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- Preoperative and postoperative endocrine disorders associated with pituitary stalk injuries caused by suprasellar growing tumors
- The opportunities of using the PSM method in neurosurgical research
- Defining the reasonability and effectiveness of decompressive craniotomy in aneurysmal subarachnoid hemorrhage
Ischemic stroke (IS) and its consequences are among the most common causes of death and persistent disability of the working-age population. According to registries, occlusion of the internal carotid artery (ICA) is detected in 15—25% of all cerebral circulation disorders [1—3] and it is one of the main causes of IS.

According to epidemiological studies [2], symptomatic ICA occlusions annually develop in more than 6 per 100 000 population, excluding patients who did not seek specialized care. Ultrasound examinations in patients with chronic cerebral ischemia symptoms show carotid occlusions in 4% of cases [4].

It is known that clinical prognosis in patients with symptomatic occlusions of the ICA is unfavorable, since the annual incidence of repeated cerebral circulation disorders is up to 27% [5]. The presence of hemodynamic stenosis of the contralateral carotid arteries, which is detected in 18% of all patients with ICA occlusions, is one of the most important factors affecting the course of cerebral ischemia in patients with carotid occlusions [5]. In these cases, the risk of developing cerebrovascular accident (CVA) in at least one of the carotid systems is up to 70% [6], which dictates the need for surgical treatment [7].

Surgical strategy is often limited to carotid endarterectomy (CEA) on the side of stenosis, which significantly reduce the risks of repeated CVA in both hemispheres with an acceptable incidence of perioperative complications [8, 9]. First of all, this is true in patients with asymptomatic course of chronic cerebral ischemia, where CEA aimed at prevention of IS is not considered as a high-risk surgery by many specialists despite the presence of contralateral occlusion [8, 9]. At the same time, the effect of CEA on the clinical prognosis of symptomatic occlusions, as well as the risks of complications associated with this operation, have not been sufficiently studied so far [10].

Extracranial-intracranial microvascular bypass (EC-IC MB) on the side of ICA occlusion is another treatment for chronic cerebral ischemia caused by ICA occlusion. In connection with this, it is important to determine the step-by-step tactics of surgical treatment, including both reconstructive and revascularization procedures.

This article analyzes the experience in surgical treatment of patients with a combination of symptomatic occlusion of the ICA and hemodynamically significant stenosis on the contralateral side.

The study was aimed at investigating the effect of CEA on the clinical prognosis of chronic cerebral ischemia in patients with hemodynamically significant stenosis of the carotid artery and symptomatic occlusion of the contralateral ICA, assessing the risks of surgical complications, and substantiating the tactics of stage-by-stage surgical treatment of patients with this pathology.

Material and methods

In the period from 2006 to 2016, 83 patients with symptomatic ICA occlusion and hemodynamically sig-
significant stenosis of more than 70% on the contralateral side were operated on at the Burdenko Neurosurgical Institute. Most patients were males, 67 (80.7%), aged 52 to 79 years (on the average, 65.7 years).

All patients had a history of chronic cerebral ischemia symptoms and episodes of ischemic CVA in the occluded carotid system. The symptoms corresponding to the stenotic ICA system were detected in 15 (18%) patients in the form of TIA in 12 and minor IS in 3 patients. In other cases, there were asymptomatic stenoses and deformations detected during the combined ultrasound of brachiocephalic arteries after CVA in the occluded ICA system.

Diagnostic algorithm included duplex scanning of the brachiocephalic arteries (Philips Sonos 5500) and transcranial Doppler ultrasound (TCDUS) with measurement of the linear velocity of blood flow (BFV) in the middle cerebral arteries (MCA) (RIMED, Israel). The reactivity index (RI) was calculated to determine cerebrovascular reserves in the form of the ratio of BFV in the MCA with underlying hypercapnic load to the baseline blood flow. Additionally, SCT perfusion study was carried out in 13 cases followed by perfusion map plotting (GE Perfusion 3.0) according to the standard procedure [11].

All patients underwent CEA on the side of ICA stenosis. Combined evasion endarterectomy was most commonly used, in 55 (66%) cases, direct endarterectomy technique was selected in 28 (34%) cases, where synthetic GoreTex patch was used to close the arteriotomy incision in 7 cases. The operations were carried out in accordance with standard methods described in detail in previous publications [7] under general anesthesia in 67 (90%) cases and locoregional anesthesia in 8 (10%) cases. In all cases of carotid artery reconstructions, the indications for the use of a temporary intraluminal shunt were determined using multimodal neuromonitoring including TCDUS with MCA localization on the side of reconstruction and cerebral oximetry. Indications for intraluminal shunt insertion after ICA compression were as follows:

— decrease in BFV in the MCA on the reconstruction side by more than 60% of the baseline level or BFV of less than 40 cm/s;
— decrease in cerebral oximetry parameters on the reconstruction side by more than 10% of the baseline level;
— the development of focal neurological symptoms (with regional anesthetic).

In total, temporary intraluminal shunts were used at the main stage of reconstruction in 28 (34%) cases.

In 43 (52%) cases, EC-IC MB procedure was performed at different stages to create a bypass between the branches of the superficial temporal artery and cortical branches of the MCA on the side of ICA occlusion according to the standard procedure [7] in addition to CEA. The decision to use EC-IC MB in the occluded carotid system was taken based on additional study of cerebral blood flow, cerebrovascular reserves, and cerebral perfusion.

The results of reconstructive interventions were evaluated in the early postoperative period and during follow-up. The follow-up ranged from 9 to 78 months (on the average, 29.3±14.7 months).

**Results**

In most cases (81 patients), we achieved good results in the form of regression of clinical symptoms on the side of stenosis in symptomatic patients and prevention of CVA in the stenotic artery system. Furthermore, 35 (42%) patients demonstrated objective signs of regression of focal neurologic symptoms on the side of occlusion (more than 1 point on the NIHSS scale). On the average, regression of neurological deficit was 1.75±0.89 on the NIHSS scale.

The tactics of surgical treatment, as well as its effectiveness, depended on the clinical course of cerebral ischemia and the level of cerebral blood flow compensation in the occluded carotid system (Table 1).

Group 1 included 40 patients with signs of compensation of cerebral circulation on the side of ICA occlusion as evidenced by moderate asymmetry of BFV in the MCA according to TCDUS (velocity higher than 60 cm/s or decrease by less than 50% compared to the opposite side); preserved cerebrovascular reserves (reactivity index of more than 1.2) and milder clinical course of chronic cerebral ischemia, where magnitude neurological deficit scored 2.5±2.1 points on the NIHSS scale. In these cases, surgical treatment was limited to reconstruction of the stenotic internal carotid artery. All patients who underwent CEA demonstrated increase in blood flow in the MCA both on the side of reconstruction (up to 13%) and in the occluded carotid system (up to 7%) (Table 1).

Compensation of cerebral blood flow in the occluded carotid system in this group of patients made it possible to avoid stage-by-stage surgical revascularization of the brain and frequent application of temporary intraluminal shunts at the main stage of reconstruction (it was used only in 12.5% of cases). In this situation, the incidence of perioperative complications did not exceed the permissible level and amounted to 2.5%.

In 43 patients, preoperative examination showed signs of severe cerebral circulatory insufficiency in the form of:

— decreased BFV in the MCA on the side of occlusion below 60 cm/s in combination with exhausted cerebrovascular reserve (reactivity index of less than 1.1);
— perfusion criteria of severe cerebrovascular insufficiency, including prolongation of mean blood transit time (MTT) on the side of occlusion by more than 8 s, increase in MTT by more than 40%, and decrease in CBF by more than 20% compared to the opposite hemisphere.
More severe clinical course of cerebral ischemia was characteristics of this group patients, which was reflected in the modified Rankine score and NIHSS score (Table 1). In these cases, reconstructive interventions were insufficient to restore the existing cerebral blood flow deficit in the occluded carotid basin (increase in blood flow after CEA did not exceed 3% compared to the baseline blood flow), which necessitated staged application of EC-IC MB. EC-IC MB on the side of carotid occlusion was performed in all 43 patients with no cerebral blood flow compensation and functioning of the created bypass was in all cases confirmed during follow-up. The flow volume in the bypass varied from 23 to 52 mL/min (on the average, 31.8±9.6 mL/min).

In this group, 24 patients underwent CEA on the side of ICA stenosis as the first stage and EC-IC MB procedure as the second stage; these patients were included in group 2. As a rule, the patients were diagnosed with critical stenoses (more than 85%, on the average 89.7±4.5%). In this group, there was a high incidence of perioperative complications (12%) compared to group 1 (2.5%), despite the extensive use of temporary intraluminal shunts (38%). In this situation, complications developed in the occluded carotid system on the contralateral side with respect to reconstruction: in 1 (4%) case, in the form of complete stroke and in 2 (8%) cases, in the form of minor stroke. An illustrative clinical case is reported below.

Patient B., 50 years old, was admitted to the Burdenko Neurosurgical Institute on 30.08.10 with complaints of headache and dizziness, episodes of speech disorders, and weakness in the right limbs. The disease manifested about 2 weeks ago, when the patient first experienced episodes of speech disturbance, progressive memory loss, increased fatigue. Neurological status at admission included mild speech disorders in the form of amnestic aphasia, acalculia, and memory impairment. The magnitude of neurological deficit was 4 points on the NIHSS scale. The patient had a transient ischemic attack (TIA) in the left MCA system in the form of increase in speech disorders up to complete aphasia within 24 hours after admission to the hospital.

MR and SCT angiography detected occlusion of the left ICA, stenosis of the right ICA up to 70—75% at the boundary of the proximal and middle third of the extracranial segment.

Ultrasound examination showed asymmetric BFV in MCA with a pronounced decrease on the left (45 vascular reserves in the left MCA system. CT perfusion study showed signs of cerebral circulatory decompensation in the left MCA system in the form of pronounced prolongation of blood transit time (MTT) to 9.55 (more than 190% compared to the right hemisphere), decrease in regional blood flow by 49.3% (up to 19.37 mL/min/100 g) (Fig. 1).

Open CEA on the right was carried out as the first stage in order to improve compensatory collateral blood flow. During neuromonitoring, BFV in MCA on the operation side decreased from 70 to 35 cm/s, which necessitated insertion of temporary intraluminal shunt. Shunt insertion and removal time did not exceed 3 minutes,

Table 1. Comparison of patients with occlusions and contralateral stenoses of the carotid arteries depending on the selected surgical strategy

<table>
<thead>
<tr>
<th>Selected tactics of surgical treatment</th>
<th>Compensation</th>
<th>Decompenation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (CEA), abs. (%)</td>
<td>Group 2 (CEA—EC-IC MB), abs. (%)</td>
</tr>
<tr>
<td>ICA stenosis level</td>
<td>87.2±5.1</td>
<td>89.7±4.5</td>
</tr>
<tr>
<td>The use of shunts2</td>
<td>5 (12.5)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Symptomatic stenoses2</td>
<td>12 (37)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Time after CVA, months</td>
<td>6.4±5.8</td>
<td>3.4±1.4</td>
</tr>
<tr>
<td>Time between operations, months</td>
<td>—</td>
<td>4.3±1.7</td>
</tr>
<tr>
<td>Mod. Rankin score, points</td>
<td>1.3±0.6</td>
<td>2.1±0.7</td>
</tr>
<tr>
<td>Initial neurological deficit, NIHSS scores</td>
<td>2.5±2.1</td>
<td>5.3±1.8</td>
</tr>
<tr>
<td>Dynamics of neurological deficit, NIHSS scores</td>
<td>1.32±0.57</td>
<td>1.6±0.47</td>
</tr>
<tr>
<td>Improvement of clinical2 symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after CEA</td>
<td>8 (20)</td>
<td>11 (45)</td>
</tr>
<tr>
<td>after EC-IC MB</td>
<td>14 (59)</td>
<td>—</td>
</tr>
<tr>
<td>Blood flow in the MCA (occlusion), cm/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>before CEA</td>
<td>63.8±6.7</td>
<td>59.7±4.7</td>
</tr>
<tr>
<td>after CEA</td>
<td>68.4±5.33</td>
<td>61.6±6.1</td>
</tr>
<tr>
<td>Blood flow in the MCA (occlusion), cm/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>before surgery</td>
<td>65.6±7.8</td>
<td>69.6±6.2</td>
</tr>
<tr>
<td>after reconstruction</td>
<td>73.0±5.7</td>
<td>75.1±6.1</td>
</tr>
<tr>
<td>Complications (persistent/Transient)</td>
<td>1 (2.5)</td>
<td>1 (4)/(2)</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>24</td>
</tr>
</tbody>
</table>

Footnote. 1All three complications developed in the occluded ICA system. 2Significant difference ($p<0.05$, Fisher's exact test). 3Significant increase ($p=0.048$, Wilcoxon's test).
while the total duration of the main phase of the reconstruction was 18 minutes.

After postanesthetic recovery, the patient demonstrated increase in right hemiparesis up to plegia and severe aphasic disorders (11 points on the NIHSS scale). MRI of the brain detected ischemia at the central gyrus and the semioval center on the left (Fig. 2a, 2b), which was indicative of the development of IS in the left MCA system (Fig. 2).

Postoperative conservative treatment resulted in only a slight increase in strength and range of motions in the right limbs (up to 3 points), while maintaining pronounced motor aphasia. NIHSS score was 7 points. Three months later, repeated cerebral perfusion study showed no significant recovery of cerebral blood flow in the left MCA system: there was interhemispheric asymmetry of blood transit time up to 148% with higher values on the left. This gave occasion to form EC-IC MB between the frontal branch of the superficial temporal artery and the cortical (frontal) MCA branch on the left.

After EC-IC MB surgery, patient’s condition significantly improved. Almost complete recovery of speech function, increased strength of the right limbs, and improved fine motor skills in the right hand were observed. NIHSS score was 3 points. Control ultrasound on day 6 showed EC-IC MB diameter up to 1.3 mm and blood flow up to 48 mL/min. Follow-up examination showed well functioning EC-IC MB and normalization of cerebral perfusion, including regression of interhemispheric asymmetry in MCA system with preserved area of reduced perfusion in the PCA system on the left and, partially, adjacent blood circulation zones (MTT asymmetry less than 20%, CBF less than 5%) (Fig. 3).

Follow-up showed almost complete recovery of lost functions except for persistent visual field disturbances. The patient is able to work and takes sports. Neurologic status: Rankin score — 1 point, NIHSS score — 2 points. Control follow-up examinations showed increase in EC-IC MB diameter to 1.7 mm and blood flow up to 76 mL/min. The duration of the follow-up was 49 months. There were no repeated cerebral circulation disorders.

Later on, EC-IC MB was formed on the side of occlusion followed by carotid reconstruction in 19 similar cases. These patients were included in group 3. The main indications for high-priority EC-IC MB procedure were as follows:

— unstable clinical symptoms on the side of ICA occlusion;
— subcritical stenosis (less than 80%) of the dominant carotid artery;
— signs of decompensation of cerebral blood flow in the occluded ICA system in the form of BFV below 50 cm/s in combination with exhausted cerebrovascular reserves according to TCDUS or prolongation of the blood transit time (MTT) on the side of occlusion by more than 10 s (increase by more than 80% compared to the opposite side) according to the MSCT-perfusion study [11].

