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GLIOBLASTOMA MULTIFORME BRAIN TUMORS LOCATED IN THE MOTOR CORTEX – SPECIFIC FINDINGS IN COMPARISON WITH LOW GRADE GLIOMAS OF THE SAME LOCALIZATION: ANALYSIS OF A SIXTY PATIENT SERIES

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SUMMARY – The verified presence of a glioblastoma multiforme (GBM) tumor in the motor area of the brain, in a patient lacking preoperative neurological deficit, offers no certainty that the tumor can be radically removed without the possibility of causing postoperative motor deficit. We present a series of 60 patients hospitalized at the Clinical Department of Neurosurgery, Clinical Center of Serbia in Belgrade between October 2011 and February 2015, harboring tumors located within and in the vicinity of the motor zone of the brain. By using Karnofsky's index (KI), the pre- and postoperative conditions of the patients were evaluated. Regarding electrical stimulation of the motor cortex, significantly lower values of the electrical current intensity, frequency, and pulse wave duration ($p<0.01$) were needed for triggering motor response in case of GBM tumor compared to a slowly growing tumor (low-grade). Patients with low-grade gliomas (LGG) had statistically significantly higher KI values pre- and postoperatively than patients with GBM ($p<0.01$). Using electrical stimulation of the cortex, a higher grade of resection of LGG could be achieved as compared with the group presenting with GBM ($\chi^2=5.281$; df=1; $p<0.05$). Our findings and review of the results reported by other authors underline the necessity of routine application of electrical stimulation of the cerebral cortex in order to identify the primary motor field (M1).

Key words: *Motor cortex; Electrical stimulation therapy; Brain neoplasms; Glioblastoma – surgery; Glioma – surgery*

Introduction

In spite of the progress in microsurgical techniques and oncologic protocols, brain tumors of the glioblastoma multiforme category (GBM WHO grade IV) have a very poor prognosis due to the average survival period of approximately one year[1-5]. The standard therapy protocol includes radical surgery followed by postoperative radiotherapy and chemotherapy[6]. The degree of surgical resection is influenced by tumor localization, age and neurological status of the patient at the time of diagnosis, and associated diseases[1-4,7-11]. It is beyond any doubt that the radicality of surgical resection of GBM is correlated with prolonged postoperative survival[2-4,8-13]. Development of new technologies, particularly the method of direct electrical stimulation (ES) of the cortex for GBM located in the motor cortex, represents a breakthrough in solving the main postulate,

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i.e. feasible maximal resection without any additional neurological deficit[8,11-22].

The objective of this study was to emphasize the particularities, i.e. biological characteristics, response to direct ES of the motor cortex, degree of surgical resection, and postoperative quality of life in GBM patients in comparison with slowly growing (low-grade) brain tumors located in the motor area.

Patients and Methods

This study included 60 patients with supratentorial tumors located in the vicinity of the motor cortex zone in front of the central sulcus, hospitalized at Clinical Department of Neurosurgery, Clinical Center of Serbia in Belgrade between October 2011 and February 2015. The pre- and postoperative status of the patients was evaluated using Karnofsky's index scale (KI). Patients with recurrent tumor and with KI less than 70 on admission were excluded from the study.

The diagnosis of expansive intracranial lesion was performed with magnetic resonance imaging (MRI). In order to achieve clear preoperative orientation and surgical planning, particularly in cases with infiltrative tumor growth and lacking clear delineation between the tumor and the adjacent brain, we measured distance between the central sulcus (the longest sulcus on high parietal scans) and coronary suture on MRI.

Craniotomy planning was based on topographic marks of the skull, i.e. identification of the coronary suture, and on the neuroradiological findings, i.e. preoperative evaluation of distance between the central sulcus and coronary suture. For electrical cortical stimulation, the 3 contact strip electrodes (AD-Tech® strip electrode, AD Technic, WI, USA) were used. The placement of the electrodes on the cortex was according to the norms, at an angle of around 65 degrees between the electrode and the brain surface. During ES, electrical current intensity, frequency and pulse wave duration were modified until we obtained motor response. Biopsy tissue was sent for histopathologic analysis. All patients underwent postoperative MRI or computed tomography (CT) scan at one month to four months. We quantified our findings according to either absence or presence of residual tumor tissue.

