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SURGICAL TREATMENT OF GLIOMAS IN MOTOR ZONE UNDER CONTROL OF NEUROPHYSIOLOGICAL MONITORING

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Background. Primary tumors of central nervous system account for about 2 % of all human tumors. Generally, the tumor removal is a necessary treatment step. The main goal of the intracerebral tumors surgical treatment is the formation removal in the most radical physiologically possible way, because this directly affects the patients' life length and its quality.

Aim. To assess the results of surgical treatment of motor zone tumors and identify predictors of development of irreversible motor disorders.

Materials and methods. A retrospective analysis of results of surgical treatment from 105 patients with tumors that affect corticospinal tract and primary motor cortex of the brain or localized in close proximity to those areas (up to 10 mm). All patients were treated in the neurosurgical department of Pirogov National Medical and Surgical Center, Ministry of Health of Russia (Moscow) in the period from 2014 to 2020. There were 48 (46 %) men, 57 (54 %) women aged from 22 to 79 (mean age – 47.6 ± 14.5) years. Tumors volume before surgery ranged from 5.16 to 283.3 (mean volume – 80.9 ± 55.1) cm^3.

The tumors' size and their relationship with the surrounding structures were assessed by pre-surgery magnetic resonance imaging and magnetic resonance tractography. For the intraoperative assessment of motor zone state dynamics, the transcranial electrical stimulation (n = 105, 100 %) and direct transcortical stimulation (with the eight-contact electrode stripe) (n = 68, 64.8 %) of the primary motor cortex were used. to assess the proximity of the motor zones, a straight cortical and subcortical bi- or monopolar electrical stimulation was used (n = 105, 100 %).

Results. Sixty-seven tumors (63.8 %) were removed completely, close to total removal was in 22 (20.9 %) tumors, 11 (10.5 %) tumors removal was subtotal and 5 (4.8 %) tumors were removed partially. Tumor volume after surgery ranged from 0 to 84.4 (mean volume – 3.54 ± 5.01) cm^3, Development of novel motor deficiency or increase in pre-surgery motor deficiency was observed in 46 (43.8 %) patients 24 hours after surgery and in 32 (30.5 %) of them 7 days after the treatment. However, during course of conservative therapy, the majority of patients showed regress of motor deficit and it remained only in 12 (11.4 %) patients on examination that was performed 6 months after surgery.

Assessment of factors affecting development of persistent motor deficiency revealed its statistically significant association with intraoperative response decrease according to transcranial stimulation ($p < 0.001$) and transcortical stimulation ($p < 0.001$) data. There were no significant changes in the functional status of patients during postoperative period depending on strength of the direct stimulation when the resection was stopped ($p = 0.9$) or depending on radicality of tumor removal ($p = 0.393$).

Conclusion:

1. Removal of tumors of motor cortex and corticospinal tract using the multimodal neurophysiological mapping allows to achieve maximal resection of the tumor tissue with good functional outcomes. All of the above leads to significant improvement of patients' life quality and allows further chemoradiotherapy.
2. Combined use of 4 methods of the neurophysiological mapping (transcranial, transcortical, direct cortical ang subcortical stimulation) helps to minimize the disadvantages of each of the methods and achieve radicality of the motor zone tumor removal with maintaining their functional status.
3. Motor deficiency in patients increases after removal of motor zone tumors and then gradually restores to the original level or is improved 6 months after surgery.
4. A predictor of development of persistent motor deficiency is decrease in amplitude of motor evoked potentials by 50 % or more from baseline (according to transcranial and transcortical neurophysiological stimulation data).
5. When the motor evoked potentials in response to 1 mA direct monopolar neurostimulation are preserved then resection of the tumor is not a predictor of irreversible motor disorders during postoperative period.

Keywords: brain tumors, gliomas, neurophysiological monitoring, motor zones tumors, corticospinal tract

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INTRODUCTION

Primary tumors of central nervous system account for about 2 % of all human tumors. According the Central Brain Tumor Registry of the United States, CBTRUS, such tumors are observed in 23.8 cases per 100 thousand population in 2017 and an annual increase in diagnosed cases is revealed [1]. The most common primary malignant tumor of central nervous system is glioblastoma (14.5 % of all tumors and 48.6 % of malignant ones).

Generally, the tumor removal is a necessary treatment step [2, 3]. The main goal of the intracerebral tumors surgical treatment was stated several decades ago: the radical formation removal in the physiologically possible way, because this directly affects the patients» life length and quality [4, 5]. But often the radicality of formation removal is linearly linked to postoperative neurological status of the patient which is especially important when motor zones are affected since motor disorders can interfere with subsequent chemoradiotherapy [6].

