

Neurophysiological status and adaptation responses upon application of electromagnetic fields in complex treatment of patients with malignant gliomas of the brain

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Aim

The aim of this paper is to discover some advantages and benefits of the complex treatment of patients with malignant gliomas of the brain with the use of electromagnetic field therapy.

Materials and methods

Our examination focused on patients suffering from malignant gliomas of the brain. One cohort of them (the reference group covering 30 patients) received surgery and chemoradiotherapy (CHRT) without electromagnetic field exposure of the brain, while the other group (the main test group which included 30 individuals) was subjected to the same therapy, but accompanied by the electromagnetic field treatment of the brain. Varying and permanent magnetic field exposure sessions were carried out from day 1 till day 20 in the context of the complex therapy. All in all, every patient received 4 courses of the systemic chemotherapy, with an interruption of 4 weeks, in combination with exposures to electromagnetic field applied to the brain area. An assessment of efficacy of the adjuvant chemoradiotherapy was performed upon expiration of 12-14 days from the date of the last injection of chemotherapy drugs according to applicable WHO recommendations for standardizing in assessment of treatment outcomes.

Results

An application of the combined magnetotherapy, which includes both the central and local electromagnetic actions, in the treatment of malignant gliomas of the brain results in a statistically significant increase in the general and recurrence-free two-year survival, improves the scale grade level of the ECOG/WHO performance status grading and the Karnofsky index ac-

ording to the Karnofsky performance status scale, provides for reduction of neurological toxicity symptoms and makes a pronounced anti-stressor effect, namely, leads to predominance of the reactions of training, calm and elevated activation in the framework of adaptation reactions of the physiological types.

Conclusions

The central and local actions by ultra-low frequency magnetic field (ULF MF) used in the therapy of malignant gliomas of the brain should be considered as a trigger of the neuro-hormonal regulation that is favorable for reducing toxicity influence by chemoradiotherapy on the brain and that is beneficial for improving life quality and prolonging a life span for the above patients.

Keywords

Neurooncology, Malignant gliomas of the brain, ULF MF, ECOG/WHO performance status, The Karnofsky index, Neurophysiological status, Adaptation reactions

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Introduction

Brain tumors range from 2 to 8 % of all neoplasms in total. It is known that recent international reports represent a picture of a considerable growth of the incidence rate of the brain tumors in populations throughout the world. As to Russia, we can state the incidence rate of the brain tumors is 10 cases per 100 000 population, with a half of the tumors located immediately inside the brain. By estimating the primary tumors of the brain in the adult population in Russia, statistics data show that gliomas of the brain accounts for 40–46 % of the cases, with 55 % of malignant tumors among them. Considering the glial tumors, the largest proportion is made by glioblastomas (16,7 %) as well as by astrocytic tumors (17,9 %), and in this case the malignant types of astrocytomas tend to occur 1,3 times more frequent-

ly in male individuals and 2 times more frequently in females as compared to the benign neoplasms [1, 2].

Within the last ten years, owing to drastic advancements in neuroanesthesia and significant improvements in microsurgery techniques, a great success has been made in the field of surgery of external brain tumors (ectopic pituitary adenoma, meningioma etc.), but the problem of therapy of patients suffering from malignant gliomas remains unresolved, and the recent results associated with the topical problem cannot be considered quite satisfactory [3–5]. An average life span of patients with malignant gliomas covers 12 months only, and the 1-year survival does not exceed 68 %; the 2-year survival is not higher than 27 %; and the 3-year survival is under 4,3 % [6].

In the last few years a trend is evident to a wider use of magnetic fields as a component in the complex therapy of tumors, the mechanism of influence of which is directed both immediately on the malignant tumor and the adaptation and protection systems of the organism of the patient to be treated [7–9]. The action on the brain by magnetic field as the component of the complex therapy of the brain malignant tumors is viewed as reasonable, since it meets the most advanced requirements, which are placed for eligible therapy of malignant tumors of the brain, as indicated below: firstly, magnetic field acts on the perifocal glia producing cytostatic, anti-edema and anti-inflammatory effects, elevating efficacy and reducing toxicity of chemoradiotherapy; secondly, magnetic field exerts an influence on hypothalamus realizing the systemic effect to enhance non-specific and anti-tumor resistance of the organism of an affected individual [10–16].

