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The phenomenon of long-term survival of patients with supratentorial glioblastomas: features of complex treatment and neuroimaging data

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Background. Glioblastoma is the most common primary malignant brain tumor with an extremely unfavorable prognosis. The frequency of the "longevity" phenomenon (>3 years of overall survival – OS) in this disease is 5–10 %. The reasons for the more favorable prognosis in these patients are still unclear.

Aim. To compare the clinical and MRI data as well as features of complex treatment of patients with supratentorial glioblastomas among the control group (OS <2 years) and study group (with the phenomenon of "longevity", OS >3 years).

Material and methods. This study included 41 patients with hemispheric glioblastomas: 17 with the "longevity" phenomenon (study group – long-term survival (LTS), prospective set); 24 patients in the control group (retrospective set). Taking into account the average age of patients, the following MRI features were examined: tumor localization relative to the frontal lobe; invasion of deep brain structures; the ratio of contrast-enhancing and non-contrast-enhancing parts of the glioma; tumor contrast intensity; localization of recurrent tumor (local/distant) in case of disease progression. Comparative analysis of complex treatment took into account the following parameters: the number of chemotherapy (ChT) courses and radiation regimens after the 1st operation and after disease recurrence; the fact and number of repeated tumor resections after recurrence; the presence of *IDH1* mutation.

Results. The localization of the lesion relative to the frontal lobe, the number of affected lobes of the brain and the invasion of deep structures did not differ significantly in the examined groups. Patients of study group (LTS, prospective set) were significantly younger than the patients of the control group (p <0.05). The tendency towards a single-lobe lesion was noted in the LTS group (p = 0.085). The average volume of the contrast-enhancing part of the tumor (according to MRI data in the T1 mode) in patients of LTS group was 34 cm^3, and the non-contrast-enhancing part (in the T2-FLAIR mode) was 105 cm^3, the ratio was 1: 3 (p >0.05). The tumor contrast intensity was 1.5 in average compared to the intact cerebral hemisphere. Among patients of LTS group, 8 patients (47 %) were re-operated due to disease recurrence, while in the control group there were no repeated operations (p <0.05). The results of the analysis of radiation therapy after the 1st operation were the follows: for LTS patients the median total radiation dose (TRD) was 58 (35–66) Gy, with no significant differences between the groups (p >0.05); the number of temozolomide courses in the LTS group were 9 (6–22), while in the control group it was 6 (3–10), p <0.05. The repeated radiotherapy (RT) in different regimens was applied in the LTS group in 52 % of patients, in the control group – 0 (p <0.05). The repeated ChT (17 (9–23) courses, mainly with bevacizumab) was applied in the LTS group in 65 % of patients, in the control group – 0 (p <0.05). The *IDH1* mutation was studied only in 15 patients: positive – in 1 (LTS group); negative – in 14 patients (7 from the control group).

Conclusion. The following significant differences were revealed: patients with supratentorial glioblastomas were younger in the LTS group. The important features of the complex treatment of patients in LTS group included statistically higher frequency of repeated resections in case of recurrence (47 %) and repeated sessions of radiotherapy (RT) in various modes (52 %); significantly more aggressive and prolonged ChT (with the predominance of temozolomide in the 1st line of treatment and bevacizumab in case of recurrence). There were no significant differences between two examined groups in tumor localization, intensity of its contrasting, the ratio of contrasted and non-contrast parts of the tumor, invasion of deep structures of the brain, involvement of functionally significant areas (FSA).

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Keywords: phenomenon of long-term survival, overall survival (OS), progression free survival (PFS), glioblastomas, magnetic resonance imaging (MRI), molecular genetic features, adjuvant treatment

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BACKGROUND

Brain glioblastomas remain a challenging problem for neurosurgeons and related specialists. Despite the fact that from 2010 to 2018 there was a doubling of the median overall survival (OS) for glioblastomas [1], the 3-year survival rate (or "longevity") for this disease remains low (Table 1).

According to the CBTRUS (Central Brain Tumor Registry of the United States) data [2], which includes 21,910 observations, the OS rate for glioblastomas is the following: 3-year – no more than 7.54 %; 5-year – less than 5 % of cases. Our previously published study [3] demonstrated predictors for favorable prognosis on patients with the "longevity" phenomenon with a verified diagnosis of "glioblastoma": young age, supratentorial location of the tumor, high Karnofsky index (KI) before surgery, surgical removal of the tumor.

The standard treatment procedures for patients with primary CNS tumors currently include surgery, radiotherapy (RT), and antitumor drug therapy. For patients with glioblastoma, the choice regimen for postoperative treatment is chemoradiation therapy (ChRT) with temozolomide: daily administration (75 mg/m^2) throughout the course of radiation therapy (RT) (30 fractions of 2 Gy), followed by 6–12 courses of temozolomide according to the 5/23 scheme [4].

While analyzing the data from 11 patients with glioblastomas and different long-term OS, the following positive prognostic factors were identified [5]:

- young age;
- individual approach to treatment;
- intensive chemotherapy (ChT) tactics – from 6 to 15 cycles of temozolomide in the 1st line and 2nd line ChT (in contrast to standard treatment protocols, limited in duration of therapy).

It is interesting to note, that patients with the "longevity" phenomenon in glioblastomas did not have the *IDH1* mutation [5]. Unfortunately, the researchers did not conduct a comparative analysis of MRI data of patients with glioblastomas in groups.

According to the world literature data, the role of repeated tumor resections in case of disease recurrence remains controversial [6]. A number of authors propose special scales for determining the prognosis of the disease in case of glioblastoma recurrence that take into account the tumor volume, the involvement of functionally significant areas (FSA) and the patient's preoperative condition according to the Karnofsky scale [7].

The search for common patterns of clinical, neuroimaging, and molecular genetic features in patients with glioblastomas and the "longevity" phenomenon is of great interest of nowadays.

The aim is to compare clinical and MRI data and features of complex treatment of patients with supratentorial glioblastomas – from the control group (OS <2 years) and with the phenomenon of "longevity" (OS >3 years, study group, LTS).