The average level of ICA stenosis in group 3 patients was 75.5±5.7%. Temporary intraluminal shunts were most often used in this group of patients (up to 73% of cases) due to more severe cerebrovascular insufficiency in the occluded carotid system. This is indicative of high surgical risk of reconstructive interventions, especially in patients with subcritical stenoses (up to 80%) that did not cause severe hemodynamic disturbances in the ICA, which is actively involved in the compensation of contralateral carotid occlusion. Prophylactic application of EC-IC MB as the first stage in this group not only prevented complications of CEA, but also provided higher clinical effectiveness in the form of partial regression of neurological symptoms (in 68% of cases, with a neurological deficit regression by 1.9±0.35 points on the NIHSS scale).

In patients with uncompensated carotid occlusions (groups 2 and 3), neurologic symptoms as a rule regressed after EC-IC MB operation (in 59 and 68% of cases, respectively). The highest clinical effectiveness of CEA was observed in group 2 patients: in 45% of cases, the patients noted improvement in non-specific cerebral symptoms in the form of regression of headaches and dizziness. Improvement in focal neurological symptoms was represented by more active speech and decrease in pyramidal symptoms within 1–2 points on the NIHSS scale. In these cases, EC-IC MB surgery at the second-stage also led to regression of clinical symptoms (a total of 59%).

Almost no changes in focal hemispheric symptoms were observed in group 3 patients after the second stage (ICA reconstruction). Neurological deficit regression was observed only in 16% of cases and did not exceed 0.65±0.55 points on the NIHSS scale. This is indicative of mostly preventive nature of reconstructive interventions carried out at the second stage.

Time interval between CVA and reconstructive surgical interventions in group 1 patients varied in a wide range from 3 weeks to 2.5 years, averaging 6.4±5.8 months. Most often, critical stenoses of brachiocephalic arteries were detected along with ICA occlusion during the diagnosis and treatment of the resulting CVA. The time elapsed before reconstructive operations was longer in patients with progressive stenosis of the opposite ICA detected during follow-up.

The decision to make EC-IC MB on the side of ICA occlusion after the carotid reconstruction performed at the first stage in group 2 patients was made in 3 months after additional examination. The average interval between the operations was 4.3±1.7 months.

In group 3 patients, the decision to form EC-IC MB was as a rule taken within the first months after ICA occlusion. The time of the second stage (ICA reconstruction) significantly varied. If patients have already been diagnosed with subcritical ICA stenoses at the time of hospitalization, reconstructive surgery was carried out
Fig. 1. Preoperative studies of the patient B.
a — stenosis of the right ICA (1) and occlusion of the left ICA (2) as shown by SCT-angiography; b — lacunar ischemia in the left frontal lobe (indicated by arrow) as shown by CT; c — complete frontal segments of the circle of Willis as shown by MRI; d, e — cerebral perfusion data (explanations in the text).
3—4 months after EC-IC MB. In the case of stenosis worsening during the dynamic follow-up (4 cases), the time between the staged interventions was up to several years. The average time interval between the step-by-step operations was 9.9±7.7 months.

The complications of reconstructive interventions were represented by transient VCA in 2 (2.4%) cases and IS in 2 (2.4%) cases. At the same time, 3 out of 4 VCAs developed in patients with unstable neurological symptoms in the occluded ICA system after contralateral CEA using a temporary intraluminal shunt due to its insufficient effectiveness. Later on, preventive surgical revascularization on the side of occlusion (group 3) as the first stage prevented these complications in similar cases.

**Discussion**

According to the data of large international multicenter studies [7, 12, 13], CEA is recognized as an effective method for prevention of IS and treatment of cerebral ischemia and is the standard treatment for patients with hemodynamically significant carotid artery stenoses of more than 70%. According to statistics, up to 10% of all carotid reconstructions are carried out in patients with ICA occlusion on the opposite side, which is considered
by most specialists as an additional factor that increases the risk of perioperative complications. Thus, according to the North American multicenter study (NASCET) [12], the presence of contralateral occlusion is associated with more than 2-fold higher risk of ischemic complications and the total incidence of ischemic CVAs after CEA was up to 18% in this group of patients. More careful selection of patients for surgical treatment, implementation of brain protection and intraoperative neuromonitoring methods into clinical practice, as well as more extensive use of temporary intraluminal shunts at the main stage of reconstruction significantly reduced the risks of complications of CEA to acceptable values (1.5—3.5%). However, the choice of surgical strategy in this group of patients is still a topical issue, especially in patients with the symptoms in the occluded carotid system.

A total of 83 patients with hemodynamically significant stenoses of the ICA and symptomatic occlusion of the ICA on the opposite side were operated on at the Burdenko Neurosurgical Institute in 2006—2016, which is 6% of all reconstructive interventions performed during this period. We developed the tactics of step-by-step surgical treatment for this group of patients aimed at improving the effectiveness of surgical treatment and reducing perioperative risks, which included both ICA reconstruction on the side of stenosis and revascularization of the brain on the opposite side.

In most cases, surgical treatment of patients began with CEA on the side of stenosis, 63 (76%) of cases. The choice of carotid reconstruction as the first stage of treatment was dictated by the need to prevent the development of IS on the side of stenosis and to improve blood supply to the brain in both hemispheres [14—16]. Indeed, the analysis of the immediate and long-term outcomes has shown that carotid reconstruction is not only effective in prevention of repeated CVA on the reconstruction side, but also improves cerebral circulation and clinical symptoms in the occluded ICA system. In this situation,
no repeated CVAs were observed in both carotid systems throughout the follow-up period despite the fact that, according to epidemiological studies, the incidence of IS during the natural course of the disease is up to 12.4% per year in this group of patients.

Our results show the interesting fact that increase in blood flow in the MCA on the side of ICA occlusion after CEA did not exceed 7% of the baseline level even in patients with critical ICA stenoses and well developed anterior sections of the circle of Willis. Therefore, in patients with severe perfusion deficiency, CEA did not lead to compensation of cerebral blood flow in the occluded system and sometimes even worsened it, which was confirmed by the aforementioned clinical observation. In these cases, additional formation of EC-IC MB on the side of occlusion was justified and was carried out in 43 (52%) patients. These revascularization interventions not only improved the clinical outcomes of staged surgical treatment, but also reduced the risks of complications of CEA. This facts pose the question about the order of the reconstructive and revascularization interventions, which was solved with allowance for assessment of the risks of complications of surgical treatment.

After CEA, ischemic complications developed in 4 (4.8%) cases with an average frequency of temporary intraluminal shunt insertion of 33.8%. This confirms the popular opinion that ICA reconstruction in the presence of contralateral carotid occlusion is an intervention associated with high surgical risk [17, 18]. At the same time, the analysis of the results showed heterogeneity of the study group of patients in terms of clinical manifestations and severity of cerebrovascular insufficiency on the side of occlusion. Thus, in patients with signs of satisfactory compensation of cerebral circulation in the occluded carotid system and minimal neurologic deficit (modified Rankin score of 1—2 points), CEA was accompanied by minimum incidence of complications (2.5%) when using temporary shunts. They developed in 13% of cases, which matches the results of CEA in patients with functioning ICA on the opposite side or asymptomatic occlusion [8, 10]. High clinical and hemodynamic efficacy of CEA in this group of patients made it possible to abandon staged cerebral revascularization.

Somewhat different results were observed in patients with initial signs of cerebral blood flow decompensation in the occluded carotid system, which manifested in the form of decrease in BFV on the side of occlusion below 60 cm/s, signs of pronounced perfusion deficiency in the form of prolongation of blood transit time on the side of occlusion by more than 8 s (or more than 180% compared to the contralateral hemisphere) accompanied by decrease in regional blood flow (CBF) by more than 30% compared to the contralateral hemisphere [19, 20]. In these cases, CEA performed as the first stage was associated with significantly higher incidence of complications (up to 12.5% of cases; 4% of them were persistent), both in the reconstructed system (4.1%) and on the side of carotid occlusion (8.4%) even despite the fact that temporary intraluminal shunts were often used (up to 38%). Contralateral IS is an extremely rare complication of CEA. It develops only in 0.4% of all carotid reconstructions and is primarily caused by systemic disorders of cerebral hemodynamics with underlying worsening of collateral blood supply or arterial pressure instability [21]. This complication is illustrated by the aforementioned clinical case, where the patient with a pronounced perfusion deficiency and clinical symptoms on the side of ICA occlusion developed IS on the opposite side as a complication of CEA. In this situation, it is likely that preventive EC-IC MB on the side of occlusion as the first stage would be a correct solution in order to stabilize the neurological symptoms and reduce the risk associated with subsequent reconstructive surgery. The use of this surgical strategy (group 3) in the future allowed us to avoid perioperative complications and improve clinical efficacy. This is especially true for patients with asymptomatic subcritical stenoses of less than 80%. In this situation, the incidence of IS in the stenotic artery system does not exceed 0.4% per year in the case of the natural course of the disease [10], and therefore more attention can be payed to the treatment of the consequences of the contralateral ICA occlusion and to perform CEA at the second stage mainly as a preventive measure. Despite the fact that this surgical strategy is not commonly used at vascular surgery departments, it is used in neurosurgical hospitals. In particular, in the international multicenter study COSS (Carotid Occlusion Surgery Study, 2010), 8% of patients with PET signs of severe cerebrovascular insufficiency on the side of occlusion underwent EC-IC MB as the first stage followed by CEA [22].

Therefore, an individual approach in required in patients with symptomatic occlusions and contralateral stenoses of the carotid arteries when determining the tactics of surgical treatment, including both reconstruction and revascularization surgery.

**Conclusions**

The effectiveness of carotid endarterectomy and associated perioperative risks in patients with hemodynamically significant ICA stenoses and contralateral carotid occlusion depend on the clinical symptoms and the degree of compensation of cerebral blood flow in the occluded ICA system. In asymptomatic patients with ICA stenosis and contralateral carotid occlusion, carotid endarterectomy is not accompanied by increased risks of perioperative complications and does not require more frequent use of temporary intraluminal shunts. Revascularization of the brain is excessive in this group of patients. In patients who had IS and demonstrate signs of cerebral blood flow subcompensation in the occluded ICA system, carotid endarterectomy on the contralateral side is associated with high risks of IS and necessitates more frequent use of temporary intraluminal shunts.
Limited effectiveness of CEA in compensating blood flow in the occluded ICA system necessitates cerebral revascularization as the second stage. Patients with unstable clinical symptoms in the occluded ICA system and signs of cerebral blood flow decompensation (prolongation of hemispheric blood transit time, MTT) on the side of occlusion by more than 10 s represent a group of increased risk of perioperative ischemic complications of CEA, both on the side of ICA stenosis and in the occluded ICA system. In this situation, it is advisable to use EC-IC MB operation on the side of occlusion as the first stage in patients with subcritical stable ICA stenoses of no more than 80%.

Authors declare no conflict of interest.
Commentary

The treatment of multiple steno-occlusion pathologies of brachiocephalic arteries is a topical problem due to its high epidemiological and socioeconomic importance. The authors of the article focus on the surgical treatment of the internal carotid artery stenoses in patients with symptomatic occlusion of the carotid arteries on the contralateral side. In these cases, reconstructive interventions are associated with high risk of ischemic complications. The authors proposed a tactic of step-by-step surgical interventions aimed at solving this problem, depending on the severity of ICA stenosis and cerebrovascular insufficiency on the side of occlusion, which reduced the incidence of complications and improved the clinical outcomes of surgical treatment.

It should be noted that, in this situation, some specialists prefer endovascular methods for correction of ICA stenoses, such as angioplasty and carotid artery stenting, which, according to the cooperative study of SAPHIRE, are recommended in patients with high risk of carotid endarterectomy. This group of patients was not deliberately analyzed in this study. Nevertheless, the comparison of open and endovascular reconstructive methods in patients with contralateral occlusions of the carotid arteries is of considerable interest and can be a subject of subsequent studies.

In general, the article deals with the urgent problem of surgical treatment of elderly and senile patients who underwent ischemic stroke, and it is of interest for vascular surgeons, neurologists, and neurosurgeons.

V.A. Lazarev (Moscow, Russia)
Neurenteric cyst (NEC) is a developmental malformation derived from persistence of the neurenteric canal that connects the primitive intestine to the neural tube. Separation failure of the canal results in NEC cavity lined with cuboidal or columnar epithelium and contains mucin-producing cells [1].

For the first time, this pathology was described by Kubie in 1928 and then by Puuseep in 1934 and currently has several names: enterogenous cyst, endodermal cyst, enteric cyst, gastroenterogenous cyst, gastrocytoma, teratomatous cyst, intestinoma, and archenteric cyst [2].

According to M. Greenberg [5], NEC is most often detected in the first decade of life, but can be diagnosed at any age and at a similar frequency in women and men [3—5]. NECs account for less than 1% of all spinal cord tumors and are more often located at the upper thoracic and cervical levels. According to A. Osborn [3, 4] the world literature described only 35 cases of intracranial NECs in 2004 and 75 cases — in 2010. The most common location of intracranial NECs is the ventral surface of the brainstem (prepontine, premedullary cysts), but they can also be found in the cerebellopontine angle and the great occipital cistern [1—4, 6]. NECs are diagnosed differentially with epidermoid, dermoid, arachnoid and colloid cysts, Rathke’s pouch cysts, and cystic acoustic neuromas [1—4].

Infants and young children with these cysts can present with cardio-pulmonary disorders resulting from cyst location at the thoracic spinal canal or compression of the cervical spinal cord. In older children and adults, the most frequent clinical manifestations are pain or myelopathy resulting from intraspinal lesion. The most frequent symptom in patients with premedullary or prepontine NECs is pain in the occipital-cervical region restricting head motion. Formation of a fistula between NEC cavity and the subarachnoid space can cause meningitis [3—5].

Neuroradiographic images

On MRI, NECs appear as sharply demarcated rounded lesions, they do not exhibit signal intensity alterations with paramagnetic (Fig. 1). The cysts are T1 isointense or hyperintense (Fig. 2), T2 hyperintense (Fig. 3), and hyperintense — in the FLAIR sequence (Fig. 4). The cysts are hypodense or isodense on CT scans and demonstrated no contrast enhancement (Fig. 5). At the site of NECs contacting to the brainstem, a solid component represented by secreting epithelium of the gastrointestinal tract can be detected [1—4, 7, 8].

NECs are diagnosed differentially with epidermoid, dermoid, arachnoid and colloid cysts, Rathke’s pouch cysts, and cystic acoustic neuromas [1—4].

Symptomatic cysts are treated surgically involving evacuation of the cyst content and, if possible, complete removal of the cyst walls [3, 4, 6, 9]. Ventral brainstem cysts are removed through the far-lateral approach [6, 9]. One of the largest surgical series of patients with intracranial NECs including only 7 patients reported evacuation and complete removal of the cyst walls for 3 (42.8%) cases. Four (57.1%) patients had postoperative aseptic meningitis; there were no lethal outcomes [9].

Abbreviations:
ICH — intracranial hypertension
PICA — posterior inferior cerebellar artery
CT — computed tomography
MRI — magnetic resonance imaging
NEC — neurenteric cyst
HCT — helical computed tomography

Intracranial Neurenteric Cysts: Experience of the Burdenko Neurosurgical Institute in the XXIth Century

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Burdenko Neurosurgical Institute, Moscow, Russia, 125047

We present a series of cases of a rare pathology, intracranial neuroenteric cysts, a review of the international literature, and the experience in treating this pathology.

Material and methods. Seven patients with intracranial neuroenteric cysts underwent surgery at the Neurosurgical Institute in the period between 2000 and 2015.

Conclusion. The main and only technique for treatment of intracranial neurenteric cysts is their resection.