Materials and methods

Our investigation was concerned with patients who suffered from malignant gliomas of the brain. One cohort of the patients (the reference group covering 30 individuals) received surgery and chemoradiotherapy without exposure of the brain to electromagnetic field, while the other cohort of the affected persons (the main test group consisting of 30 patients) received the same medical treatment, but accompanied by exposures to electromagnetic fields, targeted at the brain. The therapy procedure for the patients in the main test group was conducted as follows: upon the relevant morphological verification as the basis of the diagnosis, every patient with malignant glioma of the brain was exposed to magnetic field targeted at the

brain, namely, the hypothalamus area: applied was ULF MF at frequencies of 0,03, 3 and 9 Hz, with an exponentially changing induction from 5 to 0,8 mT, with an exposure time from 7 to 1 minute; upon expiration of 20 minutes applied was permanent magnetic field with an induction of 20 mT, under an exposure time of 15 min, to cover the surgery-affected area of the patient. Later on, the treated patient was subjected to tele-gammatherapy with Cobalt isotope (Co 60) sources using equipment Agate-R or Rocus to cover the tumor bed in the regimen of the classic fractionation: a single focus dose of 2–2,6 Gy on the field, to the total focus dose of 60 Gy plus the systemic chemotherapy based on the use of Carmustine (BiCNU) in physiological sodium chloride solution – 150 mg/m² on day 1 & day 3, and Etoposide – 60 mg/m² on days 1–3.

Exposure sessions with applied varying and permanent magnetic field were carried out from day 1 to day 20 of the treatment in the same regimens and sequences. The patient received a total of 4 courses of the systemic chemotherapy with an interval of 4 weeks, in combination with sessions of exposure to electromagnetic field.

For the patients in the reference group, the chemoradiotherapy courses were completed by giving the same dose of gammatherapy and providing the identical doses of chemodrugs as it was the case with the main test group.

An evaluation of efficacy of the adjuvant chemotherapy was performed upon expiration of 12–14 days after the last injection of chemotherapy drugs in accordance with WHO Recommendations for standardized interpretation of the treatment outcomes in grading the evidence.

An objective treatment effect was assessed upon completion of course 4 of the therapy by studying the dynamics of tumor sizes according to data obtained by roentgen ray computed tomography with the use of Toshiba-Asteion VR 2002 equipped with Workstation Vitrea-2. The immediate results of the treatment were analyzed by investigations of the observed general two-year survival and the recurrence-free survival of the patients. The survival data were calculated according to the classical non-parametric statistic method, namely, the Kaplan–Meier estimator.

In doing so, diagnosed were the following most informative parameters:

1. The immediate and nearest outcomes of the new treatment method for patients suffering from ma-

lignant gliomas of the brain, as offered by us, versus the conventional chemoradiotherapy, using the Kaplan-Meier estimator for an eligible interpretation of the results.

2. Dynamics of the general performance and quality of life for the patients at stages of their specific treatment in the groups under study by tracing changes in their ECOG Performance Status and their Karnofsky Performance Status according to the ECOG/WHO numbering scale and the Karnofsky index between 100 and 0, respectively.

3. The pattern of the adaptation reactions was assessed before and after surgery in the early post-operative period as well as after chemoradiotherapy accompanied by magnetotherapy. Blood count was performed according to Giemsa-Romanowsky blood film staining technique for a 200 cell count. In addition to the statistics data required for an identification of the actual type of the adaptation reaction, we determined a common group-related pattern of the adaptation response with calculating the synthetic parameter: it was the coefficient of relation between the anti-stressor reactions and stress ($K = AC / C$) that made possible to properly estimate the efficacy of the action of the physical factor in question.

Results and discussion

An immediate objective clinical effect (remaining in remission) upon chemoradiotherapy, accompanied by the magnetic field treatment, was achieved in 28 of the 30 patients ($93,3 \pm 4,6 \%$) who received chemoradiotherapy and magnetotherapy that was by 2,3 times more often than it was the case with that group, where the patients were subjected to the conventional chemotherapy only (12 individuals – $40 \pm 9,1 \%$). Progression of the disease was observed in the main test group in 2 patients only ($6,7 \pm 4,6 \%$), while in the group of patients, who received the conventional chemoradiotherapy only, we recorded 14 individuals with the progressing tumor ($46,7 \pm 8,5 \%$), i.e. it was 7 times more frequently as compared to the main test group. In the main test group, all individuals suffering from gliomas survived till the end of course 4 of the medication therapy, while in the reference group 4 persons died before the completion of the same therapy course ($13,3 \pm 6,1 \%$) (see Figure 1 herein).