MATERIAL AND METHODS

Characteristics of examined patients

This study included 41 patients with hemispheric glioblastomas. Some of them were operated and observed at the N.N. Burdenko National Medical Research Center of Neurosurgery (hereinafter – Burdenko Neurosurgical Institute) (Table 2).

The *study group* of "long-term survivals" (LTS) included 17 patients with glioblastomas and the phenomenon of "longevity" (OS >3 years).

The *control group* included 24 patients with a median OS <2 years.

The *supratentorial tumors*: LTS group – in 9 (52.9 %) patients; control group – in 14 (58.3 %) patients.

The *microsurgical tumor removal* was performed in all 41 patients. Among LTS group, 8 patients were re-operated on due to disease recurrence (see Table 2), 2 patients were operated on three times. In approximately 50 % of cases in both groups, tumors were located near or directly in the FSA (speech motor cortex, pyramidal tract, arcuate fasciculus).

The surgical interventions were performed using neurophysiological monitoring of motor zones (motor cortex and pyramidal tract) and speech zones in consciousness (speech cortex and arcuate tract) in all patients with tumors in the FSA.

All patients underwent MRI evaluation in T1, T2, T2-FLAIR, DWI, T1+C modes. The analysis assessed the tumor localization, its volume (contrasted part – in T1 mode with contrast, non-contrasted – in T2 FLAIR) before surgery, recurrence localization, intensity of contrast agent accumulation, invasion of deep brain structures.

The analysis of the complex treatment of patients after the 1st operation (number of ChT sessions, RT regimens) and at the onset of recurrence (repeated operations, number of ChT sessions, RT regimens) was performed. The separate analysis of the *IDH1* mutation was conducted in 15 patients from both groups using the antibody method.

Table 1. World literature data on survival (OS/PFS) of patients with brain glioblastomas in 2010 and 2018

Year	Parameter	Median, month	Range (months), 95 % CI
2010	OS	**10.0**	8.8–11.2
	PFS	9.0	7.5–10.5
2018	OS	**23.0**	17.5–28.5
	PFS	20.0	16.9–23.1

Note. *OS – overall survival; PFS – progression free survival. Growth dynamics ($p < 0.05$) was noted in 635 patients.*

During the survival analysis, the fact of death and its date were known for 24 patients in the control group and for 5 in the LTS group. The dates of recurrence were available for analysis in 16 patients of LTS group and in 5 of control group. OS was defined as the period from the first operation to the date of death (if any) or to the date of the patient's last consultation at the Burdenko Neurosurgical Institute. Progression-free survival (PFS) was calculated as the period from the last operation to the time of a new recurrence of the disease.

RESULTS

1. Clinical analysis of patients in the examined groups

The median age in the LTS group was 43 years, in the control group – 53, $p < 0.05$ (Fig. 1).

The one-lobe lesions were detected in 15 (88 %) patients of LTS group and were somewhat less common in the control group – 15 (62.5 %) patients, $p > 0.05$.

All patients of LTS group received complex treatment after the 1st operation (RT in the classical fractionation mode) and temozolomide therapy. RT analysis revealed the following: the median total focal dose (TFD) after the 1st operation in LTS group was 58 (35–66) Gy, in control group – 58.3 (45–50) Gy, the differences were insignificant. The number of temozolomide courses after the 1st operation was the following: LTS group – 9 (6–22), control group – 6 (3–10), $p < 0.05$ (Fig. 2).

The repeated tumor resections in case of disease recurrence were performed in 8 (47 %) patients of LTS group, and there were no cases in control group, $p < 0.05$ (Fig. 3).

Repeated RT upon recurrence in various modes (classical fractionation, hypofractionation and radiosurgery) was received by 9 (53 %) patients of LTS group, and none in the control group, $p < 0.05$ (Fig. 4).

The repeated courses of ChT upon disease recurrence were received by 11 (73.3 %) patients in LTS group, and none in the control group ($p < 0.05$). The number of repeated courses of ChT upon disease recurrence was 17 (9–23), with bevacizumab-based regimens mainly used (Fig. 5).

No differences were found (in all cases $p > 0.05$) during comparative analysis of the data in both groups for the following factors:

1) gender;

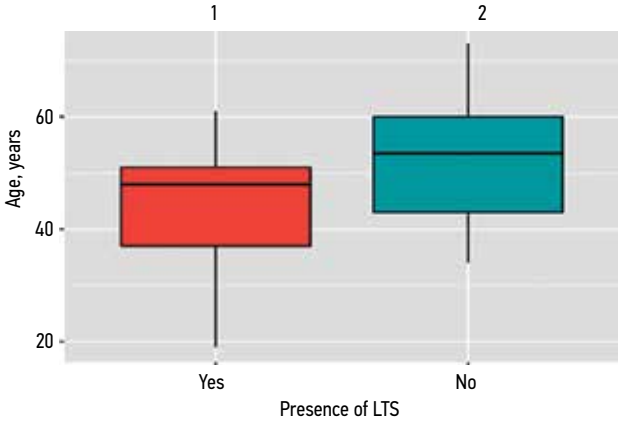

Fig. 1. *The differences in age (median) of patients in the examined groups ($p < 0.05$): 1 – group of "long-term survivals" (LTS) with overall survival (OS >3 years); 2 – control group (OS <2 years)*

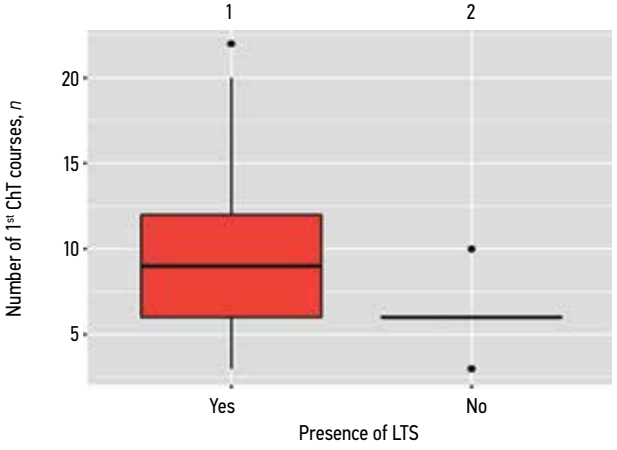

Fig. 2. *Patients with the phenomenon of "longevity" (LTS) were significantly more likely to have long courses of chemotherapy (ChT) with temozolomide after the 1st operation ($p < 0.05$): 1 – LTS group; 2 – control group*

2) the number of affected brain lobes (1 *vs* 2 or more);
3) invasion of deep structures;
4) involvement of the FSA;
5) side of the lesion;
6) frontal lobe lesion;
7) TRD during RT after the 1st operation;
8) the presence of *IDH1* mutation.

