In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the N.N. Burdenko Journal of Neurosurgery was included in the List of Leading Peer-Reviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.
Glioblastomas in children and adults are a heterogeneous group of tumors that can be divided into at least three different subgroups: pediatric glioblastomas, IDH1 mutant adult glioblastomas (a subtype with the most favorable prognosis), and IDH1 wild-type adult glioblastomas. The frequency of observed cytogenetic aberrations (amplification of MYC/MYCN, EGFR and PDGRFA oncogenes, homozygous deletion of CDKN2A and PTEN deletion) reveals that pediatric glioblastomas display similarities to the IDH1 mutant adult glioblastoma subtype.

**Keywords:** pediatric glioblastoma, IDH1 mutant adult glioblastoma
The aim of the present study was to compare the molecular and genetic features of pediatric and adult glioblastomas.

**Material and Methods**

A total of 125 patients with glioblastomas, who gave informed consent, were included in the study: 48 of them aged between 2 and 18 (the pediatric glioblastomas cohort) and 77 aged between 19 and 53 (the adult glioblastomas cohort). All patients underwent surgical resection of the tumor with histological verification, radiation therapy (for patients older than 3 years of age) and chemotherapy, following the protocols accepted at the N.N. Burdenko Neurosurgical Institute and the D. Rogachev Federal Research and Clinical Center of Pediatric Hematology, Oncology, and Immunology. All 77 adult patients with glioblastomas were operated on at the N.N. Burdenko Neurosurgical Institute in 2002—2008. The pediatric glioblastoma cohort included patients who were operated on at the D. Rogachev Federal Research and Clinical Center of Pediatric Hematology, Oncology, and Immunology and at several international centers, which kindly provided frozen tumor tissue samples for genetic studies at the German Cancer Research Center in the Helmholtz Association (DKFZ Deutsches Krebshorfschungszentrum in der Helmholtz-Gemeinschaft, Heidelberg, Germany) as a part of the "Pediatric Glioblastomas" project. Information on these patients was obtained from the DKFZ database and is publicly available at the TCGA website (https://tcga-data.nci.nih.gov).

For all patients included in the study, a fragment of tumor tissue was removed during surgical intervention and immediately frozen in liquid nitrogen; the samples were subsequently stored in liquid nitrogen at –80 °C. The availability of frozen tumor tissue allowed us to carry out comparative genomic hybridization to study cytogenetic chromosome aberrations, as well as to perform direct sequencing to identify mutations in the IDH1, TP53 and H3F3A genes.

**Comparative genomic hybridization** (performed in the DKFZ)

Array-CGH was performed for 125 glioblastomas (48 pediatric glioblastomas and 77 adult glioblastomas) according to the DKFZ protocol [25].

Polymerase chain reaction (PCR) and identification of IDH1, TP53 and H3F3A mutations by direct sequencing (performed in the DKFZ)

PCR and gene sequencing were performed for 125 glioblastomas as described in [2, 4].

**Fluorescent in situ hybridization** (performed in two centers: the N.N. Burdenko Neurosurgical Institute and the DKFZ)

Probes for the following oncogenes and chromosomal loci were used in the study: MYCN (2p24), PDGFRA (4q12), EGFR (7p12), CDK6 (7q21.2), MYC (8q24.12-24.13), CDKN2A (9p21), PTEN (10q23), CDK4 (12q14.1) and IRS2 (13q34).

**Immunohistochemical analysis** (performed at the N.N. Burdenko Neurosurgical Institute)

Immunohistochemical analysis was performed using a Lab Vision Autostainer 360 semi-automatic immunostainer (ThermoScientific) and Anti-Human IDH1 R132H astrocytoma and oligodendroglioma tumor cell marker mouse monoclonal antibody (Dianova clone: H09 dilution 1:20) [4, 5].

**Statistical analysis**

The Kaplan–Meier method was used to analyze the overall survival. The overall survival was calculated from the date of the diagnosis until death (censor) from progression of underlying disease (patients who died from other causes were excluded from the study) or until the date when the last set of follow-up data was collected.

**Results**

The “WHO Grade IV Glioblastoma” diagnosis was established based on the criteria listed in the current WHO classification of CNS tumors [14].

Microscope examination of the biopic material of pediatric and adult glioblastomas revealed the identical histological presentation of a malignant astrocyte with marked nuclear atypia, cell polymorphism, high mitotic activity, thrombosis, microvascular proliferation and necrosis.

**Cytogenetic aberrations in glioblastomas**

The comparative genomic hybridization studies of cytogenetic aberrations in glioblastomas showed that most tumors both in children and adults contain numerous irregularities in their genomes. In our cohort we found only three pediatric glioblastomas without any cytogenetic aberrations; there were no adult glioblastomas with balanced profile and neither additions nor deletions.

The amplification (increased gene copy numbers) of the MYCN, EGFR, CDK4 and PDGRA genes were the most frequent ones. In particular, MYCN amplification was observed in 12% of tumors for children and in 4% of tumors for adults; EGFR was observed, respectively, in 12 and 29% of cases; CDK4 amplification, in 6 and 18%; PDGRA amplification, in 10 and 5%; MYC amplification, in 6 and 2%; CDK6 amplification, in 6 and 7%; MDM2 amplification, in 2 and 6%; MDM4 amplification, in 2 and 8%. Therefore, MYC/MYCN and PDGFA amplifications were predominant in the pediatric cohort, whereas in the adult cohort the most frequent amplifications were those of the EGFR and CDK4 genes.

Homozygous deletion of the CDKN2A gene and chromosome 10q deletion were observed in both age cohorts at approximately equal ratios. Homozygous deletion of CDKN2A was observed in 17% of the pediatric glioblastomas and in 29% of the adult glioblastomas.
while chromosome 10q deletion was found in 54 and 60% of the glioblastomas, respectively.

The major cytogenetic aberrations in glioblastomas revealed by the comparative genomic hybridization and confirmed by fluorescence in situ hybridization (FISH) are shown at Fig. 1—8.

Analysis of mutations in the IDH1, TP53 and H3F3A genes

By employing direct sequencing analysis we found IDH1 mutation (R132H) in 29 (38%) adult glioblastomas and 4 (8%) pediatric glioblastomas (Figs. 9, 10); TP53

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Fig. 1. Cytogenetic profile of a glioblastoma with numerous amplifications of the MDM4 (locus 1q32.1), EGFR (locus 7p11.12) and MYC (locus 8q24.13) genes.

Fig. 2. Amplification (increased number of copies) of the EGFR gene (locus 7p11.12) in glioblastomas.

Fig. 3. Cytogenetic profile of glioblastoma with MYCN amplification (locus 2p24.3) and 10q deletion.

Fig. 4. Monosomy of chromosome 10q in glioblastoma.

Fig. 5. Cytogenetic profile of glioblastoma with numerous amplifications of the PDGFRA gene (locus 4q12).

Fig. 6. Amplification (increased number of copies) of the PDGFRA gene (locus 4q12) in glioblastoma.

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By employing direct sequencing analysis we found IDH1 mutation (R132H) in 29 (38%) adult glioblastomas and 4 (8%) pediatric glioblastomas (Figs. 9, 10); TP53

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N.N. BURDENKO JOURNAL OF NEUROSURGERY 2, 2014
mutation, in 33 (43%) and 24 (50%) of cases, respectively, and \( H3F3A \) mutations in 17 (35%) and 1 (1%). Two variants of \( H3F3A \) gene mutations were identified: \( K27M \) (Figs. 11, 12) and \( G34R/V \) (Figs. 13, 14). \( K27M \) mutation was identified in 11 (23%) cases for children and in 1 (1%) case for adults, whereas \( G34R/V \) mutation was observed in 6 (12%) cases in children.

Fig. 7. Cytogenetic profile of glioblastoma with amplification of the \( CDK4 \) gene (locus 12q14.1) and homozygous deletion of \( CDKN2A \) (locus 9p21).

Fig. 8. Homozygous deletion of \( CDKN2A \) (p16) (locus 9p21) and monosomy of chromosome 9q in glioblastoma.

\( CDKN2A \) (locus 9p21) is shown in red (singular signals), chromosome 9 centromere CEP 9 (loci 9p11.1–q11.1) is shown in green.

Fig. 9. Electrophoregram of studying \( IDH1 \) gene mutation by direct sequencing: no mutations in \( IDH1 \).

Here and in Fig. 10–14: the product of direct gene sequencing was isolated by capillary gene electrophoresis. For this purpose nucleotides were marked by four different fluorochrome dyes: adenine (green), guanine (black), cytosine (blue) and thymine (red). Mutation involves replacement of the base pair, leading to the replacement of one amino acid with another.

Fig. 10. Electrophoregram of studying \( IDH1 \) gene mutation by direct sequencing.

Mutation involves replacement of guanine to adenine, leading to the replacement of arginine amino acid with histidine (indicated by an arrow ↓).

Fig. 11. Electrophoregram of studying \( H3F3A \) \( K27M \) mutation (no mutation).

Fig. 12. Electrophoregram of \( H3F3A \) \( K27M \) mutation studies by direct sequencing.

The mutation involves replacement of adenine to thymine, leading to the replacement of lysine amino acid with methionine (\( K27M \), indicated by an arrow ↓).
Immunohistochemical identification of the mutant IDH1 protein

This approach was used to identify the mutant IDH1 R132H protein in parallel with direct sequencing of the genes. Marked cytoplasmic expression of IDH1 (Fig. 15) was observed in 29 (38%) adult glioblastomas and in 4 (8%) pediatric glioblastomas; with the ratios being identical to those of IDH1 mutation revealed by direct sequencing. No cytoplasmic expression of IDH1 was observed for 48 adult glioblastomas and for 44 pediatric glioblastomas. Therefore, the data of the direct gene sequencing and of the immunohistological studies aimed at identifying the mutant IDH1 protein were in complete agreement.

Glioblastoma subgroups

The glioblastomas in the study were divided in three subgroups based on patients’ age and presence or absence of mutations of the IDH1 and H3F3A genes, which are considered to be crucial for glioblastoma pathogenesis. The distribution of the observed chromosome aberrations and gene mutations across these three subgroups is shown in Fig. 16.

**MYC/MYCN** amplification was observed in pediatric glioblastomas and IDH1 mutant adult glioblastomas at approximately equal ratios of 19 and 17%, respectively, whereas amplification of **MYC/MYCN** gene in IDH1 wild-type adult glioblastomas occurred only in 4% of cases.

**EGFR** amplification was a distinctive feature of IDH1 wild-type adult glioblastomas; in this subgroup this cytogenetic aberration was observed in 42% of cases, whereas **EGFR** amplification in pediatric glioblastomas was observed only in 12% of cases and in IDH1 mutant adult glioblastomas, only in 6%.

**CDK4** amplification was observed predominantly in adult glioblastomas, irrespective of presence or absence of IDH1 mutation.

Homozygous deletion of **CDKN2A** and chromosome 10q deletion were observed in all three glioblastoma subgroups, with a minor increase in prevalence in the adult glioblastomas.

**TP53** mutations were observed in IDH1 mutant adult glioblastomas and in pediatric glioblastomas.

We have also examined the overall survival of patients with glioblastomas in the three aforementioned subgroups (Fig. 17).

An analysis of the overall survival reliably showed that the IDH1 mutant adult glioblastoma subgroup has the most favorable prognosis with the 5-year survival rate of approximately 80%. No reliable difference was observed between the overall survival in the pediatric glioblastoma and the IDH1 wild-type adult glioblastoma subgroups. The 5-year survival rates in these subgroups are approximately 8 and 0%, respectively.
Molecular classification of glioblastomas

We have developed a molecular classification of glioblastomas (Fig. 18) with three major subgroups based on the results of our studies, obtained by cytogenetic, mutational, and methylation [24] analyses, and on the overall survival rates of children and adults with glioblastomas. The first subgroup includes pediatric glioblastomas for which H3F3A mutation was observed in 40% of tumors and TP53 mutation in 50% of tumors and which are characterized by the hypomethylated genotype. The distinctive feature of the second subgroup, which includes adult glioblastomas, was mutation of the IDH1 gene; the group was also characterized by TP53 mutation observed in 80% of cases and the hypermethylated genotype. The third subgroup contained IDH1 wild-type adult glioblastomas with numerous cytogenetic aberrations (the most frequent cytogenetic distortion was EGFR amplification observed in 40% of cases) and the normomethylated genotype.

Discussion

We have investigated the molecular features in the mixed pediatric and adult glioblastoma cohort. The analysis of the molecular structures of glioblastomas in two age groups allowed us to elaborate the molecular classification that includes three main subgroups: pediatric glioblastomas, IDH1 mutant adult glioblastomas and, IDH1 wild-type adult glioblastomas.

The main features of glioblastomas in children include H3F3A mutations in 40% of tumors, IDH1 mutation in 50% of tumors, and the hypomethylated genotype. Initially described in 2012 [23], mutation of the H3F3A gene encoding H3.3 histone is an epigenetic event and is associated with post-translational histone modifications.

The main structure in the nucleus in eukaryote cells is chromatin, a complex of DNA and histone proteins. Histones are modified post-translationally and in this case it may affect their ability to interact with DNA and proteins in the nucleus. Histone modifications (the so-called “histone code”) define the status of the chromatin structure and virtually regulates all processes that involve or depend on DNA, including replication and repair, regulation of gene expression and preservation of centromeres and telomeres [23]. Histone modifications usually occur in the N-terminal region and include methylation, acetylation, and phosphorylation [6].

TP53 mutation correlates strongly with IDH1 mutation; for glioblastoma patients under 55 years of age,
TP53 mutation was observed in 80% of cases. The IDH1 mutant adult glioblastomas subgroup has the hypermethylated genotype and the most favorable prognosis compared to two other subgroups; the 5-year survival rate for this group is 80%.

In contrast to the data of M. Antonelli et al. [1], who had not observed a single case of IDH1 mutation in a cohort of 22 pediatric glioblastomas, we have identified it in four children aged 11—17. In our study all four cases of IDH1 mutation in children occurred in tandem with TP53 mutation.

The peculiar features of IDH1 wild-type adult glioblastomas are the high frequency of cytogenetic aberrations, especially EGFR amplification which was observed for 40% of cases in this subgroup, a relatively low degree of TP53 mutation compared to two other subgroups (observed only in 20% of cases), and the normally methylated genotype.

Comparison of the molecular and genetic features in the aforementioned three subgroups revealed that glioblastoma formation in pediatric and IDH1 mutant adult subgroups requires a combination of two mutations either in the H3F3A and TP53 genes (for pediatric glioblastomas) or in the IDH1 and TP53 genes (for adult glioblastomas). TP53 mutation is recognized to be crucial for the development of secondary glioblastomas [14, 18]; however, TP53 mutation also occurs in primary glioblastomas in less than 30% of cases [18]. IDH1 mutation precedes TP53 mutations during pathogenesis of glioblastomas [19].

It is possible that pediatric and IDH1 mutant adult glioblastomas are secondary glioblastomas, developed from preceding gliomas with low degree of malignancy, whereas IDH1 wild-type adult glioblastomas are primarily fast-evolving de novo glioblastomas with unfavorable prognosis.

We have shown that IDH1 mutant glioblastomas in adults under 55 years of age (the so-called “young age glioblastomas”) have the best rate of overall survival. The existence of “long-term survivors” among glioblastoma patients is a well-described phenomenon with the age under 50 years considered to be the most important favorable factor. Back in 2005, A. Korshunov et al. [13] classified “young age glioblastomas” into a separate subgroup with distinctive molecular features. By using the next-generation sequencing technique and the database containing 23,219 transcripts of 20,611 genes, D. Parson et al. [20] discovered in 2008 that glioblastomas in the patients from this age group have a heterozygous point mutation in the IDH1 gene. It became the pivotal moment in studying genetic disorders in gliomas. The discovery of IDH1 mutation provided a new explanation to the molecular classification proposed by A. Korshunov et al. [12] in 2006, which included two subgroups of glioblasto-

Fig. 18. Molecular classification of glioblastomas based on the molecular and genetic aberrations in different age groups.
mas with markedly different prognosis; the discovery of hypermethylated glioblastoma genotype in adults with IDH1 mutant glioblastomas [24] explains why the tumors from this subgroup, in contrast to pediatric glioblastomas and IDH1 wild-type adult glioblastomas, are responsive to radiation therapy and chemotherapy with alkylating agents, including temozolomide.

In daily practice of any department of pathology, IDH1 mutation and the most favorable glioblastoma subtype can be identified by an easy-to-implement immunohistochemical analysis whose results are in 100% agreement with the data of direct gene sequencing and analysis using Illumina 450k methylation array. Identification of the IDH1 mutation (or the mutated IDH1 protein, in case of the immunohistochemical analysis that we recommend) in adult glioblastomas is important not only because of the implied sensitivity to chemo- and radiation therapy, but also because of the possible targeted therapy by AGI-5198 and AGI-6780 inhibitors, which affect R132H IDH1 and R140Q IDH2, respectively [9].

As we have demonstrated in this paper, pediatric glioblastomas are a rather interesting subject for further studies; it is a heterogeneous group of tumors and despite the low overall 5-year survival rate there are some long-term survivors. In the future we intend to analyze the H3F3A mutation by direct sequencing in a large cohort of pediatric glioblastomas, to correlate different variants of K27M and G34R/V mutations with tumor location, and to determine the prognostic value of each type of mutation.

Conclusions

Glioblastomas in children and adults have similar histological presentation with some differences in frequency of cytogenetic aberrations (predominance of MYC, MYCN and PDGFA amplification in the pediatric cohort vs. predominance of EGFR and CDK4 amplification and homozygous deletion of CDKN2A and chromosome 10q deletion in adults). Despite this fact they represent a heterogeneous group of tumors, which can be divided into at least three different subgroups based on the analysis of the mutations: pediatric glioblastomas, IDH1 mutant adult glioblastomas (the subtype with the most favorable prognosis) and IDH1 wild-type adult glioblastomas.