Keywords: intracranial neurenteric cyst, skull base surgery.
Another surgical series of 6 patients reported cyst location in the third ventricle, cerebellopontine angle, pre-pontine, premedullary, and arachnoid cisterns [10]. Total resection was performed in 4 cases. Postoperative complications, such as aseptic meningitis, paralysis of the abducent nerve, pseudomeningocele developed in 3 patients [6].

Published postoperative complications include those related to surgical approach (liquorrhea, subcutaneous CSF accumulation, and pseudomeningocele), worsened neurological deficit, and aseptic meningitis. Thus, postoperative complications of NECs are similar to those associated with epidermoid and dermoid cysts, such as aseptic meningitis and resultant aggravation of neurologic symptoms [6, 9].

The prognosis is favorable. Total resection of NEC eliminates the risk of cyst recurrence, but even incomplete excision of the cyst walls neither restores the preoperative cyst volume [6—9].

Analysis of patient series

From 2000 to 2015, 7 patients with intracranial NECs (4 women and 3 men) were operated on at the Burdenko Neurosurgical Institute (Table 1). In 5 cases, NECs were located in the premedullary cistern, in 1 case — in the third ventricle, and in 1 case — in the optic thalamus. The age of patients ranged from 4 to 62 years. The duration of symptoms ranged from 6 months to 39 years. Clinical manifestations of the disease depended on cyst location. The patients with premedullary NECs (patients Nos. 1—5, 7) presented with most frequent neck pain, slight violation of the statics and gait (patients Nos. 1, 3), left without attention by the patients. In a child aged 4 years, NEC caused bulbar disorders: impaired swallowing, hoarse voice (patient No. 4). Symptoms of hydrocephalus located to the optic thalamus (patient No. 2) was the reason for examination and subsequent surgery in a female patient with the third ventricle cyst that caused epileptic seizures and pyramidal insufficiency in the form of contralateral hemiparesis (patient No. 6). The functional state was evaluated on the Karnofsky scale and was

Fig. 1. NEC with the solid component in the FIESTA mode (case No. 5).

Fig. 2. Sagittal and frontal MRI in T1 mode: the cyst is isointense to CSF (case No. 5).
Fig. 3. Axial T2 MRI slices of the brain: cyst is isointense to CSF (case No. 5).

Fig. 4. Preoperative MRI of the brain: premedullary space-occupying lesion with hyperintense contents to CSF in T2, hyperintense in T1 mode, isointense in FLAIR mode, brainstem is deformed in an anterior-posterior direction (case No. 4).
characterized by a sufficiently high level of preoperative functional performance — from 70 to 90 scores.

Neuroimaging data in our series of cases are summarized in Table 2. Thus, on MRI of the brain, the lesion is T1 isointense or hyperintense compared to CSF (Fig. 2), T2 hyperintense to CSF (Figs. 3, 4, 6), in FLAIR sequence the lesion is hyperintense compared to CSF (Fig. 4), non-enhancing signal after intravenous injection of paramagnetic agent (Fig. 6). FIESTA is the best MRI mode to image the cyst walls and the solid component (if present) (Fig. 1).

The lesion is hypodense on brain CT scan (Fig. 5) or isodense to brain tissue, non-enhancing contrast agent; there is no blood flow through the cyst in HCT-perfusion mode (Fig. 5).

Follow-up ranged from 1 to 130 months.

Postoperatively, symptoms regressed in all patients. The female patient with the third ventricle NEC developed postoperative hallucinatory delusional disorder, which regressed a few days later.

Case report

A female patient F, 43 years old (case No. 7). Previous headache intensified over the past 2 months, which became permanent: headache enhanced at the time of hospitalization in the horizontal position and was relieved with oral analgesics. In addition, vertigo appeared in the patient.

On examination the clinical findings were only pain in the cervico-occipital region and episodic vertigo. Focal neurologic, neuroophthalmologic and otorhinologic symptoms were not revealed.

MRI of the brain demonstrated a rounded irregular shaped space-occupying cystic lesion with clear margins at the craniovertebral junction level along the ventral surface of the brainstem on the midline. The cyst was hyperintense to CSF in T1 and isointense in T2. The cyst wall and cyst contents did not exhibit paramagnetic contrast enhancement, the brainstem was compressed and deformed in an anterior-posterior direction, and the size of the lesion was 26×29×17 mm (Fig. 6).

A benign, long-term existing space-occupying lesion was suspected based on the clinical and radiographic features of the disease.

At the “half-sitting” position on the operating table, the patient underwent standard median suboccipital craniectomy. The dura mater was moderately tense; it was dissected by a semicircular incision with the basis to the left side (the cyst was approached from the left side because of an insignificant lateralization). The great occipital cistern was opened (Fig. 7a).

An approach to the ventral surface of the brainstem between the brainstem, the XI—XII cranial nerve roots, the PICA loop and a variety of small perforating vessels was made (Fig. 7b). A white-yellow lesion was found under the medulla oblongata using an endoscope with a viewing angle of 30°. The lesion from the left side contacted with the vertebral artery, the brainstem was deformed in an anterior-posterior direction (Fig. 7c). The capsule was perforated with anatomical tweezers and the contents of viscoelastic consistency, white and yellow in color poured out into the wound (Fig. 7d). The cyst contents were aspirated and the cyst walls were partially excised (Fig. 7e). The remaining cyst walls adhered densely to the surrounding neurovascular structures. Since it was a congenital disease, total resection of the lesion was not performed. Reconstruction of the dura mater was performed with an aponeurosis fragment taken during an approach to the cyst.

On histological examination: the lesion was represented by fine lamellar fragments of a soft-fibrous connective tissue partially lined with prismatic epithelium, which corresponds to the wall of an enterogenous cyst. There were no postoperative complications, the wound healed by primary intention. The control MRI of the brain performed 1 year after the operation showed no signs of neurenteric cyst (Fig. 8).

<table>
<thead>
<tr>
<th>No</th>
<th>Gender</th>
<th>Age</th>
<th>Location</th>
<th>Symptoms</th>
<th>Preoperative KI</th>
<th>ICH</th>
<th>Surgery</th>
<th>Postoperative KI</th>
<th>Biopsy</th>
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<td>1</td>
<td>F</td>
<td>62</td>
<td>Premedullary and preoptine</td>
<td>Brainstem symptoms</td>
<td>70</td>
<td>No</td>
<td>15.11.05</td>
<td>90</td>
<td>Endodermal cyst</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>42</td>
<td>III ventricle</td>
<td>Hypertension</td>
<td>70</td>
<td>No</td>
<td>16.09.09</td>
<td>80</td>
<td>Enterogenous</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>42</td>
<td>Premedullary</td>
<td>Cerebellar symptoms</td>
<td>80</td>
<td>No</td>
<td>29.08.13</td>
<td>90</td>
<td>Endodermal cyst</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>4</td>
<td>Premedullary</td>
<td>VI, IX cranial nerves</td>
<td>80</td>
<td>No</td>
<td>08.06.15</td>
<td>90</td>
<td>Endodermal cyst</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>64</td>
<td>Premedullary</td>
<td>Brainstem symptoms</td>
<td>70</td>
<td>No</td>
<td>03.11.15</td>
<td>80</td>
<td>Enterogenous</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>38</td>
<td>Optic thalamus</td>
<td>Epilepsy, pyramidal insufficiency</td>
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<td>No</td>
<td>25.07.16</td>
<td>70</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
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<td>Premedullary</td>
<td>Headache</td>
<td>90</td>
<td>No</td>
<td>19.09.16</td>
<td>80</td>
<td>–</td>
</tr>
</tbody>
</table>

Footnote. KI — Karnofsky index.
Results

All patients underwent surgical resection of the space-occupying lesion. The choice of a surgical approach depended on cyst location, as well as the need to create additional spaces at the craniovertebral junction level. In 4 out of 5 patients with premedullary NECs, an operation was performed through median suboccipital approach followed by expansive duraplasty, in 1 — through retrosigmoid suboccipital approach. The third ventricle and thalamus NECs were resected through a transcavolosal approach. Due to congenital nature of the disease, the presence of a large number of fusions between the NEC wall and adjacent neurovascular structures, total excision

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>T1</th>
<th>T2</th>
<th>FLAIR</th>
<th>FIESTA</th>
<th>T1 + C*</th>
<th>CT</th>
<th>CT-perfusion</th>
<th>CT + C**</th>
</tr>
</thead>
<tbody>
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<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hypointense</td>
<td>Non-enhancing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>3</td>
<td>F</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Non-enhancing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Non-enhancing</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>—</td>
<td>—</td>
<td>Non-enhancing</td>
<td>Hypodense</td>
<td>Blood flow is not detected</td>
</tr>
</tbody>
</table>

Footnote. * — contrast-enhanced T1 MRI image of the brain with paramagnetic. ** — contrast-enhanced brain CT.

Fig. 5. Preoperative CT of the brain: premedullary isointense lesion to CSF (upper images), blood flow is absent in the lesion in perfusion mode (low images) (case No. 7).
Fig. 6. Preoperative MRI of the brain: premedullary cyst is hyperintense to CSF in FLAIR mode, T2 hyperintense to CSF, hyperintense to CSF in T1 mode with contrast, the signal is not enhanced after introduction of paramagnetic (case No. 7).

of the cyst was almost impossible and in our series only 1 of 7 patients underwent complete cyst resection.

The congenital nature of the disease influences the duration of clinical manifestations, which largely depend on cyst location. Postoperatively, at the time of discharge, the preoperative symptoms almost completely regressed in all patients. Pain syndrome in the cervical-occipital region did not regress immediately and was associated with the selected surgical approach — there was pain at the sites of incisions of soft tissues. Pain regressed 2—3 months after surgery. In all patients, preoperative symptoms almost completely regressed within 6 months.

Postoperatively, 1 patient (patient No. 2, the III ventricle NEC) had hallucinatory delusional disorder, which regressed over several days.

The patient No. 1 developed communicating hydrocephalus 10 years after surgery that was manifested by Hakim—Adams syndrome and required the implantation of ventricular peritoneal shunt. The follow-up period ranged from 1 to 130 months. All patients returned to normal functional performance, retained mental capacity and ability to work.

Discussion

Intracranial NECs are a developmental malformation of the central nervous system with an extremely low occurrence rate. The rate of surgical interventions for this pathology is even lower. Pain is the dominating presenting symptom.

The rarity of the disease and absence of specific symptoms complicates differential diagnosis.

Neuroradiographic symptoms are specific and the diagnosis of NEC on MRI presents no difficulties. MRI can differentiate NECs from other malformations of the central nervous system. Surgical resection is the mainstay and only treatment for NECs.

According to a small number of international published data on this pathology, a surgical intervention is aimed at cyst evacuation and excision of the cyst walls. The choice of approach depends on cyst location and nature. Premedullary NECs are resected through the median suboccipital approach and the far-lateral approach is used less frequently. NEC is a congenital disease, which explains the fusion between the cyst walls and the pia ma-
Fig. 7. Stages of NEC resection (case No. 7).
Description in the text.
Such a situation frequently makes it impossible to completely excise the NEC walls. Moreover, excision can lead to intraoperative brain injury. Meanwhile, NEC evacuation is not a very complicated surgical procedure because consistency of the cysts contents (mucin) allows a surgeon to use a vacuum aspirator for this manipulation. The choice of approach in our case No. 7 was dictated by the related literature. According to the published data, surgery is aimed at cyst evacuation and when possible complete excision of the cyst walls. Thus, the median suboccipital approach combining the advantages of an approach to brainstem structures and minimal injury (compared to the far-lateral approach) to soft tissues and bone structures was chosen for premedullary NECs, which causes a lower intensity of pain syndrome after surgery and reduces the number of complications associated with surgical approach. The insufficient view with a microscope was compensated by using endoscopic equipment, which allowed us to avoid excessive traction of brain structures and quickly visualize NEC on the ventral surface of the brainstem. In our opinion, resection of a space-occupying lesion of this location is advisable to add with decompression of the craniovertebral junction and duraplasty to prevent reoperation in case of recurrent NEC. Postoperatively, the patients were monitored with control MRI and neurological examinations.

**Authors declare no conflict of interest.**

### REFERENCES


Received: 24.04.17
Neurenteric cyst (NEC) is a very rare malformation that develops from separation failure of the notochord and the primitive intestine. They are commonly located in the upper parts of the spinal canal, but intracranial NECs were also revealed.

In this paper, the authors presented the results of surgical treatment of 7 patients with neurenteric cysts of different location. NECs in all these patients caused neurological symptoms, which was the reason for their resection. Most of the patients (4 out of 7) were operated on using the median suboccipital approach due to premedullary cyst location. All patients had a good functional outcome on discharge. A large number of illustrations in the paper give a clear idea of the neuroradiographic features of NECs and of the stages of surgical removal.

There are no significant comments to the paper. The work certainly represents scientific and practical interest and will be useful to neurosurgeons, neurologists, neuroradiologists, and doctors in adjacent areas.

G. Yu. Evzikov (Moscow, Russia)
The histological verification of the central nervous system tumors has some limitations: the morphological data during an analysis of a surgical material can disagree with MRI data. Molecular genetic diagnostics is a new rapidly developing direction in modern medicine. The results of such diagnostics have been reflected in the new WHO classification of CNS tumors. This classification identifies a specific entity that combines astrocytic Grade II—IV tumors — diffuse midline glioma harboring the K27M mutation in the H3F3A gene [1, 2]. Furthermore, the new classification first combined Grade II—IV diffuse gliomas having astrocytic and oligodendroglial histological features in one group based on the presence or absence of the IDH1 gene mutation [2]. Thus, the study of tumor genetics complements histological criteria and enables more correct diagnosis and precise prognosis of the disease.

Taking into account that CNS tumors are characterized by a variety of genetic and epigenetic alterations, the search and identification of genes directly involved in carcinogenesis will improve differential diagnosis and hence produce better treatment outcomes.

The aim of this paper is to perform a comparative molecular genetic study of two types of malignant gliomas: anaplastic astrocytoma and anaplastic oligodendroglioma and to compare the revealed alterations with clinical morphological data. The following molecular-genetic parameters were assessed: point mutations in 132 codon of the IDH1 gene, 5—8 exons of the TP53 gene, and 9, 14, 29 exons of the ATRX gene, 1p19q codeletion, and the methylation status of the MGMT gene.

Material and methods

Specimens of tumor tissue collected from 43 patients diagnosed with “anaplastic astrocytoma” or “anaplastic oligodendroglioma” were analyzed. All patients were operated on at the Burdenko Neurosurgical Institute and then underwent radiation therapy at the Russian Scientific Center of Roentgen Radiology between 2005 and 2015. In 2016, the biopsies were revised and discussed by doctors from the Burdenko Neurosurgical Institute together with colleagues from the Novosibirsk State Medical University and previous histological diagnoses were confirmed. Clinical data on the patients included in the study are presented in Table 1.

Tumor tissue specimens were deparaffinized with xylene and alcohol. DNA was extracted using a rapid sample preparation reagent kit (OOO Isogen Laboratory, Russia).

Codon 132 of the IDH1 gene, 5—8 exons of the TP53 gene, and 9, 14, 29 exons of the ATRX gene were amplified with PCR using the Gen-Pak PCR Core reagent kit (OOO Isogen Laboratory, Russia). The Big Dye Terminator v 3.1 cycle sequencing reagent kit (Applied Biosystems, USA) was used for Sanger’s sequencing of amplicons. Sequencing data were analyzed using the Applied Biosystems 3500 Genetic Analyzer.