Our analysis has shown that the recorded general 2-year survival in the patients of the main test group has reached $40,0 \pm 8,9 \%$ that is 2,4 times higher than

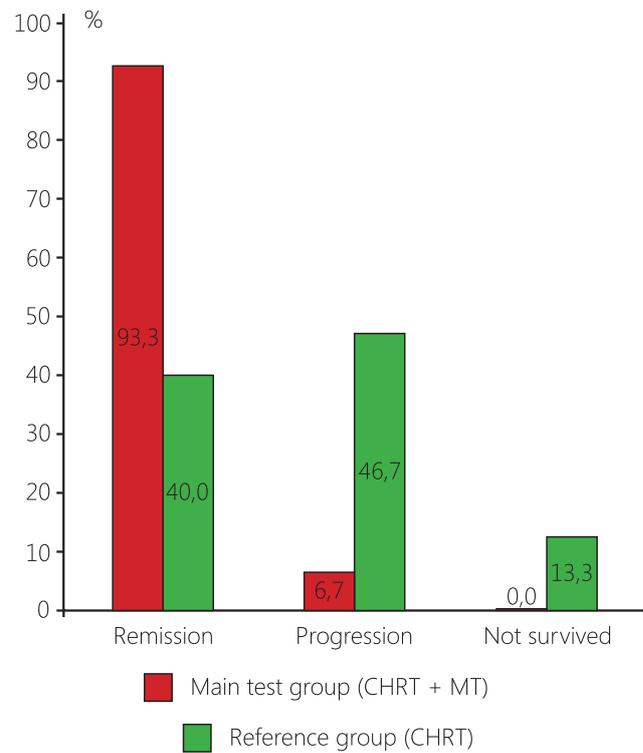


Fig. 1. Comparison of efficacy of different methods of chemoradiotherapy in patients suffering from malignant gliomas of the brain in the groups under studies upon completion of the 4 therapy courses

that indicator recorded for the group subjected to the conventional chemoradiotherapy, which amounts to $16,7 \pm 7,2 \%$.

Our investigation of the observed 2-year recurrence-free survival data for the patients with malignant gliomas of the brain, depending on the medication therapy, has demonstrated that the above mentioned indicator for those patients, who received chemoradiotherapy accompanied by magnetotherapy, has reached $20,0 \pm 7,1 \%$, i.e. it is 6 times less than that found in the main test group.

The median survival in the patients of the groups in question was reported to be as follows: in the reference group it was 9 months, and in the main test group it reached 16 months, i.e. it was established to be 1,7 times higher for the cohort received chemoradiotherapy and magnetotherapy (see Figure 2 herein).

The recurrence-free median in the patients of the considered groups was recorded to be as follows: in the reference group it was 6 months, and in the main test group we observed 12 months, i.e. the indicator was 2 times higher as compared to the reference (see Figure 3 herein). When analyzing the survival data, we obtained statistically reliable significant differences between the main test group and the reference cohort ($p < 0,05$).