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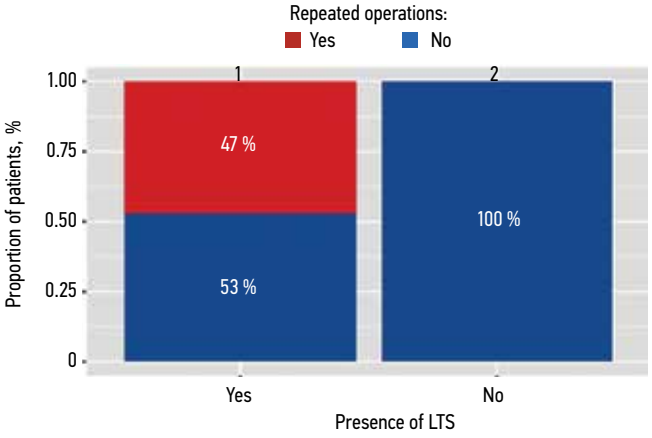

Fig. 3. *The effect of repeated operations on the fact of "longevity" (LTS) in glioblastomas (p <0.05): 1 – LTS group; 2 – control group*

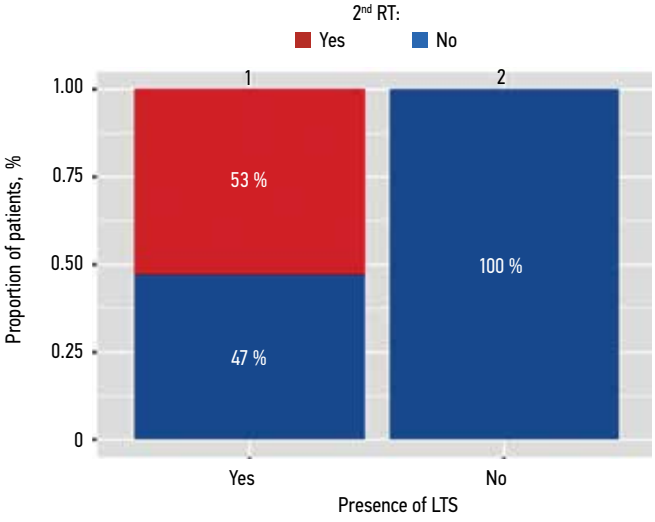

Fig. 4. *The effect of repeated radiotherapy (2nd RT) in case of recurrent glioblastoma on the phenomenon of "longevity" (LTS) (p <0.05): 1 – LTS group; 2 – control group*

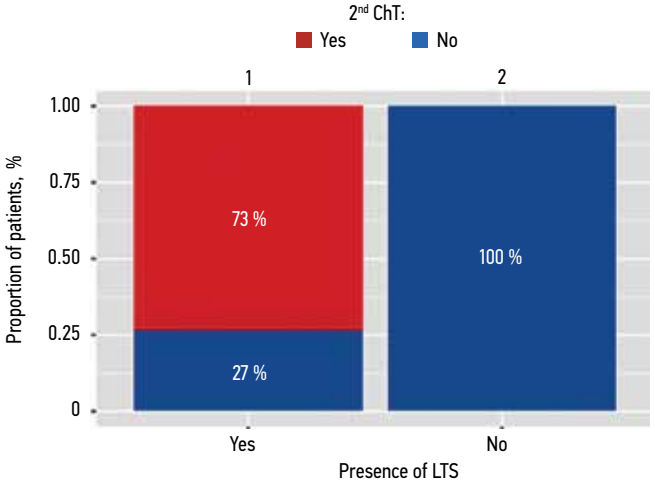

Fig. 5. *The effect of repeat chemotherapy courses (2nd ChT) based on bevacizumab in case of glioblastoma recurrence on the phenomenon of "longevity" (LTS) (p < 0.05): 1 – LTS group; 2 – control group*

Table 3 presents the analysis of the clinical factors influencing the development of the "longevity" phenomenon in the examined groups.

Thus, LTS patients with glioblastomas were significantly younger, and also tended to have a lesion of one lobe ($p = 0.085$). Important features of the complex treatment in the LTS group were the following: statistically higher frequency of repeated resections in case of recurrence (47 %) and repeated RT sessions in various regimens (52 %); significantly more aggressive and prolonged ChT (with a predominance of temozolomide in the 1st line of treatment and bevacizumab in case of recurrence).

2. Volumetric analysis of preoperative MRI data of patients with the phenomenon of "longevity"

In patients of both groups, the non-contrast-enhancing part of the tumor prevailed over the contrast-enhancing part

Table 2. Clinical data of the studied patients with glioblastomas

Parameter	LTS group (17 patients)	Control group (24 patients)
OS (from 1st operation), years	>3	<2
Age (median), years	43	53
Gender, *n*: male female	 10 7	 14 10
Tumor localization, *n* (%):	Supratentorial	
FSA one lobe of the brain	9 (52.9 %) 15 (88 %)	14 (58.3 %) 15 (62.5 %)
Surgical treatment (tumor removal), *n*	27, among them 17 – primary resection, 8 – repeated operation, 2 – three operations	24
MRI volumetric analysis, *n*	17 (before and after operation)	24 (before operation)

Note. *FSA — functionally significant areas; LTS — long-term survival (OS >3 years); MRI — magnetic resonance imaging; n — number of patients; OS — overall survival.*