The objective of the study is to evaluate the results of surgical treatment of gliomas in motor zones and identify predictors of development of irreversible motor disorders.

MATERIALS AND METHODS

The results of surgical treatment of 105 patients with gliomas in brain motor zone were analyzed retrospectively. The motor zones included formations affecting the corticospinal tract (CST) and precentral gyrus or located in close proximity to them (up to 10 mm). All patients received the therapy in the neurosurgical department of Pirogov National Medical and Surgical Center, Ministry of Health of Russia (Moscow) in the period from 2014 to 2020. There were 48 (46 %) men, 57 (54 %) women aged from 22 to 79 (mean age 47.6 ± 14.5) years, the frequency distribution of patients by age is shown in Fig. 1.

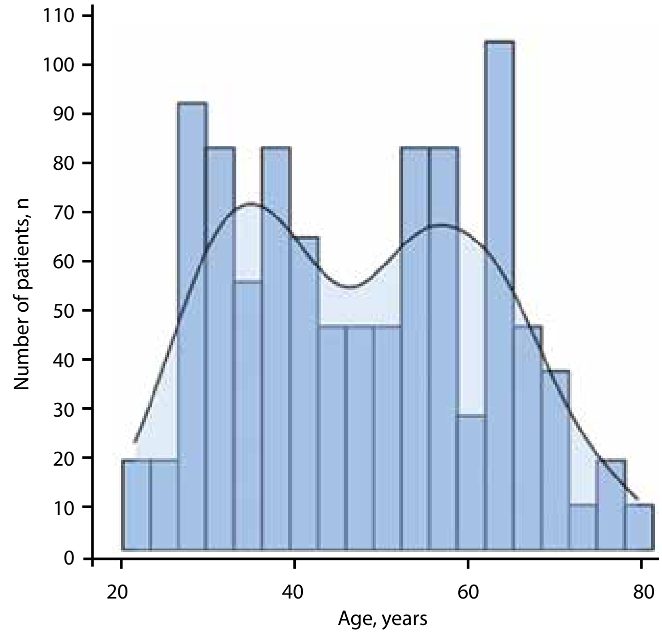

Fig. 1. *Frequency distribution of patients by age*

The study included patients with glial tumors. Grade 2 gliomas accounted for 14 (13.3 %), grade 3 – 16 (15.2 %) and grade 4 – 77 (73.3 %) cases. At the same time, 84 (80 %) patients received the surgery for the first time while 21 (20 %) patients – repeatedly due to relapse or continued tumor growth. In 54 (51.4 %) patients, the tumor was located in right hemisphere, in 45 (42.9 %) – in the left, in 6 (5.7 %) – bi-hemispherically. Isolated tumors in the frontal lobe were in 29 (27.6 %), in the parietal lobe – in 9 (8.6 %), in the insular lobe – in 3 (2.9 %) patients. In the remaining cases (64 patients, 60.9 %), localization was multilobar.

The tumor volume before surgery varied from 5.16 to 283.3 (mean volume – 80.9 ± 55.1) cm^3.

All patients underwent preoperative structural magnetic resonance imaging (MRI) with standard leads on the Magnetom Skyra 3T MR tomograph (Siemens, Germany) with a 20-channel head coil – 74 (70 %) patients and on the Magnetom Aera 1.5T (Siemens, Germany) with a 20-channel head coil – 31 (30 %) patients. In the case of the tumor location in the speech-dominant hemisphere, the functional MRI was performed with determination of speech zones in 53 (50.4 %) patients. The fMRI of movements was performed in 28 (26.7 %) patients, the study was performed when the tumor was located near the primary motor cortex. For all patients, white matter pathways were constructed on the basis of a diffuse tensor imaging study (DTI). During the DTI, the following parameters were used: repetition time – 10300 ms, echo reading time – 101 ms, b-factor – 1500, 65 slices 2 mm thick; 64 vectors in 2 scanning directions (A–P and P–A). In all cases, the data obtained was exported in the DICOM format to an external medium, after which the data was saved to the StealthStation S7 navigation station (Medtronic, Ireland). At the next stage, the DTI results were combined with structural MRI using Stealth Viz software. A multi-plane reconstruction was performed on the basis of the combined models obtained and then a CST image was constructed, the relationship of the tumor with the surrounding structures was evaluated and the volumetry was performed (Fig. 2).

The following neurophysiological mapping methods were used for intraoperative assessment of dynamics of motor zones state.

Transcranial electrical stimulation: stimulating scalp needle electrodes were installed in projection of primary motor cortex at points C3–C4 (Fig. 3, *1*, Fig. 4, *a*) according to the international electrode placement system "10–20", the stimulus strength varied from 140 to 220 mA.