The methylation status of the MGMT gene promoter was analyzed using the EpiGenTest-MGMT (ZAO Evrogen, Russia).

The 1p/19q codeletion in histological tumor specimens was assessed using the DNA probes Vysis LSI 1p36/LSI 1q25 and LSI 19q13/19p13 Dual Color Probe kit. The results were analyzed using the criteria recommended by ASCO in 2013.

Results

The TP53 gene mutations were detected in 16 (37%) tumor specimens: 3 mutations were detected in exon 5 — c. 488A>G (p.Tyr163Cys), c.428T>G (p. V143G) and c. 376_378 delTAC (p. 126 delY); 3 mutations were revealed in exon 6 — c. 652 G>A (p. V218M), c. 668 C>T (p. P223L) and c. 652_654 GTG (p. 218delV); 2 muta-
tions were revealed in exon 7 — c. 733G>A (p. G245S) and c. 735G>A(p. G245D); exon 8 carried most of the mutations — 7 mutations c. 817C>T (p. R273C) and one of each of the following mutations c. 810T>G (p. F270L), c. 799C>T (p. R267W), c. 817C>T (p. R273C), c. 843C>G (p. D281E) and c. 844C>T(p. R282W) (Fig. 1).

The IDH1 gene mutations were detected in 25 tumor specimens (58%): the mutation p. R132H (c. G395A) dominated — 22 cases; two specimens carried mutation p. R132S (c. C394A) and 1 case — p. R132G (c. C394G) (Fig. 2).

The ATRX gene mutation was detected in 9 (21%) cases: one specimen had 2 mutations affecting exons 9 and 14: the mutation c. 2648_2649delAA in exon 9 and c. 4261C>T (p. Q1421X) — in exon 14; in addition, exon 9 had the mutation c. 1149_1152delCAG and exon 14 — c. 4276C>T (p. R1426X). Six mutations were detected in exon 29: 2 mutations c.6338_6341delTTAT and one mutation of each of the following с. 6491G>A (p. R2164K), с. 6467A>G (p.Q2156R), с. 6338T>C (p. F2113S), c. 6470 C>G (p. T2157S), and c. 6488A>C (p. Y2163S).

The MGMT gene promoter was methylated in 20 (46%) tumor specimens.

The 1p19q codeletion was detected in 8 (17%) tumor specimens.

Table 2 presents the revealed genetic alterations in the studied genes in patients with anaplastic astrocytoma and anaplastic oligodendroglioma, as well as their distribution depending on the tumor location, gender and age of the examined patients.

**Discussion**

The study included two histological types of malignant diffuse gliomas — anaplastic astrocytoma and anaplastic oligodendroglioma. We did not include cases of mixed oligoastrocytoma because we tried to find clear genetic differences between astrocytic gliomas and oligodendroglial tumors.

**Table 1. Clinical-morphological characterization of the study group of patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study group (n=43), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>19 (44)</td>
</tr>
<tr>
<td>female</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>3—19</td>
<td>2 (5)</td>
</tr>
<tr>
<td>20—29</td>
<td>11 (25,5)</td>
</tr>
<tr>
<td>30—39</td>
<td>1 (2,5)</td>
</tr>
<tr>
<td>40—49</td>
<td>9 (21)</td>
</tr>
<tr>
<td>50—59</td>
<td>7 (16)</td>
</tr>
<tr>
<td>60—67</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Tumor location:</td>
<td></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>23 (54)</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Spinal</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Histological diagnosis:</td>
<td></td>
</tr>
<tr>
<td>anaplastic astrocytoma</td>
<td>29 (67)</td>
</tr>
<tr>
<td>anaplastic oligodendroglioma</td>
<td>14 (33)</td>
</tr>
</tbody>
</table>

Based on our experience, hyperdiagnostics of oligoastrocytomas by morphologists is quite common and varies slightly from one diagnostic center to another. This situation has been reflected in the new WHO classification of CNS tumors, which contains a clear definition: an area of oligodendroglial histology in diffuse astrocytoma well corresponds to the diagnosis of “diffuse astrocytoma” or “anaplastic astrocytoma” when 1p19q codeletion is absent [2]. In addition, some researchers [3] based on molecular features of diffuse gliomas tend to believe that a nosological unit of “oligoastrocytoma” does not exist.
and the reactive astrocytic component is taken as astrocytic part of oligoastrocytoma.

An analysis of the mutation status, epigenetic events and quantitative changes in chromosomes in 29 anaplastic astrocytomas and 14 anaplastic oligodendrogliomas showed a clear association of these tumors with age, location and the detected alterations. Note that the alterations under study are absent in tumors of non-hemispheric location, although the literature [2, 4] describes single cases of malignant IDH1-mutant diffuse gliomas in the cerebellum. Most of the genetic alterations we detected occurred in tumors in young people aged 30—40 years, mainly in the frontal lobe. Furthermore, several concurrent genetic alterations in one tumor specimens were frequently observed. There were some differences in the incidence of genetic abnormalities in anaplastic astrocytomas and anaplastic oligodendrogliomas: the IDH1 gene mutations were more frequent in oligodendroglial tumors (64% versus 55% in anaplastic astrocytomas); in this case patients with mutant tumors were much older: mutations in anaplastic oligodendrogliomas could be detected in patients older than 50—60 years, while the age of the patients with IDH1-mutant anaplastic astrocytomas was younger than 50 years. The MGMT gene methylation was also more common in anaplastic oligodendrogliomas (71% compared to 34% in anaplastic astrocytomas). However, the TP53 gene mutation was more common in anaplastic astrocytomas (41%) and in only about 1/3 (28%) of all anaplastic oligodendrogliomas.

Significant molecular differences between anaplastic astrocytomas and anaplastic oligodendrogliomas were also observed: 1p19q codeletion was identified in oligodendrogial tumors, while the ATRX gene mutation (with one exception) — only in anaplastic astrocytomas. The only unexplained case of concurrent ATRX mutation and 1p19q codeletion was revealed in anaplastic oligodendroglioma, which occurred in the temporal lobe of a 66-year-old woman with a long preoperative period, who was monitored for an intracranial tumor over 2 years. In addition, the IDH1 gene mutation and methylated MGMT gene were revealed in the tumor of this patient. We revised histological specimens for the presence of the astrocytic component and confirmed the diagnosis of “anaplastic oligodendroglioma” since we did not detect histological signs of astrocytic differentiation in the material. We cannot explain at present combination of the ATRX mutation and 1p19q codeletion in the tumor genome, which may be an artifact or it may be a tumor having a histological architecture similar to the diagnosis of “anaplastic oligodendroglioma”, but with the molecular features of the existing oligoastrocytoma?

Except for the above case, our data fully agree with data of other authors [5—10]. These authors recommend immunohistochemical study of the mutant ATRX protein with commercially available antibodies (HPA001906, Sigma Aldrich; anti-human ATRX antibody ab97508, Abcam in dilution 1:800) as a simple and reliable method both to assess the mutational status of the gene and to distinguish oligodendroglial tumors from astrocytomas [5, 6, 11—15]; this method is more convenient than meticulous assay of the ATRX gene with mutations affecting multiple exons.

Immunohistochemical study can also be recommended as the first stage in search for the IDH1 gene mutation. Previously, we recommended commercially available Anti-Human IDH1 R132H astrocytoma and oligodendroglioma tumor cell marker mouse monoclonal antibody manufactured by Dianova, clone H09 in dilution 1:20 [16] for this assay, which can perfectly detect the IDH1 gene mutation — R132H accounting for approximately 90% of the total number of the IDH1 gene mutations. The remaining 10% of the IDH1 gene mutations are detected by direct sequencing of codon 132 of the IDH1 gene: in our study, a substitution of arginine in po-

Fig. 2. An analysis of mutations in the 132 codon of the IDH1 gene using Sanger’s sequencing.

a — detection of the mutation p. R132H (c. G395A) (double peak is indicated with an arrow), b — variant of norm.
sition 132 by histidine (R132H) was detected in 88%; mutations with other substitutions — arginine in position 132 by serine (R132S) and arginine in position 132 by glycine (R132G) were detected in 12% of cases. The WHO recommendations advocate assaying the codon 172 of the IDH2 gene [2].

The TP53 gene mutations can only be detected by sequencing. The immunohistochemical nuclear expression of TP53 has unclear correlation with the detection of the TP53 gene mutation [9]. Methyltion-specific polymerase chain reaction (MSP) and pyrosequencing of bisulphite modified DNA requiring 0.5—1 μg of DNA are the preferred methods to assess the methylation status of the MGMT gene promoter and fluorescence in situ hybridization and microsatellite analysis for loss of heterozygosity are reliable methods to assess the 1p19q codeletion [17].

Conclusion

The assay for the ATRX gene mutation and 1p19q codeletion using Vysis (Abbott) or Kreatech probes is recommended in case of histological picture of mixed oligoastrocytoma (anaplastic oligoastrocytoma) in order to clarify the histological diagnosis. The assessment of the IDH1 and ATRX gene mutation status is better to start with immunohistochemical study. When there is no IDH1 immunoreactivity, it is advisable to assess the mutation in this gene in codon 132 by direct sequencing to detect point mutations differing from R132H. It is also necessary to investigate codon 172 of the IDH2 gene. The diagnostics algorithm of hemispheric malignant gliomas should include the assay of the BRAF and H3F3A gene mutation status, which will certainly improve the quality of molecular histological diagnosis of tumors and further treatment with targeted drugs [18, 19]. The papers [17, 20] recommend assessing the methylation status of the MGMT gene promoter in malignant hemispheric tumors in adults, when possible. Probably, in the near future the list of genes to be assessed in diffuse gliomas can be added with TERT, CIC and FUBP1 genes, whose diagnostic and prognostic value is currently studied [10, 11, 13, 15, 18, 20—24].

Authors declare no conflict of interest.
This paper is focused on an urgent issue in modern oncology — differential diagnosis of brain tumors. The authors analyzed the molecular genetic features of anaplastic astrocytomas and oligodendrogliomas in a series of 43 cases. The analysis included assay for point mutations in codon 132 of the $IDH1$ gene, point mutations in exons 5—8 of the $TP53$ gene, point mutations in 9, 14 and 29 exons of the $ATRX$ gene, 1p19q codeletion, and the methylation status of the $MGMT$ gene. Based on very convincing data of this study, despite collected on a small sample, the authors recommended molecular genetic analysis using these markers for diagnosis verification, along with analysis of histological and immunohistochemical criteria of the tumor. According to the authors, certain corrections can be made during further research mainly due to the inclusion of other molecular genetic markers, whose diagnostic and prognostic value is extensively studied.

Modern methods were used in the study such as highly sensitive research methods (PCR, Sanger sequencing), which are currently available in health care laboratories.

The text of the article is written in a good scientific language, illustrated with two tables and two figures. The results are clear and understandable. The Discussion section is well presented, where the authors describe their vision of the issue on complicated diagnostics of brain tumors. The list of references is sufficient and includes 23 papers; all the citations have been published over the past 5 years.

The presented paper is definitely relevant and presents great scientific and practical significance.

A.Kh. Bekyashev (Moscow, Russia)
Cerebrospinal Fluid Rhinorrhea in Primary Treatment of Large and Giant Prolactinomas with Dopamine Agonists


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At present, pharmacological therapy of prolactinomas with dopamine agonists (DAs) is considered the treatment of choice. In most cases, giant prolactinomas respond to treatment with dopamine agonists and decrease in size during the first months of the treatment. One of the rare but dangerous complications of conservative treatment of prolactinomas with invasive growth is cerebrospinal fluid rhinorrhea.

**Material and methods.** We present a retrospective analysis of 15 patients with macroprolactinomas who underwent surgery for cerebrospinal fluid rhinorrhea developed due to primary therapy with dopamine agonists at the Burdenko Neurosurgical Institute (BNI) in the period between 2005 and 2015. All patients had large (36—59 mm) and giant tumors (≥60 mm) (according to the classification adopted at the BNI). When cerebrospinal fluid rhinorrhea was detected, patients were hospitalized to the BNI for examination, detection of a CSF fistula, reconstruction of a defect, and resection (if possible) of the tumor.

**Results.** In the period between 2005 and 2015, 15 patients (8 males and 7 females) with prolactinomas of a large and giant size at the onset of conservative therapy underwent surgery for cerebrospinal fluid rhinorrhea at the BNI. All patients underwent transnasal reconstruction of a skull base defect, with 13 out of 15 patients undergoing simultaneous resection of the tumor. After tumor resection, reconstruction was performed using auto-fat, fascia, and glue (in 8 cases). In the remaining cases, apart from auto-fat, fascia, and glue, a mucoperiosteal flap and auto-bone were used. Fourteen patients were follow-up. In 13 cases, there was no relapse of cerebrospinal fluid rhinorrhea after skull base reconstruction. In 1 case, there was a relapse of cerebrospinal fluid rhinorrhea.

**Conclusion.** Conservative treatment of patients with giant prolactinomas should be performed under regular control of ENT doctors and neurosurgeons for timely detection and surgical treatment of cerebrospinal fluid rhinorrhea.

**Keywords:** prolactinomas, prolactin-secreting pituitary adenomas, cerebrospinal fluid rhinorrhea, dopamine agonists, hyperprolactinemia.
Oculomotor disorders in form of complete external ophthalmoplegia on the left eye were noted in one patient. One presented with extrapyramidal disorders manifested with reflexes of oral automatism, pseudobulbar syndrome, and mild secondary oral–brainstem symptoms in the form of coordination and trunk ataxia due to brainstem compression by the tumor (Fig. 1).

According to the protocol adopted an the BNI [8, 21], all patients diagnosed with macroprolactinoma undergo a course of treatment with cabergoline at a dose of 0.5 mg/week with dose correction under the control of PRL level every month. Control MRI study is performed in 3–6 months after initiation of treatment or earlier when CSF rhinorrhea appears.

When CSF rhinorrhea is detected, the patient is hospitalized to the BNI for examination, detection of CSF fistula, reconstruction of the defect and tumor resection (if possible).

Results

From 2005 to 2015, 15 patients (8 males, 7 females) with large and giant prolactinomas were operated on at the BNI for CSF rhinorrhea (Table). The average age of patients was 46.6 years (24—62 years). The mean (median) PRL blood plasma level before onset of DAs therapy was 87,000 (9,969—2,218,283 IU/L). Median period between initiation of therapy and CSF rhinorrhea presentation was 1 month (5 days — 6 years 4 months). Tumor mass significantly reduced on MRI in all patients due to cabergoline treatment. By the time of CSF rhinorrhea presentation was 3,741 (58—30,911 IU/L).

The intensity of nasal liquorheaa varied from single drops with tilting the head (or in the morning) to permanent profuse nasal discharge. Two patients developed meningitis secondary to CSF rhinorrhea, which persisted after discontinuation of DAs.

All patients underwent transnasal endoscopic skull base defect repair, with simultaneous tumor removal in 13 out of 15 cases.

Taking into account the positive effect of cabergoline and tumor invasiveness, total tumor removal was not the main purpose of surgical intervention, and therefore the tumor was resected only partially in 13 patients; the tumor was not resected in 2 cases due to significant tumor involution on MRI and the tumor remnant was detected only in the cavernous sinus. In 14 patients CSF fistula was located in an erosion of the sella floor, and in one case the defect was not clearly detected. In 8 cases, the defect was repaired using auto-fat, fascia and glue. In 7 cases, apart from auto-fat, fascia and glue, mucoperiosteal flap and auto-bone were used according to the standard procedure adopted at the BNI [22, 23]. In all cases, intraoperative external lumbar drainage was installed and removed 5—6 days after surgery.