Table 3. Analysis of clinical factors in examined groups of patients with glioblastomas

Parameter	Characteristic of parameter	LTS group (17 patient)	Control group (24 patient)	*p*
Gender, *n* (%)	Female	7 (41.2)	10 (41.7)	1.000
	Male	10 (58.8)	14 (58.3)	
Age, mean (SD)		43.00 (12.85)	52.92 (10.92)	**0.011**
Number of affected brain lobes, *n* (%)	>1	2 (11.8)	9 (37.5)	**0.085**
	1	15 (88.2)	15 (62.5)	
Repeated resections in case of recurrence, *n* (%)	Yes	8 (47.1)	0 (0.0)	**<0.001**
	No	9 (52.9)	23 (100.0)	
RT after 1st operation, *n* (%)	Yes	17 (100.0)	9 (90.0)	0.370
	No	0 (0.0)	1 (10.0)	
ChT after 1st operation (number of courses), median [quartiles]	Temozolomide	9.00 [6.00. 12.00]	6.00 [6.00. 6.00]	**0.031**
Repeated RT, *n* (%)	Yes	9 (52.9)	0 (0.0)	**0.009**
	No	8 (47.1)	23 (100.0)	
Repeated ChT, *n* (%)	Yes	11 (73.3)	0 (0.0)	**<0.001**
	No	4 (26.7)	24 (100.0)	
Mutation *IDH1*, *n* (%)	*IDH1*–	7 (87.5)	8 (100.0)	1.000
	IDH1+	1 (12.5)	0 (0.0)	
Invasion of deep structures, *n* (%)	Yes	1 (5.9)	4 (16.7)	0.382
	No	16 (94.1)	20 (83.3)	
FSA, *n* (%)	Yes	9 (52.9)	14 (58.3)	0.760
	No	8 (47.1)	10 (41.7)	
Side of lesion, *n* (%)	Both	0 (0.0)	1 (4.2)	0.271
	Left	6 (35.3)	13 (54.2)	
	Right	11 (64.7)	10 (41.7)	
Frontal lobe lesion, *n* (%)	Yes	10 (58.8)	8 (33.3)	0.125
	No	7 (41.2)	16 (66.7)	
Recurrence, *n* (%)	Yes	16 (100.0)	5 (100.0)	–
Death, *n* (%)	No	5 (100.0)	24 (100.0)	–

Note. *Mean – average value; n – number of patients; p – level of statistical significance; SD – standard deviation; LTS – "long-term survival"; RT – radiation therapy; FSA – functionally significant areas; ChT – chemotherapy; (–) no data (retrospectively, it is impossible to reliably determine the number of patients in the control group who dropped out of observation, as well as the fate of the rest in the future – whether they died or had recurrences)*

(Table 4). The average tumor volume in the LTS group according to MRI data in T1 mode with contrast was 34 (0–61) cm^3; in T2/FLAIR mode – 105 (8–213) cm^3. No significant differences in tumor volumes were found between the examined groups (p >0.05).

The intensity of tumor contrast was measured in conventional units (CU), which were obtained by the ratio of the contrast intensity values of the examined part of the tumor and the intact side, taken as one. On average, the intensity of tumor contrast did not differ in both groups (p >0.05). Also, the presence of hemorrhage in the tumor did not affect the frequency of the "longevity" phenomenon (p >0.05). The above mentioned neuroradiological features are presented in Table 4.

In addition, the lowest value of the measured diffusion coefficient (MDC) was calculated in 4 patients, the obtained data ranged from 304 to 605, the average value was 475 ± 127.29. The differences in the groups were not

Table 4. The comparative characteristics of the main neuroradiological features in glioblastomas in patients of control group and LTS group

Factor	LTS group (17 patients)	Control group (24 patients)	*p*
Mean volume of tumor part, cm^3 contrast-enhancing non-contrast-enhancing	 34 (0–61) 105 (8–213)	 38 (1–105) 99 (6–188)	 >0.05 >0.05
Ratio of contrast and non-contrast-enhancing parts of the tumor, cm^3	1 : 3	1 : 2.6	>0.05
Contrast intensity, conventional units*	1.5	1.46	>0.05
Presence of hemorrhage in the tumor, n/n_{total} (%)	11/17 (64 %)	10/24 (56 %)	>0.05
Local progression of the disease without distant foci, *n*	17	24	>0.05
Radicality of tumor resection, *n*	17 (total and subtotal resection)	–	–

Note. *n – number of patients with a certain parameter; n_{total} – total number of patients; p – level of statistical significance; (–) volume of resection was not assessed, since the control group of patients was recruited retrospectively and, according to the case records, postoperative CT was performed only to exclude postoperative hemorrhagic complications. In this regard, the assessment of the volume of glioblastoma resections was difficult to perform.*
**Conventional units are obtained by the ratio of the values of the contrast intensity of the studied part of the tumor and the intact side, taken as one.*

affected by such factors as tumor volume, the ratio of contrast-enhancing and non-contrast-enhancing parts of glioblastoma, the intensity of contrast agent accumulation, and the presence of hemorrhage into the tumor. All patients showed predominantly local disease progression without distant foci.

3. *IDH1* mutation analysis in groups

The examination was conducted to determine the presence of mutation (immunohistochemical method) in 15 patients of both groups: 8 from the LTS group, 7 from control group. *IDH1* mutation was not detected in 7 of 8 patients of the LTS group and in all 7 patients from control group. Based on the analysis of data from 15 patients of both groups, it can be tentatively concluded that the presence of *IDH1* mutation does not affect the development of the "longevity" phenomenon.

CLINICAL CASE

Patient H., *50 years old, first noticed numbness in the fingers of his left hand in October-November 2013, also he had twice tonic seizures in his left hand, as well as episodes of disorientation and short-term speech disorders. MRI data (17.03.2014) of the brain with contrast enhancement indicated an intracerebral tumor of the right frontal-parietal region with a cystic component (Fig. 6). Patient underwent surgery on 08.04.2014 at the Burdenko Neurosurgical Institute for glioblastoma of the right frontal-parietal region.*

According to biopsy No. 11615–19/14 (08.04.2014), the morphological picture and immunophenotype corresponded to glioblastoma without identified mutation of the IDH1 R132H gene. According to the WHO classification, WHO grade IV; methylation of the promoter region of the MGMT gene was not detected.

