБ було діагностовано за сукупністю клініко-радіологічних ознак; у 8 / 13,6 % хворих – патоморфологічно, після повторного хірургічного втручання. Кінцевими точками дослідження були загальна виживаність (ЗВ), безрецидивна (безпрогресивна) виживаність (БРВ) та виживаність після настання рецидиву (ВПР). Вивчався вплив на виживаність наступних кількісних та категоріальних факторів: стать, вік, функціональний статус, поєднання ад'ювантної ПТ з алкілюючою ХТ, хірургічне видалення РГБ, тип рецидивування ГБ, дозове навантаження за всі курси опромінення сумарно (за біологічно-ефективною дозою (BED_{11})) та при СРХ, кількість фракцій СРХ, об'єм мішені СРХ, термін безрецидивного періоду/виживаності (БРВ). Вплив на виживаність такого фактору як БРВ досліджувався шляхом розподілення когорти на три незалежні групи в залежності від тривалості безрецидивного періоду: група I – БРВ < 10 місяців; група II – БРВ від 10 до 20 місяців; група III – БРВ > 20 місяців. Виживаність хворих була проаналізована методом Каплана-Майера (КМ). Логарифмічний ранговий тест (для порівняння КМ кривих виживаності для різних досліджуваних груп) використовували для дослідження виживаності за бінарними предикторами. Порівняння впливу декількох категоріальних факторів на виживаність здійснювалось за допомогою χ^2-тесту (Pearson Chi-square test). Для дослідження впливу на виживаність кількісних коваріат використовували регресійний аналіз за

ISSN 1996-353X
ISSN 2311-6951

моделлю пропорційних ризиків Кокса. Співвідношення ризиків (hazard ratio, HR) розраховано з 95% довірчими інтервалами (ДІ). В результаті проведеного аналізу було виявлено наступне. Медіана ЗВ після СРХ РГБ склала 26,3 місяців (95% ДІ 17 – 45,5), медіана БРВ – 12,9 місяців (95% ДІ 8,4 – 25,6) , медіана ВПР – 9,8 місяців (95% ДІ 6,7 – 24,4). Дворічна ЗВ була досягнута більшою половиною (56%) хворих. Після СРХ 6-місячна виживаність склала 77%. Один рік після СРХ РГБ прожили 39% хворих, два роки після СРХ – 28% хворих. Такі фактори як функціональний статус за індексом Карновського (ІК) при СРХ РГБ (p = 0,00159), тривалість безрецидивного періоду (p = 0,02711) та проведення хірургічного видалення РГБ (p = 0,009391) продемонстрували статистично значущий вплив на ЗВ. Найкращу ЗВ у вибірці мали хворі із 90 балами за ІК; за умови настання рецидиву ГБ після 20 місяців і при виконанні резекції РГБ. Інші досліджені фактори не показали значущого впливу на ЗВ. Не було зафіксовано статистично значущого впливу на ВПР жодного із наступних досліджуваних факторів: стать, вік, функціональний статус за ІК, проведення ад'ювантної ПТ з алкілюючою ХТ, хірургічне видалення РГБ, тип рецидивування ГБ, дозове навантаження за всі курси опромінення сумарно (BED_{11}) та при СРХ (BED_{11}; ПД; СВД), кількість фракцій СРХ, об'єм мішені СРХ, БРВ. Хоча й хворі з РГБ відносяться до однієї з найменш обнадійливих щодо прогнозу категорій в нейроонкології, отримані нами дані підтверджують доцільність застосування СРХ з метою подовження виживаності таких пацієнтів та свідчать про відсутність асоційованої тяжкої променевої токсичності. Первинні біологічні властивості пухлини ймовірно відіграють пріоритетну роль щодо впливу на виживаність хворих із РГБ. Опромінення РГБ призводить до збільшення ВПР. Проте не можна виключити, що зміни, які відбуваються у біології рецидивної злоякісної гліоми після повторного опромінення, можуть нівелювати потенційний вплив на виживаність тих факторів, що мали предиктивну цінність до повторного опромінення.

Ключові слова: новоутворення, злоякісна гліома, гліобластома, нейрохірургічні втручання, рецидив, радіохірургія, виживаність.