

CLINICAL CASE REPORT

STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASES IN A CHILD WITH EXTRA-SKELETAL EWING'S SARCOMA

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ABSTRACT

Ewing's sarcoma is the second most common oncological disease of bones and soft tissues in children and adolescents, which is characterized by rapid growth and early metastasis. Brain metastases (BMs) occur in 10–12 % of cases and constitute a factor in the unfavorable prognosis of the disease. The possibilities of surgical treatment are often limited by the localization of a metastatic tumor, and the vast majority of chemotherapy drugs don't penetrate the blood-brain barrier, therefore radiation therapy, particularly stereotactic radiosurgery, the principle of which is a single high dose (15–24 Gy) of ionizing radiation to the pathological focus, is the most important method of treatment. High accuracy of tumor irradiation is ensured by rigid immobilization of the patient (using stereotactic frames or individual three-layer thermoplastic masks) in combination with positioning of the patient and control of his position by orthogonal X-rays. According to various authors, the use of stereotactic radiosurgery provides local control over BMs in 90 % of patients, regardless of the histological type of the primary focus, age and gender of the patient. The article describes a clinical case of successful radiosurgical treatment of a child suffering from extra-skeletal Ewing's sarcoma, in which following the complex treatment, progression of the disease, represented by multiple metastatic brain damage was revealed; the cumulative volume of metastatic foci was 2.3 cm³ and due to the proximity of the brain stem, as well as in order to avoid exceeding the tolerant load on healthy brain tissues, the total focal dose did not exceed 16 Gy. A complete response to therapy in the form of regression of all foci was noted six months after the treatment. To date, insufficient data has been published on the use of stereotactic radiosurgery in pediatric oncology, but in the available literature, the authors demonstrate the effectiveness and safety of treatment. Further research is needed to study the effect of the radiosurgical method on the children.

Keywords:

stereotactic radiosurgery, Ewing's sarcoma, brain metastases

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ОПЫТ ПРИМЕНЕНИЯ МЕТОДИКИ СТЕРЕОТАКСИЧЕСКОЙ РАДИОХИРУРГИИ ПРИ ЛЕЧЕНИИ МЕТАСТАТИЧЕСКОГО ПОРАЖЕНИЯ ГОЛОВНОГО МОЗГА У РЕБЕНКА С ВНЕСКЕЛЕТНОЙ САРКОМОЙ ЮИНГА

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РЕЗЮМЕ

Саркома Юинга – второе по распространенности онкологическое заболевание костей и мягких тканей у детей и подростков, которое характеризуется быстрым ростом и ранним метастазированием. Метастатическое поражение головного мозга (МПГМ) встречается в 10–12 % случаев и является фактором неблагоприятного прогноза заболевания. Возможности хирургического лечения зачастую ограничены локализацией метастатической опухоли, а подавляющее большинство химиопрепаратов не проникает через гематоэнцефалический барьер, поэтому важнейшим методом лечения является лучевая терапия, в частности, стереотаксическая радиохирургия, принципом которой является однократное подведение высокой дозы (15–24 Гр) ионизирующего излучения к патологическому очагу. Высокая точность облучения опухоли обеспечивается жесткой иммобилизацией пациента (использование стереотаксических рам или индивидуальных трехслойных термопластических масок) в сочетании с позиционированием пациента и контролем его положения по ортогональным рентгеновским снимкам. По данным различных авторов применение методики стереотаксической радиохирургии обеспечивает локальный контроль над МПГМ у 90 % пациентов вне зависимости от гистологического типа первичного очага, возраста и пола пациента. В статье описан клинический случай успешного радиохирургического лечения ребенка, страдающего внескелетной саркомой Юинга, у которого после комплексного лечения было выявлено прогрессирование заболевания – множественное метастатическое поражение головного мозга; кумулятивный объем метастатических очагов составил 2,3 см³, а ввиду близкого расположения ствола мозга, а также во избежание превышения толерантной нагрузки на здоровые ткани головного мозга суммарная очаговая доза не превысила 16 Гр. Полный ответ на терапию в виде регресса всех очагов отмечен через полгода после проведенного лечения. К моменту исследования период безрецидивного наблюдения составил 9 мес. На сегодняшний день опубликовано крайне мало данных о применении методики стереотаксической радиохирургии в детской онкологии, но в имеющейся литературе авторы демонстрируют эффективность и безопасность лечения. Необходимы дальнейшие исследования по изучению влияния радиохирургического метода на организм ребенка.