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Research into genetic disorders in glioblastomas is very important as it may eventually contribute to understanding of tumor histogenesis and progression and, ultimately, to development of more effective therapies. All these considerations make this paper very relevant. The relevance lies in comparative characterization of genetic aberrations in pediatric and adult glioblastomas, which shows that genetically different tumors may be united under one common name. Unfortunately, the paper does not present any information on the age groups of the children included in the study. I also believe that it is necessary to mention the importance of changes in regulatory genes in tumor development, as well as its clinical and histological parameters. The study was carried out at a very good level. The data on the complete agreement of the results of immunohistological and genetic studies are noteworthy. The discussion section is well written and even proposes a molecular classification of glioblastomas (in my opinion it is excessive because a classification should not be based on a single approach to investigation, especially in case of heterogeneous results and relatively small cohorts).

A.G. Talalaev (Moscow, Russia)
Surgery of Skull Base Tumors Extending into the Orbit, Paranasal Sinuses, Nasal Cavity, Pterygopalatine and Infratemporal Fossae: Principles of Treatment of Certain Types of Tumors

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Following the paper focused on surgery of skull base tumors invading the orbit, paranasal sinuses, nasal cavities, pterygopalatine and infratemporal fossae, the authors discuss particular issues of surgical treatment of the most common craniofacial neoplasms, including meningiomas, juvenile angiofibromas, trigeminal nerve tumors, chondroid tumors, etc.

Keywords: craniofacial neoplastic tumors, cranio-orbital tumor, meningioma, angiofibroma, trigeminal nerve tumor, chondroid tumor.

Craniofacial neuro-oncology is a specific field of surgery of skull base tumors as it concerns “borderline” pathological cases that cannot be categorized as belonging to “pure” surgical specialties like neurosurgery, ENT-surgery, ophthalmosurgery, etc. That is why the difficulty of surgical treatment of base skull tumors invading the orbit, nasal cavity, paranasal sinuses, pterygopalatine and infratemporal fossae is that one needs to get through the skull base which is an interdisciplinary “border” as well. Craniofacial neuro-oncology can be considered to rely on the following three “pillars”:

— “the art of border-crossing”, which requires the thorough knowledge of anatomy of border areas (e.g. the orbit, superior orbital fissure, infratemporal fossa, etc.) and that of the main craniofacial approaches;

— “the art of border restoration”, which requires the knowledge of plasty techniques of treating skull base defects that a surgeon always has to deal with when performing surgical excision of craniofacial neoplastic tumors. Defects mainly result from tumor resection, less often they result from tumor-caused destruction of the skull base;

— clinical practice that takes into account the diversity of histological and topographic variants of craniofacial neoplasia.

However, treatment of patients with craniofacial tumors would be impossible without an interdisciplinary approach that is essential at each stage of diagnosing (requiring a neurologist, an ophthalmologist, an ENT specialist, a radiotherapist, and a morphologist) and treatment (a neurosurgeon, an oncologist, a radiotherapist, and a chemotherapist).

Materials and Methods

The present study is based on analysis of 647 observations of patients with craniofacial tumors who were treated at N.N. Burdenko Neurosurgical Institute in 2007—2011; detailed data on these were presented in our previous article, published in Vol.5, 2013. The treatment included different surgical methods (with open and endoscopic approaches), various modes of stereotactic radiotherapy (multifraction therapy, hypofractionation, radiosurgery) and chemotherapy (in case of malignant neoplasia). The objective of this work was to describe specific ways of treating tumors of various histological origins.

Principles of treatment of specific types of tumors

Hyperostotic cranio-orbital meningiomas (285 cases) are the most frequently recorded craniofacial tumors. These are meningiomas of sphenoid bone wings extending intracranially and intraorbitally with differently manifested hyperostotic and soft-tissue components. Considering this, they can be divided into three groups in order to select optimal surgical approach: lateral (46%), medial (44.4%) and extended ones (9.6%) [6, 7]. Lateral hyperostotic meningiomas infest the superior and anterior orbital fissures, the base of the middle cranial fossa, infratemporal and pterygopalatine fossae (Fig. 1). Medial hyperostotic cranio-orbital meningiomas usually affect the anterior clinoid process, the optic canal, the superior orbital fissure, and the ethmoidal sinuses (Fig. 2). This type of tumors is characterized by vision impairments of different severity. Extensive hyperostotic cranio-orbital meningiomas have signs of both lateral and medial types.
Our experience of treating hyperostotic cranio-orbital meningiomas let us to distinguish seven stages of surgical interference [7, 11]:

1. Resection of soft tissues through a coronal incision.
2. Osteotomy aimed at forming orbitozygomatic or lateral orbital bone flap.
3. Removal of hyperostosis: excision of the osteal part of the tumor with decompression of cranial nerves in orifices and canals depending on the extension of hyperostosis (the superior and anterior orbital fissures, the optical canal, round and oval foramina). There is a risk of damaging neurovascular structures and breaking ethmoid air cells or the sphenoid sinus.
4. Removal of the intraorbital soft-tissue portion of a tumor. This stage should precede the removal of an intracranial nodule because the resection of tumor from the orbit significantly enlarges the angle of surgical manipulations. The objective of this stage is to isolate the zone of tumor infiltration from orbital structures.
5. Removal of the intracranial soft-tissue portion of a tumor. Special care is required when dissecting an infiltrated zone from the superior orbital fissure and cavernous sinus. The method of identification of III, IV and VI nerves (see above) is preferred to perform this task.
6. Reconstruction of skull base defects in the area of sphenoid bone wings is hindered as there are no points to fix the plastic material in inferomedial compartments of the middle cranial fossa. That is why fat graft is preferable for reconstruction (e.g., pedicled buccal fat pad or free fat flap from the anterior abdominal wall). There are various kinds of thrombin based fibrin glue to fix it, such as Tissucol, Tachocomb or autologous ones (made of patient’s own blood). Additional sealing is achieved by laying calvarial periosteal flap on the margins of dural defects and fixing it with sutures if possible. In case these plastic materials are not available, especially at recurrent operations, temporal muscle flap can be used (either entire or its layer). When sealing the dura mater, a microirrigator (a silicon catheter) is left in the orbit and advanced to temporoparietal area via counterincision. After the operation, hydrocortone is administrated in a dose of 50 mg for 2—3 days via a catheter to lessen the swelling of orbital tissues.
7. Grafting: sealing with titanium plates or bone cement is required in about 1/3 of cases.

In those cases when total resection of the sphenoid bone wing meningioma is impossible due to its significant medial extension, stereotactic radiotherapy is carried out after the surgery. This therapy provides possibility to control the tumor growth in about 90% of cases [3].

Despite the fact that cranio-orbital meningiomas are mostly nonmalignant, they are featured by “aggressive” behavior and tend to invade the surrounding structures. Our researches have revealed genetic aberrations stipulating such tumor behavior [17].

A specific kind of cranio-orbital meningiomas are those affecting the optic nerve (n=9). Distinctive feature of this type is that the tumor infiltrates layers of the optic nerve in the orbit, often forming an hourglass-shaped structure around the intraorbital, intracanal and intracranial segments of the optic nerve (Fig. 3). These topographic properties make the supraorbital approach a method of choice in treatment of patients with this type of meningioma. When this approach is used, the optic canal should be opened. At the first step the intraorbital portion of the tumor is resected, then the portion residing in the optic canal and, finally, the intracranial nodule. When vision recovery in patients with amaurosis appears
to be a non-option, tumor is resected together with the optic nerve. It is crucially important to repair the optic canal area to avoid orbital liquorrhea.

Although there is no such conventional term as “orbitosphenopetroclival meningioma” \((n=31)\), we were the first to describe this rare meningioma type as a separate nosological entity. It includes tumors that extend into the orbit, middle and posterior cranial fossae.

This is the terminal stage of the natural growth of meningioma of medial portions of sphenoid bone wings (Fig. 4). Since those are considered absolutely inoperable, combined treatment is used. The first step is surgical reduction of the tumor size (Fig. 5) and orbital decompression (usually using both orbitozygomatic and pterional approaches). After that, a patient undergoes a course of stereotactic radiotherapy or radiosurgery.

The specific feature of treatment of such patients is extended preoperative period during which angiography and endovascular coiling of available afferents are carried out alongside the preparation for profuse blood loss. Blood saving technologies are used (plasmapheresis, hemodilution, retransfusion).

In surgical treatment of medially located skull base meningiomas with extracranial growth \((n=68)\) various approaches are used depending on the size of intracranial nodule. If the intradural portion of the tumor (Fig. 6) is large, subfrontal craniotomy or approach through the frontal sinus are used [8]. The endoscopic endonasal approach is considered the optimal one for tumors with predominantly extracranial extension (Fig. 7) [15]. In a number of cases surgical interference is performed in two steps, considering the prolific venosity of tumor and infeasibility of preoperative embolization of afferents from the system of the internal carotid artery. This meningioma type is typically accompanied by frequent severe vision impairments up to blindness.

If the tumor affects anterior cerebral arteries, its eradication becomes impossible; stereotactic radiotherapy can be recommended as an effective adjuvant method.

**Juvenile angiofibromas** with intracranial extension into the middle cranial fossa (in some cases those may extend into the anterior cranial fossa as well) are recorded among non-meningeal mesenchymal tumors more often than any other type. True intradural invasion is observed rarely if ever [13]. These tumors are often hypervascular, so the standard preparation for the surgery with profuse blood loss is made. It includes stimulation of erythropoiesis, plasmapheresis, endovascular embolization of feeding vessels from the system of the external carotid artery. In the course of operation, blood-saving techniques are used on obligatory basis along with transfusion of donor blood components. Those include isovolumic hemodilution and retransfusion of the own washed erythrocytes. Due to the fact that tumors at this stage are characterized

![Fig. 3. Meningioma of the right optic nerve.](image)

\(a\) — MRI before surgery. The tumor is located in the orbit and extends intracranially through the optic canal affecting the anterior clinoid process, tubercle and bifurcation of the internal carotid artery; \(b\) — CT one day after the surgery. The microirrigator is indicated by an arrow; \(c\) — contrast-enhanced MRI 3.5 months after the surgery — no signs of contrast uptake.

![Fig. 4. Cranio-orbital meningioma.](image)

On the left — MRI (female patient refused to undergo the suggested surgery). On the right — SCT of the same patient 4 years later: the tumor has grown giant and occupies the anterior, middle and posterior cranial fossae, the orbit (eyebulb has protruded outside the orbit) and extends to the opposite side.
**Fig. 5.** Orbitosphenopetroclival meningioma.

On the left — view before operation; on the right — after operation. The lateral portion of the tumor was dissected from the middle cranial and infratemporal fossae from the right; the remained medial portion of meningioma is to be treated by stereotactic radiotherapy.

**Fig. 6.** Midline craniofacial meningioma with primarily intracranial extension.

On the left — MRI before operation: tumor occupies the anterior cranial fossa, frontal and ethmoidal sinuses and invades the nasal cavity. On the right — CT after transcranial resection of tumor through the frontal sinus.

**Fig. 7.** Medially located meningioma with primarily extracranial extension.

On the left — SCT before operation. Tumor fully infests the nasal cavity, ethmoidal labyrinth, sphenoid sinus and extends into the orbits and maxillary sinuses, causing compression of both optic nerves and chiasm. The intracranial portion is represented by the suprasellar mass. On the right — CT after endoscopic endonasal resection of extracranial portion of tumor with decompression of the orbits and optic canals.

by significant volume and profound lateral extension (**Fig. 8**), it is recommended that the orbitozygomatic approach with endoscopic assistance or combination of that with endoscopic endonasal approach is used [4, 9]. When total excision of tumor is impossible or there is a risk of reoccurrence, stereotactic radiotherapy or radiosurgery is administrated [14]. Juvenile angiofibromas are androgen-dependent and occur only in prepubescent and pubescent boys, so tumor remnants typically involute after the age of 20.

**Malignant craniofacial tumors** (n=51) represent a difficult interdisciplinary problem as surgical treatment in such cases requires mutual efforts of oncologists, neurosurgeons and plastic surgeons [12]. All operations can be classified into the radical and palliative ones; conditions for radical surgery depend on particular features of
the lesion in a particular patient and the possibility of restoration of extensive complex defect of the skull base. Special class of operations is craniofacial en bloc resections (Fig. 9—11). The main principle of craniofacial resection is to form a tissue mass inside which tumor would be located and dissect it. There are no clear recommendations regarding the thickness of the layer of surrounding tissues that should be included. In the anterior cranial fossa it can be 3—5 mm; in the nasopharynx and maxillary sinus, 2—3 cm. If tumor affects the skin, or the cicatrix of the previous operation and biopsy results suggest so, the skin is also included. If the skin is movable and there is an intact layer between the skin and the tumor, a surgeon does not include it in the tissue mass. Also, it also reasonable to remove suspicious tissues after the excision as those could be infiltrated by the growing tumor. It also appears helpful to verify block margins morphologically. As far as defects are concerned, the method of multilayer plastic reconstruction is used. Thus, dural defects are sealed with the free fat graft harvested from the anterior abdominal wall which is fixed with sutures and thrombin-based fibrin glue. The next layer, extradural, is made of a pedicled fascial-periosteal flap. More complex reconstruction techniques are used for extensive defects. In those, defects are reconstructed by means of omental flap, musculocutaneous flap from the rectus abdominis, greater pectoral muscle flap or musculocutaneous flap from the serratus anterior. When the process invades the pharynx to a large extent, in some cases tracheostomy is advised after en bloc resection.

**Craniofacial neurolemmoma and neurofibroma** (n=26) are exceptionally rare; they originate from trigeminal ganglion and/or the trigeminal nerve (Fig. 12). The pattern of tumor infiltration into the extracranial structures is defined anatomically. Thus, neurolemmoma of the first branch of the trigeminal nerve extends into the orbit through the superior orbital fissure. Neurolemmoma of the second branch invades through the round foramen into the pterygopalatine fossa and, in a number of cases, further into the maxillary sinus, whereas the same lesion of the third branch invades through the oval foramen into the infratemporal fossa and sometimes into the parapharyngeal space. Intracranial nodule is located in the middle cranial fossa in projection of Meckel's cavity [16]. Rather frequently it extends medially into the sphenoid sinus. Neurolemmoma is featured by degeneration of osseous structures of the skull base and symptoms of the trigeminal nerve malfunction. Contrast-enhanced MRI is recommended for more precise diagnosis. Selection of surgical approach depends on the origin and localization of tumor. In the case of small cranio-orbital tumor originating from the first branch of the trigeminal nerve it is usually sufficient to perform lateral orbitotomy, whereas the orbitozygomatic approach is used for larger tumors. Tumors of the second branch are treated surgically via both orbitozygomatic and pterional approaches; tumors of the third branch are handled by pterional or subtemporal craniotomy combined with the orbitozygomatic approach.

![Fig. 8. Extended juvenile skull base angiofibroma. The patient is 16 years old.](image)

Tumor infests the nasopharynx, nasal cavity, ethmoidal labyrinth, sphenoid sinus, maxillary antrum, pterygopalatine and infratemporal fossae; permeates the temporal fossa and profoundly extends into the middle cranial fossa. On the left — SCT before operation, on the right — CT on the 7th day after operation.

![Fig. 9. Advanced craniofacial tumor on the left (epidermoid carcinoma).](image)

MRI before operation. The tumor occupies the left half of the middle portion of the face and extends intracranially.

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The most problematic group of osteogenic tumors are those of the chondroid type \((n=18)\) that can be benign (chondroma, chondromyxoid fibroma, chondroblasto-
ma) and malignant (chondrosarcoma) \([2,10]\). Cranio-
facial chondroid tumors are mainly located medially (the sellar area, the cribriform bone). Chondrosarcoma is a rare tumor located craniofacially in 10% of cases. Most of chondrosarcomas are primary malignant, rarely they result from chondroma malignant transformation. They are characterized by aggressive growth, bone degradation and moderate vascularization. Chondromas are typically slow-progressing and less invasive than other types. As far as radiological parameters are concerned, benign and malignant tumors do not significantly differ; they look like heterogeneous extensive formations containing petrifacts, contrast-enhancing and not causing peritumoral edema \((\text{Fig. 13})\). Therapeutic approach in such cases directly depends on the degree of anaplasia. The optimal way of treating benign tumors is total resection. Even after incomplete resection, radiotherapy is not recommended as it may induce malignant transformation. Chondrosarcoma requires treatment combining surgical removal of the tumor with subsequent high-dose radiotherapy. Nevertheless, recurrent tumors are ob-
served quite often, where the extent of intradural infiltr-

\[\text{Fig. 10. Craniofacial en bloc resection — steps of operation (intraoperative photograms).}
\]

\(a —\) view before operation; \(b —\) excised mass containing the tumor; \(c —\) the first step of skull base defect reconstruction \((1 —\) calvarial peristome flap; \(2 —\) free anterior abdominal wall fat; \(3 —\) tongue in the oral cavity). We used osteomyocutaneous graft containing segment of the rectus abdominis muscle and costal arch to reconstruct face defects; \(d —\) view after operation.

\[\text{Fig. 11. CT one month after the operation.}
\]

On the left — 3D-reconstruction of skull base defect; on the right — plastic mate-
rail (indicated by an arrow) in the defect’s projection.
tion increases with each operation, thus declining the possibility of total resection.

The most diverse group of craniofacial tumors is pseudotumors \( (n=12) \). There belong sinonasal polyposis with intracranial extension, various forms of chronic inflammation of the known (debride granuloma, pyogenic granuloma, Wegener’s granulomatosis, etc.) and unknown (idiopathic pseudotumor) etiology [5]. Heterogeneity is caused not only by etiology, but completely different ways of treatment. Whereas polyposis, mucocele (pyocele), solitary eosinophilic granuloma and similar neoplastic formations are mainly treated surgically, orbitally located pseudotumors and Wegener’s granulomatosis require only morphological verification with subsequent conservative treatment. At any rate, surgical interference is always necessary either as a cure method or as a mean.

**Fig. 12.** Neurinoma of the second branch of the trigeminal nerve.
On the left — CT before operation. The tumor occupies the medial portions of the middle cranial fossa, extends into the orbit, maxillary sinus, nasal cavity and nasopharynx. Total resection was performed by combining the pterional and orbitozygomatic approaches. On the right — contrast-enhanced MRI 15 months after the operation. No signs of recurrent tumor are observed.