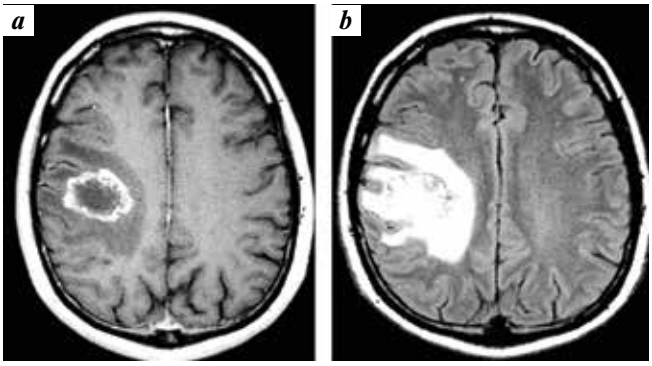

Fig. 6. *Preoperative (17.03.2014) MRI tomograms (axial scans, contrast enhancement) of patient H. with an intracerebral tumor of the right frontoparietal region with a cystic component: a – T1 mode with contrast; b – T2 FLAIR mode*

At the time of the operation, the condition was satisfactory, KI 80 points. Neurological symptoms were the following: decreased deep types of sensitivity in the left hand, mainly in the thumb and index finger; convulsive twitching of the muscles of the left hand; episodes of dizziness with spasticity in the left hand; severe coordination disorders in the left limbs (due to impaired deep types of sensitivity).

The patient underwent a course of combined ChRT to the area of the removed tumor bed (single focal dose (SFD) 2 Gy, average TRD 62 Gy), then 20 courses of chemotherapy with temozolomide at the Russian Scientific Center of Roentgenoradiology from 26.05.2014 to 26.06.2014. The patient's condition remained stable, moderate hemiparesis on the left persisted, mainly in the arm.

During the next follow-up visit (27.11.2017) the local continued tumor growth with spread downwards from the residual formation was revealed compared to the previous MRI (26.07.2017). These findings were confirmed by positron

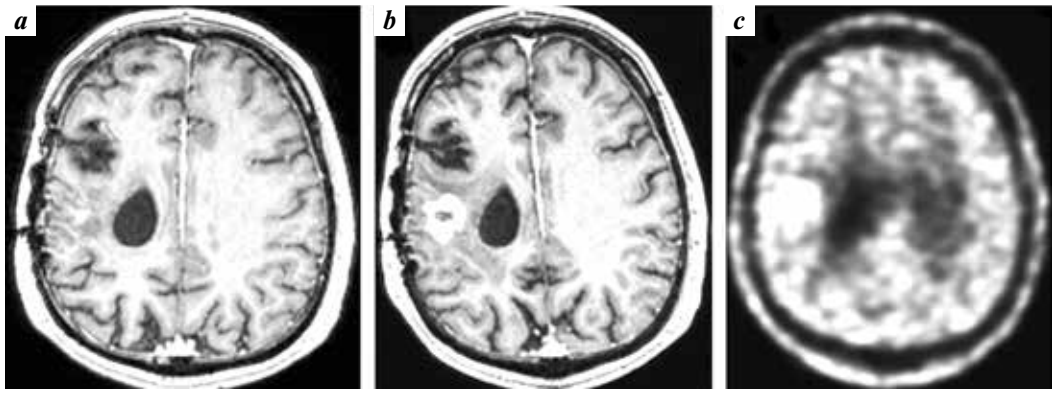

Fig. 7. *A series of control MRI scans of patient H. with an intracerebral tumor of the right frontoparietal region with a cystic component: a, b – MRI, T1 mode with contrast, axial scan; c – PET of the brain with methionine, axial scan. Local continued growth of glioblastoma with spread downwards from the residual formation is noted*

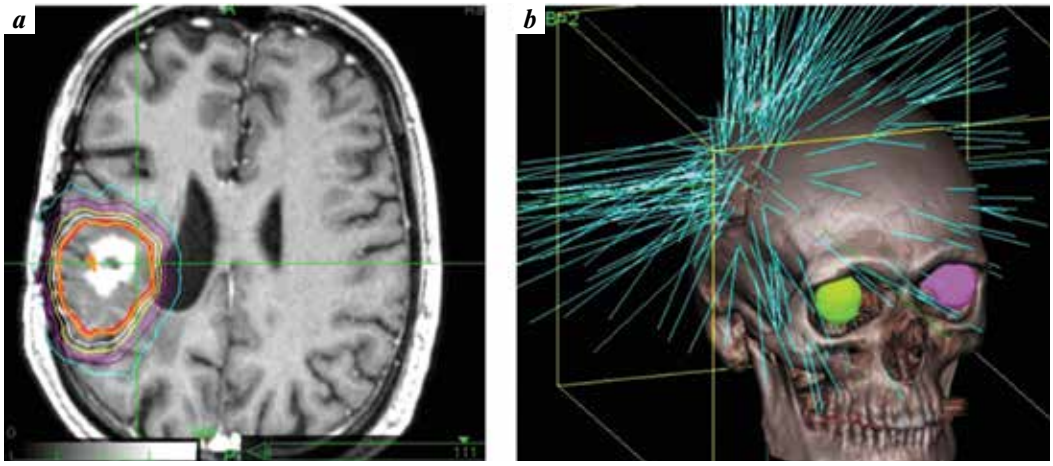

Fig. 8. *Elements (a, b) of the 2nd course planning (12.2017) of stereotactic RT using the CyberKnife device for the lesion in the parietal region of the right hemisphere in case of disease recurrence in patient H.*

emission tomography combined with computed tomography (PET-ChT) with ^{11}C-methionine (04.12.17): the amino acid accumulation index in PET in the new lesion was 2.35 (Fig. 7). The recurrence-free period was 44 months. The general satisfactory condition was maintained (KI 80 points).