Results

Histopathologic analysis showed existence of GBM tumor form in 26 and low-grade tumor presence in 44 cases. The mean age was 55.38±14.020 years in GBM patients and 40.47±12.854 years in patients with slowly growing tumors (low-grade), yielding a statistically significant between-group difference of 14.914 years (t=4.282; df=58; p<0.01).

Brain atrophy was present in 76.9% of GBM patients and 36.4% of patients harboring low-grade gliomas (LGG), also yielding a statistically significant between-group difference (χ^2=9.639; df=1; p<0.01).

The values obtained by parallel analysis of the electrical wave parameters (electrical potential, frequency and amplitude) that were applied for ES of the motor cortex in order to provoke motor response are shown in Table 1. The results showed that statistically significant lower values of the individual electrical wave parameters (p<0.01) were needed to cause motor response in patients with GBM when compared to those presenting slowly growing tumors.

Table 1. Electrical stimulation: intensity, frequency, pulse wave and motor response

	HP finding	n	Arithmetic mean	Median	Min	Max	SD	Test result
Intensity	Glioblastoma	26	8.12	8.00	6	12	1.479	t=-3.214; df=58; p<0.01
	Low grade	34	9.26	9.50	7	11	1.286	
Frequency	Glioblastoma	26	16.42	16.00	15	20	1.653	Z=-3.98 ; p<0.01
	Low grade	34	18.32	18.00	15	20	1.609	
Pulse wave	Glioblastoma	26	298.08	300.00	260	340	22.094	t=-3.711; df=58; p<0.01
	Low grade	34	319.12	320.00	270	360	21.514	

HP = histopathologic

The mean electrical current intensity value in the GBM group was 8.12±1.479 mA, whereas in the slowly growing glioma group it was 9.26±1.286 mA (t=-3.214; df=58; p<0.01). The mean value of electrical frequency in the GBM group was 16.42±1.653 Hz, whereas in the slowly growing glioma group it was 18.32±1.609 Hz (Z=-3.98; p<0.01). The mean pulse wave duration was 298.08±22.094 ms in the GBM group and 319.12±21.514 ms in the slowly growing glioma group (t=-3.711; df=58; p<0.01).

Using KI, the pre- and postoperative clinical conditions of the patients were compared for each individual and among other patients according to the histologic type of their tumor.

The mean pre- and postoperative KI value in the GBM group was 75.38±8.593 and 79.23±8.910, respectively, while the respective figures in LGG group were 90.59±10.133 and 92.94±8.359. There was a statistically significant difference in pre- and postoperative KI values (F=48.856; df=1; p<0.01; Eta^2=0.457), indicating that patients with slowly growing brain gliomas had statistically significantly higher pre- and postoperative KI values than patients with GBM (p<0.01).

The degree of surgical resection was evaluated by control MRI brain scan one month after initial surgery. In the group of patients with GBM, postoperative MRI showed the absence of tumor recurrence in 44% (n=11) of cases, while the presence of a recurring tumor was confirmed in 56% (n=14) of cases.

The level of surgery radicality in LGG was substantiated by the absence of tumor recurrence in 73.5% (n=25) of cases; whereas relapsing tumors were identified on MRI scan in 26.5% (n=9) of cases. From statistical standpoint, the ES technique enabled a significantly higher degree of surgical resection of LGG than of GBM of analogous location (χ^2=5.281; df=1; p<0.05).