**Fig. 13.** Giant craniofacial chondrosarcoma extending intracranially into the anterior cranial fossa and infiltrating the nasal cavity, nasopharynx, ethmoidal sinus, maxillary sinus and sphenoid sinus, orbits, pterygopalatine and infratemporal fossae on the left side.
Almost total vision impairment in both eyes. The tumor was dissected through the frontal sinus with endoscopic assistance. On the left — MRI before operation; on the right — CT on 7th day following the operation. Since the patient had not undergone radiotherapy, three more operations were carried out on recurrent tumors.
of refining diagnosis (biopsy); in some cases decompression of the orbit and/or the optic canal is needed. Current less traumatic treatment methods using the transnasal approach with endoscopic assistance or ophthalmological approaches are the best option for most patients with craniofacial pseudotumors (Fig. 14).

Plasmacytoma is a lymphoproliferative lesion \((n=3)\) characterized by monoclonal proliferation of plasma cells secreting immunoglobulins. This malignant tumor may infest both the calvaria and skull base, though the cranio-orbital location is among the most frequent ones. Plasmacytomlas can be of the solitary (bones or soft tissue) and multiple types. Multiple plasmacytoma prognosis is much worse than that of solitary plasmacytoma. Tumor causes degradation of the entire bone thickness and uniformly absorbs contrast media (Fig. 15). Venosity formed as a result of exaggerated branches of the external carotid artery is typical of this tumor type. Plasmacytomlas are successfully treated by radiotherapy; another therapeutic option is total surgical excision with adjuvant therapy [1].

**Conclusion**

Craniofacial tumors are a very diverse group of lesions having absolutely different origins, growing patterns, clinical signs and, consequently, requiring various means of treatment. That is why there are no standard ways of treatment; one only can speak of the common approach to treating the most frequent pathologies such as cranio-orbital meningiomas. Current trends in the surgery of skull base tumors extending into the orbit, nasal cavity, paranasal sinuses, infratemporal and pterygopalatine fossae, can be summed up in two — making the approach less traumatic and surgical manipulations more invasive by means of intraoperative control techniques (such as neuronavigation, endoscopy, neuromonitoring, etc.). Here, endoscopy may serve either as assistant means or as the main means of removing the tumor (at transnasal approach). It should be mentioned once again that diagnosis and treatment of craniofacial tumors should be carried out on an interdisciplinary basis. Despite the fact that microsurgical and endoscopic equipment are advancing more and more, nowadays decision against inappropriate and risky radical interference in

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**Fig. 14.** Considerable pyocele of the base of the anterior and middle cranial fossae on the right side was a reason for vision and oculomotor impairment that regressed after endoscopic endonasal drainage.

On the left — SCT before operation; on the right — 2 months after operation.

**Fig. 15.** Cranio-orbital plasmacytoma.

On the left — CT before the operation, on the right — after the operation.
many cases lets one to keep a considerably high level of the patient’s life quality at benign and malignant processes. It has become possible due to evolution of contemporary methods of highly precise stereotactic radiotherapy that has recently been growing into an essential component of the complex treatment of skull base neoplastic tumors. The results of treating various tumors will be reported in our further publications.

REFERENCES

Intraoperative Fluorescence Diagnosis and Laser Spectroscopy in Repeated Operations for Brain Gliomas


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A method of fluorescence diagnosis (FD) using 5-aminolevulinic acid (5-ALA) has been widely employed in surgery for primary intracerebral tumors over the recent years. The issue of FD application in surgery of brain gliomas with continued growth has remained less studied. Objective. To study the efficacy of using FD with 5-ALA and laser spectral analysis in surgery of brain gliomas with regrowth. Material and methods. 19 patients with recurrent WHO Grade II-IV gliomas of different localization were included in the study. All tumors were localized supratentorially. 5-aminolevulinic acid hydrochloride, “Alasens”, (Research Institute of Organic Intermediate Products and Dyes, Moscow, Russia) was used in the study. The equipment used during surgery included an operating microscope with an attachment for fluorescent navigation. Along with an expert qualitative assessment of the fluorescence intensity, a computer analysis of the fluorescence and light scattering (diffuse reflection) spectra was performed on a LESA-01-BIOSPEC spectrum analyzer (Russia). Results. Detectable fluorescence was observed in all the cases. Protoporphyrin IX (PP IX) fluorescence indices ranging from 9.05 to 53.97 were determined by a quantitative analysis of the spectrograms (the study was conducted in 12 cases). An analysis of light scattering revealed its inverse relationship with respect to the fluorescence index. A high sensitivity of the method in surgery of recurrent gliomas requires clarification of the method specificity because nonspecific accumulation of PP IX in the area of post-radiation necrosis may occur in these patients. Conclusions. The FD method can be used for intraoperative demarcation of tumor resection boundaries in surgery of cerebral gliomas with regrowth. However, it is necessary to be critical about the high sensitivity of the method in patients with post-radiation pathomorphism due to possible nonspecific accumulation of PP IX in tissues. A light scattering study may provide additional information about the structure of tissues in the surgical wound.

Keywords: fluorescence diagnosis, 5-ALA, gliomas, continued growth, spectroscopy.

Glioblastomas are among the most common tumors of the central nervous system, which account for up to 62% of all astrocytic tumors [14]. Currently, a combined treatment approach is used in most cases, which includes surgery followed by chemotherapy and radiotherapy [23, 31]. Unfortunately, the 5-year survival rate does not exceed 10% for all kinds of the treatment [30]. The crucial factor influencing the efficacy of all subsequent stages of this scheme remains the maximum possible surgical removal of the tumor. J. Nazzaro and E. Neuwell [27] define the role of surgery in treatment of supratentorial gliomas in the following way: reducing the mass effect and intracranial hypertension; reducing the mass of the tumor itself and establishing the correct histological diagnosis. Intraoperative demarcation of glial tumor boundaries is a very complicated process due to the infiltrative nature of growth. During the recent decade, the intraoperative fluorescence diagnosis with 5-aminolevulinic acid (5-ALA) has gained ground in glioma surgery [4, 29]. The principles of fluorescence diagnosis in glioma surgery were expounded by J. Tonn and W. Stummer [33] in 2008. Thus, 5-ALA-fluorescent navigation was demonstrated to be capable of increasing the rate of radical resection of malignant gliomas compared to the conventional microsurgery (65% and 35%, respectively), while the authors achieved the 2-fold increase in the 6 month relapse free survival [29].

In the case of malignant glioma recurrence, the neurosurgeon inevitably faces the indications for reoperations, attitude to which, according to the literature, is contradictory (Table 1).

Thus, M. McGirt et al. [22], using an example of 949 patients with Grade III–IV gliomas, note the positive role of repeated operations, while other authors [21] tend to refuse repeated surgical intervention in the case of continued growth in surgery of recurrent malignant gliomas. In a group of repeatedly operated patients, it was possible to increase the overall survival upon recurrent glioblastomas by 3 months only [17]. The resection volume of a relapsed glioblastoma is an important overall survival predictor. In the case of a subtotal removal upon the disease relapse, the maximum overall survival is achieved...
Table 1. The role of repeated surgical interventions upon glial tumor recurrences

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Grade</th>
<th>Effect of reoperation</th>
</tr>
</thead>
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<td>33</td>
<td>II—IV</td>
<td>Unpronounced</td>
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<td>M. Pinsker, C. Lumenta (2001) [28]</td>
<td>38</td>
<td>IV</td>
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<td>32</td>
<td>IV</td>
<td>Negative</td>
</tr>
<tr>
<td>M. McGirt et al. (2009) [22]</td>
<td>949</td>
<td>III—IV</td>
<td>Pronounced</td>
</tr>
<tr>
<td>T. Gorlia et al. (2012) [16]</td>
<td>300</td>
<td>IV</td>
<td>Unpronounced</td>
</tr>
<tr>
<td>P. De Bonis et al. (2012) [15]</td>
<td>76</td>
<td>IV</td>
<td>Pronounced</td>
</tr>
</tbody>
</table>

regardless of an initial removal volume of the tumor [10]. Undoubtedly, the initial patient condition, along with his somatic and neurological status, is taken into consideration when evaluating indications for recurrent operations. In connection with these data, the maximum possible, with allowance for the tumor localization, surgical removal of recurrent malignant gliomas is relevant.

Intraoperative orientation in a wound is substantially complicated due to previous surgery and performed radiation therapy, which causes massive gliosis and significantly complicates the determination of tumor boundaries. Modern metabolic “navigation” provides the surgeon with a possibility of fast optical differentiation of tissues in the surgical wound and identification of the areas with increased accumulation of protoporphyrin IX (PP IX), which, in turn, allows one to change rapidly, if required, the operative tactics. The literature does not cover comprehensively enough possibilities for the use of intraoperative fluorescence diagnosis with 5-ALA in surgery of gliomas with regrowth.

Material and Methods

The study included 19 patients (12 males and 7 females) with recurrent gliomas of the different malignancy grade (Grade II — 1 person; Grade III — 3 people; Grade IV — 15 people). The median age of patients with recurrent gliomas was 43 years (35–58 years on average). In all the patients, the tumors were located supratentorially: in the frontal region — in 8 patients, in the temporal region — in 3, in the parietal region — in 5, in the occipital region — in 1, lesions of the deep parts of the hemispheres — in 1, and multifocal growth — in 1 (Table 2). All the patients underwent a complex preoperative examination, including compulsory brain MRI with contrast enhancement. Virtually all the patients underwent chemotherapy and radiotherapy after the first operative intervention (from 1 to 7 courses of chemotherapy and radiotherapy at standard doses). Time after the first surgery varied from 6 to 78 months (25.6 months on average). When tumors were localized near functionally important areas, neurophysiological monitoring with intraoperative identification of the cortical speech and motor areas and pyramidal tract was used.

5-Aminolevulinic acid (5-ALA) hydrochloride, “Alasens”, (Research Institute of Organic Intermediate Products and Dyes, Moscow, Russia) was used in the study. The preparation in the form of a white crystalline powder was dissolved in 150–200 ml of water at room temperature to obtain 20 mg per 1 kg of the patient’s body mass. Patients ingested the resulting solution 4 hours before the beginning of tumor removal. The equipment, used during surgery, included a Carl Zeiss OPMI Pentero operating microscope with an attachment for fluorescent navigation. In some cases, detectable fluorescence was assessed on a 4-point scale (0 — no fluorescence, 1 — weak, 2 — moderate, 3 — bright fluorescence). Apart from an expert qualitative assessment of the fluorescence intensity, a computer analysis of the fluorescence and diffuse reflection spectra was performed on a LESA-01-BIOSPEC spectrum analyzer (Russia). As a diagnostic criterion, the fluorescence index (FI) value was used, which is calculated as the ratio of the PP IX fluorescence intensity in the range of 690–730 nm to the backscattered laser signal intensity. Also, as a marker for structural changes, the scattering (diffuse reflection) coefficient was studied, which was calculated as the ratio between the intensities of laser radiation backscattered by an analyzed tissue and the intact brain (generally, by the cortex).

Results

As seen from Table 2, detectable fluorescence was detected in 19 observations (the general method sensitivity was 100%). A qualitative assessment of the detectable fluorescence (+/−) was performed in 6 patients, the qualitative assessment according to the 4-point scale (0 — no fluorescence, 1 — weak, 2 — moderate, 3 — pronounced fluorescence) was done in 13 patients. According to the intensity, weak fluorescence was detected in 5 patients, moderate fluorescence — in 3, and bright fluorescence — in 5.

A quantitative analysis of the fluorescent effect using a laser spectroscopy method was performed in 12 patients; the maximum PP IX fluorescence index was 53.97, the minimum one was 9.05, with the background level from the intact cortex ranging from 0.85 to 3.7 (Table 3; Fig. 1).
Table 2. Data of patients with regrowth of brain gliomas

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age, years</th>
<th>Grade after the first surgery</th>
<th>Grade after the second surgery</th>
<th>Time after the first surgery, months</th>
<th>Histology</th>
<th>Localization</th>
<th>DF</th>
<th>Karnofsky index before surgery</th>
<th>Karnofsky index after surgery</th>
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<td>III</td>
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<td>2</td>
<td>60</td>
<td>70</td>
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</tr>
<tr>
<td>2</td>
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<td>+</td>
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<td>IV</td>
<td>10</td>
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</tr>
<tr>
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<td>IV</td>
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<td>IV</td>
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<td>70</td>
<td>CRT</td>
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</table>

from Table 3. Two last columns of this table contain the data on relative light scattering by tumor tissues compared to normal ones. It is easily seen that the minimum level of light scattering by a tumor is always less than 1, i.e. a tumor scatters the light more poorly than a normal tissue. However, the maximum level of light scattering in some cases is higher than 1, i.e. a tumor scatters the light better than a normal tissue. This is caused by the fact that the neoplastic process development is accompanied not only by the myelin destructurization, but also by an increase in the number and size of cell nuclei, which are also good scatterers. The presence of necrotic changes also influences the level of backscattered laser radiation.

Clinical case 1

A 35-year-old female was diagnosed with a recurrent intracerebral tumor of the left parietal parasagittal region with extension to the splenium and subcortical ganglia on the left. The past medical history: she had suffered since November 2006, when headache, attacks of dizziness

<table>
<thead>
<tr>
<th>№</th>
<th>Intact cortex FI</th>
<th>Minimum FI from tumor</th>
<th>Maximum FI from tumor</th>
<th>Minimum level of light scattering by tumor</th>
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Footnote. FI – fluorescence index.

The analysis of light scattering (in 11 patients) with the morphological control of biopates revealed a statistically significant feedback between the PP IX accumulation level and the light scattering coefficient value ($p<0.05$). An increase in the fluorescence parameters in the active tumor growth area is well explained by the presence of a large number of actively proliferating cells (Table 3). A decrease in light scattering occurs due to the destructurization of myelin and white matter fibers as glioma progresses.

The quantitative analysis of structural changes occurring in tissues during the neoplastic process development is based on interpretation of the level of laser radiation backscattered by a tissue. Tissues containing a larger number of optically dense inclusions (e.g. cell nuclei or nerves’ myelin sheaths) better scatter the light, and a spectrometer detects a higher level of the backscattered laser signal. The neoplastic process development is accompanied by the destructurization of myelinated nerve fibers that leads to a decrease in light scattering, as it can be seen from Table 3. Two last columns of this table contain the data on relative light scattering by tumor tissues compared to normal ones. It is easily seen that the minimum level of light scattering by a tumor is always less than 1, i.e. a tumor scatters the light more poorly than a normal tissue. However, the maximum level of light scattering in some cases is higher than 1, i.e. a tumor scatters the light better than a normal tissue. This is caused by the fact that the neoplastic process development is accompanied not only by the myelin destructurization, but also by an increase in the number and size of cell nuclei, which are also good scatterers. The presence of necrotic changes also influences the level of backscattered laser radiation.

Clinical case 1

A 35-year-old female was diagnosed with a recurrent intracerebral tumor of the left parietal parasagittal region with extension to the splenium and subcortical ganglia on the left. The past medical history: she had suffered since November 2006, when headache, attacks of dizziness
and spasms in the right leg started. On June 4, 2007, surgery was performed: astrocytoma of the left parietal lobe was removed using intraoperative neurophysiological monitoring. Biopsy №4572-75/07 on June 4, 2007, revealed a Grade II diffuse (fibrillary protoplasmic) astrocytoma with moderate nuclear polymorphism and regions of closely packed cells. The patient’s condition had become worse since April 2012. Brain MRI revealed signs of a recurrent tumor in the form of multiple nodes with a ring-shaped pattern of contrast agent accumulation, which were predominantly located in the parietal parasagittal region up to the splenium in the form of multiple nodes of various sizes with extension to the subcortical structures. The largest parts of the tumor were represented by the necrosis area and located along the convexity with extension onto the cortex of the left parietal and occipital lobes; the smaller parts were located deeply in the splenium region, in the subcortical ganglia and internal capsule on the left, with permeation into the posterior horn of the left lateral ventricle. A partial removal of the tumor was performed during repeated operative intervention (May 16, 2012). The method of fluorescence diagnosis with the use of an OPMI Pentero microscope was employed during the surgery. The bright crimson fluorescence was observed under illumination of the altered brain cortex regions in the BL 400 mode. During the tumor removal, the bright heterogeneous fluorescence and high values of PP IX accumulation were observed, according to the laser spectroscopy data, (Fig. 2), with an increase in the fluorescence index up to 20 units (the background level from the intact brain tissue was 2 units).

Clinical case 2
A 42-year-old male was diagnosed with a recurrent anaplastic astrocytoma of the left frontotemporal area. The patient was operated on for the first time on November 21, 2005; resection of a glioma of the frontotemporal area on the left was performed. The morphological conclusion was the anaplastic astrocytoma. A course of radiotherapy (60 Gy) and 7 courses of Temodal therapy were given. Continued growth of the tumor was detected in May 2012 (6.5 years later), when MRI revealed a space-occupying lesion in the left frontotemporal area with the intense accumulation of the contrast medium, with the heterogeneous structure and size of 72×81×44 mm. Positron emission tomography (PET) with methionine performed at the Institute of Human Brain, the Russian Academy of Sciences, showed that the accumulation index in the area of interest was 2.58. During the repeated surgery (July 5, 2012), a removal of the recurrent tumor in the left frontotemporal area was performed using intraoperative neurophysiological monitoring, ultrasonic scanning, and fluorescent navigation. The bright fluorescence of the tumor solid part was observed during the operative intervention (Fig. 4).

The postoperative period proceeded smoothly, the wounds were healed by the first intention, stitches were taken out on the 7th day. The morphological conclusion was an anaplastic astrocytoma. Currently, a course of adjuvant therapy is given domiciliary; no signs of tumor recurrence have been observed during the case follow-up.