The 2nd course of stereotactic RT was performed (18–20.12.17) using the CyberKnife apparatus (Fig. 8): an average dose of D_{av} = 30 Gy was delivered to the lesion (volume 28.5 cm^3) in the parietal region of the right hemisphere (GTV + 5 mm, according to PET-ChT with ^{11}C-methionine) in 5 fractions, with the maximum dose for the target D_{max} = 27 Gy. The condition during radiation was satisfactory. Neurological status was without negative dynamics. After each session, 4 mg of dexamethasone was administered intramuscularly.

Another 12 courses of ChT with temozolomide were administered; patient H. was diagnosed with thrombocytopenia (up to 104 × 10^3 U/μl) and suffered from herpes zoster.

Control MRI (14.11.2018) revealed negative dynamics compared to the previous ones: the appearance of small foci of contrasting downwards and medially from the previously existing lesion. Neurological status without pronounced negative dynamics. Recurrence-free period is 10.8 months. It was recommended to change the ChT line to bevacizumab (400 mg intravenously drip) + irinotecan (200 mg intravenously drip once every 2 weeks), provided that blood counts are satisfactory.

The 3rd course of stereotactic 3D conformal RT was performed (26.11.2018 to 17.12.2018) to the lesion in the temporoparietal region of the right hemisphere with a marginal capture of 3 mm (PTV volume = 93 cm^3). The 15 fractions were delivered with a single boost dose (SBD) of 3 Gy to a TRD of 45 Gy on the TrueBeam linear electron accelerator, radiation was performed from three sides – from three independent arcs of conformal dynamic rotation using volumetric intensity-modulated arc therapy (Volumetric Modulated Arc Therapy, VMAT) technologies (Fig. 9).

The 12 injections of bevacizumab in combination with irinotecan and 6 injections of bevacizumab in monotherapy were performed. The local continued growth was noted (MRI dated 03.10.2019) compared to the previous MRI. The recurrence-free period was 10.2 months. The chemotherapist's recommendations were the following: bevacizumab (400 mg

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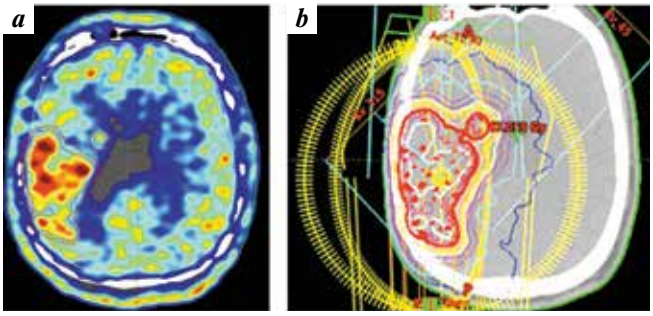

Fig. 9. *Elements (a, b) of planning the 3rd course of stereotactic 3D conformal radiotherapy (12.2018) of a lesion in the right temporo-parietal region because of disease recurrence in patient H.*

intravenously drip) + irinotecan (200 mg intravenously drip once every 2 weeks).

The control PET/ChT of the brain with ^{11}C-methionine in the right frontal-parietal region, an ametabolite area of post-radiation and postoperative changes is determined periventricularly to the dilated posterior parts of the body of the right lateral ventricle. Around this area, a zone of hyperfixation of the radiopharmaceutical drug with a maximum accumulation index (uptake ratio) UR_{max} up to 2.01, metabolic volume of 23 cm^3 is detected. A decision was made to conduct the 4th course of ChT.

The 4th course of stereotactic conformal RT was performed (16–22.10.2019) on the TrueBeam linear electron accelerator in accordance with the plan: an average dose for the target D_{mean} of 32.5 Gy (in 5 fractions) from 4 arches using VMAT technology was delivered to the target in the right temporal lobe, taking into account the PET-ChT data with ^{11}C-methionine (PTV volume = 20.4 cm^3). The load on critical structures is within the tolerance limits. Patient H. tolerated the radiation satisfactorily, without an increase in neurological symptoms and radiation toxicity (Fig. 10).

Subsequently, ChT was continued according to the scheme: bevacizumab + irinotecan. According to RANO criteria, disease stabilization lasted until March 2020, at which time continued growth began. Neurological status without significant negative dynamics. Recurrence-free period was 5 months.

Since April 2020, the patient received ChT according to the different scheme: bevacizumab + mustoforan. Control MRI (05.30.2020) revealed progression in the frontoparietal region and corpus callosum: an increase in the size of previously detected foci. At the same time, structures in the brainstem region did not progress. The next MRI (08.03.2020) showed continued growth.

Compared to the previous brain PET/ChT data, the next control showed a tendency towards an increase in the metabolic activity of ^{11}C-methionine of the tumor tissue along the contour of the postoperative cyst in the right frontal-parietal region: UR_{max} 2.29, V 48.09 cm^3 (03.24.2020) and UR_{max} 2.44, V 48.6 cm^3 (08.10.2020). Due to the lack of nivolumab, it was decided to prescribe and administer (08.17.2020) carboplatin (300 mg) + bevacizumab (400 mg). Patient H. continued to be observed 76 months after the diagnosis.

The presented clinical case demonstrates the importance of clinical and demographic factors: relatively young age (50 years), hemispheric localization of the tumor, absence of distant foci of the disease, long-term repeated courses of ChT and RT in case of disease recurrence.

DISCUSSION

In the recent years, there has been an improvement in outcomes with combined treatment in the surgery of high-grade gliomas and, above all, glioblastomas. Thus, the median OS was the following: in 2001–2003 – 7.4 months; in 2010–2012 – 10.6 months; in 2015–24.1 months with repeated resections and up to 20.4 months in the case of one surgical intervention followed by combined treatment. The 2-year survival rate for glioblastomas was: in 2001–2003 – 8.2 %, in 2012–2012 – 18.3 % [8].