Fourteen patients were followed-up. The mean follow-up period was 32 months (from 3 to 103 months). Postoperatively, all patients continued to receive cabergoline. In 13 of 14 cases, there was no tumor growth or the tumor decreased in size with further decline in PRL (or its normalization). In one case, in a female patient aged 62 years old with a primary positive effect from cabergoline therapy in the form of decrease in PRL levels from 9,969 to 1,945 IU/L after surgery (partial tumor resection and reconstruction of CSF fistula), tumor growth continued, vision function deteriorated to OS amaurosis and PRL increased to 35,618 IU/L in 3 years after appli-
cation of maximum cabergoline doses (3.5 mg/week). The clinical situation was defined as secondary resistance to cabergoline. The patient underwent repeated endoscopic endonasal partial tumor removal and stereotactic radiotherapy was recommended.

In 13 cases, there was no recurrent CSF rhinorrhea after skull base repair. In one case, a 48-year-old female patient with giant prolactinoma had an episode of CSF rhinorrhea 2.5 years after surgery. As the patient refused reoperation, cabergoline dose was reduced to 0.125 mg/week resulting in cessation of CSF rhinorrhea. The tumor size on MRI did not increase, but hyperprolactinemia persisted with 143,500 IU/L. Test repeated cabergoline dose increase to 0.25 mg/week caused recurrent CSF rhinorrhea.

**Case report**

Fig. 2 presents MRI scans of the brain (Fig. 2a, b) of a female patient aged 44 years with a giant pituitary tumor extending to the skull base structures and the nasopharynx (the level of PRL was 545,000 IU/L). The treatment (Fig. 2c, d) reduced significantly tumor size after 3 weeks and profuse CSF rhinorrhea occurred (PRL 6,300 IU/L). The patient underwent endonasal endoscopic surgery — resection of endosellar tumor remnant and skull base defect repair using auto-fat, a bone fragment of the nasal septum, hemostatic sponges and glue. Postoperatively, PRL fell to 3,412 IU/L. Cabergoline therapy was resumed at a dose of 0.5 mg/week; 1 month after surgery, the PRL level
### Demographic, clinical and follow-up data of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Tumor size</th>
<th>Location</th>
<th>PRL level prior to treatment with DAs, IU/L</th>
<th>PRL level in CSF rhinorrhea, IU/L</th>
<th>Time from initiation of treatment with DAs to CSF rhinorrhea presentation, days</th>
<th>Complications (resulting from CSF rhinorrhea)</th>
<th>Clinical symptoms prior to use of DAs</th>
<th>Clinical symptoms after surgery (PD — positive dynamics)</th>
<th>Follow-up (CG — continued growth)</th>
<th>PRL level, IU/L after treatment</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>Giant</td>
<td>Endosupralateral (S)</td>
<td>228,260</td>
<td>5384</td>
<td>120</td>
<td>No</td>
<td>Chiasmatic syndrome, erectile dysfunction</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>55</td>
<td>Large</td>
<td>Endosupralateral (S)</td>
<td>49,672</td>
<td>19,716.0</td>
<td>14</td>
<td>No</td>
<td>Cephalgic disorder</td>
<td>No</td>
<td>75 months no CG</td>
<td>935</td>
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<td>3</td>
<td>F</td>
<td>56</td>
<td>Large</td>
<td>Endosupra</td>
<td>30,952</td>
<td>1,431</td>
<td>21</td>
<td>No</td>
<td>Cephalgic disorder</td>
<td>No</td>
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<td>374</td>
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<td>F</td>
<td>35</td>
<td>Giant</td>
<td>Endosupralateral (S, D)</td>
<td>2,218,283</td>
<td>758</td>
<td>2,280</td>
<td>No</td>
<td>Cephalgic disorder</td>
<td>No</td>
<td>11 months no CG</td>
<td>1,400</td>
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<td>57</td>
<td>Large</td>
<td>Endosupra</td>
<td>17,265.6</td>
<td>1,262.8</td>
<td>120</td>
<td>No</td>
<td>N/A</td>
<td>No</td>
<td>5 months no CG</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>27</td>
<td>Giant</td>
<td>Endosupra</td>
<td>150,712</td>
<td>30,911</td>
<td>30</td>
<td>Meningitis</td>
<td>Chiasmatic syndrome, cephalgic disorder</td>
<td>No</td>
<td>0 months no CG</td>
<td>4,026</td>
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<tr>
<td>7</td>
<td>M</td>
<td>56</td>
<td>Giant</td>
<td>Infrasupra</td>
<td>58,000</td>
<td>58</td>
<td>210</td>
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<td>Chiasmatic syndrome, cephalgic disorder, insignificant, convulsive attacks</td>
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<tr>
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<td>Large</td>
<td>Endosupra</td>
<td>87,000</td>
<td>638</td>
<td>30</td>
<td>No</td>
<td>Chiasmatic syndrome</td>
<td>No</td>
<td>17 months no CG</td>
<td>310</td>
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<td>F</td>
<td>48</td>
<td>Giant</td>
<td>Endosupralateral</td>
<td>198,891</td>
<td>29,201</td>
<td>120</td>
<td>Meningitis</td>
<td>Chiasmatic syndrome</td>
<td>Chiasmatic syndrome 36 months no CG</td>
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<tr>
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<td>Giant</td>
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<td>15,500</td>
<td>2,692</td>
<td>150</td>
<td>No</td>
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<td>Endosupra</td>
<td>140,370</td>
<td>9,833</td>
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<td>267</td>
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<tr>
<td>12</td>
<td>M</td>
<td>52</td>
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<td>Endosupra</td>
<td>8,418.6</td>
<td>5,561</td>
<td>14</td>
<td>No</td>
<td>Cephalgic disorder</td>
<td>No</td>
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<td>1,744</td>
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<td>Giant</td>
<td>Endosupra</td>
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<td>3,741</td>
<td>5</td>
<td>No</td>
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<td>Chiasmatic syndrome 17 months no CG</td>
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<tr>
<td>14</td>
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<td>62</td>
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<td>Endosupra</td>
<td>9,969</td>
<td>1,945</td>
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<td>Endosupra</td>
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<td>6363.4</td>
<td>30</td>
<td>No</td>
<td>Cephalgic disorder, extrapyramidal disorders, brainstem symptoms</td>
<td>No</td>
<td>103 months no CG</td>
<td>261</td>
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</table>
dropped to 971 IU/L and completely normalized after another 2 months (110 IU/L). After 2 years from the onset of treatment, the patient continues to take cabergoline at a dose of 0.25 mg/week, normal prolactinemia remains (250—276 IU/L). On MRI in 18 months after surgery: secondary empty sella turcica occurred; there were post-operative changes and reconstruction materials in the cavity of the sphenoid sinus (Fig. 2e, f).

Discussion

CSF rhinorrhea is clear leakage of CSF resulting from fistula formation in the skull base structures [24]. The standard for detection of CSF rhinorrhea adopted at the BNI includes: examination by ENT doctor, presence of glucose in the leaked fluid and CT-cisternography. Another test is β2-transferrin assessment in leaked CSF. It is a more accurate diagnostic option, with higher sensitivity (~100%) and specificity (~95%) compared to standard glucose measurement [24, 25]. This test can differentiate CSF rhinorrhea and allergic rhinitis [12]. Unfortunately, we have no experience of its use.

CSF rhinorrhea can be caused by trauma, neurosurgery, tumors, inflammation and congenital defects. In our case, we consider CSF rhinorrhea as a complication of conservative therapy of macroadenomas using DAs [15, 25].

Macroadenomas can be the only tumors accompanied by CSF rhinorrhea due to conservative therapy [19, 26—36]. CSF rhinorrhea is caused by prolactinoma shrinkage and unplugging of an fistula in the dura mater and skull base bone erosion [27, 36].

The complications of CSF rhinorrhea can be meningitis, pneumocephalus and intracranial abscesses; untreated these have a mortality of 25—50% [37].

Despite the risk of meningitis in patients with CSF rhinorrhea due to conservative treatment of prolactinomas, prophylactic administration of antibiotics remains controversial [29, 38].

Although the literature [15] describes sporadic cases of spontaneous CSF rhinorrhea resolution in such patients, we advocate for surgical management. We believe that the optimal treatment is surgical reconstruction of CSF fistula with possible simultaneous tumor resection; however, infiltration of the skull base bones and dura mater by the tumor can hamper total resection [16]. An insignificant liquorhea can be managed by repair of the skull base defect with glue and/or artificial dura mater [9]. In case of more severe liquorhea, autologous fat, fascia and mucoperiosteal flap are recommended for reconstructive surgery [39]. When surgical treatment is contraindicated, conservative therapy can be stopped for some time and external lumbar drainage can be installed [16].

Median period of CSF rhinorrhea presentation in our study was 1 month after imitation of cabergoline treatment due to rapid tumor shrinkage in patients with high sensitivity to cabergoline. However, in one case we observed a female patient with delayed presentation of CSF rhinorrhea — 76 months after imitation of treatment.

We advocate initiating treatment of macroadenomas with a low dose of cabergoline regardless of tumor size and PRL level in order to prevent rapid tumor size reduction and CSF rhinorrhea. It is advisable to warn the patients for occurrence of such complication when that are started on DAs treatment for large and giant invasive prolactinomas and the patients should be urgently referred to ENT doctor and neurosurgeon when CSF rhinorrhea is suspected.

Authors declare no conflict of interest.

REFERENCES


This paper focuses on the conservative treatment of large and giant prolactin-secreting pituitary adenomas with dopamine agonists. Conservative treatment of these tumors causes CSF rhinorrhea due to shrinkage of the tumor that plugs a skull base defect. Such shrinkage or involution of a tumor mass exposes a CSF fistula between tumor eroded areas of the chiasmatic cistern, sella turcica and the sphenoid sinus.

Fifteen patients who underwent surgery for CSF rhinorrhea with skull base repair were monitored. Fourteen patients were followed-up; tumor growth was absent in 13 of the 14 cases or there was a decrease in tumor size and subsequent decline in PRL level (or its normalization). This work is of great practical importance, since it gives the basic algorithm for management of patients with large and giant prolactinomas, the tactics of conservative treatment and, if necessary, surgical treatment for CSF rhinorrhea. Tests for differential diagnosis of CSF rhinorrhea and other nasal CSF discharge conditions are described in detail. The main stages of surgical skull base reconstruction using autologous and synthetic materials are listed.

This retrospective study analyzes medical records of patients with giant and large prolactinomas, surgical outcomes and follow-up.

All cases are analyzed adequately; case report and the treatment process are described quite fully. The results of the study are significant; the conclusions are justified by the data collected during study.

The literature list comprises 39 references, including 6 Russian and 33 foreign citations. Early papers and the most recent publications have been reviewed, indicating interest to this issue in modern medicine.

The abstract is brief, but fully describes the content of the paper and is well structured. The translation into English is exact to the Russian abstract.

In general, the work is of interest both for a narrow circle of neurosurgeons dealing with this issue and for a wide range of endocrinologists, therapists, neurologists and otolaryngologists managing patients with prolactinomas.

A.Yu. Grigor’ev (Moscow, Russia)
Transient Enlargement of Craniopharyngioma Cysts after Stereotactic Radiotherapy and Radiosurgery


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Stereotactic radiotherapy/radiosurgery (RT/RS) is an effective technique for treating craniopharyngiomas (CPs). However, enlargement of the cystic part of the tumor occurs in some cases after irradiation. The enlargement may be transient and not require treatment or be a true relapse requiring treatment.

Material and methods. In this study, we performed a retrospective analysis of 79 pediatric patients who underwent stereotactic RT or RS after resection of craniopharyngioma.

Results. Five-year relapse-free survival after complex treatment of CP was 86%. In the early period after irradiation, 3.5 months (2.7—9.4) on average, enlargement of the cystic component of the tumor was detected in 10 (12.7%) patients; in 9 (11.4%) of them, the enlargement was transient and did not require treatment; in one case, the patient underwent surgery due to reduced visual acuity. In 8 (10.1%) patients, an increase in the residual tumor (a solid component of the tumor in 2 cases and a cystic component of the tumor in 6 cases) occurred in the long-term period after irradiation — after 26.3 months (16.6—48.9) and did not decrease during follow-up in none of the cases, i.e. continued growth of the tumor was diagnosed. A statistical analysis revealed that differences in the terms of transient enlargement and true continued growth were statistically significant (p<0.01).

Conclusion. Enlargement of a craniopharyngioma cyst in the early period (up to 1 year) after RT/RS is usually transient and does not require surgical treatment (except cases where worsening of neurological symptoms occurs, or occlusive hydrocephalus develops).

Keywords: craniopharyngioma, cyst, transient enlargement, continued growth, radiotherapy, radiosurgery.

Abbreviations:
RFS — recurrence-free survival
CP — craniopharyngioma
RT — radiotherapy
MRI — magnetic resonance imaging
OS — overall survival
RS — radiosurgery
TBD — total boost dose
IMRT — Intensity modulated radiotherapy

CPs are rare (1.3 cases per year per 1 million population [1]) benign epithelial tumors of dysembryogenetic origin most often located in the chiasm-sellar or third ventricle regions. They grow from remnants of the Rathke’s pouch. There are two morbidity peaks: in childhood and in the sixth decade of life [1].

The current treatment of choice for CPs is surgical removal [2, 3]. However, even after total resection, recurrent tumors occur in 10—30% [4—6]. In addition, the features of the growth of these tumors often limit complete resection [3, 7, 8]. Incomplete resection raises the risk of continued growth [9], comprising up to 50—70% according to various data [10, 11] and even up to 85% [5, 12, 13].

The use of RT or RS can significantly enlarge RFS after subtotal or partial CP resection [14—18]. Thus, in a meta-analysis conducted by J. Clark et al. [18] in 2013 (109 papers, 531 case reports), the 5-year RFS after total tumor removal was 77%, after incomplete removal without RT/RS — only 43%, and with complex treatment — 73%. Hence, based on published data, stereotactic RT/RS is an effective method in the complex treatment of CPs.

The vast majority of pediatric CPs have adamantinolike histology subtype and hence they contain both solid and cystic component. While RT commonly reduces or stabilizes the solid tumor component, cyst dimensions can increase during and after RT [19, 20]. Traditionally, enlargement of the residual tumor is regarded as continued growth, but in some cases CP cyst may temporarily increase in size post-radiation with eventual spontaneous shrinkage [20] without further intervention. Although in most cases such an expansion is asymptomatic, in some patients it can aggravate neurologic symptoms requiring surgical management. Therefore, differential diagnosis between transient cyst enlargement after RT/RS and true continued growth is extremely important.

We conducted a retrospective study and identified criteria for differential diagnosis between transient en-
largement of CP cysts and true continued tumor growth after stereotactic RT/RS.