Clinical case 3
A 39-year-old male was diagnosed with a recurrent glioblastoma of the left frontal lobe. According to the past medical history, he had suffered since September 2010 (the disease onset started with an epileptic attack). Brain
MRI revealed a space-occupying lesion in the left frontal lobe with compression of the left lateral ventricle and the displacement of midline structures. Resection of the tumor was performed at the N.N. Burdenko Neurosurgical Institute on September 23, 2010. The morphological conclusion was a glioblastoma. A course of stereotactic radiotherapy using a Primus apparatus was given after the surgery; 30 fractions by 2.2 Gy at the isocenter were delivered with simultaneous administration of Temodal (10 courses). Since September 2012, the patient had noticed an increase in the epileptic seizure frequency; anticonvulsant therapy was intensified and seizures were controlled. However, in connection with headache augmentation, MRI was performed on October 5, 2012, which revealed signs of the tumor progression (size of 5.6×2.7 cm, accumulating the contrast medium). Repeated surgery was performed on October 15, 2012; the recurrent glioblastoma in the left frontal region was removed using intraoperative sonography, fluorescence diagnosis, neurophysiological monitoring of the motor areas and pyramidal tract, and laser spectroscopy. During operation, the weak heterogeneous fluorescence was observed at the initial stage, which gradually intensified and became bright and homogeneous (Fig. 5).

At the end of operation, control fluoroscopy of the removed tumor bed was performed, in the course of which, a residual fluorescence in the bed was observed. The tumor remnants were removed. No augmentation of neurological symptoms was observed in the postoperative period. The postoperative period proceeded smoothly, the wound was healed by the primary intention, stitches were taken out on the 8th day. The patient was discharged in a satisfactory condition for subsequent domiciliary therapy.

**Discussion**

Fluorescent navigation increases the accuracy in determining tumor margins and allows one to perform a fast optical analysis of tissues in the surgical wound [29]. Intraoperative visualization for highly malignant recurrent gliomas after preceding adjuvant therapy is significantly complicated due to epiphenomena of post-radiation pathomorphism [19]. According to our data, observable fluorescence of a tumor was detected in all 19 observations. A spectral analysis, performed in 12 observations, revealed the increased PP IX fluorescence indices. This is consistent with the data of A. Nabavi et al. [25], according to which, the detectable fluorescence was observed in 34 of 36 patients with Grade III—IV recurrent gliomas, with the intensive detectable fluorescence being observed in 24 of the patients. In addition, the bright fluorescence

---

**Fig. 3. Correlation of the parameters of fluorescence diagnosis and light scattering in different parts of glioblastoma.**

High values of PP IX accumulation in a tumor upon low values of light scattering are noted. In the area of composite bioplates (solid part of a tumor + intact tissue + necrosis), the fluorescence decreases while the light scattering increases.
**Fig. 4. Preoperative and intraoperative metabolic navigation in a patient with anaplastic astrocytoma of the left frontotemporal area.**

a, b – preoperative Single Photon Emission Computed Tomography-Computed Tomography and PET (methionine accumulation index is 2.58); c – preoperative MRI with contrast enhancement; d – intraoperative photograph, a view in white light; e – intraoperative photograph, a view in the BL400 mode (intensive detectable fluorescence is observed); f – intraoperative laser spectroscopy in various tumor areas; g – postoperative brain Spiral Computed Tomography on the first day after the surgery.

**Fig. 5. Intraoperative fluorescence diagnosis in a patient with recurrent glioblastoma of the left frontal lobe at different stages of operative intervention.**

a, b – preoperative MRI before and after contrast enhancement, axial sections; c, d – intraoperative photographs in white light and the BL400 mode at the initial stage of surgery; weak fluorescence is detected; e, f – intraoperative photographs in the middle of the tumor removal stage; observable fluorescence intensity increased significantly, a view in white light and the BL400 mode; g – residual fluorescence at the end of the tumor removal stage, intraoperative photograph in the BL400 mode; h – postoperative brain Spiral Computed Tomography within the first 24 hours.

was noted in the area of the solid tumor part; the fluorescence was weak in the infiltration area.

Unfortunately, the fluorescence diagnosis method does not allow one to differentiate specific PP IX accumulation in a tumor and nonspecific accumulation in the radionecrosis area. Thus, in a study of 354 biopsies taken from sites with the positive detectable fluorescence in 40 patients, the authors revealed false-positive biopsies.
only in 12 (3.4%) cases. In these cases, the positive observable fluorescence was detected in the absence of tumor cells in bioplates [25]. The literature describes cases of the observable fluorescence in demyelinating diseases and post-radiation necroses. In these observations, the false-positive results may be explained by infiltration of the perifocal region with reactive astrocytes and macrophages accumulating 5-ALA [24]. Analogous cases were also observed in general oncology after operative interventions on the bronchi [7].

5-ALA accumulation is known to depend on the cell division rate in a tumor, however, nonspecific 5-ALA accumulation can be observed in association with radionecrosis and post-radiation pathomorphism [24]. In surgery of recurrent brain gliomas, the sensitivity and specificity of the method of intraoperative metabolic navigation with 5-ALA need to be clarified; however, it was found that increased PP IX accumulation in a recurrent glioma can be a consequence of inflammatory alterations around the tumor after performed adjuvant therapy without high proliferation of the very tumor [35, 36]. In connection with this fact, preoperative PET with methionine needs to be performed to increase the specificity of intraoperative navigation with 5-ALA. This method of analysis helps distinguish between regrowth of glioblastoma and a radiation necrosis area after preceding radiation therapy in a considerable amount of cases [6]. Thus, in recent studies, the sensitivity and specificity of 11C-methionine PET for the differentiation of continued growth of cerebral gliomas and post-radiation alterations of the brain were 75 and 75%, respectively, with the threshold value of the accumulation index (AI) being 1.58 [32], or, according to another sample, 85.7% and 77.8%, with AI being 2.0 [26]. However, slightly increased accumulation of 11C-methionine can also be detected in the radiation necrosis area [6]. The reasons of this phenomenon are not well established yet. Histological studies of the radiation necrosis area have revealed inflammatory perivascular infiltration and elements of microvascular proliferation, i.e. inflammatory and vascular components that may affect active uptake of the amino acid [6, 37]. In some cases, a combination of radionecrosis sites and areas of active tumor growth is possible. Perfusion examinations and MR spectroscopy can be used as methods alternative to PET for preoperative identification of radiation necrosis [6].

In these cases, further research is required to clarify capabilities of intraoperative fluorescent metabolic navigation with 5-ALA and spectroscopy. This will allow one to specify the sensitivity and specificity of the method of fluorescence diagnosis with 5-ALA in surgery of recurrent brain gliomas after radiation therapy.

To quantify PP IX accumulation, the laser spectroscopy method is currently employed, which helps identify the margins of infiltratively growing tumors when the standard fluorescence methods are ineffective [34]. In recent times, the method has been used in surgery of meningiomas, metastases, and other brain and spinal cord tumors [1, 5, 18]. The use of laser spectroscopy allows one to decrease the error rate in the course of operation during identification of the margin for resection of malignant glial tumors [9]. In recent years, there has been a tendency for extension of the intraoperative spectral analysis with concomitant measurement of parameters of light scattering by tissues, oxygenation, and blood filling [5, 35, 36]. In this work, the increase in PP IX accumulation parameters was found to be accompanied by the decrease in the parameters of light scattering by tissues. This occurs due to the destructurization of the myelin fibers upon the tumor invasion. Thereby, the use of two spectroscopic parameters may provide additional information on the intraoperative demarcation of tumor margins.

The obtained data on the use of fluorescence diagnosis (FD) in patients with brain gliomas suggest that this method, due to its high sensitivity, allows one to better evaluate tumor margins during surgery as well as, probably, to achieve more radicality and to avoid excessive resection of the surrounding tissues, which may determine the risk of postoperative complications. The use of combined spectroscopy with a concomitant analysis of the parameters for light scattering and PP IX accumulation provides additional information for intraoperative demarcation of tumor boundaries. Further clinical research is necessary to evaluate the effect of intraoperative fluorescence diagnosis and combined spectroscopy on improvement of results of surgery for brain gliomas.

REFERENCES


According to recent literature data, depending on histology and the results of this treatment (the patient’s life expectancy), an informed decision for repeated operative intervention, the removal of recurrent intracranial malignant gliomas. Neurosurgery 1987; 21: 607—614.


Retreat-ment of recurrent malignant gliomas, it is not always possible intraoperatively to delimit clearly the tumor areas from cicatrical and post-radiation scar tissue. Exp Rev Anticancer Ther 2013; 13: 5: 583—587. doi: 10.1586/era.13.32.


rather conclusively distinguish the recurrent glioblastoma and radionecrosis area. However, in some cases, increased accumulation of methionine may be detected also in the radionecrosis area.

In these situations the authors suggest using various modalities of fluorescent navigation: not only the parameters of PP IX accumulation, but also data of an intraoperative spectral analysis with a concomitant measurement of the PP IX accumulation parameters and light scattering from tissues. The results of these studies are currently somewhat ambiguous, however, research in this direction has very significant scientific and practical perspectives.

O.N. Dreval' (Moscow, Russia)
Treatment of patients with intracranial aneurysms in the acute phase of subarachnoid hemorrhage has the highest risk of unfavorable outcomes due to developing vasospasm in most cases. According to the International Subarachnoid Aneurysm Trial (ISAT), the 30-day mortality rate after aneurysm repair in the acute phase of subarachnoid hemorrhage was 13.4% and the overall incidence of severe disability and mortality during the first year after aneurysm treatment was 30.9% [5]. Similar results were obtained in Russian studies focused on the outcome of aneurysm repair in the acute phase of subarachnoid hemorrhage. The postoperative mortality rate for the group of patients who mostly underwent microsurgery was 11%; the disability rate, 14.1% [2]. The group of patients with 62% of them treated using endovascular therapy had the mortality rate of 9.3% and the disability rate of 13.6% [4].

Although the outcome of aneurysm repair performed in the late phase of subarachnoid hemorrhage is much better [8], a number of clinical factors contribute to the high risk of postoperative complications. It makes decision making on the choice of aneurysm treatment rather complex.

The objective of the study was to evaluate the frequency and pattern of complications after microsurgery and endovascular therapy of intracranial aneurysms of various topography and localization in patients operated on in the late phase of subarachnoid hemorrhage and to assess the risk of intervention in these patients.

Material and Methods

Characteristics of the study group

The study group included patients who underwent microsurgery or endovascular therapies of single intracranial aneurysms.

The exclusion criterion for the study group was the acute phase of subarachnoid hemorrhage corresponding to 21 days from the aneurysm rupture [3].

The study group included a total of 1074 patients, 552 (51.4%) of which were females and 522 (48.6%) were males aged 18 to 75 years (mean age 45.3 years) who were treated at the N.N. Burdenko Neurosurgical Institute in 2005—2012. There were 877 patients with aneurysmal subarachnoid hemorrhage (SAH) and 197 with recurrent SAH.

Microsurgery (also known as surgical clipping) and endovascular therapy (endovascular coiling) were performed in 887 (82.6%) and 187 (17.4%) patients, respectively. Treatment types are presented in Table 1.
Classification of aneurysm repair complications in the patients of the study group

All complications of surgical aneurysm repair are divided into intraoperative and postoperative ones.

The complications potentially causing clinical aggravation in patients during the postoperative period were classified as intraoperative ones (aneurysm rupture, thrombosis, etc.). The postoperative complications were of two types: cerebral (neurological) and extracerebral ones. The neurological complications were divided into transient (resolved within 24 hours) and persistent ones.

When assessing the severity of neurological complications, the following gradation was used: moderate, severe impairments, and death. Moderate impairment implied the emergence or exacerbation of neurological symptoms not confining patient’s mental, speech and motor capabilities. Severe impairment was inferred as the emergence or exacerbation of the patient’s psychiatric, aphasic, motor or bulbar disorders.

Considering that patients with complications in the postoperative period could stay in the hospital for a long time and the fact that the study was based on the examination of the immediate surgery outcomes, the changes in the neurological status were assessed for the period of 1—3 weeks after surgery.

Results

Postoperative complications were observed in 163 (15.2%) patients of the study group. Most of the complications (14.2%) were cerebral. Severe impairment was observed in 6% of all cases, the mortality rate was 0.9% (Table 2).

The cerebral complications were observed in 13.8 and 16% of patients who had undergone microsurgery and endovascular therapies, respectively. The mortality rates were 1 and 0.5%, respectively (Table 2).

Extracerebral complications

The extracerebral complications were observed only in 11 cases of microsurgeries, accounting for 1.2% of all open surgeries. Five (0.6%) patients developed nasal liquorhea as a result of opening of the frontal sinus during pterional craniotomy. In all cases this symptom could be stopped using lumbar drainage.

Noteworthy, opening of the frontal sinus during the pterional craniotomy was performed in 12% of cases. In most cases, nasal liquorhea was reliably prevented by proper sealing of the nasal cavity in frontal sinus reconstruction (autologous muscle fragment and fibrin glue were typically used).

Infectious complications were rare. Thus, pneumonia and sepsis were detected only in 2 (0.2%) patients staying in the intensive care unit for a long time due to the postoperative neurological complications. Postoperative meningitis was diagnosed in 2 (0.2%) patients and treated with systemic and intrathecal administration of antibiotics.

Transient neurological complications

The total number of transient neurological complications was relatively low, 2.1% (see Table 2). The neurological status of these patients at discharge from the hospital corresponded to their preoperative status. Transient cognitive disorders developing after open surgeries on aneurysms of the anterior communicating artery (ACA) and rare cases of single generalized convulsive seizures in

<table>
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<th>Table 1. Types of aneurysm repair treatments</th>
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<tr>
<td>Endovascular therapy (17.4%)</td>
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<th>Table 2. Postoperative cerebral complications associated with microsurgeries and endovascular therapy, number of patients (%)</th>
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<td>Neurologic deficit</td>
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<tr>
<td>Transient</td>
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<td>Persistent:</td>
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<tr>
<td>Death</td>
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the early postoperative period that were most likely caused by pneumocephalus are included in this group.

Among the transient neurological complications, the patients of the endovascular therapy group had focal hemispheric symptoms of varying severity that were most likely associated with vasospasm.

The persistent neurological complications were observed in 106 (12%) and 23 (12.3%) patients of the microsurgery and endovascular therapy groups, respectively.

The most common cause of neurological disorders and mortality in the microsurgery group was ischemic abnormalities identified by postoperative computed tomography (CT) of the brain in 4.9% of the patients. In most cases, in 37 (4.2%) patients, the isolated ischemic regions were found within the same lobe. Apparently, small arteries were compromised upon the aneurysm repair resulting in progression of the complications.

Extensive ischemic lesions affecting multiple lobes were diagnosed in 6 (0.7%) patients. The reasons for such complications often included improper clipping of the neck of an aneurysm associated with occlusion of large arteries due to complex anatomical characteristics or intraoperative rupture of the aneurysm resulting in longer time required for temporary clipping of the aneurysm-carrying arteries.

We classified all cases of localized edema and bleeding in the brain (21 patients (2.4%)) together with those of postoperative meningeal and intracerebral hematomas (1 patient (1.1%)) as the consequences of direct surgical trauma.

Recurrent intraventricular hemorrhage (IVH) during the early postoperative period occurred only in 1 patient (0.1%). It was caused by incomplete clipping of the large aneurysm of the internal carotid artery (ICA) bifurcation and resulted in death of the patient.

A group of 26 patients (2.9%) with the psychoneurological symptoms after ACA aneurism treatment should be distinguished among 47 patients (5.3%) with complications after surgical clipping who demonstrated no clear focal ischemic and hemorrhagic disorders in brain tissue as was revealed by CT.

The postoperative dysfunction of cranial nerves (optic, oculomotor, caudal) was observed in 2.4% (n=21) of the patients often as a result of surgical clipping of ICA and vertebrobasilar junction aneurysms.

In the endovascular group of patients, the ischemic disorders worsened the neurological complications in almost a half of cases. Thus, according to the postoperative brain CT, ischemic lesions within the same lobe after endovascular clipping were observed in 13 (7%) patients, while extensive ischemic damage was observed in 2 (1.1%) patients. Thromboembolic complications were presumably the major cause of these disorders.

The neurological complications associated with the pressure of thrombosed aneurysm on the adjacent brain structures and cranial nerves (a symptom progression) were typical for the endovascular group. These symptoms developed in 2 patients (1.1%) after endovascular coiling of large aneurysms.

Severe subarachnoid and intraventricular hemorrhages were diagnosed by CT following the treatment in 3 (1.6%) and 2 (1.1%) patients, respectively, and were mainly associated with the intraoperative aneurysm rupture. No changes were found in 8 (4.3%) patients of the endovascular group.

Factors influencing the incidence of postoperative neurological complications

**Gender.** The postoperative complications were observed in 93 (16.8%) out of 552 females and in 59 (11.3%, p=0.0049) out of 522 males. It may be explained by the age factor. The mean age of the females with the postoperative complications was 47.8 years while that for males was 46 years.

**Age.** We found no substantial statistical difference in the percentage of complications between different age groups that could indicate more complications in elderly patients. Thus, in the group of 105 elderly patients (over 60 years old), the neurological complications were 16.2%, while in the group of 969 younger patients (under 60 years of age) they were 13.9% (p=0.2603). The mortality rate in these groups was 1 and 0.9%, respectively.

**The number of hemorrhages.** A total of 197 patients with recurrent hemorrhage and 877 patients who had only one hemorrhage were compared. No significant difference in the amount of the postoperative complications (14.3 and 13.7%, respectively) and mortality rates (1 and 0.3%, respectively) was revealed.

**Aneurysm size** is one of the main factors affecting the number of postoperative complications (Table 3).

The fewest complications (11.6%) and no fatal outcomes were registered in the patients with aneurysms less than 5 mm in size.

Large and giant aneurysms, which are the most complex ones from the surgical standpoint, were observed in 21 and 5.3% of the cases, respectively. Correspondingly, the overall complication rates of their treatment were 15.9 and 33.3%, while the surgical clipping and endovascular clipping complication rates were comparable.

**Aneurysm shape.** Most aneurysms (95%) were of the typical saccular shape. Fusiform aneurysms were diagnosed in 54 patients (5%) and located in the area of vertebrobasilar junction (40.7%) and ICA (29.6%) in most cases.