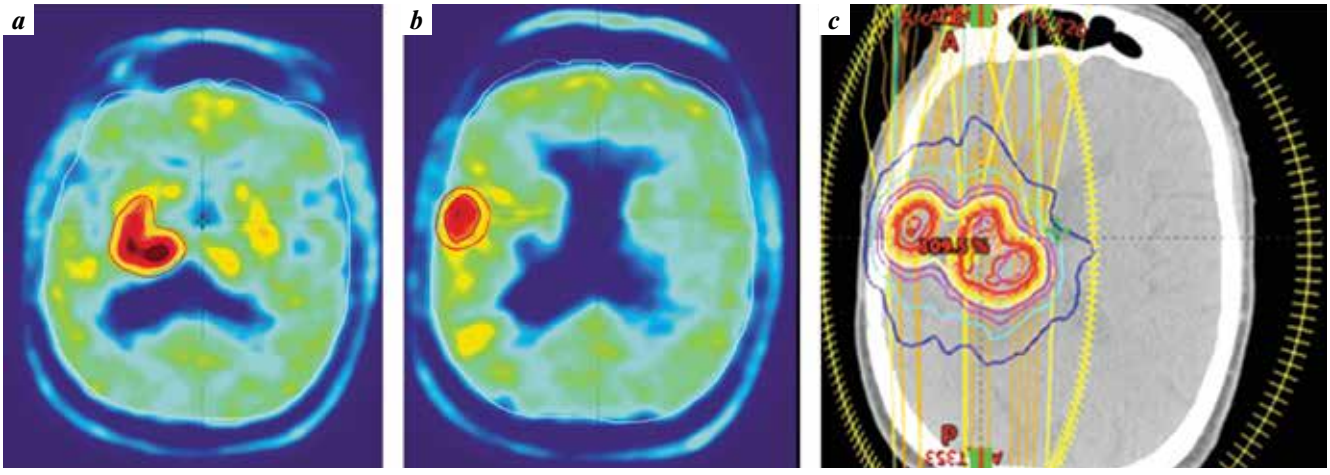

Fig. 10. *Elements (a, b, c) of planning the 4th course (10.2019) of stereotactic conformal radiation therapy on TrueBeam (linear electron accelerator) to a lesion in the right temporal lobe because of disease recurrence in patient H.*

Table 5. Increase in median overall survival of patients with glioblastomas from 1999 to 2020 due to changes in chemotherapy regimens

The literature source	Year	Adjuvant treatment regimen after surgery	Median OS, months
[10]	1999	RT	12.6
[11]	2009	RT	12.5
[12]	2014	ChRT (temozolomide)	17.6
[13]	2020	ChRT (temozolomide + bevacizumab)	21.5

Note. *OS – overall survival; RT – radiation therapy; ChRT – chemoradiation therapy.*

The literature source [9] presents an approximate picture of the dynamics of the median OS for patients with glioblastoma in cases of different chemotherapy regimens:

- with temozolomide – from 12.6 months [10] and 12.5 months [11];
- without temozolomide, but also without bevacizumab: up to 17.6 months [12];
- in a series of patients with recurrent glioblastoma: temozolomide + bevacizumab in case of recurrence – up to 21.5 months [13] (Table 5).

Thus, in the last decade, there has been a tendency towards an increase in the median OS for patients with glioblastomas, and in the last few years, according to various authors, an increase in life expectancy cannot help being associated with the use of bevacizumab (probably in the 2nd line of treatment) [9]. Younger age, surgical intervention to reduce the tumor volume, ChRT treatment and methylation of the *MGMT* gene promoter are associated with the longer survival of patients with glioblastomas [14].

Our trial also revealed a significant impact on the fact of "longevity" of such clinical factors as age, duration of ChT with temozolomide after the 1st operation and bevacizumab after the recurrence onset [15].

However, in our opinion, the role of repeated resections and repeated RT courses in case of disease recurrence is also important. They contribute to the development of "longevity" in glioblastomas. Thus, a major role of repeated resections in improving the survival rates of patients with glioblastomas is noted by A.M. Stark et al. [16] on a large clinical material (492 patients with glioblastomas). Repeated RT plays an important role in patients with the LTS phenomenon [17], which is consistent with our data.

According to S. Mukherjee et al. (2020) [18], a significant effect of the following factors on OS in patients with glioblastomas was revealed: repeated tumor resection (in this group of patients, OS increases by 4 months); young age; high Karnofsky score; later recurrence dates; resection volume of the contrasted part of the tumor more than 80 %; positive expression of *MGMT* [17].

At the same time, according to [5], the radicality of the operation did not significantly affect on the survival of patients over a period of more than 3 years. Long-term survival was affected by the young age of patients and a positive response to ChT with temozolomide. The following clinical signs did not have a statistically significant effect (2017 and 2019) [5] on survival for more than 3 years: patient gender, Karnofsky performance status; tumor localization; lesion volume or number of affected lobes; number of surgeries and volume of cytoreduction. According to our data, patients with one-lobe lesion without invasion of deep brain structures (lateral ventricles, basal ganglia, corpus callosum) were somewhat more common in the LTS group compared to the control group.

In the present study, when analyzing MRI data in examined groups, no significant differences were found in the overall tumor volume and its contrast-enhancing and non-contrast-enhancing parts. It was also found that long-term survival in glioblastomas was not affected by the fact of hemorrhage into the tumor, the intensity of contrast agent accumulation, and the localization of the tumor relative to the frontal lobe.

One of the most important parameters determining the duration of OS and PFS in glioblastomas is radicality of the surgery [19]. New surgical treatment techniques that have allowed to increase the radicality of surgical interventions for glioblastomas include metabolic navigation, the use of intraoperative ultrasound scanning, and MRI. Thus, the surgery of high-grade gliomas, the frequency of total resections increased from 36 % to 74.5 % when using 5-aminolevulinic acid (5-ALA) [20]. It should be noted that, according to the literature, over past 10 years, there has been increase in the number of more radical operations for brain gliomas. Thus, the frequency of radical operations for resections of low-grade gliomas has significantly increased from 21.5 % (2006) to 60.8 % (2017) [21].