Direct cortical stimulation of primary motor cortex of the brain: an 8-pin cortical electrode strip (Fig. 3, *2*, Fig. 4, *b*); batches of 5 stimuli (motor responses from control muscles were recorded at stimulation strength of 25–30 mA).

Transcortical stimulation (TCoS): in 68 (64.8 %) patients were performed using a strip electrode.

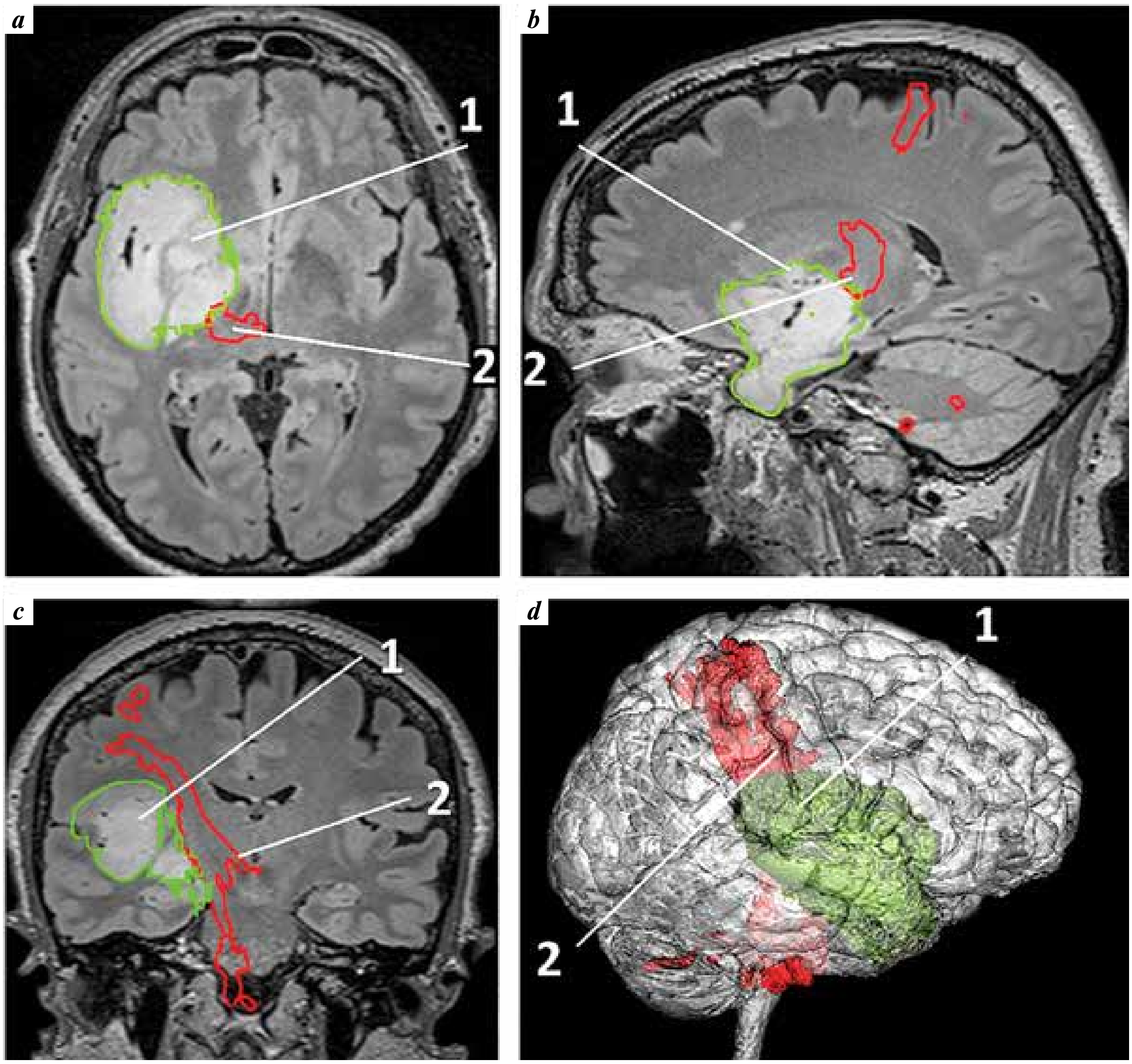

Fig. 2. *Magnetic resonance imaging (MRI) of brain for patient with diffuse astrocytoma (WHO grade 3) in right frontal, temporal and insular lobes with superimposed 3D models of corticospinal tract (CST) and tumor. Image in FLAIR mode: a – axial projection; b – sagittal projection; c – coronary projection; d – 3D combined model of the brain, tumor and CST in the StealthStation S7 navigation station. On the MRI series (FLAIR), a volumetric formation in the right frontal, temporal and insular lobes is determined, spreading into the subcortical nuclei on the right; adjacent to CST and partially dislocating it medially and posteriorly. The contours of the tumor (1) are marked in green, the CST (2) is marked in red*

To assess proximity of the motor zones, the direct cortical (Fig. 3, *3*, Fig. 4, *c*) and subcortical bi- and monopolar electrical stimulation (Fig. 3, *4*, Fig. 4, *d*) were used in all patients.