Discussion

Due to the risk of causing *de novo* motor deficit, the surgery of tumors situated in the motor region of the cortex is considered as a highly challenging procedure. Intrinsic tumors may infiltrate both the cortical and subcortical structures, sometimes lacking signs of functional worsening. However, clear presentation of a large tumor in a patient without preoperative neurological deficit cannot guarantee that tumor can be radically removed while excluding the possibility of subsequent motor deficit[23]. Authors argue that postoperative survival and the degree of surgical resection are concurrent in both low- and high-grade gliomas, and that an extensive resection within a supplementary motor field may cause complete akinesia[24]. Electrical stimulation of the cortex in infiltrative brain gliomas located in the motor cortex prevents additional damage to the functionally important areas of the cortex while enabling radical surgery[25,26]. Skirboll *et al.* emphasize that it is difficult to establish whether the new postoperative neurological deficit is a result of intratumorous emplacement of motor fibers, a consequence of surgical manipulation proximate to the motor area, or if both these mechanisms play a part[27]. The mass effect of the tumor and its invasion of the functional cortex, along with the organization of the motor area, are factors that strengthen the need for uncovering the shortest and safest approach to these lesions in order to achieve the highest feasible surgical radicality. Sir Victor Horsley identified the centers for the hand and leg movement by using experimental ES of the cortex in monkeys[28,29]. Up to now, this primary method has been modified, including actual electro-cortical stimulation of awake patients, which was founded by Cushing[30], Gruenbaum and Sherrington[31], and recommended by Penfield and Boldrey[32] as a safe surgical approach to the lesions located in eloquent cortical areas.

Surgical resection of tumors can be considered a brain injury by itself, being able to induce GABAergic inhibition and NMDA receptor-dependent excitation in the structures adjacent to the cavum. This, in turn, leads to synaptic plasticity and reorganization by accelerating the long-term heterosynaptic potentiation[33]. These changes in local synaptic activity can activate preexistent regional functional centers and remote cortico-cortical connections[33,34]. Some of the mechanisms of the motor area reorganization and somatosensory organization were confirmed in experimental studies on animals[35,36]. It has been proven that this swift initial reorganization, sometimes transient, can become permanent with continuous exercise[37-39].

In their expansion, tumor cells are able to split surrounding axons, neurons, and glia, as well as separat-

ing tracts. Little is known about the factors that are restraining tumor growth in this phase, aside from that they are the result of the humoral and cellular immune response to astrocytic tumors and that the immune response towards a GBM is generally weak[40]. In its wake, tumor growth compresses and shifts the sulci and the venous system. This centripetal process of enlargement progresses towards the periventricular white matter, respecting the basal ganglia and the thalamus. It should be emphasized that, in general, the gliomas of the neocortex do not invade the mesocortex, the ventral cores, or the ventricles. GBMs located in primary motor cortex, primary sensitive cortex, and primary auditive cortex display a specific pattern of growth. The high-grade gliomas arising from these localizations have a tendency to grow diffusely and expand anarchically, since the phylogenetically younger parts of the brain are considerably more vulnerable to mutations than the 'primitive structures'.

The actual consensus places LGG in the malignant tumor group, with an average survival of 4 to 9 years[41-45]. Numerous series of results show that radical surgical resection may delay malignant transformation and prolong survival[42,45-47].

Following surgical removal of the tumor, there is swift neurological recovery, while the motor field itself becomes wider and endowed with ability of obtaining the same motor response on several regions of the M1 cortical segment. The absence of preoperative motor deficit in rapidly growing tumors may be the cause of synergetic action of the M1 segment on the contralateral hemisphere, fulfilled by various collateral connections[34]. Duffau *et al*. recommend the standard use of intraoperative ES of the brain during surgery within eloquent areas as a method of improving postoperative functional outcomes[33,48,49,50-53]. Direct ES is a safe, precise, and easily applicable technique to identify the eloquent cortical and subcortical fields[24,53,54].

The absence of neurological deficit in LGG is a frequent outcome, explained by local regrouping of the functional neural network, which encourages total surgical removal of the lesion[33,55-59]. On the other hand, functional nerve tissue can be found within the tumor, which sometimes hinders radicality[27,60]. Alterations in spatial organization and the direction of tumor growth can be caused prior to surgery. The tumor itself may trigger peritumoral functional reorganization of the motor cortex, with the absence of neurological deficit. This could be the case even if part of the eloquent zone is within the tumor borders, while the lesion itself may induce functional compensation of ipsilateral regions assigned to a common purpose (such as speech)[33,49,53,61].