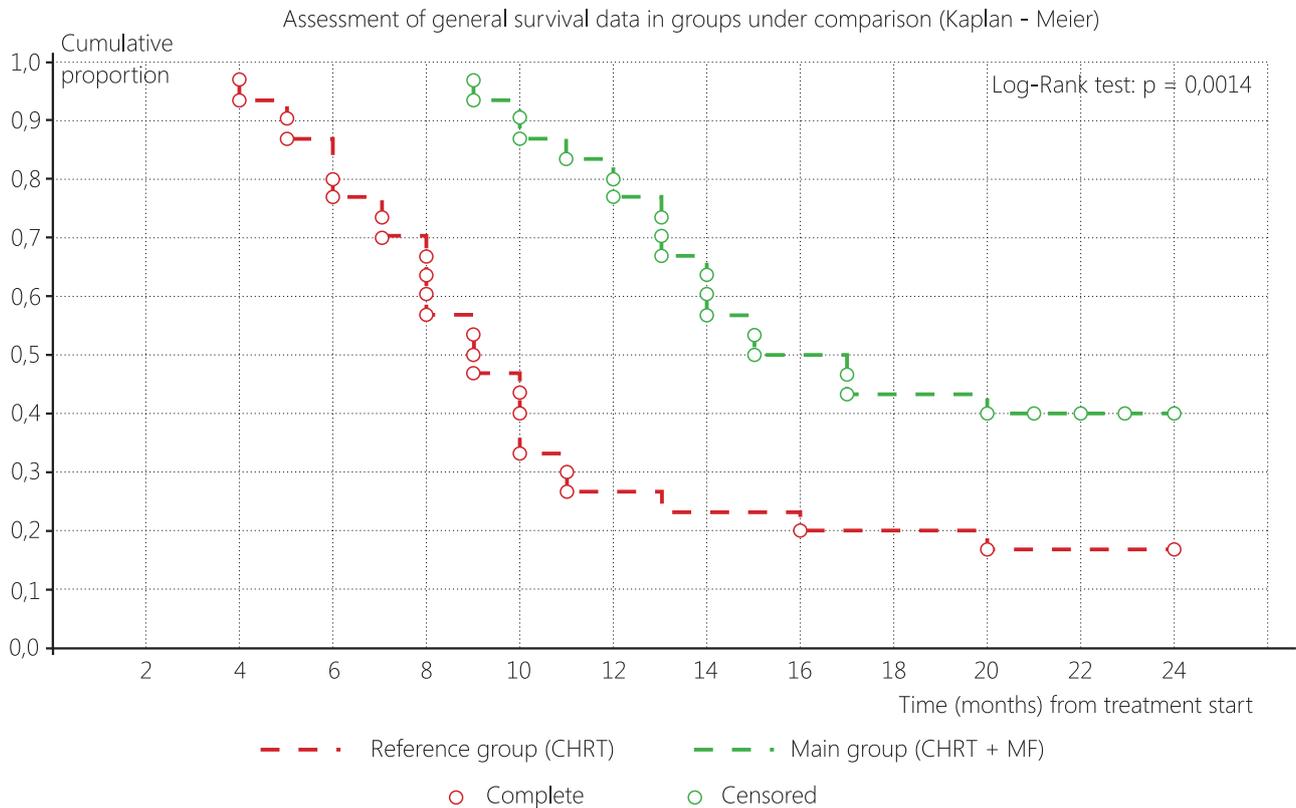


Fig. 2. General 2-year survival data in patients suffering from malignant gliomas of the brain upon completion of chemoradiotherapy with magnetic field treatment versus chemoradiotherapy without magnetotherapy, based on the Kaplan–Meier estimator.