Direct cortical mapping was performed with bipolar electrode, and subcortical mapping was performed with monopolar electrode in the cathode polarity. to verify the motor zones, the parameters offered by M. Taniguchi were used: the frequency of 250–500 Hz in batches of 5 stimuli with an interstimulus interval of 0.2 ms. Cortical stimulation was performed at a pulse strength of 10 mA. Stimulation of the white matter was started using the same parameters with stimulus strength of 20 mA, applying gradual attenuation in the stimulation strength to minimum that was still capable to produce motor evoked potentials (MEP). For verification of speech zones, the parameters offered by W. Penfield were used: frequency of 50 Hz with a single stimulus lasting up to 3 s. Neurophysiological monitoring was carried out using the NIM ECLIPSE device (Medtronic, Ireland).

During the surgery with intraoperative awakening of patients, the "anesthesia–awakening–sedation" technique was used. For induction of anesthesia microdoses of muscle relaxants for intubation were used as well as short – acting drugs (propofol, xenon, dexdor) in various combinations including narcotic analgesics. After patient positioning on the operating table and rigid fixation of its head, analgesia of scalp and thorn points was performed using local anesthetics. The patient was awakened after the standard stages of surgical access and opening of the dura mater. Transcranial stimulation (TCrS) was performed only before the patient woke up. During the patient's awakening with consciousness level sufficient for speech testing, an electrode strip for TCoS was implanted. The first stage of cortical mapping was verification of motor zones using a bipolar electrode employing parameters proposed by M. Taniguchi. After motor mapping was completed and when patient reached sufficient level of consciousness, the speech mapping of cortex was performed with a bipolar electrode employing the stimulation parameters according to W. Penfield. Mapping was carried out when the patient continuously performed the tests that were selected depending on the mapping area. The testing was repeated when speech disorders occurred during stimulation of certain cortex area. In case of retention of testing errors, the specific cortex area was marked and considered as a zone participating in production and perception of speech. After completion of mapping of cortical motor and speech zones, the corticotomy was performed outside the identified functional areas of cortex and tumor resection was started having continuously communicating patient. The resection was started from the speech zones to shorten the patient's testing time in order to reduce the associated risks. When removing the tumor in the projection of speech pathways, the direct subcortical stimulation was performed in parallel with neurolinguistic testing of the patient. After the removal of tumor of the speech zones, the patient was sedated and resection was continued using the above described algorithm for removal of tumors in motor zones.

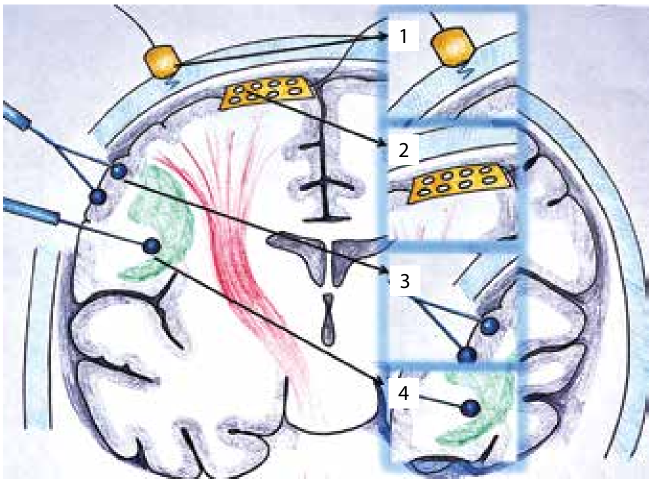

Fig. 3. *Scheme of multilevel intraoperative neurophysiological monitoring. Stimulation: 1 – transcranial; 2 – transcortical; 3 – direct cortical; 4 – direct subcortical*