The complications of treating typical saccular aneurysms were detected in 12.5% of the cases with the mortality rate of 1% (Table 4).

The complexity of the fusiform aneurysm repair procedure observed both for surgical clipping and endovascular coiling caused a high percentage of postoperative complications (44.4%) but no fatal outcomes.

**Partially thrombosed aneurysms** were found in 15.1% of the cases. Most of them were large (38.4%) and giant (29.5%). The percentage of postoperative complications...

---

Table 4

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<th>Factor</th>
<th>Postoperative Complications</th>
<th>Mortality Rate</th>
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<tr>
<td>Gender</td>
<td>Female (93) 6.2%</td>
<td>1%</td>
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<tr>
<td></td>
<td>Male (59) 11.3%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Age</td>
<td>105 (16.2%)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>969 (13.9%)</td>
<td>0.3%</td>
</tr>
<tr>
<td>Aneurysm Size</td>
<td>21 (15.9%)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>5.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Aneurysm Shape</td>
<td>Saccular (95%)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Fusiform (5%)</td>
<td>1%</td>
</tr>
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</table>
in patients with partially thrombosed aneurysms was higher (17.3%) than that in patients whose aneurysms had no signs of thrombosis (13.6%). However, no statistically significant difference was observed ($p=0.1067$) (Table 5).

**Aneurysm location.** Aneurysms of the anterior cerebral artery occurred most frequently (39.6%) in the study group.

The anterior cerebral artery aneurysms were surgically in most cases (95.8%).

The repair of distal anterior cerebral artery aneurysms, also known as pericallosal artery aneurysms, caused complications relatively seldom (4%); and no fatal outcomes were observed.

The complications after surgical clipping of ACA aneurysms were detected in 13% of the cases with the mortality rate of 1.1%. Open surgeries on the ACA aneurysms were most often associated with mental disorders, such as amnestic ones in 9.4% of patients. 2.8% of patients developed Korsakoff’s syndrome without any obvious improvement within two weeks after ACA aneurysms had been clipped.

The incidence of complications associated with endovascular coiling of ACA aneurysms was 16.7%. Comparison of the ACA aneurysm repair outcomes of the clipped and coiled patients was not statistically significant ($p=0.3252$) due to the small number of the coiled patients ($n=18$).

ICA aneurysms were observed in 26.2% of the patients. The overall incidence of postoperative complications associated with the ICA aneurysms was 15.7% and the mortality rate was 0.4%.

The largest number of complications occurred after surgical clipping ($n=63$) of aneurysms of the ophthalmic segment of the ICA (25%). In most cases these complications were associated with the direct injury to the optic nerve, and the corresponding visual impairment. Noteworthy, endovascular coiling ($n=43$) of aneurysms of the ophthalmic segment of the ICA resulted in a much fewer number of complications (7%) ($p=0.0095$).

The total numbers of complications after surgical clipping and endovascular coiling of aneurysms of the supraclinoid segment of the ICA were comparable (12 and 14.2%).

**Aneurysms of the middle cerebral artery** made up to 22.3% of all cases. A vast majority of the patients with aneurysms of the middle cerebral artery (98.7%) were operated on using open surgery. A relatively small number of postoperative complications (7.2%) and the mortality rate of 1% were observed when aneurysms were typically located at the bifurcation of the middle cerebral artery.

**Aneurysms of the basilar artery** were observed in 8.6% of the patients.

Postoperative neurological complications for the patients in this group were observed in 30.4%; the mortality

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**Table 3. Effect of aneurysm size on the incidence of postoperative neurological complications in all treated patients**

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td></td>
<td>small (up to 5 mm)</td>
<td>medium (6—14 mm)</td>
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<tr>
<td>Number of patients</td>
<td>172</td>
<td>619</td>
</tr>
<tr>
<td>Complications</td>
<td>20 (11.6%)</td>
<td>77 (12.4%)</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>8 (4.7%)</td>
<td>32 (5.2%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>5 (0.8%)</td>
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</table>

**Table 4. Effect of aneurysm shape on the incidence of postoperative neurological complications in all treated patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Aneurysm shape</th>
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<tr>
<td></td>
<td>saccular</td>
<td>fusiform</td>
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<tr>
<td>Number of patients</td>
<td>1020</td>
<td>54</td>
</tr>
<tr>
<td>Complications</td>
<td>128 (12.5%)</td>
<td>24 (44.4%)</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>55 (5.4%)</td>
<td>9 (16.7%)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 5. Effect of partial aneurysm thrombosis on the incidence of postoperative neurological complications in all treated patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Partially thrombosed aneurysms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Number of patients</td>
<td>912</td>
<td>162</td>
</tr>
<tr>
<td>Complications</td>
<td>124 (13.6%)</td>
<td>28 (17.3%)</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>52 (5.7%)</td>
<td>12 (7.4%)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (0.8%)</td>
<td>3 (1.9%)</td>
</tr>
</tbody>
</table>
rate was 3.3%. These high rates are primarily due to complex anatomy of such aneurysms and the proximity of the brain stem structures.

Endovascular coiling was performed in 83% of these aneurysms. Temporary disturbances such as transient ischemic attack were among the complications associated with endovascular treatment in most cases. One patient died from intraoperative thrombosis of the P1 segment of the posterior cerebral artery that happened after coil occlusion of the basilar artery bifurcation aneurysm.

When endovascular coiling was not possible for aneurysms of the posterior cerebral and distal portions of the basilar arteries because of their anatomical features, surgical clipping was used. During the postoperative period after the clipping, oculomotor nerve palsy was often observed (80%) but it was transient in most cases.

Open surgery on the basilar artery bifurcation aneurysms resulted in severe ischemic brain stem disorders in 2 of 7 cases.

Aneurysms of the vertebral artery were least common (3.4%) and almost equally often treated by surgical clipping (n=19) and endovascular coiling (n=18) with no fatal outcomes. The complications after endovascular coiling and surgical clipping of the vertebral artery aneurysms developed in 11.1 and 16.7% of the cases, respectively. It should be emphasized that surgical clipping on aneurysms of the vertebral artery was usually performed in patients with a high risk of occlusion of the posterior inferior cerebellar artery terminal area or trunk during endovascular coiling.

Intraoperative aneurysm rupture. According to our data, intraoperative aneurysm ruptures during surgical clipping and endovascular coiling occurred in 7.4 and 4.3%, respectively.

The neurological complications of surgical clipping associated with intraoperative aneurysmal hemorrhage were likely to be caused by longer time required for temporary clipping of blood vessels and, as a consequence, ischemia in some brain regions.

Endovascular clipping complicated by intraoperative aneurism rupture resulted in the formation of subarachnoid clots and often intraventricular blood clotting that led to the disruption of cerebrospinal fluid circulation, vasospasm, edema, etc.

In general, the neurological complications associated with aneurysm rupture during its repair developed in 39.1 and 71.4% of cases after surgical clipping and endovascular clipping, respectively.

Discussion

Aneurysm repair treatment sometimes cannot be provided within the next few weeks after subarachnoid hemorrhage (SAH). The reasons vary but often they are associated with organizational problems [1]. The overall percentage of patients who survived a series of acute pathological reactions associated with SAH (vasospasm, edema, ischemia, hydrocephalus, etc.) is unknown. Nevertheless, there are quite a few such patients in Russia and many of them can be operated on in the late phase of SAH. The surgery in this case is aimed at preventing the recurrent SAH, the risk of which during the first six months reaches 50%, and subsequently 3—5% annually [6, 7, 10].

Surgeons typically do not have to deal with brain edema when performing surgical clipping of aneurysms three weeks after SAH. Subarachnoid adhesion, more pronounced in patients with recurrent SAH, may increase the time required for surgical dissection of the blood vessels. Yet, it does not affect the occurrence of the postoperative neurological complications as it was demonstrated by our study.

The main statistically significant risk factors for surgical clipping and endovascular coiling in the late phase of SAH are giant and fusiform aneurysms as well as aneurysms of the basilar artery. Elderly patients and patients with partially thrombosed aneurysms have a tendency for the slightly worse surgery outcomes. Noteworthy, most of the postoperative complications are observed in female patients.

Currently, there exists a broad range of medical and technical manuals for prevention of intraoperative complications.

Thus, most surgeries including those in the late phase of SAH are performed at the N.N. Burdenko Neurosurgical Institute using cerebral relaxation with osmotic diuretics in order to reduce traction complications.

Aneurysms with complex anatomical characteristics with a high risk of intraoperative rupture are repaired by performing a sequence of short (less than 4 min) clippings of the artery bearing the aneurysm to prevent its rupture. Large and giant aneurysms of the ICA, which are not suitable for endovascular clipping, are treated using retrograde suction decompression.

We believe it is important to use modern certified clips to exclude the possibility of slipping and separation of the clip blades during atherosclerotic aneurysm repair that can cause serious hemorrhagic complications during surgery and in the early postoperative period.

To prevent ischemic complications, it is necessary to monitor blood flow in the arteries after aneurysm clipping using Doppler ultrasound, flowmetry and endoscopy. Intraoperative indocyanine green (ICG) angiography is a promising method that was proven effective abroad. This technique is used to detect blood flow in both large and small perforating blood vessels which do not appear on Doppler ultrasound images. It also allows identification of the continuing inflow of the contrast dye in the incompletely clipped aneurysm [9].

Annual technical innovations in endovascular therapy help reduce the number of postoperative complications associated with intracranial aneurysm clipping. The use of stent-assisted coil embolization in the late phase of SAH is essential to secure aneurysm occlusion.
To prevent the intraoperative and postoperative thrombotic complications in patients undergoing stent-assisted coil embolization, antiplatelet therapy has to be properly chosen. It is known that some patients have resistance to certain antiplatelet drugs that set up conditions for the ischemic complications [11]. The platelet function test (platelet aggregation in vitro in response to antiplatelet agents) has recently been conducted at the N.N. Burdenko Neurosurgical Institute prior to endovascular treatment for all patients in which stent-assisted coil embolization is supposed to be used.

In our opinion, a detailed analysis of various factors associated with intracranial aneurysm determines the optimal choice of the treatment and, therefore, reduces the overall percentage of postoperative complications. The repair of complex aneurysms is discussed together by surgeons specializing both in microsurgery and in endovascular therapy. The choice of the treatment is usually made in favor of the one that can provide complete to near-complete aneurysm occlusion with the minimal risk of postoperative complications.

Aneurysm location is the most important factor influencing decision making regarding the therapy type. As in many other clinics, at the N.N. Burdenko Neurosurgical Institute patients in the late phase of SAH with aneurysms of the anterior and posterior sectors of the circle of Willis usually undergo open surgery and endovascular therapy, respectively. However, exceptions are not rare. Thus, most of the patients with the ICA ophthalmic segment aneurysms, including large and giant, have recently been treated by endovascular therapy to achieve better functional outcomes.

**Conclusions**

The postoperative complication and mortality rates in patients treated in the late phase of SAH were 6 and 0.9%, respectively.

Taking into account the study of untreated aneurysms [6, 7, 10], we can conclude that the overall risk of disability and death associated with the recurrent SAH is significantly higher than the risks of aneurysm repair in the late phase of SAH, especially for young patients.

Thus, the ruptured intracranial aneurysm is needed to be treated regardless of the SAH phase.

**REFERENCES**


**Commentary**

In their article, Yu.V. Pilipenko et al. address the major causes of the occurrence of complications in patients who underwent intracranial aneurysm repair in the late phase of SAH. Authors review the data on complications after microsurgical and endovascular treatment of aneurysms. The complications are classified by type (cerebral and extracerebral) and divided into persistent and transient ones. Clinical features associated with these complications are described. The study analyzes the causes of the complications and describes the ways to eliminate and prevent them. Factors influencing the complication occurrence and progression, such as gender, age, number of hemorrhages, size, shape and location of aneurysms, intraoperative aneurysm rupture, are discussed.

The authors found that female patients had more complications than males (16.8% versus 11.3%). There was a slight increase in the complication rate in patients older than 60 years (16.2%) vs patients under 60 (13.9%).

Size, shape and location of the aneurysm influenced the complication occurrence the most. Thus, as indicated in the study, the overall complication rate for aneurysms up to 5 mm
did not exceed 11.6%, while this rate for large aneurysms was 15.9%, and reached 33.3% for giant aneurysms. Also, according to the authors, the incidence of complications differs significantly depending on the aneurysm shape (12.5% for saccular versus 44.4% for fusiform aneurysms).

The article shows that the aneurysm location can significantly affect the overall incidence of complications. Thus, the complication rate was 13% for the anterior communicating artery aneurysms, of which 9.4% corresponded to mental disorders. This is probably due to the necessity of the partial resection of the gyrus rectus, which is sometimes required to provide better imaging of the anterior cerebral and anterior communicating arteries. The incidence of complications in patients with the basilar artery aneurysms was the highest compared with aneurysms at other sites (30.4%). It can be explained by complex anatomy of the basilar artery and the proximity of cranial nerves and the brain stem. The complications after surgical clipping were more severe and mainly manifested as oculomotor nerve palsy.

Intraoperative aneurysm rupture was less frequent in patients who had undergone endovascular coiling (4.3% vs 7.4% in the clipped patients). Nevertheless, the authors note that more neurological complications occurred after intraoperative aneurysm rupture in coiled patients (71.4% compared with 39.1% in patients who had undergone open surgery). This is primarily due to the inability to adequately remove subarachnoid blood from the basal cisterns and, as a consequence, more frequent development of vasospasm after endovascular therapy.

Today, there are not so many neurosurgical clinics in Russia that can provide a complete set of options to choose the optimal treatment for patients with intracranial aneurysms. In most clinics one type of treatment prevails over another: either endovascular therapy or open surgery is used. However, these treatments are not equally applicable for all types of aneurysms. In this regard, more complications occur due to the improper choice of the type of aneurysm treatment than it could be.

A thorough analysis of the features and causes of complications associated with aneurysm repair in the late phase of subarachnoid hemorrhage presented in this article makes a significant contribution to the choice of aneurysm treatment in order to reduce the incidence of complications and improve the treatment outcomes.

A.V. Dubovoy (Novosibirsk, Russia)
A Model of Cerebral Arterial Aneurysm for Microneurosurgical Training

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Clipping of cerebral arterial aneurysms is one of technically complex neurosurgical interventions. There is no information in the literature regarding simulation models of aneurysm clipping that have realistic tactile properties. The study presents a technical rationale for the development of a new aneurysm model using human placental vessels to train isolation and clipping skills under the conditions of a ruptured and unruptured aneurysm.

Keywords: simulation, microneurosurgery, training, model, aneurysm.

Currently, simulation technologies in medicine have been developed intensively and improved owing to the up-to-date requirements to medical professionals training [4, 8, 9, 11, 22]. Training of a surgeon is compared to training of an aircraft pilot who spends many hours practicing on a simulator, which simulates flight and emergency situations, before actually flying a plane. Supplementary materials for the January and October issues of the journal N.N. Burdenko Problems of Neurosurgery, 2013, are fully focused on the virtual reality and simulation technologies in neurosurgery, which characterizes the relevance of this direction [23].

Surgical interventions on the cerebral vessels are known to be the most complex ones in the neurosurgical practice [1, 20]. As the endovascular method of aneurysm treatment spreads, the possibility for neurosurgeons to receive practical experience in open interventions decreases progressively. The anticipated dominance of the number of conducted endovascular surgeries over open ones in the routine neurosurgical practice will ultimately result in a decrease in the number of neurosurgeons who will be capable of open exclusion of arterial aneurysms [9, 25]. Given that the group of endovascularly excluded aneurysms includes the most “simple” ones, neurosurgeons will more often face aneurysms that are technically difficult for open exclusion [2, 17, 25]. Modern trends in surgical education require mastery of manual skills using various simulators [4, 5, 7, 8, 12]. There are known models of cerebral vascular aneurysms developed using laboratory animals [13, 19, 21, 26], synthetic materials [10, 14], and the 3D stereolithography technology [15]. Thus, the development of new simulation models for neurosurgical training is a promising research direction.

The objective was to create a model of a cerebral vascular aneurysm on the basis of the human placental vessels for microneurosurgical training.

Material and Methods

The study was conducted at the department of neurosurgery of the Scientific Center of Reconstructive and Restorative Surgery of the Siberian Branch of the Russian Academy of Medical Sciences (SCRRS SB RAMS) (Irkutsk, Russia) and at the Skull Base Surgery Laboratory of the Barrow Neurological Institute (Phoenix, USA) and approved by the ethics committees of the SCRRS SB RAMS and the Barrow Neurological Institute. Simulation models of wide- and narrow-neck aneurysms were created using vessels of 20 human placentas. Surgical microscopes (Olympus 5000, Zeiss OPMICS), a bipolar coagulation unit (Grieshaber), an aspirator, a microsurgical instruments set, neurosurgical clips (Aesculap), a clip holder (Aesculap), 5, 6, 8 FR Foley silicone catheters, venous catheters, intravenous infusion systems, isotonic solutions, red and blue food dyes were used in this work.

The placentas of parturient women who gave a voluntary informed consent were obtained, in accordance with the stated protocol of the study, from morbid anatony departments. The placenta with prepared aneurysms was stored at 4 to 10 °C in isotonic saline up to 6 days. Morphometric parameters of the simulated aneurysms as well as the time required for their fabrication and training of isolation and clipping skills were evaluated. Statistical processing was done with the Statistica 8.0 software using methods of descriptive statistics. The quantitative data were represented by the median and interquartile range in the form of Me [25; 75].
Aneurysm simulation procedure. The placenta was washed out of blood clots with running water and prepared, and then the amnion was removed. The umbilical cord was cut, with a 5 cm segment being left. Both umbilical arteries and the umbilical vein were catheterized with subclavian catheters and washed with isotonic saline under pressure using a syringe till complete blood and clot removal. Intravascular thrombi were manually removed. The placental vessels are located on the dense choroid that strengthens the bottom wall, partially lateral walls, and also occasionally the top wall of arteries and veins, which prevents them from the aneurysm formation. The formation of a wide-neck aneurysm model can occur at the most thinned regions of the vessels when injecting isotonic solution under high pressure. To form the broad-based and also fusiform aneurysms, the Foley catheter was inserted into the umbilical artery and advanced distally until impacted in a small branch. Next, the balloon was inflated by injecting a fluid (Fig. 1a) and positioned in such a way that it would expand towards the top wall. The expanded balloon was left in the vessel lumen for 6−12 h. Then it was decompressed and removed.