Ключевые слова:

стереотаксическая радиохирургия, саркома Юинга, метастатическое поражение головного мозга

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RELEVANCE

Ewing's sarcoma ranks second among bone and soft tissue tumors of childhood and adolescence. The disease is characterized by an extremely rapid and aggressive course; distant metastases are detected in a third of patients by the time of diagnosis [1; 2]. The lungs (40–85 %), bones (30–70 %), lymph nodes (10–35 %), as well as the brain are most often affected, where metastases develop in 10–12 % of cases. The localization and size of the metastatic focus are of paramount importance for the prognosis of the disease [3]. Metastatic brain injury (MPGM) is an unfavorable prognosis factor with a median survival of 51 days [4]. The possibilities of surgical treatment are often limited by the localization of a metastatic tumor, and the vast majority of chemotherapy drugs do not penetrate the blood-brain barrier, therefore radiation therapy is the most important method of treatment.

Stereotactic radiosurgery (SRS) is a modern method of radiation therapy based on a single application of a high dose (15–24 Gy) of ionizing radiation to a pathological focus, while radiation therapy in the mode of classical fractionation provides a single focal dose of 1.8–2.2 Gy for several fractions, depending on the prescribed total focal dose. High accuracy of tumor irradiation is ensured by rigid immobilization of the patient (using stereotactic frames or individual three-layer thermoplastic masks) in combination with positioning of the patient and control of his position by orthogonal X-rays. According to various authors [4–6] local control over intracranial neoplasms of secondary genesis can be achieved in 90 % of patients, regardless of the histological type of the primary focus, age and gender of the patient.

To date, very little data has been published on the use of the SRS technique in pediatric oncology, but in the available literature, the authors demonstrate the effectiveness and safety of treatment. In the study carried out by Napieralska et al. [7] radiosurgical treatment at a dose of 6 to 15 Gy for relapse of medulloblastoma or ependymoma was received by 14 patients, including four children aged 3 to 10 years. The authors state the development of local post-radiation cerebral edema in all patients, which was not clinically manifested and was determined only on MRI images. With further dispensary observation for two years, no other early or late post-radiation injuries were detected, and the edema was eliminated

by the administration of systemic glucocorticosteroids within a week. Nicolato et al. [8] studied the irradiation of arteriovenous malformations with high doses (from 9 to 26.4 Gy) in 100 children aged 3 to 18 years. Bleeding was observed in 9 % of patients and was due to the peculiarity of the pathology, no other complications were reported.

The purpose of the study: to demonstrate the clinical effectiveness of the stereotactic radiosurgery technique in children with metastatic brain damage.