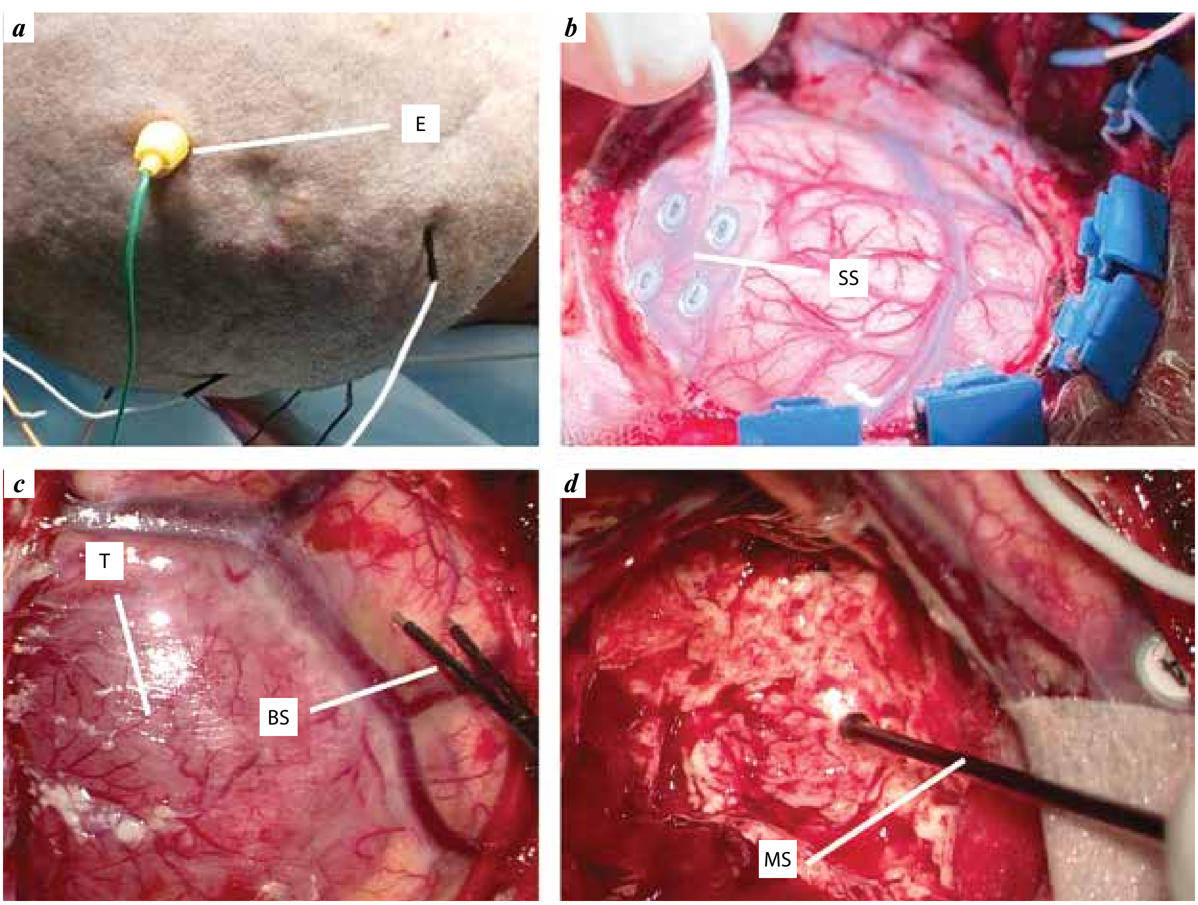

Fig. 4. *Intraoperative neurophysiological multimodal neuromonitoring. Intraoperative photographs: a – transcranial neurostimulation, positioning of the electrode (E); b – transcortical neurostimulation, positioning of the 8-pin stimulator strip (SS); c – direct cortical mapping of motor zones, T – tumor, BS – bipolar stimulator; d – direct subcortical mapping of motor zones, MS – monopolar stimulator*

The radicality of tumor removal was assessed during the first day after the surgery according to MRI data: in T2, FLAIR modes for tumors that do not accumulate a contrast agent, and in T1 with contrast – for accumulating ones. For assessing the degree of radical removal, the following arbitrary criteria were used: total – removal of 100 % of the tumor, close to total – 95–99 %, subtotal – 85–94 %, partial – less than 85 %.

The patients» condition was assessed according to neurological examination data (sensory, motor, speech disorders) and according to the Karnovsky Scale: before surgery, 24 hours and 6 months after surgery. The severity of paresis was assessed by the use of the Medical Research Council 5-point Scale.

Statistical analysis of the data obtained was performed with IBM PC class personal computer using the jamovi v. 1.6 (Jamovi project, 2021) and Excel 2010 (Microsoft, USA) software. For evaluation of normality distribution of quantitative variables, the Shapiro – Wilk criterion was applied, while for groups of more than 50 patients the Kolmogorov–Smirnov criterion was used. Differences between 2 independent groups were analyzed by the use of the Mann–Whitney test and Student's t-test. For comparison of 3 or more groups, the Chi-square test was used with assessment of its critical value. The results are presented as mean value plus and minus standard deviation and a probability ratio with a 95 % confidence interval. The significance level was 0.05 for each statistical analysis.