**Material and methods**

Since 2005, only stereotactic RT and RS have been used as part of combined treatment for CPs at the Burdenko Neurosurgical Institute (the former Moscow Institute of Neurosurgery). From the beginning of 2005 to 13 October 2016, i.e., over a little more than a decade, a total of 706 operations for CPs were performed on 455 pediatric patients (under 18 years of age at the time of surgery). Indications for radiation treatment were formulated together by a radiologist, neurosurgeon, endocrinologist and neuroophthalmologist. After surgery, 159 (34.9%) patients received stereotactic RT/RS. Seven patients underwent radiation treatment 2 or more times; during the analyzed period a total of 168 courses of stereotactic RT and RS for CPs in children were conducted. RT was performed using the Primus, Novalis and CyberKnife instrumentation, RS — using the GammaKnife machine. Standard fractionation (1.8—2.2 Gy per fraction) and hypofractionation modes (more than 2.2 Gy per fraction) were used. In standard fractionation RT (n=31), the mean total boost dose (TBD) was 54±1.5 Gy in 30 fractions (27—33); in hypofractionation (n=33) — 25±2.4 Gy in 5 fractions (in 2 cases — 3 fractions). The median boost dose for RS (n=15) was 16 Gy (10—32).

Eighty patients who received first radiation treatment were available for full follow-up; they had pre- and postoperative MRI scans, pre- and post-radiation MRI scans, and all subsequent images stored on electronic media in the DICOM format. One patient was excluded from the analysis due to ectopic recurrence (implantation metastasis) 2 years after removal of endosuprasellar CP and RS, but there was no continued growth in the site of primary location of the tumor. Thus, 79 pediatric patients were analyzed. Their medical records and available MRI scans were assessed. These patients were operated on through transtemporal (n=42) and transnasal (n=25) approaches for tumor removal or cyst evacuation; an Ommaya reservoir was installed in 12 patients. The surgical extent varied from total (n=4) and subtotal (n=19) to partial (n=27) resection of the tumor or cyst evacuation (n=17).

The first tomography after RT was performed approximately in 2 months (from 1 to 5) after irradiation, then every 3—6 months during the year and then once a year. Enlargement of the cystic component of CP after RT/RS followed by gradual decrease on follow-up MRI was regarded as transient expansion. In other cases, roentgen enlargement of residual tumor (both solid and cystic components) was regarded as true continued growth, even if it was asymptomatic. Repeated growth of the tumor after total removal was regarded as recurrence.

A residual tumor expanded post-radiation in 18 patients, in 16 of them due to the cystic component and 2 — due to the solid component. Volumetric analysis for assessing tumor response to irradiation during follow-up was performed using the Osirix MD software (Pixmeo Sarl, Switzerland). The outline of the tumor was traced manually on each slice and the tumor volume was automatically calculated. The surveillance time was counted from the date of RT/RS initiation. RFS and OS were estimated using the Kaplan—Meier estimator. Statistical analysis was performed using the Statistica software version 8.0 (StatSoft, Inc., 2007, USA). All the sets of random variables were tested for compliance with the normal distribution using the Kolmogorov—Smirnov test. The mean values and standard deviation are indicated for normal distribution. Median, the maximum and minimum values are given for non-normal distributions. Difference significance for non-normal variables was estimated using the nonparametric Mann—Whitney test. Difference significance between survival curves was estimated using the log-rank test.

**Results**

The mean age of patients at the time of RS or the beginning of RT was 11.4±4.7 years. The number of females and males was approximately similar: 47 (59.5%) boys and 32 (40.5%) girls.

The median length of follow-up was 45.1 months (from 1 to 121). The 5-year RFS after complex treatment of CPs was 86% (Fig. 1). Fifty nine (74.7%) patients received RT or RS for residual tumor soon after subtotal or partial resection of CP (approximately in 2.5 months) and 20 (25.3%) — when there was recurrent or continued growth. The 5-year RFS in these groups was 83 and 93%, respectively, the differences were insignificant (log-rank test: p>0.05).

Control MRI scans after irradiation revealed an enlargement of residual CP in 18 patients. Ten of them had an increase in the cystic component of the tumor in the early post-radiation periods— approximately in 3.5 months (2.7—9.4 months). Two of these patients received standard fractionation RT, 7 — hypofractionated RT, and 1 — received RS. One of the patients in this group, with cyst enlargement in 4 months after irradiation, had a sharp decline in acuity and required surgical treatment (case report 3). This patient was not analyzed for cyst volume in dynamics. In the remaining 9 (11.4%) cases, the cyst reached its maximum size approximately in 4.7 months (2.9—12.4 months) after RT/RS and began to gradually shrink without any treatment approximately in 8.5 months (6.1—16.4 months), i.e. cyst enlargement was transient. There was no re-accumulation of the cyst fluid in any of these patients. The median volume of cyst before RT/RS was 0.36 cm³ (0.07 to 6.2), the maximum volume — 4.02 cm³ (1.3 to 39.3), and the minimum (after cyst reduction) — 0.05 cm³ (0 to 2.3). In transient enlargement, cyst volume increased approximately by 6.5 times (1.4 to 294.6).
Eight (10.1%) patients were diagnosed with continued growth: 6 — due to cystic enlargement and 2 — due to enlargement of the solid component. In this group, cyst volume increased in later periods (median 26.3 months, from 16.6 to 48.9) and did not regress in follow-up. Thus, they were diagnosed with true continued growth of CP. Of these patients, 2 underwent standard fractionation, 5 — hypofractionated RT, and 1 patient received RS.

A statistical analysis revealed that differences in the periods of transient CP cyst enlargement and true continued growth after stereotactic RT/RS were significant (Mann—Whitney; \( p<0.01 \)) (Fig. 2).

The 5-years OS after irradiation in the analyzed group of 79 patients was 93%. Two patients died for reasons not related to tumor progression (one — from esophageal vein bleeding due to liver cirrhosis; another — from septic complication of pneumonia). The cause of death of the other two patients is unknown, but they did not have recurrent CP at the time of the last follow-up.

Case report 1
Patient E. with endosuprasellar CP (Fig. 3a) was operated on at the age of 4 years. Endoscopic endonasal transphenoidal evacuation of the tumor cyst was performed (Fig. 3b). After a month, the patient underwent hypofractionated RT — in 5 fractions, TBD was 27.5 Gy. In 3.5 months, the cyst almost reformed its original size (Fig. 3c). Since there was no neurologic aggravation and visual functions were stable, it was decided to monitor the cyst. In 9.5 months post-radiation, the cyst significantly shrank (Fig. 3, d) and during the next 2 years there was no continued growth.

Case report 2
Patient K., 12 years old (Fig. 4a) underwent transcranial partial removal of CP. Postoperative MRI visualized residual CP, which included 3 cysts (Fig. 4b). A month after tumor resection, standard fractionation RT (TBD — 54 Gy in 30 fractions) was performed, and a small increase in one of the cysts and a decrease in the other two were revealed in 2.7 months after RT. It was decided to continue on surveillance. After another 3.5 months, the cyst reached a large size (Fig. 4c) and the child developed symptomatic epilepsy — epileptic seizure with a sensation of unpleasant odor. Anticonvulsant therapy at the place of residence was not prescribed, and by the time of admission to the Burdenko Neurosurgical Institute — a month after the MRI — attacks ceased. With spontaneous regression of paroxysmal symptoms, repeat brain MRI was performed that showed tumor volume reduction by 4 times (Fig. 4d). During the next 3 years (up to the present) the patient was followed at the Burdenko Neurosurgical Institute, tumor dimensions remain stable on control MRI.

Case report 3
Patient F. underwent transcranial resection of endosuprasellar craniopharyngioma at the age of 3 years. After 2 years, the patient underwent multi-beam (94) hypofractionated RT in 5 fractions of 5 Gy with TBD of 25 Gy
Acuity on both eyes was 1.0. In 4 months after irradiation, MRI revealed an increase in the cystic component of the tumor (Fig. 5b) accompanied by a sharp decrease in acuity on the right eye to 0.02; the child was reoperated. Within 6.5 years after surgery, no recurrence was detected. This patient was excluded from the analysis.

**Discussion and conclusions**

Treatment of patients with CPs is a complex and multidisciplinary task. In some cases, complete tumor resection is impossible or unwarranted due to the risk of injury to eloquent structures. In such cases, stereotactic RT/RS allow one to achieve indicators of RFS comparable with the outcomes after total tumor resection. The indicators of effectiveness of stereotactic RT/RS in this study: the recurrence rate (10.1%) and 5-year RFS after surgical treatment and irradiation (86%) are comparable with the published data and confirm the efficacy of this treatment for CPs.

The literature describes cases of transient increase of CP cysts after irradiation. As early as in 1989, L. Constine et al. [22] reported on post-radiation cyst enlargement in 4 of 11 patients followed by decrease in size in 3 of 4 showing that not all such patients require an intervention. In 1993, B. Rajan et al. [23] reported enlargement of CP during irradiation in 11 (6.4%) of 173 patients.

Traditionally, enlargement of residual tumor is regarded as a disease progression, requiring active treatment (most often surgery). Since post-radiation expansion of CP cysts is not always true continued growth of the tumor, it is important to create an algorithm for managing such patients.

In 2012, Z. Shi et al. [20] prospectively reviewed the occurrence and natural course of this response. The analysis included 21 patients (median age was 8.2 years), who received standard fractionation RT (median TBD — 54 Gy with 1.8—2.0 Gy/day). The mean follow-up was 3.5 years. In a volumetric analysis of the tumor response to RT, 52.4% of subjects had transient cystic enlargement soon after RT (approximately in 1.5 months), which could remain for 5—6 months, with eventual shrinkage. Ten of these subjects had asymptomatic enlargement and one had neurologic symptoms requiring surgical cyst evacuation.

In our study involving more patients (79 patients), the rate of this response was significantly lower — only 11.4%. In addition, probably, due to a larger sample, our study showed a larger increase in cyst volume — approximately by 6.5 times, i.e. by 550% compared to 150% in paper by Z. Shi [20]. In our work, we also compared the periods of detecting transient cyst expansion and continued tumor growth and there were significant differences.

According to our results, the likelihood of transient enlargement in cyst volume is comparable to the risk of continued growth — 11.4 and 10.1%, respectively, but the mean periods of their occurrence differ significantly — 3.5 (from 2.7 to 9.4) for transient expansion and 26.3 months (from 16.6 to 48.9) for continued growth.

Our data show (Fig. 2) that all cases of transient cyst enlargement were observed up to 10 months after irradiation and true recurrences — in 16 months.

A. Bishop et al. [24] reviewed records from 52 children treated with proton beam therapy or intensity modulated radiation therapy for CPs and reported transient increase in cyst volume for 14 of 17 patients in the early...
period after radiation (up to 3 months), in contrast to our series with transient cystic expansion in the first 10 months observed for all 9 patients. Perhaps this difference is due to the type of radiation: in our study, 8 out of 9 patients with transient cyst enlargement received either RS or hypofractionation RT. These types of irradiation are apparently associated with lower likelihood of outfield tumor growth due to shorter length of treatment (1 fraction in RS and 5 — in hypofractionated radiation in contrast to 30 fractions in standard fractionation).

Therefore, cystic expansion on control MRI in a patient with CP after tumor resection and subsequent stereotactic RT or RS within a period less than 1 year post-radiation is most likely transient, not requiring any treatment for a patient with stable clinical picture. Such cases require only surveillance and regular tomography (at least 1 time in 3 months). Cyst evacuation, implantation of an Ommaya reservoir or other surgical intervention may be required for evident symptoms, such as occlusive hydrocephalus with symptoms of intracranial hypertension, neurologic deficit, decreased acuity or constricted visual fields. Cystic enlargement occurring later than 12 months after RT/RS more likely represent true continued growth, requiring treatment.

In our study similar to a paper by Z. Shi et al. [20], MRI was not performed during radiation and in some cases cyst enlargement could have occurred in earlier periods (before complete RT) than at those indicated. In recent years (since 2005 at the Burdenko Neurosurgical Institute), only stereotactic conformal radiotherapy

![Fig. 3. Case 1. Patient E., 4 years old.](image)
a — preoperative MRI; b — MRI after cyst evacuation, prior to RT; c — cyst enlargement to almost initial sizes in 3.5 months after RT; d — cyst reduction in 9.5 months post-radiation.

![Fig. 4. Case 2. Patient K., 12 years old.](image)
a — preoperative MRI; b — MRI after operation prior to RT; c — reduction of 2 cysts and an increase in 1 cyst in the temporal lobe in 6.1 months post-radiation; appearance of symptomatic epilepsy; d — reduction of size of all cysts in 8.1 months after RT, regression of epilepsy.

![Fig. 5. Case 3. Patient F., 5 years old.](image)
a — recurrent CP; MRI prior to RT; b — an increase in the cystic component of the tumor associated with an acute deterioration of acuity.
which ensures accurate delivery of radiation with reduction in the volume of normal tissue irradiated has been used for treating patients with CPs. In this case, outflow tumor growth (most frequently cystic expansion) can occur due to fluctuations in tumor configuration during treatment. K. Winkfield et al. [19] first described fluctuations in CP cystic volume during radiation with linear accelerators and in proton therapy. In 4 out of 17 cases such response required correction of the radiation plan, in one case cyst drainage was performed, and cystic component decreased in size in another patient in response to treatment.

According to A. Bishop et al. [24], cyst growth during RT was observed in 10 of 24 children with CPs, 5 cases required changes in the radiation plan and 2 — cyst decompression. Therefore, patients with cystic CPs treated with standard fractionation should be followed with MRI during irradiation for timely correction of the radiation plan [19, 25].

**Conclusion**

With different periods in the occurrence of transient cystic enlargement and true continued growth of CPs, we can recommend surveillance for cases of early post-radiation/post-radiosurgery cystic expansion (up to 1 year) that do not cause occlusive hydrocephalus or neurologic aggravation (in particular, a decrease in acuity or narrowing of visual fields). Late cystic expansion should be regarded as a continued growth that requires decision on further treatment tactics.

A long course of radiation therapy for treating the cystic component of CPs should be paralleled with MRI and correction of the radiation plan, when necessary.

**Authors declare no conflict of interest.**
Quite often, post-radiation expansion of the cystic component of craniopharyngioma is a dilemma for the doctor: whether it is regrowth of the tumor requiring repeat treatment or the patient can only be monitored in dynamics. An error in the interpretation of the situation can lead to serious consequences. Therefore, the topic of this work focused on differential diagnosis in this situation is important. The work corresponds to the profile of the journal. The conclusions on the role of the periods of cyst enlargement are based on a thorough analysis of the results of surveillance in dynamics on a sufficient number of patients (79 patients) and are important for the formation of optimal treatment tactics during monitoring of this category of patients. Statistical methods confirm the significance of the results. The case reports and illustrations prove the authors’ conclusions. The literature list reflects both modern and important publications of the past years. The abstract is fully consistent with its content. The limitations found during primary reviewing were removed. This paper will be very useful for practicing neurosurgeons and radiologists.

O.I. Shcherbenko (Moscow, Russia)
Biodegradable Fixation Systems in Pediatric Craniofacial Surgery: 10-year Experience with 324 Patients

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Introduction. Over the past 15 years, resorbable materials have been successfully used for osteosynthesis, but their high cost prevents widespread application. However, the use of resorbable systems could be the method of choice, especially in treatment of children, since these materials are not only highly competitive with known metal constructs in terms of fixation rigidity, biocompatibility, and low risk of infection, but they are also resorbable, which is an undeniable advantage allowing quick recovery of damaged bones to the physiological condition.

Materials and methods. Over the past 10 years, we have used biodegradable systems in 324 patients. Conventional (plate/screw) systems were used in 244 of them, and an ultrasonic welding system was used in 80 cases.