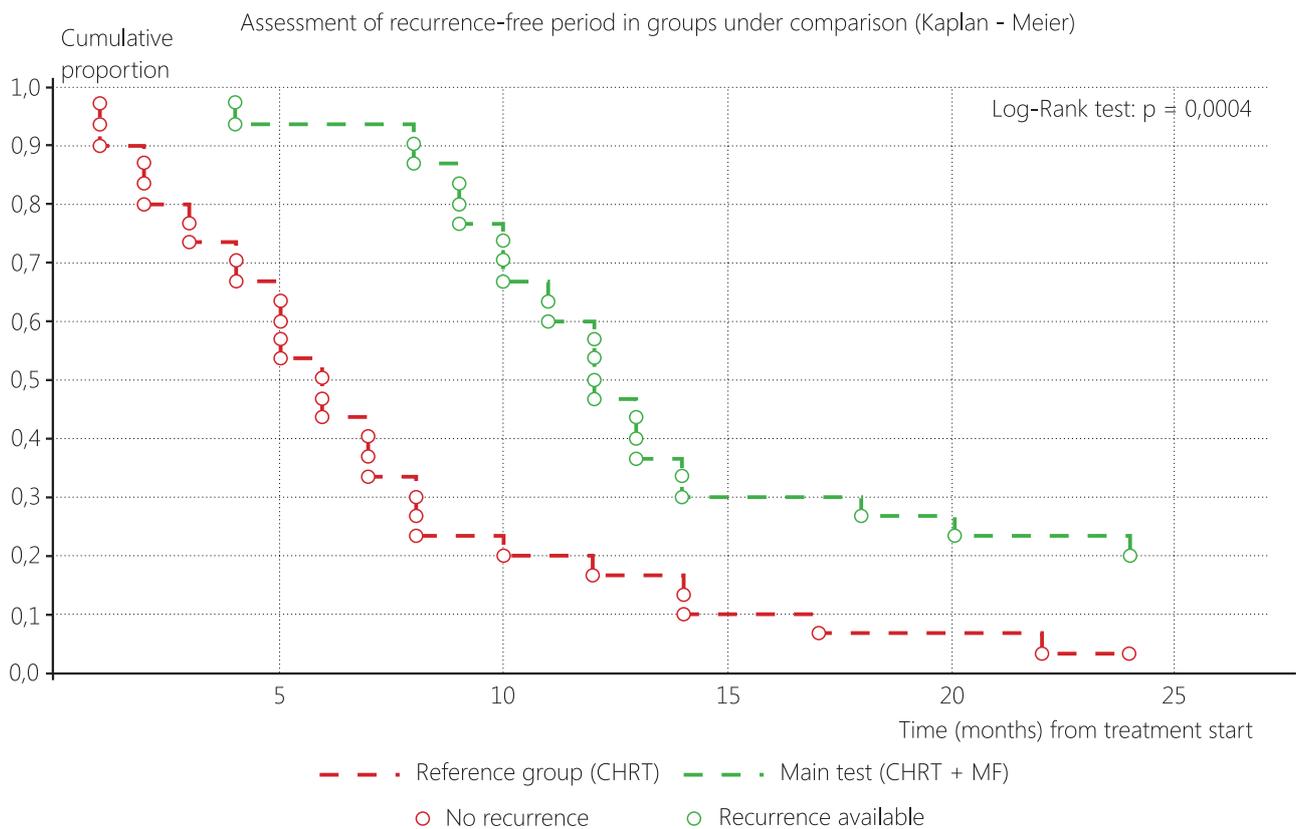


Fig. 3. Data on two-year recurrence-free survival of patients with malignant gliomas of the brain upon completion of chemoradiotherapy accompanied by magnetic field treatment vs. chemoradiotherapy alone, based on the Kaplan–Meier estimator

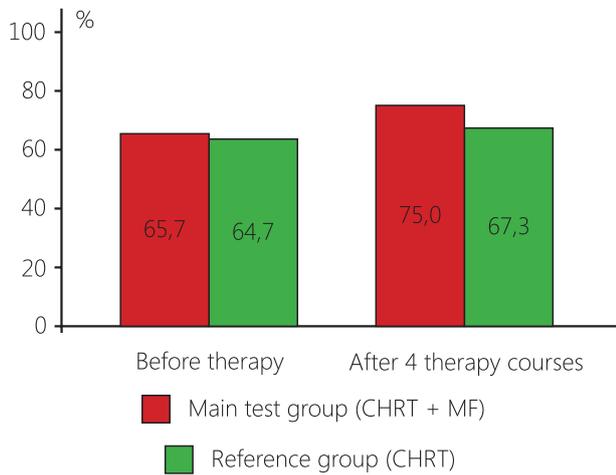


Fig. 4

Our enquiries into the topics of the dynamics of the ECOG performance status grading and the Karnofsky indices in the patients under studies, which should be considered as parameters reflecting the subjective general response by an organism to chemoradiotherapy exposures, demonstrated that the same data, which showed before their therapy practically no differences in the patients from the groups under studies, upon completion of the 4 therapy courses were found to be statistically significantly better for those patients, who additionally received magnetotherapy.

The differences in the Karnofsky index values, established between the groups, increased from 1 % to 7,7 % ($p < 0,05$) (see Figure 4 herein). Whereas an average grade according to the ECOG Performance Status Scale for patients with malignant gliomas of the brain was recorded to be $2,20 \pm 0,08$ in the main test group and $2,25 \pm 0,09$ in the reference group, the

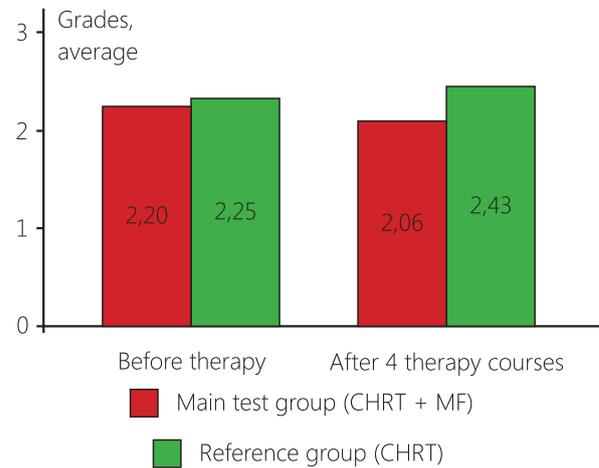


Fig. 5

Figures 4 and 5. Dynamics of the Karnofsky index values and the ECOG Performance Status grades in patients suffering from malignant gliomas of the brain, when conducting different variants of chemoradiotherapy

respective indicators identified in both groups upon completion of the 4 therapy courses were reported to be $2,06 \pm 0,09$ and $2,43 \pm 0,014$, respectively, that allowed us to establish the presence of a statistically significantly better dynamics of the indicator in those patients, who received magnetotherapy in addition to the conventional therapy ($p < 0,05$). The patients with the better dynamics were capable of all selfcare and even able to carry out everyday work of a light nature.