RESULTS

A total of 105 operations were performed in patients with tumors affecting the CST, primary motor cortex and precentral gyrus or located in their proximity.

Sixty-seven (63.8 %) tumors were removed totally, 22 (20.9 %) were – close to total, 11 (10.5 %) removal were subtotal and 5 (4.8 %) tumors were partially removed (Fig. 5). The volume of the tumor after surgery varied from 0 to 84.4 (mean volume 3.54 ± 5.01) cm^3.

Initially, 44 (41.9 %) of patients had motor disorders (the mean score of muscle strength was 3.9). Twenty-four hours after surgery the average score of muscle strength was 2.7. Seven days after surgery – it was 3.5. After a period of conservative therapy, the deficit regressed in most patients; after 6 months it persisted only in 12 (11.4 %) patients (the mean score of muscle strength was 4.3).

Based on the literature data, a selection of signs that may have an impact on outcomes of surgical treatment of patients with motor zones tumors was made [7]. The signs are combined into a table, then a statistical analysis is carried out (Table 1).

When assessing the factors influencing development of persistent motor deficits, a statistically significant association was obtained with an intraoperative decrease in response amplitude by 50 % or higher from baseline according to TCrS ($p < 0.001$) as well as to TCoS ($p < 0.001$).

Speech disorders were detected before surgery in 28 (26.7 %) patients, 24 hours after surgery – in 42 (40 %),

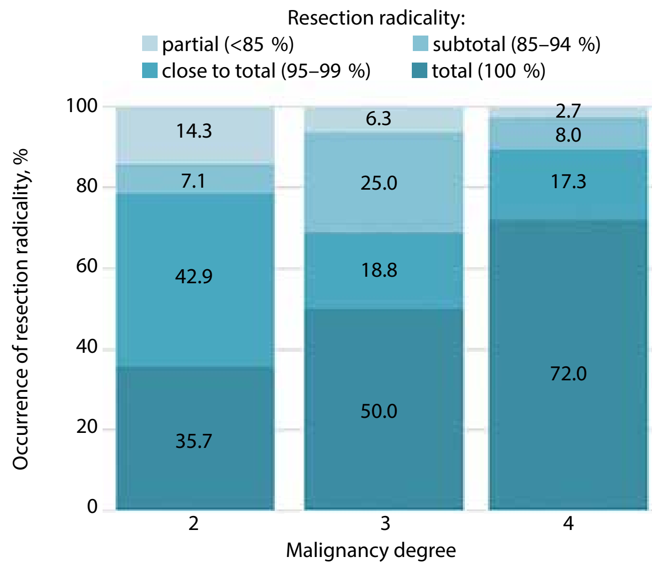

Fig. 5. *The radicality of tumor removal depending on its malignancy degree according to the classification of the World Health Organization*

during examination 6 months after surgery – in 12 (11.4 %) patients. However, an increase in preoperative speech disorders or novel disorder were not observed in any of the patients.

Sensitivity disorders were detected before surgery in 22 (21 %) patients, 24 hours after surgery – in 26 (24.8 %), after 6 months – in 17 (16.2 %). Thus, hypesthesia regressed in 5 (22.7 %) patients as compared with preoperative deficiency. In all cases of sensitivity deficiency, the tumor also affected the postcentral gyrus.

Symptomatic epilepsy before surgery was detected in 46 (43.8 %) patients, while during examination 6 months later it persisted only in 2 (4.3 %) patients. The preoperative condition of patients by the Karnovsky Scale varied from 50 to 100 points (mean value 78.9 ± 13.5). On the 7th day after surgery, the majority (82 of 105, 78.1 %) of patients had the Karnovsky Scale score higher or equal to 70 points (mean value 72.8 ± 13.5). After 6 months, the mean value of the patients» the Karnovsky Scale score was 82.2 ± 13. Their state dynamics estimated by the Karnovsky Scale depending on the tumor malignancy degree is shown in Fig. 6.

In the present study, the results of treatment of 105 patients were analyzed; in 63 (60 %) of them the muscle responses were obtained in response to direct stimulation of 4 mA or less stimulus intensity; in 44 (41.9 %) – to stimulus strength of 2 mA or less (Table 2). There were no statistically significant differences in the functional status of patients during postoperative period ($p = 0.9$) as compared with group of patients with muscle responses to the stimulus strength of 5 mA or more. Analysis of effect of minimal stimulus strength on presence of complications revealed a negative correlation that, however, was not statistically significant (rho – 0.448; $p = 0.144$).