Results. We found no technical difficulties when working with a standard set of fixing mini-plates and mini-screws, as well as using an ultrasonic welding system. We determined differences in indications for the use of these methods: the conventional screw-and-plate system was the method of choice when working in difficult to approach areas, while pin riveting with ultrasound was the only possible fixation method when working with very thin bones. The difference between the two groups in average operation time was one minute. Consumption of mini-screws and pins was also comparable. Complications that necessitated removal of the material developed in 5 (1.54%) cases.

Conclusion. Experience in application of biodegradable materials in craniofacial reconstructions reliably suggests that this fixation method is technically comparable to conventional metal osteosynthesis methods, but its safety is much lower. Despite the high cost of bioresorbable systems, the benefits from their use compensate for all costs by reducing the number of reoperations and preventing secondary deformations, which can be formed when using of non-resorbable materials.

Keywords: craniosynostosis, resorbable plates and screws, ultrasonic bone welding.

Osteosynthesis is an essential step in any craniofacial reconstruction and its reliability determines the final outcome of the treatment. A large number of materials have been suggested for fixation of broken or osteotomised bone fragments, wire, metal screws, plates, and mesh being the most popular of them. Currently, metal osteosynthesis is widely used in the treatment of both adult and pediatric patients. Modern metal structures are mainly made of titanium. In most cases, extraction of the plates at the end of bone fragment consolidation period in adults can be avoided due to high bioinertia and low radiopacity of this material. However, many authors [1] prefer to remove titanium plates in children due to the continued growth of facial and back skull bones and some of them even advise to abandon metal osteosynthesis. This approach is based on the popular belief that too rigid fixation in young children can restrict the growth of skull and face bones [2—5]. Osteosynthesis with resorbable materials proposed in recent years both reduced the risks associated with growth restriction and eliminated more real and threatening complications, such as intracranial migration of metal structures [6].

Most modern biodegradable systems are made of polylactide, a mixture of L and D stereoisomers of the polylactic acid (poly-L/DL-lactic acid, PLLDL). Polymeric nature of this material enables its application not only in the form of conventional plates and screws, but also in the form of riveted pins, which are melted by ultrasound in the drill hole and fill bone channels, resulting in reliable pin fixation in the bone. In our view, high cost is the only major disadvantage of polylactic acid-based materials, which considerably limits application of biodegradable osteosynthesis and therefore hinders accumulation of wide clinical experience.

The present work is the first Russian study describing the use of biodegradable materials in a large group of patients. We report the results of the use of two fixation systems, conventional one (screw and plate) and ultrasonic welding, in 324 craniofacial interventions that were carried out in children over the last 10 years.

Materials and methods

Biodegradable materials are used at the Maxillofacial Surgery Department of the Russian Children’s Clinical Hospital (RCCH) of the Russian Ministry of Health since 2005. Since that time, these materials were used for surgical interventions in 324 children (183 boys and 141 girls aged 4 months to 18 years). The vast majority of children were operated on for craniosynostosis and craniofacial dysostosis (292 operations). Additionally, resorbable materials were used to repair 18 post-traumatic and 14 post-resection of bone defects of the craniofacial area. In 244 cases, the standard system consisting of miniplates and miniscrews (Synthes, Switzerland, DePuy Synthes, USA since 2013) was used for fixation. In 80 pa...
Results

We found no significant technical difficulties when working with standard set of fixing miniplates and miniscrews, as well as with ultrasonic welding system. However, our subjective sensation was that slightly longer time was required for standard fixation process (drilling, threading, screwing) than for Sonic Weld fixation system. Howev- er, statistical analysis showed that the average operation time differed only by 1 min between the two groups, which was not statistically significant and not important in routine practice. The amount of spent miniscrews and pins was also approximately the same (Table).

The complication in the form of primary infection occurred in 3 patients. Suppuration of the subgaleal hematoma, which was formed after a small injury in the early postoperative period, occurred in a 6-month-old boy, who was operated on for scaphocephaly. Infected hematoma was evacuated at the place of residence, but the wound did not close despite the general and local antibacterial treatment for 2 weeks. Wound revision found that its bottom was formed by fixation plate (Synthes). The latter was removed and secondary intention healing of the osteotomised bone fragments were assessed. This group included 58 patients with scaphocephaly, who belonged to the same age group (7 to 12 months) and underwent multi-flap craniotomy with remodeling of the parietal-temporal-occipital region of the calvarium adopted in our clinic. A standard set was used for fixation in 37 patients, and a set for ultrasound fixation was used in 21 patients. Student’s t-test was used for statistical analysis to determine the equality of mean values in two patient settings.

Discussion

Silk and wire sutures have been successfully used in craniofacial surgery for fixation of bone fragments for a long time. In the late 1960s — early 1970s, more reliable osteosynthesis system represented by metal plates and screws have been developed and popularized [7—9]. At first, they were made of stainless steel, vitallium, ticonium, and other alloys. Then, it was found that titanium is the best material for fixation systems, which rapidly replaced other metals and their alloys [10]. However, working process revealed some issues related to the use of rigid fixation in children. Animal experiments have shown the
potential possibility of craniofacial bone growth restriction when using traditional rigid fixation in growing subjects [5, 11]. The cases of intracranial migration of mini-plates and wire sutures in children after craniofacial reconstructions [2—4, 12] have been reported. The incidence of this migration was similar for miniscrews, mini-plates, and wire sutures [13]. In a series of 27 patients who underwent calvarial reconstruction for craniosynostosis, ingrowth of fixing material into the bones was observed in 14% of cases, and the plate penetrated into the cranial cavity in 6.6% of cases [14]. The problems associated with growth disorders, transecranial or intracranial migration of metal plates, as well as the need for their subsequent removal in children, facilitated the development of biodegradable fixation systems based on polylactic, polyglycolic, and polydioxanone acids [15—17].

It is believed that an ideal system for bone fragment fixation should be not only biocompatible and sufficiently rigid to ensure early consolidation of the fragments, but it should also gradually reduce its own rigidity to enable formation of normal bone structure under natural physiological loads. These qualities are characteristic of biodegradable materials. Modern absorbable materials consist of linear amorphous polymer of polylactic acid (PLA), a polylactide synthesized from monomers, L— and D-stereoisomers of polylactic acid (poly-L/ DL-lactic acid, PLLDL). Isolated L-polylactides are the semicrystalline substances characterized by high mechanical strength and long degradation time (approximately 6 years). On the contrary, D-stereoisomers are an amorphous substance, which makes them less stable and shorter degradation time to 6—12 months. The combination of L and D-lactides in the polymer provides the required characteristics due to increase or decrease in the amount of each component. The polylactide consisting of 70% of L-isomer and 30% of D-isomer demonstrate the best quality characteristics due to increase or decrease in the amount of each component. The polylactide consisting of 70% of L-isomer and 30% of D-isomer demonstrate the best quality in terms of fixation. Strong microstructure, easily degrading in the body, is a significant advantage of this chemical compound. Material resorption process occurs as follows: first, water penetrates into the polylactide as a result of hydrolysis, the material swells, which is accompanied by opening of chemical bonds forming the scaffold of the polymer chain. Polymer degradation results in shorter chains, whose molecular weight is gradually reduced due to hydrolysis. Then, the smallest particles are phagocytosed and metabolized to lactic acid, which is in turn decomposed to carbon dioxide and water (CO₂ and H₂O). Rigidity of the material gradually decreases with degradation process. Thus, the material retains about 68% of the original rigidity in 8 weeks and only 30% in 6 months. Complete resorption is observed within approximately 24 months.

The first attempts to use resorbable materials for craniofacial osteosynthesis were associated with the use of bone sutures made of absorbable suture materials in children during the active growth period. The procedure was ineffective when bone extension by more than 1 cm was required, but good result was obtained when there was no soft tissue tensioning associated with bone movement, e.g., in the treatment of trigonocephaly or operations in very small children, where the strength of fixation is not particularly important [1, 18]. Bioreabsorable materials have been used to produce plate and screw systems since 1990s. Later on, and ultrasound fixation system was developed. Another option in the form of nails was also proposed, but it is not widely used [1, 19].

The conventional plates-and-screw system was represented on the Russian market by Synthes until 2013, and by DePuy Synthes after 2013. The technique of insertion of resorbable screws is not much different from the use of metal structures: a hole is drilled in the bone and thread is cut, followed by screwing. The only difference from metal screws lies in the fact that polylactide is less durable and cannot be used to produce self-tapping and self-drilling screws, and therefore great attention is payed to step tapping.

Another system is based on pin fusing into the bone in the form of ultrasonic welding. Exposure to ultrasound results in heating and softening of the polylactide pin. If it is placed into the drilled channel simultaneously with heating under light pressure, the material remains firmly fixed after cooling due to filling of all the small irregularities of the bone canal. This fixation option is known under the brand Sonic Weld and is represented in the world by the only KLS Martin company.

Conventional fixation systems are quite common and have been successfully used for a long time. The main complications include material palpability under the skin, local inflammatory reactions, infection, and plate fracture as a result of trauma. C. Sanger et al. [20] reported self-resolved palpability of the material in 5 out of 52 patients, who underwent skull reconstruction. In another study including 100 patients and 912 resorbable plates inserted during craniofacial reconstructions, there were only 4 cases where the material was removed due to pronounced contouring under the skin [21]. Analysis of 22 other craniofacial reconstructions with resorbable

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DePuy Synthes</th>
<th>KLS Martin</th>
<th>Significance of differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time, min</td>
<td>192.43±4.3</td>
<td>193.33±7.9</td>
<td>t 0.20 &gt;0.05</td>
</tr>
<tr>
<td>The number of plates, pcs</td>
<td>2.54±0.02</td>
<td>2.57±0.2</td>
<td>p 0.17 &gt;0.05</td>
</tr>
<tr>
<td>The number of screws/pins, pcs</td>
<td>98.54±6.2</td>
<td>100.47±8.2</td>
<td>p 0.37 &gt;0.05</td>
</tr>
</tbody>
</table>
plate fixation showed only two cases, where the material was clearly palpable under the skin [22].

We did not interpret palpability as a complication since complete resorption of the material occurs within 2 years. However, it should be noted that there were many cases when patient’s parents expressed concern about the fact that they found "some irregularities" under the child’s head skin. In the early stages of the use of this material, we often had to explain the safety of this phenomenon. Later on, we warned of possible “irregularities” in advance and the attitude of parents to this side effect of resorption process changed.

In the paper of C. Sanger et al. [20], plate fractures as a result of post-surgical trauma was observed in 3.8% of patients, but in all cases, fusion of bone fragment occurred without removal of damaged plates. Only 0.3% of plate fractures resulting from trauma were observed in the multicenter study by D. Eppley et al. [23], which included 1883 patients with craniofacial surgery for craniosynostosis. In the same study, local inflammation was observed in 0.7 to 14% of cases and infection in 0.2 to 2% of cases. The incidence of plate removal as a result of any of these events ranged 0.3 to 4%.

T. Turvey et al. [6] obtained 716 satisfactory results after 761 (94%) the operations in an extensive analysis of their own cases. Unsatisfactory outcomes were observed in 45 (6%) operations. Of these, 14 (2%) patients had complications associated with material fracture and 31 (4%) — with material infection. In all 14 patients with plate fractures, complications were observed in the lower
jaw. Inflammatory complications were most common in the upper jaw (87%) and least common in the lower jaw (7%) and orbit (7%). The overall incidence of complications in this study (6%) was comparable to that when using titanium plates. It is important to note that only those cases that required reoperation in the operating room were considered as unsatisfactory. The cases not requiring interventions, for example chronic inflammation with fistula formation, were not considered by the authors as bad outcomes.

Our data are fully consistent with international experience. We observed no cases of plate fracture and material infection rate was 1.07%.

Sonic Wield system is characterized by the same features as the standard fixation systems. Transient material contouring is quite common, infection and plate fracture are very rare [24].

E. Arnaud et al. [1] analyzed 20 cases where ultrasonic welding system was used and noted that the strength of pin fixation was superior to that of miniscrews as evidenced by the results obtained in animal experiments [25, 26]. According to E. Arnaud, the possibility to fix very fine bone fragments is the most important feature. C. Freudlsperger et al. [27] concluded that ultrasonic fixation method provides more rigid structure in the craniofacial osteosynthesis in children. The authors noted that exclusion of the step tapping process prevents thin bone fracture, which is quite common during this manipulation. In our study, we not only confirmed these data, but also noted the additional features. First, it is impossible to reuse pins in the case of improper insertion. Therefore, we often conduct preliminary fixation with metal structures to avoid mistakes and then replace them by biodegradable materials during the operation. Second, it is difficult to use ultrasonic activator in some areas, such as infratemporal fossa or anterior cranial fossa. Conventional resorbable systems should be used in these areas. Therefore, we believe that the presence of both fixation systems in the operating room is the best option, especially since no contraindications to their concomitant application were found.

Low radiopacity of the material is another quality that was not properly reflected in the literature. Modern fixing materials based on polylactic acid are so much radiolucent that they are almost impossible to detect with standard radiography. Computed tomography can only approximately estimate the position and state of the material in the “soft tissue” modes. In the “bone” mode, plate position becomes visible in a child in 6—8 months, when bone embankment is formed around the plate due to aseptic inflammation. This characteristic of the material has both positive and negative sides. High radiolucency gives an undoubted advantage over other fixation systems, since any neuroimaging examinations can be carried out without limitations in the postoperative period. At the same time, evaluation of the integrity of the plate itself and fixating screws (pins) is impossible. In our opinion, the true incidence of plate fractures and bone fragment instability cannot be confidently assessed due to this fact. As mentioned above, we observed no plate fractures. However, when fixing bone fragments with substantial post-tension of soft tissues, e.g. in cases of coronal synostosis with anterior extension of the fronto-supraorbital complex by more than 1.5 cm, sometimes it seemed that the level of postoperative relapse was higher than in the case of metal osteosynthesis under similar conditions. Unfortunately, we have no accurate data on this phenomenon at the moment, but this assumption forced us to use a greater number of resorbable plates in those cases where significant tension of soft tissue is expected in the postoperative period to strengthen the structure.

Conclusion

The use of biodegradable fixation materials significantly increased the possibilities of children’s craniofacial surgery and neutralized the negative impact of rigid fixation on the continuing bone growth. This eliminated the need for reoperation aimed at removal of metal structures, which was previously practiced. The development of ultrasonic fixation, which creates a reliable rigid three-dimensional structure based on very thin bones, is another important step. At the same time, conventional resorbable systems also remain popular and, sometimes, indispensable. Our experience in the use of biodegradable materials in 324 children who underwent craniofacial reconstructions allows us to say with confidence that this fixation method is technically comparable to the conventional metal osteosynthesis methods, but it is much safer. Despite the high cost of bioresorbable systems, benefits from their use in patients during the active growth period completely covers all costs both in terms of reduced need for reoperations and prevention of secondary deformities, which can be formed when using non-resorbable materials.

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REFERENCES


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The article is of undoubted scientific and practical interest since it focuses on osteosynthesis methods in craniofacial surgery for craniosynostosis in children using modern biodegradable materials. The authors analyzed application of two different biodegradable systems based on their own clinical material. The results were summarized, adverse effects and complications of this osteosynthesis method were discussed.

The detailed analysis of extensive clinical material showed undoubted advantages of biodegradable materials compared to commonly used earlier osteosynthesis methods. Nevertheless, the authors concluded that biological properties of the organic material used to produce biodegradable plates and screws (pins) have a number of drawbacks, including plate fragility and associated risks of unstable fixation, aseptic inflammation during material resorption, possibility of sustained infection, and contouring of plates and screws because of their greater thickness compared to most titanium structures, etc. The authors demonstrated the absence of any systemic reactions of the organism associated with the use of biodegradable materials based on a large material.

