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Experience of Using Hyperbaric Oxygenation in the Treatment of Radionecrosis That Developed as a Complication of Stereotactic Radiosurgical Treatment of Meningioma on the Example of a Clinical Case

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SUMMARY In contrast to conventional microsurgery, stereotactic radiosurgery has an advantage in the treatment of intracranial masses, avoiding severe complications associated with open surgery. In rare cases, the use of the method is associated with the development of radiation-induced injuries, one of which is radiation necrosis (RN). This is a late complication of radiosurgery, developing mainly 6 months after radiation exposure. The neurological manifestations of this complication depend on location, and the clinical picture is very diverse. The method of magnetic resonance imaging (MRI) with intravenous contrast enhancement is quite often the first link in neuroimaging, which helps to suggest the presence of this complication based on the X-ray picture and to clarify the location of changes.

We presented the experience of radiation necrosis treatment in a 47-year-old patient who was referred to our department with a diagnosis of frontal meningioma. The patient underwent stereotactic radiosurgical treatment using the Elekta Leksell Gamma Knife Perfextion device, and 6 months later the gradual deterioration began, the patient complained of headache, nausea; central prosoparesis developed. Considering the clinical picture and control MRI data, the changes were interpreted as radionecrosis. In order to control the complication, the patient underwent standard glucocroticosteroid therapy, supplemented by hyperbaric oxygenation (HBO), which made it possible to achieve regression of the adverse clinical and radiological manifestations of the complication. Thus, on a clinical example, it was demonstrated that the combined use of glucocorticosteroids and HBOs is highly effective in the treatment of RN.

Keywords: stereotactic radiosurgical treatment, radionecrosis, magnetic resonance imaging, meningioma, hyperbaric oxygenation

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WHO – World Health Organization
HBO – hyperbaric oxygenation
DWI – diffusion-weighted images
RN – radiation necrosis
MRI – Magnetic Resonance Imaging
SRST - stereotactic radiosurgical treatment
FFD – Facies basalis ossis frontalis dexter
FLAIR– Fluid attenuation inversion recovery
FSPGR– Fast spoiled gradient echo
SWAN– Susceptibility-weighted angiography

TE– Echo time
TR– Repetition time

INTRODUCTION

Stereotactic radiosurgery is an effective method of treating neoplasms of the brain, however, in rare cases, when it is used, complications develop, one of which is radiation necrosis (RN). RN refers to delayed complications that are difficult to treat. The use of hyperbaric oxygenation (HBO) as an adjunct method helps to improve the effectiveness of RN treatment.

This clinical case reflects the dynamics of the resolution of radionecrosis that developed as a result of stereotaxic radiosurgical treatment of meningioma. Treatment of the complication was carried out by a combination of therapy with glucocorticosteroids and HBO, as a result of which complete remission of RN was achieved.

Clinical case

Patient Y., 47 years old, with complaints of headache for a long time was referred by a neurologist to magnetic resonance imaging (MRI) of the brain. When performing this study with intravenous contrast enhancement (Gadobutrol, at a dose of 0.1 mmol / kg), an extracerebral mass formation (meningioma) was revealed. Based on the results of the examination, the patient was referred for a consultation with a neurosurgeon at the N.V. Sklifosovsky Institute. Taking into account the basal location of the tumor and the increased risk of infectious complications during open neurosurgical surgery, due to sinusotomy at access, it was decided to perform a radiosurgery in order to prevent further tumor growth: "Stereotaxically oriented external beam treatment using the device *“Leksell Gamma Knife Perfexion”.*

At the stage of preoperative preparation, the patient underwent MRI on an ultra-high-field tomograph with a magnetic field of 3 T *(GE Signa HDxT 3.0T, Milwaukee, WI, USA)*. The images of the brain in the axial plane, weighted by T1, were obtained in the mode *FSPGR (fast spoiled gradient echo)* with the following parameters: slice thickness 1.0 mm; relaxation time (TR) — 5,8; echo time (TE) — 2,0, matrix size 256x256 pixels, field of view 25.6x25.6 cm. The presence of a space-occupying lesion of the right frontal region, according to radiological signs corresponding to a meningioma [1] with dimensions of 20.5x20.0x19.5 mm with deformation of the perifocal substance of the brain, without edema and displacement of the median structures was detected (Fig. 1).