DISCUSSION

At present time, the dominant paradigm in brain tumor surgery implies the identification of so-called functionally

Table 1. *Factors that may have an impact on development of persistent motor deficits after surgery*

Factor	For all patients	For patients with motor disorders 6 months after surgery	P-value
Number of surgeries, abs. (%)	105 (100)	12 (11.4)	
Mean age, years	47.6	45	0.501
Sex, abs. (%): F M	 57 (54) 48 (46)	 7 (12.3) 5 (10.4)	0.751
Tumor hemispheric localization, abs. (%): left right bi-hemispherically	 45 (42.9) 54 (51.4) 6 (5.7)	 7 (15.6) 4 (7.4) 1 (16.7)	0.415
Tumor location, abs. (%): with lesion of insular lobe without lesion of insular lobe	 47 (44.8) 58 (55.2)	 5 (10.6) 7 (12.1)	0.874
Type of surgery, abs. (%): primary repeated	 84 (80) 21 (20)	 9 (10.7) 3 (14.3)	0.645
Tumor malignancy degree, abs. (%): grade 2 grade 3 grade 4	 14 (13.3) 16 (15.2) 75 (71.5)	 1 (7.2) 4 (25) 7 (9.3)	0.175
Intraoperative reduction of MEP by more than 50 % from the baseline according to TCrS data, abs. (%): is present is absent	 43 (41) 62 (59)	 12 (27.9) 0	**<0.001**
Intraoperative reduction of MEP by more than 50 % from the baseline according to TCoS data, abs. (%): is present is absent stimulation was not applied	 35 (33.3) 39 (37.2) 31 (29.5)	 7 (20) 0 5 (16.1)	**<0.001**
Intraoperative approach to CST based on the strength of the direct stimulation stimulus, abs. (%): ≤4 mA ≥5 mA	 63 (60) 42 (40)	 7 (11.1) 5 (11.9)	0.900
Resection radicality, abs. (%): 100 % 95–99 % 85–94 % <85 %	 67 (63.8) 22 (20.9) 11 (10.5) 5 (4.8)	 9 (13.4) 2 (9.1) 0 1 (20)	0.393

***Note.** MEP – motor evoked potentials; TCrS – transcranial stimulation; TCoS – transcortical stimulation; CST – cortical-spinal tract.*

significant zones and, accordingly, their preservation from direct and indirect intraoperative injuries (as a result of ischemic disorders, cerebral edema, thermal trauma) [8]. Malignant glial formations requiring adjuvant therapy are most frequently located in the area of motor zones [1–3]. The surgical deficit of motor functions reflects the patient' functional status which may prevent this group of patients from being selected for the necessary chemoradiotherapy [1–3].

There are various methods of preoperative neuroimaging aimed to preserve the oncofunctional balance (increase in tumor removal radicality while maintaining the patient' functional status). These include MRI, fMRI, computed tomography, MR-tractography, transcranial magnetic stimulation, etc., as well as their various modifications. By the use of those methods, it is possible to identify cortical motor zones, CST, assess their link to the tumor, plan the surgery and select methods of neurophysiological control. However, intraoperative neurophysiological monitoring is still accepted as "gold standard" for determination of functional state of specific brain regions [9].

Combinations of the neurophysiological monitoring methods are most frequently used during removal of motor zones tumors [10]. The greatest efficacy was shown for use of 4 techniques combination: TCrS, TCoS, direct cortical and subcortical neurostimulation [10]. That is due to limitations existing for each of the techniques when used

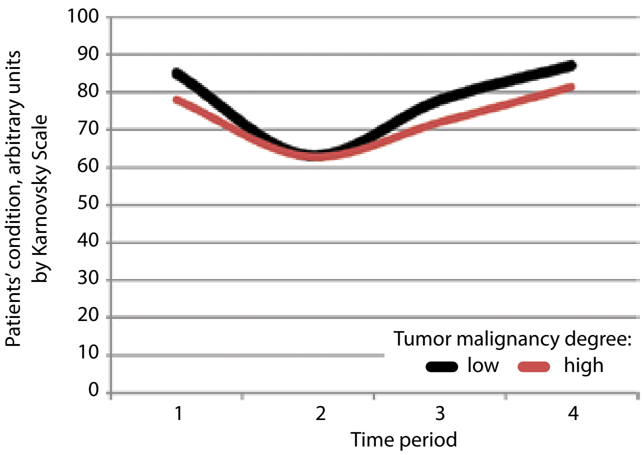

Fig. 6. *Dynamics of patients' condition according to the Karnovsky Scale depending on tumor malignancy degree in different periods: 1 – before surgery; after surgery: 2 – after 24 hours; 3 – after 7 days; 4 – after 6 months*