A narrow-neck aneurysm was formed in two stages. Dilation of the arterial segment immediately after the bifurcation was conducted using the Foley catheter balloon, according to the aforementioned technology, and then the vessel was ligated distal of the extension. The formed aneurysm quality was tested by means of its connection to the intravenous infusion system and injection of a dye solution. Some aneurysms had small perforating branches, which were visualized by injection of the dark red or blue food dye solution into the vessel.

Isolation and clipping of an aneurysm. The created aneurysms were used to train microdissection skills on the surface and in the deep surgical field. For this purpose, the placentas with formed aneurysms were placed on a sample stage and connected to the infusion system for continuous infusion of dyed saline; the red dye was used for arteries and the blue dye was used for veins.

Simulation of the Sylvian fissure dissection. A large vein was selected on the placental surface, and a sharp microsurgical technique was used for its isolation and for a deep approach to the chorionic villi (Fig. 2a). Bipolar forceps were used to practice the dissection with jaws opening (see Fig. 2b). Bayonet microsurgical scissors along with an aspirator were used to train skills of sharp dissection in different directions: sideward, backward, and forward and using the left and right hands as well. The possible errors included damage to the vein and its small tributaries.

Aneurysm isolation. The aneurysm was isolated from the placental chorion using the sharp technique. Isolation closer to the aneurysm wall was carried out to increase the training complexity. The perforating vessels can be found on the back wall of the aneurysm during its isolation (Fig. 3a). Maintaining a constant high pressure of the colored solution, with different colors used for venous and arterial networks, allowed us to visualize the dissection plane and small perforating branches.

Aneurysm clipping. After the preparation process, the skills for application of clips with various configurations were trained (see Fig. 3b). Particular attention was paid to the evenness of manipulations with a clip-holder, holding clips and their rearrangement as well. The possible manipulation errors included: slipping of the clip, aneurysm rupture, luminal occlusion of the aneurysm-bearing vessel, pinching of the perforating vessels and adjacent tissues along with the aneurysm neck, and incomplete aneurysm exclusion.

Deep surgical field. To simulate dissection and clipping of aneurysms in the narrow and deep wound (mini-approach), one placenta (simulation of the Sylvian fissure dissection) was placed onto another (simulation of the aneurysm) in such a way that the area of the surgical approach was located above the aneurysm (see Fig. 3c). The placenta provides the capability of training the skills for the placement of brain spatulas or for microsurgery without the use of retractors, when the manipulation area is formed between the jaws of bipolar forceps and the aspirator tip [26].

Simulation of aneurysm rupture. Microsurgical dissection of the simulated Sylvian fissure down to the an-
eurysm was carried out, and its wall was incised with micro scissors (see Fig. 3d). To achieve realistic bleeding, it is better to use opaque solutions and to produce an increased pressure by compressing a bag with the solution using the infusion cuff. At that, the larger the aneurysm wall defect is, the more massive bleeding occurs. Under the conditions of aneurysm rupture and persistent bleeding, various techniques to stop it were practiced: 1) proximal control (search for the afferent vessels and application of temporary clips); 2) the use of two aspirators to control bleeding; 3) increase in the rate for isolation and clipping of the aneurysm.

**Results**

The vascular aneurysm model was successfully performed on all obtained placentas. Sizes of the simulated aneurysms are given in the Table. Preparation of the pla-
centa required 20 min, on average, while catheterization of blood vessels and the aneurysm formation took 10 min. Remodeling of the vascular wall and the formation of dilation after balloon decompression required 6 h. Additionally, ligation of the vessel to create the narrow-neck aneurysm required about 20 min.

Each exercise is aimed at training of various specific neurosurgical skills with a different complexity level: dissection of membranes, dissection inward using bipolar forceps and an aspirator, hemostasis, isolation of the aneurysm from the surrounding tissues, applying clips, taking and holding the clip with a clip-holder, changing the clip position, applying the clip under the conditions of significant bleeding and poor visualization. Execution of all the described exercises required 1 h 40 min, on average (Fig. 4).

Discussion

Currently, there is growing interest in the development of aneurysms models for microsurgical training that possess elastic properties of a living tissue, which are the most relevant to the neurosurgical practice. To practice the manual skills of cerebrovascular surgery, aneurysms models have been developed using the arteries of rat, rabbit, swine, dog, and cadavers as well as synthetic and virtual models, [11, 16, 17, 19, 21, 22].

Virtual computer simulation models (neuro-touch [17], robo-sim [16], dextroscope [18]) along with a high technological potential have a significant drawback, namely, the lack of tactile feedback, which prevents these models from being recommended for complete microneurosurgical training. In addition, special expensive equipment with the software is required for virtual computer simulators. To our opinion, they are the perfect complement for developing a strategy for surgical approaches and mastering the three-dimensional anatomy.

U. Spetzger et al. [24] presented a model of the aneurysm based on synthetic vessels and a plastic model of a rat artery for practicing a microvascular neurosurgical technique. The lack of tactile properties of a living vascular tissue and the arachnoid membrane, as well as a high cost, is the disadvantage of synthetic models. One of the types of the synthetic model is a 3D aneurysm model described by T. Kimura et al. [15], which was obtained using a stereolithography method. It was used by the authors for clarification and elaboration of the tactics of upcoming surgery. N. Hashimoto [13] in 1978 was one of the first who demonstrated the possibility of induction of cerebral aneurysms in a mouse. A series of experimental works under his supervision has been devoted to studying molecular and genetic mechanisms of the arterial aneurysms development. J. Olabe et al. [21] described a model of the aneurysm formed on the porcine carotid arteries by stitching a vein graft in the bifurcation region and application of fibrin glue to simulate the arachnoid dissection. This model allows one to create an aneurysm using a living tissue with real blood flow. However, its preparation is laborious, resource-intensive and requires plenty of time. H. van Alphen et al. [7] described creation of a saccular aneurysm at the bifurcation region of the rat carotid arteries by damaging the artery internal elastic membrane. H. Cloft et al. [11] described an aneurysm model that was prepared endovascularly using balloon occlusion of the rabbit common

### Method of creation, sizes and types of simulated aneurisms

<table>
<thead>
<tr>
<th>Aneurysm creation method</th>
<th>Aneurysm type</th>
<th>Number of aneurysms formed</th>
<th>Aneurysmal neck size, mm</th>
<th>Aneurysmal dome size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion of solution under pressure</td>
<td>Wide neck</td>
<td>10</td>
<td>6 [5; 10]</td>
<td>4 [3; 6]</td>
</tr>
<tr>
<td></td>
<td>Fusiform</td>
<td>5</td>
<td>25 [15; 30]</td>
<td>10 [8; 10]</td>
</tr>
<tr>
<td>Using a balloon</td>
<td>Wide neck</td>
<td>10</td>
<td>10 [10; 10]</td>
<td>3 [2; 4]</td>
</tr>
<tr>
<td></td>
<td>Narrow neck</td>
<td>20</td>
<td>2 [1.5; 4]</td>
<td>10 [7; 15]</td>
</tr>
<tr>
<td></td>
<td>Fusiform</td>
<td>5</td>
<td>10 [10; 10]</td>
<td>7 [5; 10]</td>
</tr>
</tbody>
</table>

Footnote: *l* — dilation length, *d* — dilation diameter.

Unlike animal aneurysm models, the human placenta is an available object, which allows simulating highly realistic aneurysms. The disadvantages of this model include a risk of infectious disease transmission in the case of unsafe practices as well as a relatively short term of its use (storage up to 6 days at 4−10°C). At the same time, the advantages of the proposed model include the presence of biological tissue properties, membranes, and capabilities of modeling blood flow. The placenta can be obtained from an anatomic pathology department of a hospital and used for creation of 3−10 aneurysms, which can be used for training of a different complexity level within a week. In the described model, constant dye solution infusion under pressure makes it possible to simulate an emergency situation such as aneurysm rupture. In addition, the aneurysm itself or its bearing vessel may be damaged during aneurysm isolation. This allows one to simulate the algorithm of neurosurgeon’s actions under the conditions of realistic arterial bleeding.

Conclusion

In summary, the presented model of the aneurysm based on the human placental vessels can be used for receiving, mastering, and maintaining the basic manual neurosurgical skills required for open exclusion of cerebrovascular aneurysms from the circulation.

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REFERENCES

Commentary

The present article is undoubtedly of interest and deserves special attention. The proposed method for creation of the aneurysm model using the human placental vessels can be used in organization of workshops for training of young neurosurgeons.

Ideally, a young professionals training course should be combined with virtual computer simulation models to couple mastering of the three-dimensional brain anatomy with tactile sensations during dissection of veins and arteries.

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Biological Features and Long-term Results of Comprehensive Treatment of Brain Tumors in Infants

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Complete resection is the treatment standard for the majority of brain tumors. The outcomes of subsequent comprehensive treatment depend on biological features and histological structure of the tumor, and radicality of surgery. The aim of this work was to study the morphological features of brain tumors in infants and to analyze long-term outcomes of surgical and comprehensive treatment. Material and methods. The study included 80 infants with brain tumors aged 1—12 months who had been operated on at the Burdenko Neurosurgical Institute in 2000—2010. Results. The maximum radicality was achieved in the group of tumors of the lateral and third ventricles (85%), in the group of tumors of hemispheric localization (82%), and in the group of tumors of the posterior fossa (83%). The lowest percentage of radical tumor removal (15%) was related to tumors of the chiasmosellar area, most of which were large visual pathway gliomas. The overall five-year survival rate associated with the treatment in the studied series of patients was 92% and 48% for Grade I—II and Grade III—IV tumors, respectively. Conclusion. The biological features of brain tumors in infants include the increased proliferative activity (high Ki-67 index of 10% and higher) not affecting the clinical course and revealed at the diagnosis of choroid papillomas, some pilocytic astrocytomas of the chiasm and Grade III astrocytomas. The best long-term results of the treatment were obtained in infants with complete resection of Grade I and III astrocytomas and in infants with choroid papillomas. Radical removal of such histological forms as anaplastic astrocytoma, choroid carcinoma and anaplastic ependymoma improves the prognosis, provides favorable conditions for adjuvant therapy and increases the period of relapse-free survival in infants.

Keywords: brain tumors, infancy, surgery, morphology, biology of tumors, adjuvant therapy, long-term outcomes.
(7p12), MYC (8q24.12-q24.13), CDKN2A (9p21), PTEN (10q23), 6q, 9q and chromosome 17.

The long-term outcomes of treatment were analyzed using Statistica 8.0 software package. The nonparametric Kaplan-Meier method for estimating the survival rate was used in addition to the standard methods for statistical analysis of long-term outcomes.

Results

Topographical and morphological characteristics

The tumors predominantly had supratentorial localization — 85% cases (n=68). Subtentorial localization of tumors was observed in 15% cases (n=12). Tumors with supratentorial localization were subdivided into three groups according to the maximal topographical distribution: tumors of the lateral and III ventricle (n=33; tumors with hemispheric localization (n=22); and tumors of the chiasmosellar area (n=13). The frequency of tumors with various histological structures in infants, according to our data, slightly differed from that of other analogous series: the most frequent were gliomas — 29% (n=23) and choroid plexus tumors — 27% (n=22), followed by ependymomas — 12% (n=10), then in the declining order: embryonic tumors (medulloblastomas, atypical teratoid/rhabdoid tumors (AT/RT) and primitive neuroectodermal tumors (PNET)) — 10% (n=8), glioneuronal tumors — 9% (n=7), malignant germinocellular tumors — 4% (n=3), pineoblastomas — 4% (n=3), and craniopharyngioma — 1% (n=1).

Table 1 shows the dependence of histological distribution of brain tumors on their topography.

Primary brain tumors were diagnosed in 77 observations; meningeal tumors with dissemination into the brain tissue, in 3 observations (infantile fibrosarcoma, malignant schwannoma (also known as malignant peripheral nerve sheath tumor, MPNST) and infantile myofibroma.

In total, tumors with high malignancy rate were diagnosed in just over a half of all observations — 51% (n=41).

Histological features of brain tumors in infants were reviewed according to the topographical groups.

Tumors of the lateral and III ventricle (n=33)

Choroid plexus tumors (papillomas and atypical papillomas) — 64% (n=14) and choroid plexus carcinomas — 36% (n=8) were diagnosed in more than half of the observations — 67% (n=22).

Choroid plexus papilloma was structurally similar to the choroid plexus, but had globular shape, in some cases (30% of observations) with traces of old hemorrhages. It was microscopically presented in a form of multiple papillomatous excrecences covered by cuboid or prismatic epithelium. Plexus stroma was composed of connective tissue and small blood vessels.

The characteristic features of choroid plexus carcinomas were the loss of papillar structure in a substantial por-
tion of the tumor; nuclear atypia, multiple mitotic figures and necrotic changes; evident infiltrative growth with destruction of ependymal lining of the ventricle and para-ventricular parenchyma. These tumors required mandatory immunohistochemical verification for carrying out the differential diagnosis with other poorly differentiated tumors of CNS (PNET, glioblastomas, AT/RT).

It is necessary to note that atypical choroid plexus papillomas were not characterized by a large number of mitotic figures in our series of observations. The diagnosis of atypical choroid plexus papillomas was confirmed only after immunohistochemical analysis, based on the high Ki-67 labeling index (10% and more) (Fig. 1).

For Gr II—III astrocytomas (n=3) in this topographical group, the characteristic histological picture (cellular and nuclear polymorphism, sites of dense cell localization and mitotic figures) was observed in only one case. The malignancy rate (Gr II and Gr III) in 2 observations was determined after immunohistochemical investigation, based on the high Ki-67 labeling index.

**Tumors with hemispheric localization (n=22)**

The most frequent tumors with hemispheric localization were those of the glial line — 76% (n=17), predominantly with high grade of malignancy — 65% (n=11): anaplastic ependymomas, glioblastomas and anaplastic astrocytomas.

The signs of malignization in anaplastic ependymomas appeared as a large number of mitotic figures, presence of proliferation of vascular endothelium cells and formation of necrotic foci, including those with the presence of palisade structures.

Necrosis made them hardly distinguishable from the other malignant gliomas in some observations. In these cases the immunohistochemical study allowed one to verify the histological diagnosis.

The histological picture of pilocytic astrocytomas and anaplastic astrocytoma with hemispheric localization in infants was similar to that of older children.

Glioblastomas (Gr IV) were diagnosed in 2 observations; the morphological picture did not differ from that of glioblastomas in other age groups and included evident proliferation of vascular endothelium, cellular and nuclear polymorphism and presence of necrotic foci, often with palisade structures. Immunohistochemical studies revealed the positive expression of INI-1 and GFAP in tumor. Fluorescent in situ hybridization revealed a homozygous deletion of CDKN2A indicating unfavorable disease prognosis in one case only (Fig. 2).

Tumors with low malignancy grade and hemispheric localization were represented by gangliogliomas (n=4) and pilocytic astrocytomas (n=3).

A case of large glioneuronal tumor with hemispheric localization (desmoplastic infantile astrocytoma with areas of anaplasia) should be particularly noted. Histological analysis revealed the presence of foci of low differentiated rounded cells clusters with frequent mitotic figures and Ki-67 labeling index up to 20% (Fig. 3), along with typical desmoplastic areas prevailing in tumor and composed of fibroblast-like spindle-cell tumor astrocytes expressing GFAP.

**Tumors of the chiasmosellar area (n=13)**

Chiasmal gliomas with low malignancy grade were predominant in the group of tumors of the chiasmosellar area — 77% (n=10). It should be noted that in 2
cases a rare histological form of pilocytic astrocytomas (pilomyxoid astrocytoma) was diagnosed. Immunohis- tochemical study with evaluation of the Ki-67 labeling index was performed for 8 infants. High Ki-67 index (10% and higher) was detected for 4 infants (45%) (Fig. 4).

Tumors of posterior cranial fossa (n=12)

Tumors of posterior cranial fossa were represented by tumors with high grade of malignancy (predomi- nantly medulloblastomas, anaplastic ependymomas and AT/RT) in 75% cases (n=9). Medulloblastoma is a poorly differentiated tumor composed of densely packed neuroepithelial cells with small rounded nuclei. Mitotic figures are a typical feature; cytoplasm is poorly represented. Other characteristic features include expression of neuronal markers Syn (synaptophysin) and NSE (neuron-specific enolase) and focal expression of GFAP (glial fibrillar acid protein). Molecular genetic studies revealed no cytogenetic aberrations (amplification of the MYC gene, amplification of the MYCN gene, isochromosome 17q, deletion of 6q MYB locus or deletion of the PTEN gene) in any of the cases. Classical medulloblastoma had very unfavorable prognosis in infants compared to its desmoplastic/nodular variant.

AT/RT in some cases was hard to distinguish from classical medulloblastoma, PNET or glioblastoma. AT/ RT was characterized by marked heterogeneity, presence of poorly differentiated regions interlaced with foci of large cells with eosinophilic cytoplasm – rhabdoid cells (Fig. 5a) and clusters of cells with epithelial and mesenchymal differentiation. AT/RT cells can express smooth muscle actin (SMA), epithelial membrane antigen (EMA) and general cytokeratin (AE 1/3). However, the main diagnostic criterion was the absence of nuclear expression of BAF-47 (INI-1) in the immunohistochemical study (Fig. 5b). This marker is required in all cases to verify diagnosis in infants with malignant tu- mors to avoid misdiagnosis.
Long-term outcomes of treatment for different morphological types of brain tumors in infants

It is known that long-term outcomes directly depend on the following factors: 1) radicality of tumor resection; 2) tumor histology; 3) adjuvant therapy.