Clinical case description

Patient B., 3 months old, was directed by a pediatrician to the National Medical Research Center for Oncology of the Russian Ministry of Health (Rostov-on-Don) for examination and determination of treatment tactics for education in the field of soft tissues of the back, which, according to parents, is marked from birth. Ultrasound of the soft tissues of the back from 09/27/2017 – in the soft tissues of the back on the left, a hypoechoic formation is located with smooth, clear contours, heterogeneous structure, with dimensions of 1.4 × 2.7 cm. CT of the thoracic, abdominal cavity, pelvic organs from 10/13/2017. – the lung tissue is without foci, there is no fluid in the pleural cavities, the pleura is not changed, the liver is diffusely heterogeneous, the spleen, the pancreas is not changed, there is no ascites. Adrenal glands, kidneys without pathology, retroperitoneal l / n are not enlarged, intra-thoracic l / n are not enlarged. In the ribs, sternum, pelvic bones without destruction. On the left, a paravertebral multi-nodular soft tissue formation of 4.5 × 3.7 × 3.0 cm with an inhomogeneous structure, calcinates, spreads through 6.7 intercostals into the soft tissues of the back. 16.10.2017 in the conditions of drug-induced sleep, in order to verify the tumor process, the patient underwent a core biopsy of the tumor. Histological analysis No. 70830/17 dated 16.10.2017 – the morphological picture is most characteristic of Ewing's sarcoma, it is necessary to differentiate with neuroblastoma, rhabdomyosarcoma, lymphoma. IHC from paraffin block No. 70830/17 dated 10/23/2017 – morphological picture and immunophenotype of tumor cells are most characteristic of extra-skeletal Ewing's sarcoma. Based on the above data, a clinical diagnosis was made: Ewing's sarcoma with paravertebral growth at the level of 6, 7, 8 intercostal space on the left, with growth in the soft tissues of the back, T3N0M0, stage III. Clinical group 2.

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In the period from November 2017 to November 2018, the patient underwent 6 courses of neoadjuvant chemotherapy according to the EURO Ewing 2008 protocol. On 04/02/2018, surgical intervention was performed in the following volume: removal of a residual soft tissue tumor of the middle third of the back on the left, histological conclusion No. 30576–81/18 of 04/06/2018 – Ewing's sarcoma with pronounced

dystrophic changes in tumor cells, extensive foci of fibrosis, with areas of angiomatosis. The formation is removed within healthy tissues. Remote radiation therapy was performed on a Novalis Tx, Varian linear accelerator, according to the planned plan: from 2 arches using the technology of volume-modulated arc therapy (VMAT) to the area of primary tumor spread against the background of drug-induced sleep, from 1.8 G to

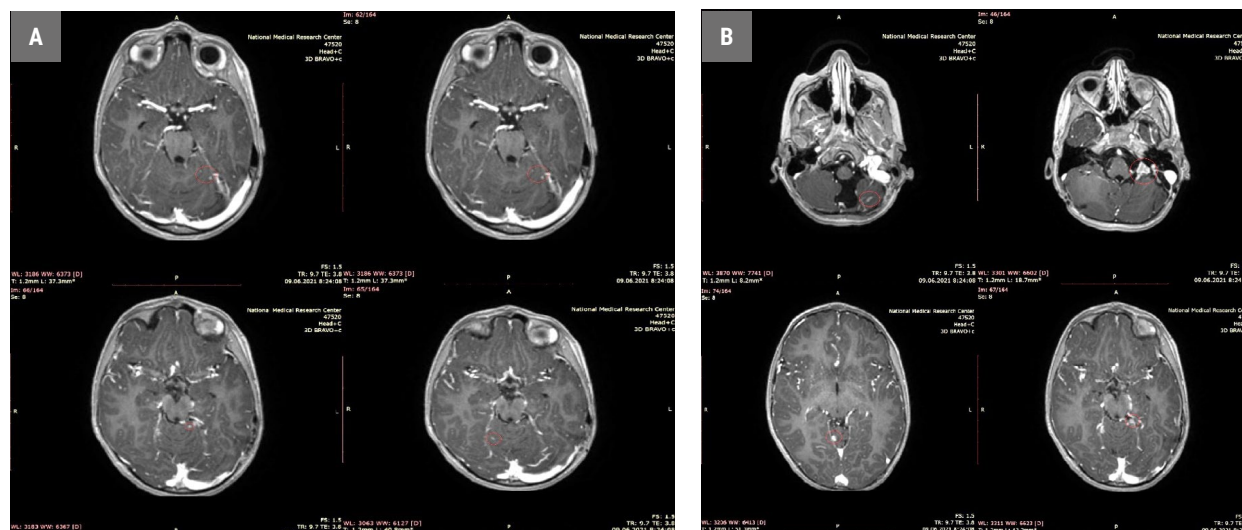


Fig. 1. Revealed metastatic foci on MRI of the brain from 06/09/2022.