Table 2. *Distribution of patients depending on minimum strength of direct subcortical stimulation*

Minimum strength of stimulation, mA	Total number of patients, abs. (%)	Number of patients with complications, abs. (%)
1	19 (18.1)	0
2	27 (25.7)	4 (14.8)
3	11 (10.45)	2 (18.2)
4	8 (7.6)	3 (37.5)
5	9 (8.6)	1 (11.1)
6	5 (4.8)	0
7	1 (0.95)	1 (100)
8	5 (4.8)	0
9	10 (9.5)	1 (10)
10	8 (7.6)	0
12	1 (0.95)	0
16	1 (0.95)	0

separately. For example, brain displacement during the tumor removal will lead to alteration in the MEP obtained with TCrS; at the same time, the transcortical stimulator located on the cerebral cortex will allow correct interpretation of the data obtained. The use of direct subcortical mapping will allow to understand only the proximity of the brain pathways, but will not give an understanding of safety of the overlying elements of CST.

The technique of TCrS and TCoS is standardized, but there are currently no generally accepted recommendations for direct stimulation. The question of choice of stimulation parameters, as well as their numerous modifications remains under discussion. Some authors recommend use of high – frequency stimulation when mapping motor pathways in the cortical and subcortical levels, and low-frequency stimulation when mapping speech zones [9, 11]. Other authors believe that in all cases it is worth to use the stimulation parameters proposed by W. Penfield [6]. At the same time, there are recommendations appealing to increased risk of seizures in response to low-frequency stimulation and advising in all cases the use the parameters proposed by M. Taniguchi [12]. In addition, it is possible to switch between these parameters during cortical and subcortical stimulation [13, 14].

In the present study, the parameters by M. Taniguchi were used in all cases of stimulation of motor zones, and the parameters by W. Penfield were used for stimulation of speech zones. In cases where the tumor affected both motor and speech centers, the verification of motor and then speech zones was consistently carried out.

Another modifiable parameter is the use of a bi- or monopolar stimulator. Recommendations for the use of these distinct tools are comparable with choice of frequency of stimulation parameters. Previously, it was proposed to use a bipolar stimulator when approaching motor zones [9]. These recommendations are based on the idea that electrical stimulus has a conical orientation and, thus, a bipolar stimulator provides greater predictability of signal propagation. On the contrary, when applying monopolar stimulator, the pulse propagates from the active tip of electrode towards passive electrode located distantly. However, the physical experiment did not support these ideas: when using the bipolar stimulator, the impulse is formed initially and mainly at the anode and then – at the cathode in a much smaller volume. Thus, the original theory regarding the benefits of use a bipolar stimulator has not been confirmed [15].

In the present study, cortical mapping in all cases was carried out with the bipolar electrode and subcortical mapping with the monopolar one. If the unreliability of the data obtained from monopolar stimulation was suspected, then in several cases a bipolar stimulator was additionally used, however, the data turned out to be comparable so this was not taken into account during analysis of the results.

One more issue under discussion is the minimally safe approach to CST which is comparable to the minimum strength of white matter direct stimulation at which the MEP from the control muscle groups is preserved. A number of authors suggest stopping the tumor resection when response to stimulation with current strength of 2 mA is observed [16, 17]. Other studies have shown dependence of development of irreversible neurological deficit when tumor resection is stopped at the time of appearance of MEP at minimum stimulus strength of 3 mA [14]. According to recommendations of the International Association of Neurophysiological Monitoring, the minimum safe stimulus strength is 5 mA [18]. In the study by R. Schucht and coworkers it is recommended to stop resection at 7 mA [19, 20].

In the group of patients studied by us, the resection was stopped when approaching CST at the stimulus strength was

1 mA in 19 (18.1 %) patients and none of them developed persistent neurological disorders.

CONCLUSIONS

1. Removal of motor cortex tumors of the brain and CST using multimodal neurophysiological mapping, allows for the maximum resection of tumor tissue with good functional outcomes, which leads to significant improvement in patients' life quality and allows for further chemoradiotherapy.
2. The use of 4 methods of neurophysiological mapping – TCrS, TCoS, direct cortical and subcortical stimulation – helps to neutralize the disadvantages when each of the methods is applied separately and makes it possible to achieve radical removal of motor zones tumors while maintaining the patient' functional status.
3. When removing the motor zones tumors, the motor deficit in patients is increased and gradually recovers to baseline or is improved 6 months after surgery.
4. A decrease in the amplitude of the MEP by 50 % or more from the baseline according to TCrS and TCoS is a predictor of development of persistent motor deficit.
5. When the MEPs in response to 1 mA direct monopolar neurostimulation are preserved then resection of the tumor is not a predictor of irreversible motor disorders during postoperative period.

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