By this means we succeeded to achieve the better dynamics in the ECOG Performance Status grading and the Karnofsky index values in patients of the main test group subjected to CHRT accompanied by MT. Our analysis of such a subjective criterion like neurologi-

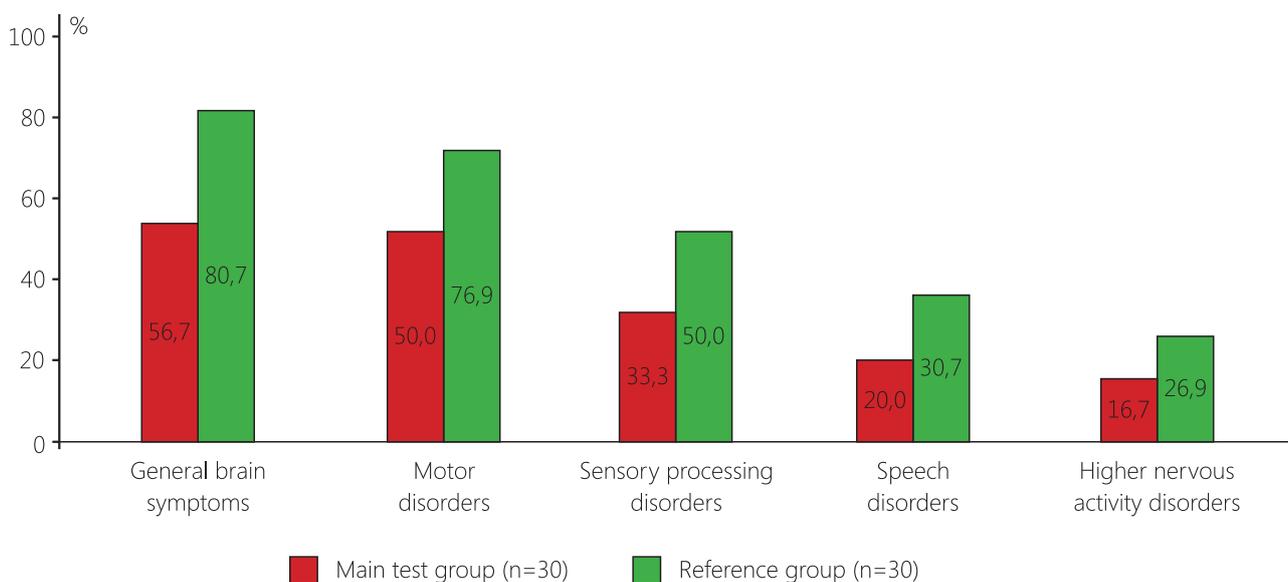


Fig. 6. Neurological disorders upon completion of the 4 therapy courses in the studied groups of patients suffering from malignant gliomas of the brain.

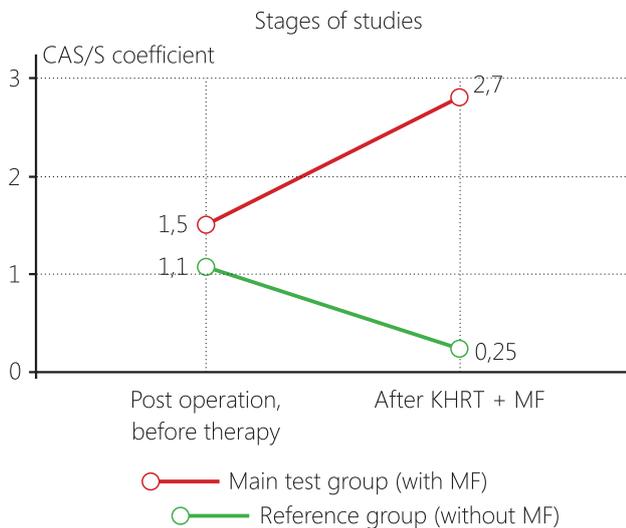


Fig. 7. Intergroup differences in the coefficient of the relation between the anti-stressor reactions and stress upon completion of the complex therapy comprising magnetotherapy in patients with malignant gliomas of the brain