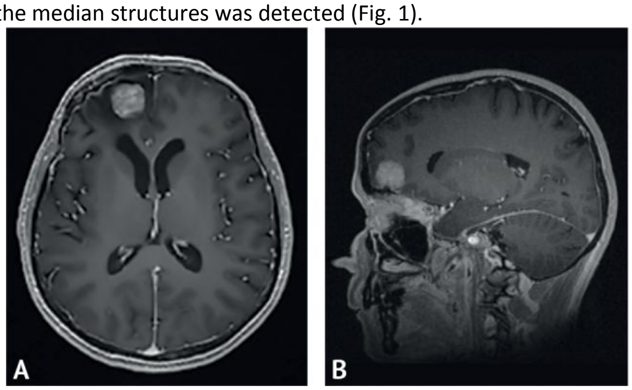

Fig. 1. Results of preoperative magnetic resonance imaging with intravenous contrast enhancement in T1 FSPGR mode in axial (A) and sagittal (B) projections. In the basal parts of the right frontal region, an extracerebral formation of a rounded shape, with a clear even contour, actively and uniformly accumulating contrast agent is determined

Subsequently, remote stereotaxically oriented irradiation of the meningioma was performed using the device *“Elekta Leksell Gamma Knife Perfexion”* within the tolerance of the surrounding tissues with the prescribed marginal dose (Table 1, Fig. 2).

Table 1

Prescribed Dose, Isodose, and Maximum Dose Values Used in Stereotactic Radiosurgery for Meningioma

Localization	Prescribed dose, Gy	Prescribed isodose, %	Maximum dose, Gy
Basal surface of the frontal bone on the right	12	50	24

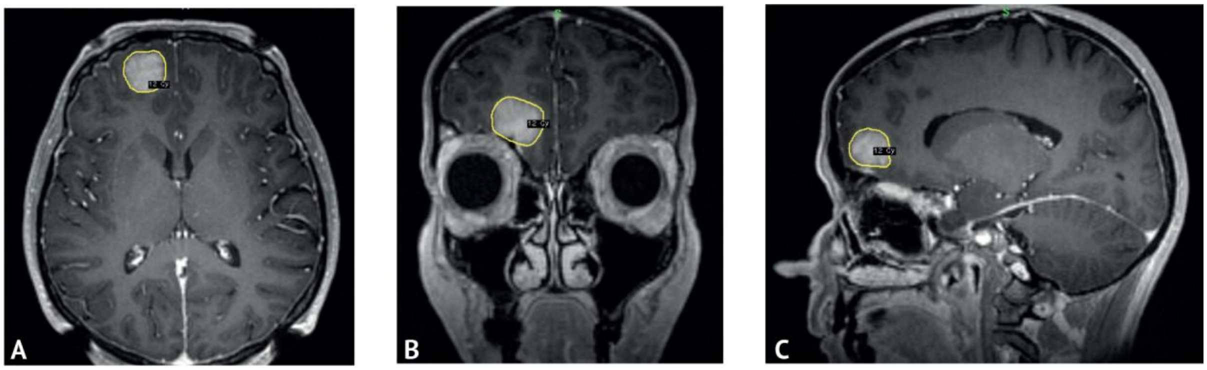

Fig. 2. Plan of stereotactic radiosurgical treatment. The images were obtained from the Gamma-Plan radiosurgical treatment planning station. On T1-weighted MRI scans, obtained after intravenous administration of a contrast agent, the yellow line indicates the prescribed dose limit of 12 Gy, corresponding to the edge of the tumor. The letters A, B, C denote images in axial, coronal and sagittal planes, respectively

The patient underwent the operation satisfactorily, without negative dynamics in the somatic and neurological status and she was discharged from the hospital for further outpatient observation.

Six months after stereotaxic radiosurgical treatment (SRT), the patient developed a gradual deterioration, she complained of headache and nausea, and central prosoparesis. Control MRI revealed an increase in the size of the irradiated meningioma up to 25.0x23.0x25.0 mm (previously 20.5x20.0x19.5 mm), which is permissible at different times after irradiation [2, 3]. However, in addition to this, such signs as indistinctness of the tumor contour and diffuse signal dropout in the *SWAN (susceptibility weighted angiography),* regarded as hemosiderosis was detected. In the perifocal substance of the right frontal lobe, pronounced edema up to 88 mm thick developed, and transverse dislocation of the midline structures up to 12 mm as a consequence. In the area of edema, a weak accumulation of contrast agent was noted (Fig. 3). Given the presence of neurological symptoms, the revealed MRI changes were interpreted as radionecrosis [4, 5]. To stop the edema, therapy with glucocorticosteroids was prescribed in the form of intramuscular administration of the drug dexamethasone for 4 weeks, according to the scheme presented in table 2.