This phenomenon can be explained by type III in-space configuration of the LGG, as described by Daumas-Duport *et al*. Thus, tumor cells infiltrate the surrounding brain without the loss of essential connections or functions[62].

Presumably, the M1 region is detected and protected during surgery, whereas the secondary fields tasked with the excitation and inhibition of the primary motor area are not. This might justify the reason why transient neurological deficit occurs even when the utmost care towards the motor cortex is considered, and why these deficits can mend over time, with the help of secondary compensatory mechanisms[54,63].

Conclusion

Our results underline the necessity for the routine application of ES of the brain cortex with the objective to identify the primary motor area (M1) during the surgery of intrinsic primary brain tumors located in front of and around the central sulcus. The ES technique itself is precise and easy to perform. Without any ambiguity, it has been proven that orientation on the exact location of the tumor, on the basis of anatomical landmarks, i.e. MRI findings and distance between the central sulcus and the coronary suture, is not entirely reliable, with an error of 6-10 mm observed with the naked eye and 1.5-4 mm when applying neuronavigation. Even errors that may seem as small as these may cause definitive and lasting neurological deficit. The ability of the motor cortex to establish interconnections, in the event that postoperative neurological deficit develops within a short period of time, leads to visible recovery in over 90% of cases. This allows us to consider our approach toward cases previously declared as inoperable, with tumors located in the primary motor area and a formerly unacceptable risk of producing and/or increasing neurological deficit.

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Sažetak

MULTIFORMNI GLIOBLASTOM LOKALIZIRAN U MOTORNOM KORTEKSU: SPECIFIČNOSTI U ODNOSU NA GLIOME NISKOG STUPNJA ISTE LOKALIZACIJE – ANALIZA SERIJE OD ŠEZDESET BOLESNIKA

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Jasna prezentacija tumora mozga u području motorne zone kod bolesnika koji prijeoperacijski nisu imali slabost ekstremiteta nije jamstvo da se on može radikalno odstraniti bez poslijeoperacijskog neurološkog deficita. Prikazujemo niz od 60 ispitanika sa supratentorijalnim tumorima lokaliziranim u i oko motorne zone mozga, koji su hospitalizirani na Institutu za neurokirurgiju KCS u Beogradu u razdoblju od listopada 2011. do veljače 2015. godine. Procjena prije- i poslijeoperacijskog stanja bolesnika je vrednovana ljestvicom Karnofski indeksa (KI). Iz serije su isključeni bolesnici s recidivom tumora i bolesnici čiji je KI kod prijma bio manji od 70. Tijekom procedure elektrostimulacije motornog korteksa potrebne su značajno manje vrijednosti jačine struje, frekvencije i pulsnog vala ($p<0,01$) za izazivanje motornog odgovora u slučaju postojanja tipa tumora multiformnog glioblastoma (*glioblastoma multiforme*, GBM) u odnosu na spororastuće gliome (niskog stupnja) mozga. Nađena je statistički značajna razlika u prije- i poslijeoperacijskim vrijednostima KI ($F=48,856$; $df=1$; $p<0,01$; $Eta^2=0,457$), naime, bolesnici s gliomima niskog stupnja imali su statistički značajno veću vrijednost KI prije- i poslijeoperacijski u odnosu na vrijednosti KI kod skupine bolesnika s GBM ($p<0,01$). Uporabom elektrostimulacije korteksa postignut je veći stupanj radikalnosti kirurške resekcije glioma niskog stupnja u odnosu na skupinu bolesnika s GBM ($\chi^2=5,281$; $df=1$; $p<0,05$). Kirurgija tumora lokaliziranih u motornom korteksu predstavlja izazov zbog pratećeg rizika od *de novo* nastanka motornog deficita. Naši rezultati kao i rezultati drugih autora pokazuju neophodnost rutinske primjene direktne elektrostimulacije moždane kore radi identifikacije primarnog motornog polja (M1).

Ključne riječi: *Motorička kora; Električna stimulacija, terapija; Moždani tumori; Glioblastom – kirurgija; Gliom – kirurgija*