cal deficit incidence rate in the groups under studies demonstrated that, upon completion of the 4 therapy courses, the indicated rate was found in patients of the reference to be at a higher level as compared to that in the main test group that might be illustrated as follows: general brain symptoms were recorded as $80,7 \pm 9,0 \%$ against $56,7 \pm 4,9 \%$; motor disorders as $76,9 \pm 9,4 \%$ against $50,0 \pm 7,6 \%$, sensory processing disorders as $50 \pm 9,8 \%$ against $33,3 \pm 8,5 \%$, speech disorders as $30,7 \pm 8,4 \%$ against $20 \pm 7,3 \%$ and higher nervous activity disorders as $26,9 \pm 8,7 \%$ against $16,7 \pm 6,0 \%$. Finally, we achieved a statistically significantly better dynamics in changes of the neurological status in the patients of the main test group, who were subjected to CHRT with MT ($p < 0,05$).

The quintessence of the inter-group differences was calculation of a synthetic parameter: it was the CAS/S coefficient to represent the relation between an integral of the anti-stressor reactions and stress that is capable of quantifying the final result of the application of magnetotherapy by testing the types of reactions and identifying the frequency of the occurrence of development of anti-stressor reactions and stress in patients with malignant gliomas of the brain. The dynamics of adaptive resetting patterns, as illustrated in Figure 7 herein, exhibited essential intergroup differences in CAS/S both at the initial and final stages of therapy.

At the post-operative observation stage, before the beginning of the adjuvant therapy, we noted a tendency of bringing the CAS/S values in the groups under

studies closer together, i.e. equalization of the CAS/S values. But upon completion of the basic therapy accompanied by the electromagnetic field treatment we detected the predominance of the anti-stressor reactions that was favorable for an increase in resistance and beneficial for the functional rehabilitation; that promoted an improvement in the quality of life of the patients.

Conclusions

1. The application of the adjuvant chemoradiotherapy accompanied by the magnetic field treatment, targeted at the brain in the context of therapy of malignant gliomas of the brain, results in a statistically significant increase in the general 2-year survival by 2,4 times ($40,0 \%$ against $16,7 \%$) as well as an increase in the 2-year recurrence-free survival by 6 times (from $3,3 \%$ to $20,00 \%$), ($p < 0,05$).

2. The use of adjuvant chemoradiotherapy in combination with magnetotherapy in treatment of malignant glial tumors of the brain improves the ECOG Performance Status grades and provides for the better Karnofsky index values. The established intergroup differences in the Karnofsky indices have shown a rise from 1% to $7,7 \%$ ($p < 0,05$). Before the therapy, an average ECOG Performance Status grade in patients suffering from malignant gliomas of the brain has been found to be $2,20 \pm 0,08$ in the main test group and $2,25 \pm 0,09$ in the reference group, respectively, whereas upon completion of the 4 therapy courses the relevant status has been assessed as $2,06 \pm 0,09$ and $2,43 \pm 0,014$, respectively, that allows identifying a statistically significant better dynamics of the data in patients, who received MT ($p < 0,05$).

2. The utilization of the adjuvant chemoradiotherapy combined with magnetotherapy in treatment of malignant glial tumors of the brain reduces symptoms of neurological toxicity, as compared to the reference group, as follows: general brain symptoms by 24% ; motor disorders by $26,9 \%$, sensory processing disorders by $16,7 \%$, speech disorders by $10,7 \%$ and higher nervous activity disorders by $13,9 \%$ recorded within the time close to surgery (6 months after the surgery operation). It contributes to a better dynamics of the ECOG Performance Status grading ($0,32$ against $0,18$) and in the Karnofsky index values ($9,3$ against $2,6 \%$).

3. The application of magnetic field exposures in the complex treatment of patients with malignant gliomas of the brain produces a pronounced anti-stressor ef-

fect: it provides for predominance of training, calm and elevated reactions in the pattern of the physiological reactions in 73,4 % of the cases; it decreases the stress share by 2,9 times that promotes increasing of the coefficient of the relation between the anti-stressor reactions and stress by 10,8 times, as against the level identified in chemoradiotherapy treatment without magnetotherapy ($p < 0,05$).

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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