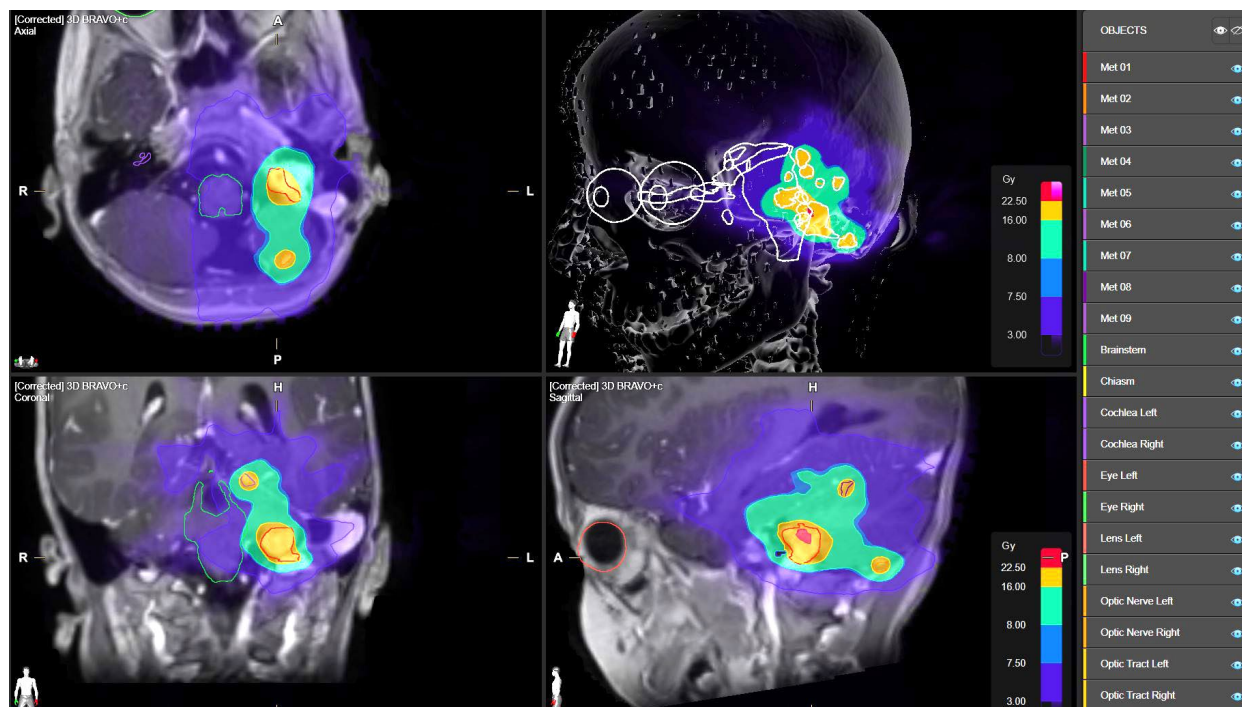


Fig 3. Stereotactic radiosurgery plan.

SOD 40 G. The treatment was carried out against the background of drug-induced sleep. Subsequently, the patient received 8 courses of adjuvant chemotherapy according to the above protocol.

03/21/2020, according to his parents, he fell off the sofa in a dream, screamed a lot. On 03/22/2020, the parents noted the unsteadiness of the gait, the tilt of the head to the left. A CT scan of the brain was