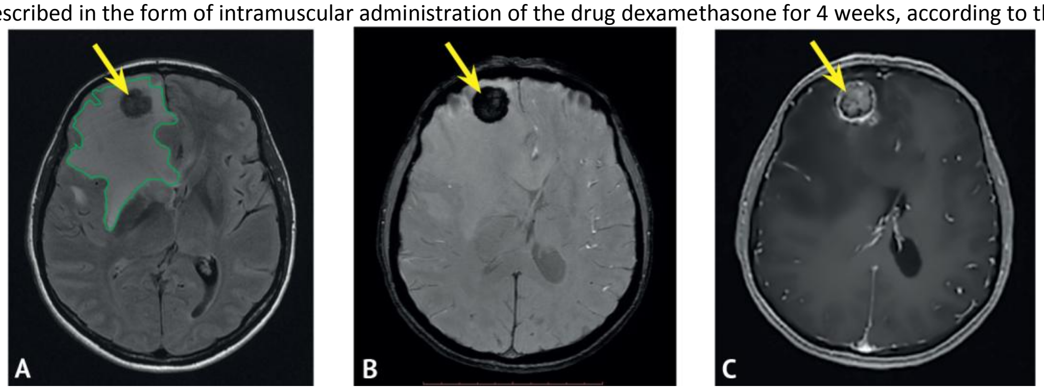

Fig. 3. Results of control magnetic resonance imaging performed 6 months after stereotactic radiosurgical treatment: A - axial projection in FLAIR mode; B - axial projection in SWAN mode; C - axial projection in T1 FSPGR mode with intravenous contrast enhancement. There is a change in the structure of the meningioma (arrow) to a more heterogeneous one, with a fuzzy outline and diffuse hemosiderosis according to the SWAN mode. In the perifocal substance of the right frontal lobe, there is a zone of significant edema (circled by a green line). With intravenous contrast enhancement, the accumulation of a contrast agent is noted not only in the tumor, but also in the substance of the right frontal lobe (a sign of a violation of the integrity of the blood-brain barrier)

Table 2

Scheme of intravenous administration of dexamethasone to control the developed edema

Week no	Morning dose, mg	Evening dose, mg
1st week	16	8
2nd week	12	8
3rd week	12	8
4th week	8	8

8 months after SRST, a convulsive seizure developed against the background of the therapy was noted as a result of which the patient was re-hospitalized. As part of the hospitalization, a course of conservative treatment was carried out with positive dynamics in the form of the absence of repeated convulsive seizures.

Control native MRI scans performed 9 months after treatment showed a decrease in edema in the perifocal substance of the right frontal lobe to 62 mm, as well as a decrease in the transverse dislocation of the median structures to 7.5 mm. Despite the improvements that arose against the background of conservative treatment, the size of the RN zone did not change significantly. Due to the high risk of recurrence of radiation complications, a course of HBO was prescribed as an auxiliary method of treatment [6, 7]: 15 sessions in a pressure chamber "Sechrist 2800" (USA). The patient received therapy every day, one session lasting 40-50 minutes on treatment modes 1.3–1.4 ATA.

Control MRI with intravenous contrast enhancement performed 3 and 7 months after the HBO course showed a gradual decrease in the perifocal edema zone to 40 mm and regression of the transverse dislocation of the midline structures of the brain. There was no accumulation of contrast agent in the brain substance in the area of edema. The contour of the meningioma became clear and even. The size and structure of the tumor remained unchanged.

Subsequently, control MRI studies were performed 22 and 33 months after SRST, which determined the stabilization of the process without changes in the size and structure of the tumor (Table 3, Fig. 4), which is a manifestation of local control over the irradiated meningioma. There were no signs of RN at the time of the last study.

Table 3

Dynamics of changes in the size and volume of the tumor and perifocal edema

Study	Linear tumor size, mm	Tumor volume, cm3	Volume perifocal edema, cm3
Preoperative	20,5x20,0x19,5	4,11	absent
Control after 6 months	25,0x23,0x25,0	6,94	164,05
Control after 33 months	21,0x22,0x23,0	3,87	10,68

Fig. 4. Results of control magnetic resonance imaging performed 33 months after stereotactic radiosurgical treatment: A - axial slices in FLAIR mode; B - axial slices in SWAN mode; C - axial slices in T1 FSPGR mode obtained after intravenous contrast enhancement. There is a change in the tumor contour to a clearer one (arrow), a decrease in the edema of the right frontal lobe (the area of edema is outlined with a green line). With intravenous contrast enhancement, the accumulation of contrast agent in the substance of the right frontal lobe is not detected

DISCUSSION

Hyperbaric oxygenation (HBO) – a method of using 100% oxygen at elevated atmospheric pressure [8]. During this procedure, the patient breathes pure oxygen inside the hyperbaric chamber, where an increased atmospheric pressure is created (in clinical practice, the pressure range from 1.2 to 3 ATA is usually used, depending on the treatment objectives and the patient's condition) [9].

Under HBO conditions, the amount of dissolved oxygen in the blood plasma increases by 100 times, from 0.03% to 3%, thereby enhancing the role of hemoglobin-independent oxygen transport in the RN zone. Oxygen dissolved in blood plasma reaches areas inaccessible to red blood cells, thereby increasing oxygenation of damaged tissue. HBO also has a number of other positive effects: reduces platelet aggregation and interstitial edema, activates neovascularization [7, 10]. Thus, we can talk about the significant effectiveness of HBO as a method of treating radionecrosis.