In the present study, all patients in the LTS group underwent total and subtotal resection of the contrast-enhancing part of the tumor. Unfortunately, there were no early postoperative MRI data in the control group to perform a comparative analysis of the effect of resection radicality on survival in our LTS group. However, in our opinion, the radicality of glioblastoma resection also contributes to "longevity".

Infiltrative growth of glioblastomas remains a major problem for neurosurgeons. A number of authors have shown that the degree of glioblastoma invasion, according to postmortem studies, is variable: 20–27 % of tumors have infiltration less than 1 cm from the edge of the primary

tumor; 20 % – more than 3 cm; 8 % – pronounced dissemination beyond the tumor [22–24].

One of the most important factors limiting a neurosurgeon in tumor resection (in addition to its localization) is the severity of infiltration, which determines the resectability of the tumor. Naturally, the greater radicality of the operation can be expected in the case of hemispheric, well-demarcated gliomas without invasion of deep structures and FSA of the brain. The influence of the infiltrative properties of gliomas, as well as the ratio of the contrasted and non-contrast parts of glial tumors on surgical tactics are important aspects for future study.

In the present study, no differences were found between the patients of the two groups (LTS and control) in the predominance of the non-contrast-enhancing part of the tumor over the contrast-enhancing part, as well as in the intensity of contrast (see Table 4). The non-contrast-enhancing part of the glioblastoma is where the disease most often relapses, therefore, this part of the tumor (if possible) should also be subjected to combined treatment [25].

It should be taken into account that the non-contrast-enhancing part of the glioblastoma is extremely difficult for a neurosurgeon due to the difficulty of intraoperative determining the tumor borders [26].

The expected difference in the volume of the non-contrast-enhancing part of the tumor in the compared groups of patients with glioblastomas was not found in the present study. At the same time, a worse prognosis regarding OS in patients with glioblastomas (both initially and during treatment with bevacizumab) was noted [27] with an increase in the MR signal in the T1 and T2 FLAIR mode in the tumor and the adjacent brain area.

In the considered series of patients with glioblastomas with the phenomenon of "longevity", a low frequency of invasion of deep brain structures was noted (6 %), which is extremely important for a neurosurgeon during surgical intervention. The involvement of the corpus callosum and basal ganglia in glioblastoma leads to a decrease in survival rates: OS <6 months [28]. The involvement of the lateral ventricles in tumor growth is also a poor prognostic factor [29].

According to the world literature, tumor localization near the FSA affects OS in glioblastomas. Based on the study of 322 patients, special prognostic scales Sawaya (I, II, III) and Friedlein (A and B) were created, which take into account the proximity of the tumor to the FSA. Using these scales, significantly lower OS periods were shown when glioblastomas were localized in or near the FSA [30]. In the present study, the effect of tumor localization near the FSA on the prognosis of the disease was not revealed. This may be due to the equal distribution in percentage of tumors located in or near the FSA in the compared groups.

There were also no differences in the frequency of detection of positive *IDH1* mutation in the study groups, possibly due to the small number of patients in this study (15 people), as well as the previously used method [5] of immunohistochemical study of this mutation. The most informative molecular markers in the study of the phenomenon of "longevity" in glioblastomas are mutations of the *IDH1/2* gene and methylation of the *MGMT* gene promoter, which are associated with a better response to standard clinical care [31].

The role of decreased expression of the *CHI3L1, FBLN4, EMP3, IGFBP2, IGFBP3, LGALS3, MAOB, PDPN, SERPING1* and *TIMP1* genes is also discussed in the literature. Due to the small number of patients with glioblastomas and with the LTS phenomenon, comparative studies of genetic differences with patients with standard OS periods are difficult to conduct. To improve patient management and clinical outcomes, a thorough "omics" or multimodal approach is needed to identify the differences between short-term and long-term survival of patients with glioblastomas [31].

CONCLUSION

In the presented series of patients, "long-term survival" patients with glioblastomas were significantly younger, had a tendency for one-lobe localization of the tumor, and no invasion into deep brain structures (corpus callosum, basal ganglia, thalamus). Long-term survival was not significantly affected by the total tumor volume, the presence of hemorrhages in tumor, the intensity of contrast, the ratio of the volumes of the contrast and non-contrast parts of the glioblastoma, the side of the lesion, and the proximity of functionally significant areas.

About 50 % of patients with the "longevity" phenomenon, in contrast to patients with low survival, were re-operated upon recurrence of the disease. All patients in the "long-term survival" group received significantly longer courses of chemotherapy both after the 1st operation and during recurrence of the disease. The high frequency of repeated radiation therapy for tumor recurrences in patients with the "longevity" phenomenon seems important. Patients in both study groups did not differ in the frequency of *IDH1* mutation detection.

LIMITATIONS OF THE CURRENT STUDY

A comparative analysis of the effect of glioblastoma resection radicality on the "longevity" phenomenon was not performed, since there were not enough early postoperative MRI scans in the retrospective control group.

IDH1 mutation was detected in only 15 of all 41 patients in the series; immunohistochemistry (R132H) was used in all cases.

A more detailed genetic study of patients with glioblastomas and the "longevity" phenomenon requires the use of next-generation sequencing to analyze *IDH1/2, ATRX, TERT*, *p53*, *EGFR, PDGFRA, MGMT*, and *H3F3*, which was performed in single cases (4 patients) in this study.

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N.N. Maslova, N.V. Yuryeva: editing of the article;
A.Yu. Belyaev: collection and analysis of archival documents;
D.R. Akhmadullina, A.I. Batalov, K.S. Solozhentseva, D.V. Gusev: collection and analysis of archival documents, data analysis and interpretation;
M.V. Ryzhova, G.L. Kobyakov, O.V. Absalyamova: data analysis and interpretation;
D.I. Pitskhelauri, D.Yu. Usachev, N.E. Zakharova, A.V. Golanov, I.N. Pronin: research idea and design of the study;
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