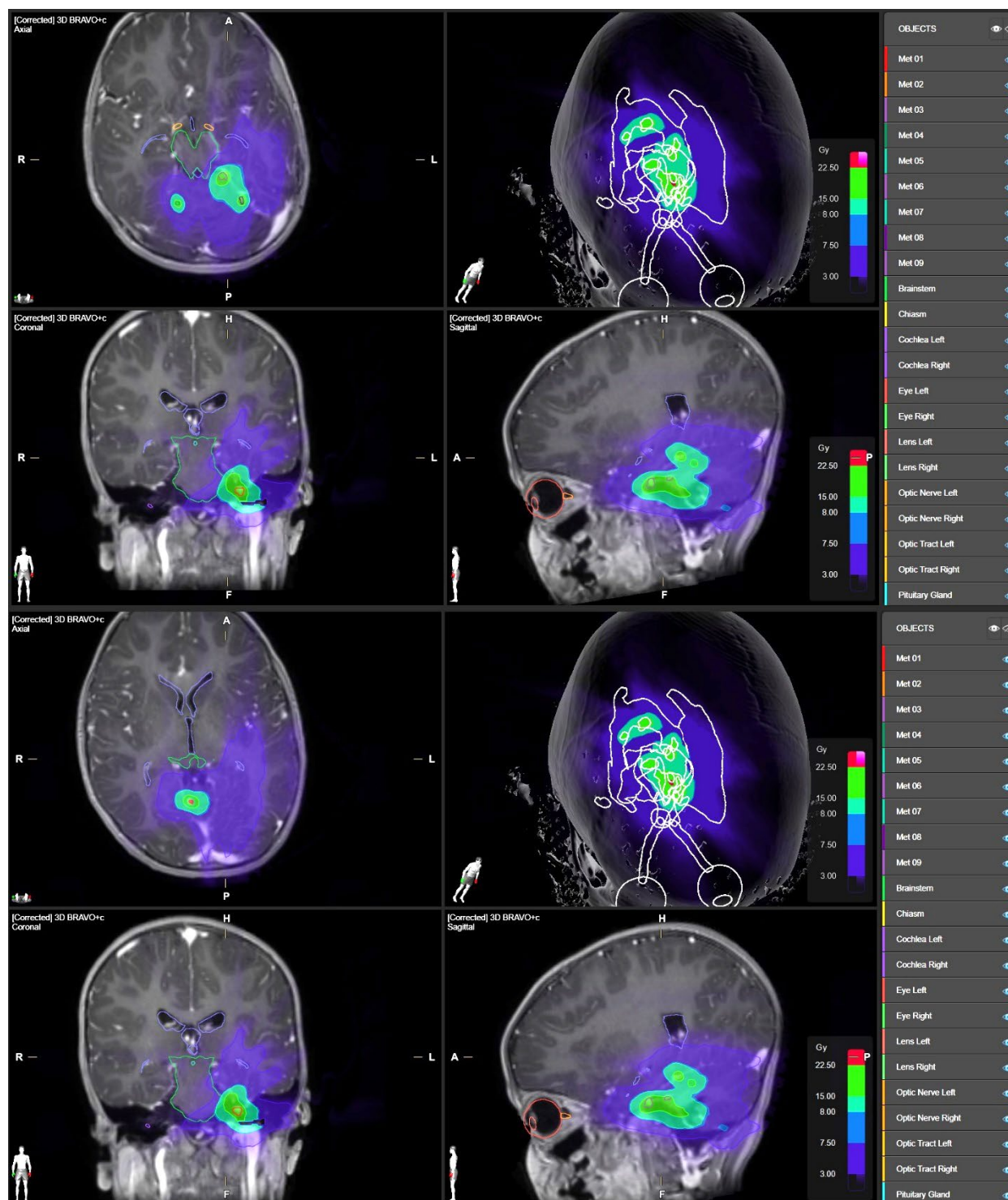


Fig. 4. Stereotactic radiosurgery plan.