Maximum radicality was achieved in the group of tumors of the lateral and third ventricles (85%), in the group of tumors with hemispheric localization (81%), and in the group of tumors of posterior cranial fossa (83%). The lowest percentage of radical tumor removal (15%) was related to the tumors of chiasmosellar area, most of which were chiasmal gliomas that will be reviewed separately.

Adjuvant therapy was mainly represented by diverse chemotherapy (CT) protocols developed specially for infants: HIT SKK 2000, SIOP 2000/LGG, Baby-POG. In some cases (anaplastic ependymomas, anaplastic astrocytomas, medulloblastomas) a local stereotactic radiation therapy was performed for children after they turned 1 year old.

Gliomas (n=23). Tumors with low grade of malignancy were diagnosed in 74% cases (n=17) in the group of glial tumors (n=23). Ten of them were chiasmal gliomas that will be reviewed separately.

Low-grade astrocytomas (n=7, Gr I—II) had the most favorable prognosis: all infants were alive and without relapses; the follow-up period was from 1 to 8 years. Functionally, an interior hydrocephaly increased in 1 case (localization — posterior cranial fossa) 1 year after surgery; the condition stabilized after ventriculoperitoneal shunting; right-side hemiparesis (3 points) arisen in early postoperative period persisted in one case; good functional result was achieved in 5 cases.

High-grade astrocytomas (n=4, Gr III; PCT protocol — Baby-POG/99) — all infants were alive; the follow-up period varied from 1 to 7 years. Polychemotherapy (PCT) was performed in 2 cases, in one of them local radiation of the bed of the removed tumor (after tumor relapse after 61 months) was performed in addition to PCT. Functionally, left-side hemiparesis persisted in one child with symptomatic focal epilepsy (PCT + radiation therapy); in one case resection of the gliotically changed right temporal lobe was conducted because of drug-resistant epileptic seizures 3 years after the tumor had been removed.

It should be mentioned that adjuvant therapy was not given to two children with high Ki-67 index (10% and higher) with good functional result; no relapses were detected in the follow-up period of 3 and 7 years.

Glioblastomas (n=2, Gr IV; CT protocol — Baby-POG/99). One child died from tumor regrowth one year after the second PCT course; the second child died from tumor relapse 6 months after the 4th PCT course.

Gliomas of visual pathways (n=10, Gr I—II; CT protocol — SIOP-LGG/2000—2004, HIT-2000/08-GLG). These tumors had large dimensions despite the low grade of malignancy; resection of the exophytic portion was predominantly partial, all children were further given PCT.

Table 2. Surgery of brain tumors in infants (2000—2010, general data, n=80), abs/%

<table>
<thead>
<tr>
<th>Tumor resection (n=80)</th>
<th>Radical resection (&gt;85%)</th>
<th>Partial resection (&lt;85%)</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors of the lateral and third ventricles (n=33)</td>
<td>28/85</td>
<td>5/15</td>
<td></td>
</tr>
<tr>
<td>Tumors with hemispheric localization (n=22)</td>
<td>18/82</td>
<td>4/18</td>
<td></td>
</tr>
<tr>
<td>Tumors of the chiasmosellar area (n=13)</td>
<td>2/15</td>
<td>9/70</td>
<td>2/15</td>
</tr>
<tr>
<td>Tumors of posterior cranial fossa (n=12)</td>
<td>10/83</td>
<td>2/17</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>58/72</td>
<td>20/25</td>
<td>2/3</td>
</tr>
</tbody>
</table>
after 6 years. In one of these cases stabilization occurred after brachytherapy had been performed, in 3 other cases a repeated removal of tumor was performed with further PCT.

Functionally, 5 children develop according to age and are socially adapted; there is a decrease in vision with various degree of manifestation in all children; total loss of vision occurred in one child.

**Choroid plexus tumors (n=22).** The group of vascular plexus tumors comprised 11 choroid papillomas, 3 atypical choroid papillomas and 8 choroid carcinomas.

The catamnesis is known for 13 of 14 operated children with choroid papillomas of Gr I—II: all children are alive, with good functional outcome, without relapses; the follow-up period was from 1 to 11 years. Noteworthy, adjuvant therapy was not given to 3 children with atypical forms of tumor, with the same results as those for children with choroid papillomas.

**Choroid carcinomas (n=8, Gr III; CT protocol — SIOP-CPT/2000).** Four children out of 8 with diagnosed choroid carcinomas died in the perioperative period. Among the four survived infants, one with radically removed tumor had a small local relapse detected after 1.5 years by brain MRI while receiving PCT, functionally characterized by severe pyramidal symptoms. Three other children with radically removed tumor also received PCT and had the relapse-free period of 3, 5 and 9 years and good functional results.

**Anaplastic ependymomas (n=10, Gr III; CT protocol — HIT-2000/2002-SKK).** A problem with adjuvant therapy is that anaplastic ependymomas have low sensitivity to PCT, and radiation therapy cannot be given to infants younger than 1 year old. PCT was conducted in order to postpone radiation therapy as much as possible and to perform it after the child reaches the age of 1 year old. Two out of 10 operated children died (one in the early postoperative period, another child — one year after the tumor had been removed, as a result of somatic complications while receiving PCT); in one more case the catamnesis was not known.

PCT was given to children in 7 cases; in 3 cases of non-radical removal the tumor relapsed after 5 months, 1 year and 4 years. The process was stabilized after the repeated removal and stereotactic radiation therapy. The follow-up period varied from 1 to 6 years.

The children who survived demonstrated good functional results in 50% observations, development delay in 25% cases, and pyramidal symptoms in 12.5%.

**Glioneuronal tumors (n=7, Gr I).** Catamnesis is known for 5 infants. Adjuvant therapy was conducted in one case, after subtotal removal of a giant ganglioglioma of the chiasmomellar area; the infant died of the relapse 5 years after the tumor had been removed. Two infants were alive 3 and 4 years after the surgery, with good functional results; one child with ganglioglioma was alive after 4 years, but with a pronounced development delay (localization — posterior cranial fossa). Adjuvant therapy was not performed in one case of a child with radically removed large infantile desmoplastic astrocytoma having areas of anaplasia, no relapse was observed.

Embryonic tumors: medulloblastomas, PNET (n=5, Gr IV; CT protocol — HIT-2000/2002-SKK, Neuro-COH/2006 — RCRC); ATRT (n=3, Gr IV; CT protocol — ATRT-ZNS 2004). Embryonic tumors were diagnosed in 8 observations. Four cases (67%) were medulloblastomas, one — PNET with hemispheric localization. Two patients are alive: a child with the desmoplastic form of medulloblastoma (relapse-free period 3 years; the parents refused the adjuvant therapy) with good functional result; and a child with PNET with hemispheric localization (relapse-free period 4 years, with PCT, local radiation therapy and transplantation of stem cells performed), with severe growth retardation but psychological development and speech corresponded to the age. Three children with the classical forms of medulloblastomas died 10, 11 and 12 months after the surgery despite the absence of unfavorable prognostic marker of MYC gene amplification revealed by molecular genetic analysis. All children had tumor relapse and metastases to the brain and spinal cord tunics while given with PCT.

AT/RT were diagnosed in 3 observations. In 2 cases, the infants died 2 and 8 months after the surgery while given with PCT as a result of intensive continuous growth of the tumor. In one case, reoperation was performed for tumor relapse one year after PCT; the PCT regimen was then changed, but the relapse occurred again after 6 months.

**Germ cell tumors (immature teratomas, n=3, Gr IV; CT protocol — SIOP-GCT/96-2004).** Malignant teratomas were diagnosed in 3 observations. One child died of uncontrolled intraoperative bleeding (histological diagnosis — malignant teratoma of unspecified type). Tumor biopsy and histological diagnosis for the second infant showed a mixed germ cell tumor having the regions of germinoma and teratoma with malignant transformation. The relapse-free period was 1 year, with no tumor growth while conducting PCT; functionally, the child demonstrated severe delay in psychomotor development. In the third case (histological diagnosis — teratoma with malignant transformation, presence of epithelial and neuronal components and large quantity of pigment) the child died one year after the surgery as a result of rapid tumor regrowth despite PCT received.

Pineoblastomas (n=3, Gr IV; CT protocol — HIT-2000/2002-SKK, Neuro-COH/2006 — RCRC). Pineoblastomas were diagnosed in 3 observations. In one case the relapse-free period was 3 years, with 2 courses of low-dose CT + 2 courses of high-dose CT and transplantation of stem cells conducted in Wurzburg. Functionally, pyramidal symptoms were preserved in the child who generally developed according to the age. In another case a child died 1.5 years after the surgery despite the performed PCT and radiation therapy, with the tumor re-
lapse and metastasis to the brain and spinal cord tunics. In one case the catamnesis was unknown.

The death of an infant with craniopharyngioma occurred in early postoperative period due to persistent electrolytic disturbances and hyperthermia of central genesis. The relapse-free period in case of malignant schwannoma (MPNST) with hemispheric-basal localization was 5 years; adjuvant therapy was not conducted, no relapses were observed. Functional result was good after delayed cranioplasty of the defect of temporal and parietal bones that remained after the surgery.

The relapse-free period in case of infantile myofibroma was 4 years, also with a good functional result.

A child with infantile fibrosarcoma of the temporal-occipital area died 2 years after the surgery as a result of decompensation of progressive hydrocephaly.

In case of hamartoma of hypothalamus stereotactic irradiation was performed 3 years after tumor biopsy; attacks of spasmodic laughter became less frequent; the process was stabilized according to the data of control brain MRI with the catamnesis of 8 years.

The relapse-free period in case of infantile myofibroma was 4 years, also with a good functional result.

Discussion

High-grade tumors were diagnosed in more than half of all patients in our series of observations (51%), corresponding to the data of other asimilaralogue studies where the share of Gr III—IV tumors varied from 45 to 60% [6, 10, 16]. Low-grade tumors (Gr I—II) with the predominance of choroid plexus tumors were diagnosed in half of all observations in the group of tumors of the lateral and III ventricles (n=33).

The diagnostic criteria of atypical choroid plexus papillomas (Gr II) are poorly defined. Signs of atypia include: emergence of papillae with the presence of multiple outgrowths covered with multilayer cylindrical epithelium and containing mitotic figures [2, 3, 14]. This “classical picture” of atypical choroid papillomas was not observed in the present study. The diagnosis of atypical choroid papilloma was made after immunohistochemical study, based on the high Ki-67 labeling index (higher than 10%). However, favorable clinical course of these tumors raises the question whether this approach is correct. These tumors should be probably considered as choroid papillomas with the increased proliferative potential.

Choroid carcinomas in infants had an extremely unfavorable surgical prognosis: tumors with high degree of anaplasia and infiltrative growth, originating from choroid plexus and therefore intensively supplied with blood, reached large sizes and were too challenging for the radical surgery. S. St. Clair et al. [18] proposed to perform PCT before the surgery to improve the outcomes of surgical treatment of choroid carcinomas. According to the authors, the 3-year relapse-free survival in the group of 5 infants was less than 40%. In our series of 8 infants diagnosed with choroid carcinomas, 4 infants died in the perioperative period. The 3-year relapse-free survival in the remaining 4 observations was 75% in case of the radical removal and PCT performed.

A problem with adjuvant therapy of anaplastic ependymomas is that these tumors have low sensitivity to PCT, and radiation therapy cannot be given to infants younger than 1 year old. PCT was conducted to postpone radiation therapy as much as possible and to perform it after the child reaches the age of 1 year old. T. Merchant et al. [13] studied the group of 48 children younger than 3 years old and demonstrated the possibility and safety of conformal irradiation after the surgery, the 3-year relapse-free survival being 75%. In our study, infants with ependymomas (Gr III) showed the 3-year relapse-free survival in 65% of observations, with good functional results in 50% of cases.

Infants with astrocytomas (Gr I and Gr III) demonstrated 100% survival (with the maximum catamnesis being 10 years) with good functional results in 50% of observations. It should be noted that infants with Gr III astrocytomas and high index of proliferative activity did not receive any adjuvant therapy in more than half of observations; no relapse was observed (during 3 years at most). According to J. Geyer et al. [9], infants with Gr II—III astrocytomas may respond to CT even without radiation therapy, with the survival rate better than that of older children and adults. The prognosis in case for glioblastomas is extremely unfavorable in infants as well as in all age groups.

![Fig. 6. 5-year survival rate in a group of infant patients with brain tumors: Gr I—II — 92%, Gr III—IV — 48%](image-url)
A single case of large desmoplastic infantile astrocytoma in a 3-month-old child was observed in our study. The tumor was radically removed with no relapse detected within 3 years. According to the 2007 WHO classification, desmoplastic infantile astrocytomas are Gr I glioneuronal tumors. The presence of anaplasia regions with high proliferative index or lower differentiation is described in the literature; the prognosis for these tumors is defined by the completeness of neoplasm resection, with possible aggressive course of the process in case of subtotal removal [5, 19]. Our observation confirms the data on the importance of radical removal of these tumors.

Most diagnosed tumors of the chiasmosellar area \( (n=13) \) were Gr I—II chiasmal gliomas — 10 (77%), with high index of proliferative activity revealed by immunohistochemical analysis in almost half of all observations. The pilomyxoid form of glioma, a rare morphological form of tumor with Gr II malignancy, was diagnosed in 2 cases. The 3-year relapse-free survival of infants with chiasmal gliomas (Gr I—II) in our study was 70%. According to M. Massimino et al. [12], survival without progressing in non-operated infants younger than 1 year old with chiasmal gliomas was 33%.

Tumors of posterior cranial fossa in the present study were represented by high-grade tumors, predominantly medulloblastomas, in 75% of observations. S. Rutkowski et al. [17] noted that the prognosis for medulloblastomas depended on the extent of tumor resection, absence of metastases and the histological type of tumor; the prognosis was better for desmoplastic medulloblastomas than that for the classical type. According to the authors, the 10-year relapse-free survival of infants younger than 3 years old, with the absence of metastases as a low-risk factor, was more favorable and reached 50% in case of high-dose CT and craniospinal irradiation. In the present study, three children with the classical form of medulloblastoma died; all children belonged to the high-risk group despite the absence of unfavorable prognostic marker of MYC gene amplification revealed by molecular genetics analysis.

One child with desmoplastic form of medulloblastoma is alive, with the relapse-free period of 3 years in the absence of adjuvant therapy.

The series of observations of infants with brain tumors published in the literature differ by the survival time-frames and functional outcomes. According to different authors, the survival rate up to 1 year and up to 5 years varies significantly: from 45 to 85% and from 21 to 81%, respectively. Excellent results presented by H. Young, H. Johnston [20] can be explained by the large number of histologically benign tumors in their series of observations. According to C. Di Rocco et al. [6], C. Lapras et al. [10], A. Raimondi et al. [15], the 5-year relapse-free survival ranged from 30 to 40%, with satisfactory functional results observed only for 1/3 of the patients who had survived. The different data obtained in the studies are explained by differences in histogenesis and ratio between benign and malignant tumors rather than different methodological approaches in different series of observations.

In our opinion, it would be more correct to evaluate treatment outcomes in infants with brain tumors in each morphological group based on the malignancy grade, histogenesis and localization of tumors.

The results of the present study were evaluated according to different histological types and malignancy grades. The best long-term outcomes of treatment were obtained for children with Gr I and Gr III astrocytomas and those with choroid papillomas.

Table 3 shows the long-term outcomes of treatment of brain tumors with different histology achieved in the most representative series including the present study.

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Authors</th>
<th>Number of children (abs.)</th>
<th>Adjuvant therapy (CT, RT, CSI)</th>
<th>Relapse-free survival (RFS), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Our study</td>
<td>4</td>
<td>CT+RT (n=2)</td>
<td>3-RFS — 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not performed (n=2, Ki-67 &gt;10%)</td>
<td>3-RFS — 100</td>
</tr>
<tr>
<td>Gliomas of visual pathways Gr I—II</td>
<td>M. Massimino, 2002 [12]</td>
<td>7</td>
<td>CT</td>
<td>3-RFS &lt;33</td>
</tr>
<tr>
<td></td>
<td>Our study</td>
<td>10</td>
<td>CT</td>
<td>3-RFS — 70</td>
</tr>
<tr>
<td></td>
<td>S. St. Clair, 1992 [18]</td>
<td>5</td>
<td>CT before tumor removal</td>
<td>3-RFS &lt;40</td>
</tr>
<tr>
<td></td>
<td>Our study</td>
<td>4</td>
<td>CT</td>
<td>3-RFS — 75</td>
</tr>
<tr>
<td></td>
<td>Our study</td>
<td>10</td>
<td>CT+RT</td>
<td>3-RFS — 65</td>
</tr>
<tr>
<td>Medulloblastomas Gr IV</td>
<td>A. Gaijar, 1994 [8]</td>
<td>4</td>
<td>CT+CSI</td>
<td>5-RFS — 25</td>
</tr>
<tr>
<td></td>
<td>Our study</td>
<td>4 (3-RR)</td>
<td>CT+1 CSI</td>
<td>3-RFS — 25</td>
</tr>
</tbody>
</table>

Footnote: CT — chemotherapy; RT — radiation therapy, CSI — craniospinal irradiation. 3-RR — high-risk group 3 (metastases). LR — low-risk group (no metastases).
Conclusion

One feature of brain tumors biology in infants is the increased proliferative activity (high Ki-67 index: 10% and more) revealed during the diagnosis of choroid papillomas and some chiasmal astrocytomas and not reflected in the clinical course. This behavior of tumors allows one to review the increased proliferative index differentially; the morphological picture of tumor in infants in the absence of evident malignization signs should probably be given higher priority, pointing to the high proliferative activity without changing the malignancy grade. It may be supposed that the increased proliferative activity in these histological forms does not have conclusive prognostic importance and is explained by intensive myelination and synaptogenesis during the first year of infant’s life [1].

The best long-term results of treatment were obtained in infants with complete resection of Gr I and Gr III astrocytomas and in infants with choroid papillomas, with 100% 3-year relapse-free survival.

The 3-year relapse-free survival of infants with operated chiasmal gliomas (Gr I—II, partial removal) was 70%, which was better than in the foreign studies where surgical treatment of these tumors was either not performed or limited by the biopsy.