Initially, the use of hyperbaric oxygenation was directed only to the treatment of acute decompression sickness and gas embolism, later it was proved that the use of oxygen in high concentrations under high pressure is possible in other pathological conditions, such as carbon monoxide poisoning, prolonged compression syndrome, necrotic soft tissue infections, refractory osteomyelitis [3]. In addition to the above indications, hyperbaric oxygen therapy is an effective method of treating delayed radiation damage to the brain resulting from radiation therapy [11]. There is some evidence that HBO during radiation therapy enhances tumor destruction, reduces the frequency of local recurrence and increases patient survival [12–15]. In addition, HBO is used not only for independent, but also for combined treatment of various malignant tumors for the purpose of radiomodification (changing the radiosensitivity of tumor cells and normal tissues), radioprotection (weakening radiation damage to healthy tissues) and enhancing the effect of chemotherapy. Radiation therapy is an effective treatment for brain tumors, but the method is not devoid of side effects, such as radiation damage to healthy tissue. Symptoms caused by radiation therapy depend on the time of onset and can be divided into acute encephalopathy occurring within a month after therapy, early delayed changes developing after 1-4 months, and more delayed effects of radiation therapy, which occur on average 6 months after treatment and can lead to the development of RN. According to various studies, the incidence of this complication ranges from 5 to 37% [16, 17]. It depends, first of all, on the accuracy of the chosen technique and the individual characteristics of the patient.

The pathogenesis of radionecrosis is a complex and not fully understood process, represented by a number of links in pathological reactions in response to ionizing radiation.

As a result of the action of radiation, the endothelium of small arteries and arterioles is primarily affected [18]. Water molecules undergo radiolysis with the formation of unstable hydrogen and hydroxyl radicals. The latter, in turn, reacting with oxygen molecules, form perhydroxyl radicals and hydrogen peroxide, which damage DNA and lead to the death of endothelial cells. [10]. In this case, the brain substance undergoes hypoxia, a violation of the blood-brain barrier occurs, the permeability of the vascular wall increases and, as a result, the extravasation of albumin, which initiates the development of interstitial cerebral edema. Disruption of the blood-brain barrier and hypoxia lead to the expression of factor-1a (HIF-1a) and vascular endothelial growth factor (VEGF), thereby increasing interstitial edema. Through the damaged vascular wall, the brain substance is infiltrated by T-cell lymphocytes, macrophages and microglia. Macrophages and damaged endothelial cells activate the secretion of cytokines, triggering the inflammatory process. The inflammation, in turn, initiates the activity of the chemokine network, such as CXCL12/CXCR4, causing even greater infiltration of immune cells and leading to microbleeds, thrombus formation, demyelination and coagulation necrosis in the irradiated brain matter [18].

Many of the acute and early delayed effects of radiation therapy resolve on their own or with the help of glucocorticosteroid therapy, but when radionecrosis occurs in some cases, the effectiveness of such treatment may be low. To date, there have been several studies proving the effectiveness of HBO use in the treatment of RN. One of these is research of K. Kohshi et al. A 68-year-old man with metastases to the left hemisphere of the cerebellum of renal cell carcinoma underwent several stages of SRST. After 9 months, radiation necrosis developed during treatment, and neurological status worsened. In the treatment of this complication, glucocorticosteroid therapy was used and 60 sessions of HBO were carried out at 2.5 atmospheres for 60 minutes. At the same time, an improvement in the neurological status was revealed, according to the MRI data, regression of the RN zone was revealed. Subsequently, the patient was only on steroid therapy, after 2.5 months he again developed neurological symptoms, according to MRI data an increase in the zone of radionecrosis was revealed. In this regard, 50 courses of HBO were re-prescribed, after 11 months an improvement in the patient's condition was detected, according to the MRI data, a decrease in the RN zone was determined, and after another 22 months, a complete regression of radiological signs occurred and the absence of neurological symptoms was noted [10, 19].

In other studies conducted by B. Uysal et al., E. John et al., patients with radionecrosis after stereotaxic radiosurgical treatment for arteriovenous malformations and astrocytomas (grade 2 according to the WHO classification) were treated with HBO. Against the background of HBO therapy, all patients showed a significant improvement in the form of a decrease in the severity of neurological symptoms and edema according to imaging data [6, 7, 19].

Thus, taking into account the mechanisms of action and the experience of using HBO in clinical practice, it is possible to formulate the significance of barotherapy in oncological rehabilitation for the prevention of postoperative complications and weakening the side effects of radiation, chemotherapy and hormone therapy. This becomes especially relevant in view of the active development of stereotactic radiosurgery for intracranial neoplasms and, consequently, the number of detected complications.

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