performed, conclusion: the formation of up to 16 mm is determined on the right in the hemisphere of the cerebellum. In the left hemisphere of the cerebellum, a 33 × 38 × 30 mm volumetric formation with a cystic component of 32 × 22 × 30 mm with calcinates is parasagittally determined, squeezing and deforming the 4th ventricle, the median structures are not displaced. On 03/27/2020, an MRI of the brain was performed: the median structures were shifted to the right at the level of the PH up to 8.3 mm. In the right hemisphere of the cerebellum, there is a cystic-solid formation with moderate vasogenic edema along the periphery, with a total size of up to 28 × 42 mm. The formation of a cystic solid structure of the worm, the left hemisphere, the middle leg of the cerebellum, the left parts of the Varolian bridge with a slight edema on the periphery, dimensions 55 × 51 mm. Compression of the IV ventricle, the plumbing of the brain, the trunk, the legs of the cerebellum, the left leg of the brain. Displacement of the left amygdala of the cerebellum below the BZO level by 6.4 mm. After intravenous amplification, an active heterogeneous accumulation of contrast is determined by a solid component of tumors: on the right, the size is 18 × 17 × 13 mm, on the left, 29 × 26 × 33 mm. The presence of tumor contact with the walls of the left sigmoid venous sinus, without intraluminal invasion. The lateral ventricles of the brain are asymmetric D < S, moderately dilated, without periventricular edema.

ma. III ventricle up to 5.5 mm. Conclusion: MR is a picture of the same type of cystic solid formations in the right hemisphere of the cerebellum, in the left parts of the cerebellum, brain stem. Differentiate metastasis and hemangioblastoma. Compression of the plumbing of the brain and the IV ventricle with compensated internal hydrocephalus. Lateral displacement of median structures at the RF level, initial manifestations of descending axial wedging. On 03/27/2020, an operation was performed – removal of metastatic tumors of the cerebellum. GA, IHC No. 32105/20, 800/20: Morphological picture and immunophenotype of tumor cells, taking into account clinical data, are characteristic of Ewing sarcoma metastasis, Ki 67–60 %.

From 04/15/2020 to 09/21/2020, 6 anti-relapse courses of polychemotherapy were conducted (irinotecan, temozolomide.) In the future, he was under dynamic observation, MRI of the brain 1 time in 3 months, CT scan of the chest, abdominal cavity, pelvis 1 time in 3 months.

On the next control MRI of the brain with contrast enhancement from 06/09/2021, multiple metastatic foci of the following sizes and localizations were found: 7 × 4 mm, 2 × 2 mm and 2 × 1 mm in the left hemisphere of the cerebellum, 13 × 11 mm in the left bridge-cerebellar corner, 5 × 6 mm and 2 × 2 in the cranial part of the cerebellar worm, 5 × 4 mm and 3 × 3 mm in the left hemisphere of the cerebellum at

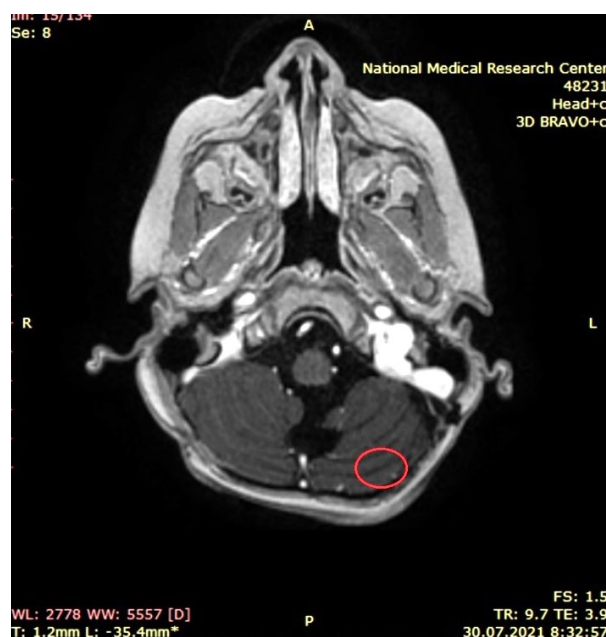
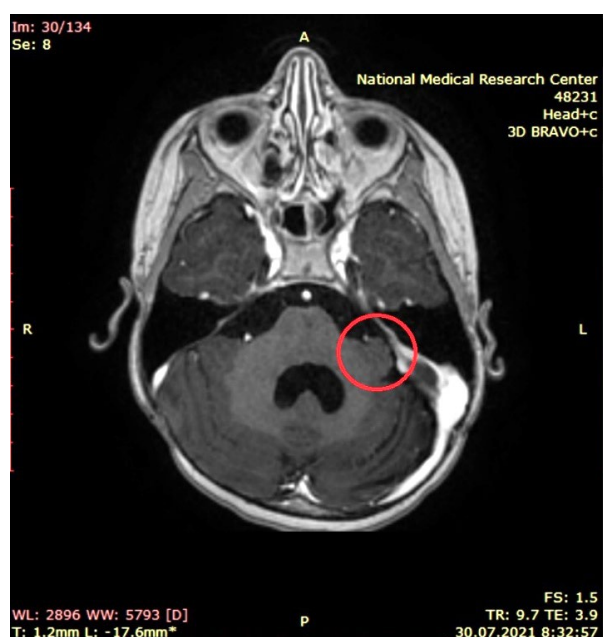