Radical removal of histological forms such as anaplastic astrocytoma, choroid carcinoma, anaplastic ependymoma, infantile desmoplastic astrocytoma with areas of anaplasia influences the relapse-free survival of infants and promotes further favorable prognosis and adjuvant therapy.

Prognosis in infants with medulloblastomas (classical type), AT/RT, immature teratomas, and pineoblastomas remains pessimistic despite the radicality of removal; the search for new protocols of adjuvant therapy is necessary.

REFERENCES


19. WHO Classification of Tumours of CNS 4th Ed. Lion 2007; 96—98.


Commentary

The article is interesting due to the fact that it is the first catamnestic study of brain tumors in infants on the first year of life in the Russian literature, with the analysis of the patients’ survival depending on different initial data: histological type of tumor, its localization and treatment performed. I would like to note several things related to the histopathological details. According to the authors of various handbooks on histopathology of CNS tumors, as well as the WHO Classification of Tumors of the CNS as the consensus publication, atypical choroid plexus papilloma is the papilloma with high mitotic index (more than 2 mitotic figures in 10 visual fields under x400 magnification) and some probable but not obligatory morphological features (e.g. focal loss of papillary structure). The proliferative index evaluated as the expression组织实施。
level of Ki-67 (MIB-1) and reviewed separately is not a criterion for differential diagnosis between papilloma and atypical papilloma of choroid plexus.

Regarding the correlation between the survival of patients with medulloblastomas and genetic basis of these tumors, distribution of medulloblastomas into four prognostically different molecular genetic groups has been made only recently; therefore, the study of the catamnestic patients with these tumors should be conducted in accordance to the revealed molecular group.

The authors are absolutely correct in assuming that the adequate interpretation of therapy results is possible only by using the integral approach, based on the complex evaluation of localization, histological diagnosis, molecular and genetic aberrations of tumors, the extent of surgical intervention, radiation therapy and protocols of chemotherapeutical treatment.

A summary table of long-term outcomes of treatment with the data of the authors’ studies and those of foreign researchers is given at the end of the article. In my opinion, a complete comparison of the results is not correct due to methodological differences in the studies (no histological types are assigned for medulloblastomas; age groups and relapse-free survival periods differ in the works of foreign authors). Nevertheless, a significantly higher 3-year relapse-free survival of patients with partially removed tumors as compared to children who had not received surgical treatment was noted in the group of chiasmal gliomas.

A.V. Kislyakov (Moscow, Russia)
Choroid plexus papilloma (CPP) is a rather rare benign neoplasm that arises from choroid plexus cells. CPP prevalence is 0.3 per 1,000,000 [26]. CPPs amount to 0.5 to 0.6% of all intracranial tumors in all age groups [17, 22]. Choroid plexus tumors are most frequently encountered in the children population, where they account for 1.8—2.9 to 2—5% of all intracranial space-occupying lesions [5, 15, 23, 43].

Analyzing the literature, we have not found any reports on the use of the endoscopic technique with implementation of two operation ports to remove CPP in early childhood. In this connection, the analysis of a clinical case given in this paper and the examination of surgical aspects in terms of this case are of practical interest.

The objective of this work is to analyze the literature devoted to the application of the endoscopic method for surgical treatment of CPP as well as presenting our own experience with this technique using a specific example of the patient follow-up for 22 months.

Clinical case

An 8-month-old infant Z. had undergone inpatient treatment at the Department of Pediatric Neurosurgery, the Federal Center of Neurosurgery (Tyumen’, Russia) from August 1, 2011 to August 15, 2011. At the age of 3.5 months, 4.5 months before admission to the hospital, a space-occupying lesion up to 3 mm in the right lateral ventricle was suspected during the ultrasound examination of the brain. Computed tomography (CT) of the brain was performed on April 12, 2011; the conclusion was: a vascular malformation of the choroid plexus on the right side, a space-occupying lesion? Internal communicating hydrocephalus. Upon the neurological examination on April 20, 2011, a significant increase in the head circumference up to 47.5 cm (+12.5 cm) was observed. During this period, complaints of regression of previously acquired skills arose. On April 22, 2011, due to progressive internal hydrocephalus, ventriculoperitoneal shunting (VPS) on the left side was performed with an improvement in the form of reducing the effects of hypertension-hydrocephalic syndrome. On July 27, 2011, the VPS exploration was carried out. The patient’s status improved after the surgery.

The child was referred to the Federal Center of Neurosurgery in Tyumen’ to determine further treatment. At admission to the clinic, complaints (according to the child’s mother) of that the child was unable to hold his head, sit, turn, swallowed poorly, and had a high muscle tone in the limbs. The child was somatically compensated. The head circumference was 51 cm, the anterior fontanelle was tense. Consciousness was clear; vision was reduced to distinguishing between light and shadow; fixation and tracking reflexes were absent. Eyeball movements were involuntary and conjugate. There were pseudobulbar disturbances in the form of reflexes of oral automatism, dysphagia, and dysphonia, muscular hypertonicity of the upper limb flexors, of the extensors and adductors of the lower limbs. Active and passive movements of the limbs were limited due to the high muscle tone, the tendon reflexes from the upper and lower extremities were spastic, D=S. The pain protective response had the form of a generalized activation with
irregular protective flexion of the limbs without localizing a stimulus. Meningeal signs were absent.

Ophthalmoscopy revealed congestion in the fundus on the right and the left side. According to magnetic resonance imaging (MRI) of the brain and spinal cord with intravenous contrast in the MPRAGE sequence with 1 mm slice thickness, a cauliflower-like tumor nodule with the size of 33×20×24 mm on the vascular pedicle was diagnosed in the posterior horn of the right lateral ventricle associated with pronounced internal hydrocephalus. Hypoplasia of the cerebellar vermis, mega cisterna magna, was also detected, which widely communicated with the IV ventricle (variant of the Dandy-Walker malformation) (Fig. 1). The analysis of the cerebrospinal fluid (puncture of the VPS pump) revealed 13 cytosis cells (8 lymphocytes and 5 neutrophils), 0.62 g/L of protein, 116 mmol/L of chlorine, 3.25 mmol/L of glucose. For additional visualization of the tumor vascular pedicle, CT with angiography and 3D reconstruction was carried out (Fig. 2). On August 5, 2011, surgery was performed for complete endoscopic removal of the right-sided lateral ventricle choroid plexus papilloma. The tumor vascular pedicle was clipped. The Arendt test was performed. VPS removal was carried out (the surgeon was Prof. Sufianov A.A.). The operation was performed with the child in the supine position with a soft hold of the head in a DORO frame (PMI, Germany). A set for endoscopic surgery on the brain (Gaab KARL STORZ, Germany) and HOPKINS II Karl Storz (0°, 30°, 45°) optics were used. The parasagittal approach was used, on the right side, in the parietal region through the burr hole. The tumor located in the posterior horn of the lateral ventricle and its vascular pedicle were visualized through a neuroendoscope. The second operational approach in the parietal region on the right was formed; an additional 6 mm endoscopic port (Johnson & Johnson, XCEL ENDO-PATH) was placed (Fig. 3). The vascular pedicle for

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Fig. 1. MRI of the brain with intravenous contrast before operation.

a — sagital section: 1 — mega cisterna magna communicating with the IV ventricle (a variant of the Dandy–Walker malformation). Cerebellar vermis hypoplasia is marked; b — axial section: 2 — a cauliflower-like tumor nodule on the vascular pedicle, located in the posterior horn of the right lateral ventricle, associated with severe internal hydrocephalus; c — sagittal section: 3 — the tumor vascular pedicle.

Fig. 2. CT angiography with 3D reconstruction.

a — frontal view: 1 — the tumor; b — top view: 2 — the tumor vascular pedicle (venous component of which is formed from the thalamostriate vein), 3 — the thalamostriate vein; c — side view: 1 — the tumor located in the posterior horn of the lateral ventricle, 2 — the tumor vascular pedicle.
clipping was isolated using bipolar coagulation. The vascular pedicle was clipped with titanium clips using an endoscopic clip applier and transected. The tumor was removed in pieces through an additional endoscopic port (Fig. 4). The blood loss was 10 ml, most of which was due to skin incisions. After performing the Arendt test (positive), the VPS was removed. The postoperative period proceeded satisfactorily. After surgery, CT of the head was performed; there were no data on hemorrhage. The control MRI and CT with 3D reconstruction of the skull with intravenous contrast visualized the condition after complete removal of the tumor of the choroid plexus of the right lateral ventricle; the vascular pedicle was clipped. Open internal hydrocephalus was of the former size (Fig. 5).

At the time of discharge from the department on the 10th day after the operation, the child was conscious. The motion activity was minimal: the child performed flexion–extension of the limbs, the muscle tone in the limbs was elevated, the tendon reflexes from the upper and lower limbs were spastic, with minor clonus. Appetite improved, the head circumference decreased by 2 cm. The pyramidal insufficiency events decreased signifi-
cantly, oculomotor and vision disturbances remained. Postsurgical wounds healed by first intention (Fig. 6). The follow-up period for the child was 22 months. Hydrocephalus had not progressed over the entire follow-up period. There were no data on the continued growth of the tumor (Fig. 7).
Results and Discussion

In the analyzed literature [40], among the many reports devoted to the etiology, pathological anatomy, diagnosis, and surgical aspects of this pathology (including combined stepwise removal of a choroid plexus papilloma using endoscopy in a 6-week-old infant), there are very few publications on the use of endoscopy alone in this pathology. We found two reports on the use of the endoscopic method only upon manipulations on the choroid plexus. For example, in one case, endoscopic removal of a choroid plexus cyst with obstructive hydrocephalus caused by it was performed in a 25-year-old female [31]. In the second case, endoscopic removal of a cystic choroid plexus papilloma of the III ventricle was performed in an 18-year-old male [35]. In some publications, the authors have stated, based on the analysis of techniques, the importance of endoscopic assistance in performing these microsurgical manipulations [28]. Only several of them have emphasized advisability of using endoscopy to remove tumors with intraventricular localization and proved the anatomic accessibility to different areas of the cerebral ventricles [19, 44]. Few works [6, 9, 37] have been devoted to analysis of the efficacy and technical features of endoscopic removal of intraventricular tumors. Papers [13] devoted to partial removal or biopsy of intraventricular tumors with the use of endoscopy in adults were published more often. There are few works dedicated to this analysis in pediatric practice [16].

A description of choroid plexus papillomas was first given in 1832 by a pathologist M. Guerard [27] in autopsy of a 3-year-old child. G. Perthes reported for the first time successful removal of a lateral ventricle choroid plexus papilloma in an adult in 1919. E. Sachs in 1922 and then D. Cushing in 1927 reported removal of a choroid papilloma of the IV ventricle. In 1932, D. Cushing in his monograph “Intracerebral Tumors” [34] described 12 observations of choroid plexus papillomas among 2,023 cases. Removal of this tumor in pediatric practice was first performed by W. Dandy [15] in 1927 in a 14-year-old child. The tumor was located in the III ventricle, and he used the transcallosal approach to remove it. It should be noted that surgical treatment had been accompanied by a large number of complications and high mortality: 62% for tumors localizing in the lateral ventricle and 27% for those localizing in the IV ventricle [7].

14 [20] to 12.8% of tumors of the choroid plexus [23] are accounted for the first year of life. According to K. Laurence [30], 75% of all tumors of the choroid plexus develop during the first 10 years of life, and 70–90% of these tumors occur in children younger than 2 years [8, 32, 38].

The most common tumor localization in adults and children is the lateral ventricle (50%). Also, it can be located in the IV and III ventricle in 40 and 5% of cases, respectively [3]. The remaining 5% of the tumors can be localized in very different areas including the cerebello- pontine angle, suprasellar region, frontal lobe, posterior commissure, pineal region, and cerebellum [29]. The supratentorial localization is mostly prevalent in infants [47]. The infratentorial localization is more common in adults [16, 39, 45]. CPPs in very rare cases have an aggressive course and a tendency to infiltrative growth, spreading to the brain parenchyma, developing structural atypia of the choroid plexus villi at the invasion site [32, 42].

The most common and characteristic symptom of a choroid plexus papilloma is hydrocephalus and an increased intracranial pressure [16, 29]. According to R. Humphreys et al. [25], hydrocephalus occurs in 78% of cases; according to R. Ellenbogen et al. [15], it occurs in 95% of cases. In 80% of cases, ventriculomegaly develops without obstruction of cerebrospinal fluid (CSF) circulation pathways. The development of hydrocephalus in this case is a consequence of the CSF overproduction by the hypertrophic choroid plexus or a comorbid disorder of CSF resorption [11, 14]. Sometimes tumor removal is accompanied by regression of hydrocephalus, but it can persist even after the tumor was removed successfully [21]. Shunt placement is required in up to 50% of patients [12, 38].

Since a choroid plexus papilloma always has an ample blood supply, its pronounced contrasting is observed when introducing a contrast medium. Tumor calcification occurs in 25% of lesions, but it is rare in children [1, 33]. Although, K. Koeller and G. Sandberg [29] reported, based on CT studies, that calcification is present in 14% of cases.

The main sources of tumor blood supply are the anterior and posterior choroid arteries. The venous drainage is carried out into the internal cerebral venous system [36, 41]. These vessels form a vascular pedicle. Its localization is the most important aspect of surgical treatment. Attempts to begin tumor resection without visualizing feeding vessels may result in a significant blood loss at the very beginning of operation [10, 12, 38]. According to some authors, a certain problem with vascular pedicle visualization during endoscopic removal is one of the reasons in favor of open surgery rather than endoscopy [18]. Corticotomy, performed in an open approach to resection, may subsequently establish a permanent communication between the brain ventricle and the subdural space. Therefore, an important aspect of this method is the need to close an intracortical defect by means of biological adhesive to minimize the risk of postoperative subdural hygromas [4, 24, 38]. Development of these complications increases the risk of surgery adverse outcome [38]. To our opinion, the use of endoscopy does not bear these risks, because the transcortical approach performed in this case and the diameter of the tools used are very small, and shaft canal walls occlude easily.

J. Wolff et al. [47] noted that the 1-, 5-, and 10-year survival rate for CPP is 90, 81, and 77%, respectively.

It should be emphasized that biportal approaches are not common in neurosurgery as yet. To date, only a
few studies mention the use of two endoscopic ports in intraventricular neurosurgery. A publication by F. Veto et al. [46] can be referred as an example. The authors used this procedure for surgical treatment of 3 patients with tumors of the III ventricle with aqueduct occlusion and hydrocephalus development and came to the conclusion about the efficacy of this approach. The multiportal approach (with more than two ports) has been worked out in detail and widely introduced into clinical practice by A.A. Sufianov in 2000 [2]. The multiportal principle means the creation of a larger, but just required, number of ports during endoscopic surgery in order to achieve the safest, minimally invasive, and most curative surgery. Our experience allows us to speak about advantages of the multiportal approach in endoscopic neurosurgery, especially in severe cases. In this situation, multiportality allows one to use the required amount of tools, to control visually the situation in almost all parts of the brain ventricle and at different angles of view (e.g., in the opposite ventricle) as well as to visualize panoramically the microtool tip relative to the brain structures with any power magnification and in the maximum brightness. For example, it is especially important when passing an endoscope through the narrow foramen of Monro. The use of ports of the same diameter is important to ensure the possibility for passing any tool through any port. All this greatly reduces the risk and dramatically increases possibilities of surgical intervention. Under certain favorable conditions (e.g., small intraventricular tumors), even bimanual manipulation is possible at some stages. Our judgments are consistent with data of other authors [18, 35, 46].

Conclusion

In spite of the fact that choroid plexus papilloma occurs relatively rare in the general structure of intracranial tumors of the central nervous system, the relevance and necessity of studying this pathology should be recognized, which is particularly important for pediatric neurosurgery. To date, there are few works devoted to this problem, which cover issues relating to the features of surgical tactics in relation to CPP. This tumor occurs most often in pediatric practice, where the selection and use of the minimally invasive treatments are vital and relevant.

The given clinical case demonstrates clearly the use of the minimally invasive technique (as exemplified by complete biportal endoscopic removal of CPP) for resection of an intraventricular tumor in a child.

REFERENCES

Commentary

The article by Prof. A.A. Sufianov et al. “Biportal endoscopic removal of choroid papilloma of the lateral ventricle in a child” is remarkable first of all in that the authors demonstrate the successful application of minimally invasive techniques, namely biportal endoscopic removal, in pediatric neurooncology. The publication reasonably indicates that the foreign literature describes procedures for endoscopic-assisted microsurgical removal of a tumor, that there are publications on endoscopic removal of colloid cysts and small benign tumors of the ventricular system, but publications on biportal or multiportal neuroendoscopic removal are very few. As a consequence, the indications and contraindications to the use of this technique are the matter of considerable debate.

Our experience of using endoscopy (more than 80 observations) in pediatric neurooncology allows us to make an assumption that the limitation for this technique is the size of the tumor and the extent of its blood supply/malignancy. The provided observation demonstrates the case of a choroid plexus papilloma with the well-visualized long vascular pedicle feeding the tumor. CPP is known to be a benign tumor and its removal is not accompanied by bleeding unless the feeding arteries are damaged. Therefore, the primary task of the surgeon who is planning surgery is to identify the tumor feeding vessel by means of modern neuroimaging techniques (neurosonography, CT, MRI), which was successfully done in the observation. The bimanual endoscopic approach certainly creates more comfortable conditions for manipulations and control in the surgical wound for the surgeon. The authors clearly demonstrated the capability and technique of application of this procedure.

Another problem in CPP surgery in infants is disorders of cerebrospinal fluid dynamics during the postoperative period, such as progressive hydrocephalus and tense subdural accumulations (28 to 75%). In modern literature, some authors recommend preoperative embolization of the tumor feeding arteries to prevent these complications. However, given the small caliber of arteries in infancy, their superselective catheterization cannot always be performed. Another disadvantage is the risk of embolizing the terminal branches of the anterior choroidal artery and questionable economic benefits too.

In conclusion, the authors are to be congratulated on the successful use of the biportal neuroendoscopic technique in pediatric neurooncology. This observation will undoubtedly arouse the interest among Russian and foreign neurosurgeons.

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