Fig. 5. Regression of metastatic foci a month after treatment, control MRI of the brain from 02/28/2022.

the level of the quadrilaterals, 3×2 mm in the right hemisphere of the cerebellum (Fig. 1). A consultation of doctors of the National Medical Research Centre for Oncology recommended a session of stereotactic radiosurgery. The patient was hospitalized in the radiotherapy department of the National Medical Research Centre for Oncology, Rostov-on-Don.

On 06/15/2021, preliminary topometric preparation was carried out: in the conditions of drug-induced sleep, an individual fixing device was made – a three-layer thermoplastic mask for stereotactic radiation therapy, X-ray contrast tags were installed, the isocenter was determined using the LAP Laser laser navigation system, topometric tomography was performed on a Siemens Somatom computer tomograph, the effective dose for the study was $3.7 \text{ m}^3\text{v}$. Preliminary topometry data was processed at the Singo Via virtual simulation station. Segmentation was performed using the Elements (BrainLab) software. The calculation and formation of a treatment plan (3D planning) (Fig. 3, 4) for the Novalis Tx linear accelerator (Varian, USA) were carried out.

On 06/17/2021, in the conditions of drug-induced sleep, a SRS session was conducted on a Novalis Tx linear accelerator, Varian on the identified metastatic foci, the total volume of which was 2.3 cm^3 , using the SRS technique with an irradiation energy of 6 MeV and the following target coating parameters: $V_{100} \% \geq 95 \%$, $D_{\max} \leq 150 \%$ (Fig. 3). Due to the close location of the brain stem, as well as to avoid exceeding the tolerant load on healthy brain tissues ($V_{12\text{Gy}} \leq 10 \text{ cm}^3$), the prescribed focal dose was 16 Gy. Positioning was performed using the Exactrac system (BrainLab). The period after irradiation took place against the background of standard decongestant therapy. No radiation reactions were observed, the treatment was carried out satisfactorily.

A month after the SRS session with a control MRI of the brain from 07/30/2021, according to the criteria of RANO-BM, stabilization of the process in the brain is noted: regression of the metastatic focus in the left area of the cerebellum and the focus in the left bridge-cerebellar corner (Fig. 5). The total volume of foci decreased by 23 % and amounted to 1.77 cm^3 (previously 2.3 cm^3). A complete response to therapy in the form of regression of all previously determined metastatic foci was noted six months later with a control MRI of the brain from 12/01/2021.

Currently, supportive chemotherapy is being performed. Dynamic examination is carried out. There is no data for progression.

DISCUSSION

Modern methods of treatment can prolong the life of patients in difficult clinical situations. Despite multiple metastatic brain damage, with the help of radiosurgical treatment, it was possible to achieve complete regression of foci without reducing the quality of life of the child. By the time of the study, no early symptoms (nausea, vomiting, headache, fever, post-radiation dermatitis) were detected or late (delayed growth of the skull bones) post-radiation injuries. The period of relapse-free follow-up is 9 months.

CONCLUSION

The technique of stereotactic radiosurgery in pediatric oncology can prove itself as a safe and effective non-invasive method of treatment. Further research is needed to study the effect of the radiosurgical method on the child's body.

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