The complication rate obtained by the authors when using resorbable materials does not exceed the data reported in the literature. Formation of surface irregularities of calvarial bones at the plate fixation site due to irregular appositional growth of the skull bones is another undesirable phenomenon associated with biodegradable materials. Unfortunately, no recommendations to avoid potential complications have been formulated.

These problems are nevertheless fully compensated by undoubted advantages of the method: significantly reduced operation time, which in turn leads to lower blood loss, lower traumatization, faster postoperative recovery of the patient; there is no need for reoperation to remove the materials used for osteosynthesis; thermoplastic properties of biodegradable materials can be used not only to fix bone fragments, but also for bone modeling.

The authors compared two different systems of biodegradable materials in the same type of surgery and formulated differentiated approach to the use of these materials: application of KLS Martin system is optimal in young children with thin bones, where step tapping is impossible or there is a risk of bone fracture. No statistically significant differences in the duration of operations were found when using these two systems. Despite the same number of plates, screws, and pins, the difference was only 1 min. This result seems to be paradoxical, since there is no need for step tapping when using biodegradable materials KLS Martin.

Resorbability of materials is the most important characteristic when choosing biodegradable system for osteosynthesis. The authors point out that they did not evaluate the degree of resorption and did not check the integrity of the plates after use, since they are non-radiopaque. There are published studies on these issue, which will enable practitioners to make an optimum choice of the system for each specific case [1].

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REFERENCES

Drainage-Associated Meningitis in Neurocritical Care Patients. The Results of a Five-Year Prospective Study

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Aim — to determine the incidence rate and risk factors for drainage-associated meningitis in neurocritical care patients.

Material and methods. The prospective study included 539 patients who spent more than 48 h at the Department of Neurocritical Care and underwent external ventricular drainage. The incidence rate and risk factors for drainage-associated meningitis were evaluated.

Results. Over a 5-year period, 2140 patients have been hospitalized to the Department of Critical and Intensive Care (DCIC) for more than 48 h; of these, 539 patients underwent external ventricular drainage (EVD). Drainage-associated meningitis developed in 99 patients, which amounted to 19.8 (CI 16.3—23.3) per 100 patients with drainage and 18.3 (CI 14.3—22.2) per 1000 days of drainage. The incidence rate of drainage-associated meningitis did not significantly correlate with different neurosurgical diseases, but there was a tendency for meningitis to predominate in EVD patients with vascular pathology of the central nervous system (CNS). The rate of artery catheterization for direct measurement of systemic BP and the use of vasopressor agents were significantly higher in the group of patients with drainage-associated meningitis (p<0.05). ALV was used in 98 (99%) of 99 patients with drainage-associated meningitis; respiratory support was used in 325 (80.8%) patients without meningitis (p<0.01). An analysis of the ventricular drainage duration revealed a significantly (p<0.05) larger number of days of using EVD in the group of patients with drainage-associated meningitis. In most critical care patients (57.6%), meningitis developed during the first week of drainage. Cerebrospinal fluid leakage occurred significantly more frequently in patients with drainage-associated meningitis than in patients with EVD and without meningitis (p<0.01). Based on a microbiological examination, the etiology of drainage-associated meningitis was established in 57.1% of cases. The leading pathogens were coagulase-negative staphylococci (48.3%) and Acinetobacter baumannii (18.3%).

Conclusion. The incidence rate of drainage-associated meningitis was 19.8 per 100 patients and 18.3 per 1000 days of drainage. The risk factors significantly predominating in patients with drainage-associated meningitis include the duration of drainage, association with external CSF leakage, as well as factors associated with indicators of the overall severity of the condition.

Keywords: nosocomial meningitis, external ventricular drainage, drainage-associated meningitis, department of critical and intensive care (DCIC).

External ventricular drainage (EVD) is a common neurosurgical intervention for CSF drainage, continuous monitoring of intracranial pressure, and direct drug administration into the ventricular system in patients with various intracranial diseases [1—3]. Although intraventricular catheters were first introduced at the end of the XIX century, the technique was not widely used until the 1960s, when Lundberg refined the technique and demonstrated its usefulness for bedside analysis [4]. While placement of an EVD may be a lifesaving intervention, the benefits can be counteracted by several complications, such as hemorrhage along the catheter tract, catheter malposition, and CSF infection [5]. Since ventriculostomy significantly raises the risk of central nervous system (CNS) infection, drainage-associated meningitis is recognized as a separate group of diseases [1, 6—13].

Most researchers [14] refer nosocomial meningitis occurring in patients with EVD to drainage-associated meningitis. At present, clinical and laboratory criteria developed by CDC (Centers for Disease Control and Prevention) are commonly used for diagnosis and surveillance of nosocomial meningitis in international literature. Most frequently, the diagnosis is established from pathogens yielded by CSF culture in conjunction with systemic manifestations of infection and/or biochemical and cellular changes in CSF composition [9—13, 15—18]. Several papers [6, 18—20] diagnose meningitis based on only pathogen isolation from CSF while inflammatory changes in CSF and blood are less taken into account. The lack of a common definition for EVD-related infection complicates monitoring over the incidence rate of drainage-associated meningitis [10, 11]. The standardized CDC (Centers for Disease Control and Prevention) definition documents the rate of drainage-associated meningitis based on duration of ventriculostomy treatment [14]. However, papers that estimate the incidence and rate of drainage per 1000 catheter-days are limited [10, 18].

Doctors during diagnosis of drainage-associated meningitis in patients of the Critical and Intensive Care Unit (CICU) first focus on laboratory markers of CSF infection and then take into account clinical manifestations of the disease. The reason for the low informativity of clinical signs is easily explained: CICU patients can have a variety of neurological symptoms, including coma [8].

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The risk of drainage-related meningitis depends on many factors: the ventricular drainage duration, technique of catheter insertion, catheter care and manipulation (CSF sampling frequency, catheter irrigation, disconnections), CSF leakage along the catheter tract, length of patient stay in CICU, and presence of other foci of infection [1, 6—8, 10, 12, 13, 21]. There is an opinion that presence of blood in the ventricular system (for example, in case of ruptured intracranial aneurysm or arteriovenous malformation (AVM) increase the incidence of CSF infection [8, 10—12, 21, 22]. Many urgent issues related to insertion and use of external ventricular drainage were considered by a professional society and were published in guidelines in 2016 [5]. A committee of experts found that the available data concerning several issues are contradictory or insufficient, necessitating further research [5].

The aim of this study is to evaluate the incidence and risk factors for drainage-associated meningitis in neurocritical care patients using own data.

Materials and methods

This is a prospective study. All patients treated at CICU of the Burdenko Neurosurgical Institute for at least 48 hours in the period from October 2010 to October 2015 were analyzed. Data on all patients were documented daily into electronic medical records. Drainage-associated meningitis was diagnosed using standard Definitions of Nosocomial Infections developed by the Centers for Disease Control in the United States [14]. The following criteria were essential: 1) isolation of specific types of a microorganism/microorganisms from CSF using cultural or non-cultural microbiological methods; 2) a combination of clinical (fever or headache, meningeal signs, other neurologic symptoms) and laboratory predictors of meningitis (pleocytosis, protein level increase and glucose level decrease in CSF, the visualization of bacteria in CSF in a gram stain procedure). The drainage-associated meningitis rate per 1000 catheter-days was estimated as an additional indicator to characterize the effect of the leading risk factor. The formula was:

\[
\text{Drainage-associated meningitis rate} = \frac{\text{Total number of meningitis in patients with EVD}}{\text{Total number of catheter-days} \cdot 1000}
\]

Difference significance in the incidence rate of drainage-associated meningitis in the two groups was estimated using the \( \chi^2 \) test. Continuous random variables in two groups were compared using the Wilcoxon—Mann—Whitney test. Differences were significant at \( p<0.05 \).

Results and discussion

During a 5-year period, 2,140 patients who met the above criteria were hospitalized to the CICU; of these, 539 underwent an EVD. The total number of catheter-days was 5,418. Thirty eight patients who developed meningitis before catheter insertion were excluded from analysis. Therefore, the analysis included 501 patients. External drainage prior to meningitis was not performed in 1633 neurocritical patients. In this population, nosocomial meningitis developed in 81 (5%) patients.

Drainage-associated meningitis was diagnosed in 99 patients, comprising 19.8 (95% CI 16.3—23.3) per 100 patients with drainage and 18.3 (95% CI 14.3—22.2) per 1,000 catheter-days. According to published data, the incidence of drainage-associated meningitis varies widely within 5.6—23.2% [1, 6—9, 23, 24]. The overall incidence rate of ventriculostomy-associated CSF infection was approximately 11.4 per 1,000 catheter-days and shows significant heterogeneity due to several factors: criteria used for the diagnosis of drainage-related infections, duration of drainage, and use of antibiotics [18]. Thus, the incidence rates among a population of neurocritical care patients in our study are consistent with the literature data.

We compared two groups of patients: with EVD and drainage-related meningitis (\( n=99 \)) and patients with EVD and without drainage-related meningitis (\( n=402 \)). An analysis of patient and disease data revealed no significant differences in the following characteristics: age, gender, and Charlson comorbidity index (\( p>0.05 \)). The Charlson index is a scoring system of predicting long-term prognosis by classifying or weighting age (when the age is above 50 years) and comorbid conditions [25]. The Charlson index scores are higher for older patients and more severe grade of organ damage. There were no significant differences in the rate of drainage-associated meningitis in relation to the nature of neurosurgical diseases, but meningitis tended to predominate in patients with EVD with vascular pathology of the central nervous system (stroke, intracranial aneurysms and AVM) (Fig. 1).

An artery catheter to directly measure systemic blood pressure (BP) was required significantly more frequently in a group of patients with drainage-associated meningitis (41.4 and 28.1%, respectively; \( p<0.05 \)). A similar correlation was observed for vasopressors, which were required in half of the patients with meningitis (50.5%) versus 36.8% of patients requiring drugs to maintain systemic BP without CNS infections (\( p<0.05 \)). In the group of patients with drainage-associated meningitis, artificial lung ventilation (ALV) was performed in 98 (99%) of 99 patients, while in the group without meningitis respiratory support was provided to 325 (80.8%) patients (\( p<0.01 \)). In our opinion, more frequent use of ALV can indicate an overall critical condition of neurocritical care patients. The literature [26—30] identifies grade of organ damage, requirement for invasive devices and techniques as the main risk factors that substantially raise the incidence of nosocomial infections in CICU patients. An analysis of the EVD duration revealed a significantly
greater \( p<0.05 \) number of days of an EVD use in patients with drainage-associated meningitis. EVD was inserted for 3 days in half of patients without meningitis (221 people, 55%) and in general the duration of an EVD was no longer than 12 days in such patients. An EVD was inserted for at least 13 days in half of the patients with drainage-associated meningitis (50 people, 50.5%) and the duration of EVD was up to 55 days in 90% of such patients (Fig. 2).

An analysis of the periods of nosocomial meningitis development due to EVD revealed two periods of increased rate of drainage-associated meningitis: on 1—2 days of an EVD insertion, when meningitis was diagnosed in 20 people and on 6—7 days, when meningitis was detected in 22 patients (Fig. 3). An analysis of 20 early drainage-associated meningitis cases showed that placement of an EVD occurred in the operating theater in 8 cases, in CICU at the patient’s bedside — in 9 cases, and at dressing neurosurgical department in 3 patients. Thus, there are no convincing data on the association between the risk of drainage-associated meningitis and the place where placement of ventricular drainage occurs. In general, the majority neurocritical care patients (57.6%) developed drainage-associated meningitis in the first week of drainage (up to 7 days inclusive) (Fig. 3). This is consistent with literature data showing that a positive correlation between the duration of an EVD and the risk of infection is more common for the first week of catheter use. The results from different authors on subsequent days of an EVD are contradictory and generally indicate

###Fig. 1. The incidence rate of drainage-associated meningitis in relation to neurosurgical diseases.

###Fig. 2. The cumulative incidence of drainage-associated meningitis at different durations of external ventricular drainage.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Abs.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr(+)</td>
<td>34</td>
<td>56.67</td>
</tr>
<tr>
<td>Including:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoNSI (coagulase-negative staphylococci)</td>
<td>29</td>
<td>48.33</td>
</tr>
<tr>
<td>other Gr(+)</td>
<td>5</td>
<td>8.33</td>
</tr>
<tr>
<td>Gr(−)</td>
<td>25</td>
<td>41.67</td>
</tr>
<tr>
<td>Including:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>11</td>
<td>18.33</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>7</td>
<td>11.67</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3</td>
<td>5.00</td>
</tr>
<tr>
<td>other Gr(−)</td>
<td>4</td>
<td>6.67</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
<td>1.67</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

*Footnote. Gr(+) — gram-positive pathogens; Gr(−) — gram-negative pathogens.*
that the risk can decrease [8, 18], increase [6] or remain unchanged over time [11, 13].

A comparison of patient groups with and without liquorrhea revealed that patients with drainage-associated meningitis had significantly more frequent CSF leakage than patients with EVD without meningitis (41.2 and 17.3%, respectively; \( p<0.01 \)). In our study, the term “liquorrhea” in the vast majority of cases (95%) implies wound liquorrhea, which included: postoperative wound liquorrhea, CSF leakage along ventricular drainage tract, CSF rhinorrhea when endoscopic surgery was performed through a transsphenoidal approach.

Microbiological testing established the etiology of drainage-associated meningitis in 56 (57.1%) patients. In 42 cases, the causative organism of infection was not identified, in 4 cases there was an association of microorganisms. A total of 60 microorganisms were isolated (Table).

The etiology of diseases was made of 56.67% (\( n=34 \)) gram-positive pathogens, 41.67% (\( n=25 \)) — gram-negative pathogens and 1.67% (\( n=1 \)) — Candida albicans. The leading pathogens of drainage-associated meningitis were coagulase-negative staphylocoeci (48.3%), Acinetobacter baumannii (18.3%), and Klebsiella pneumoniae (11.7%) (Fig. 4). Staphylocoeci dominate in the etiology of infection suggesting that contamination of drain devices with normal skin flora colonizing the wound site is the leading pathway of CSF infection.

The total mortality rate in the CICU at the Burdenko Neurosurgical Institute for the last 3 years was 1.7%. Adverse outcomes in patients with drainage were evaluated in the group of complicated neurocritical care patients hospitalized to the CICU for a period of more than 48 hours. The percentage of such patients was 14.6% of the total number of patients admitted to CICU. The mortality rate among patients with drainage-associated meningitis did not differ significantly from the group of patients with drainage but without meningitis (23.2 and 20.2%, respectively; \( p>0.05 \)), indicating different causes of death of neurocritical care patients.

According to the empirical antibacterial therapy protocol adopted at our clinic, initial systemic treatment for drainage-associated meningitis included a combination of carbapenems (meropenem, doripenem) and vanco-

**Fig. 3.** The number of cases of meningitis diagnosed over different periods of external ventricular drainage.

**Fig. 4.** The percentage of pathogens in the etiology of drainage-associated meningitis.

CoNSi — coagulase-negative staphylocoeci.
mycin (linezolid) in form of prolonged infusion at maximum dosage. Antibacterial therapy was corrected taking into account the antibiotic susceptibility of CSF yielded pathogens. When a pathogen was not yielded from CSF, empirical treatment was continued. The duration of therapy depended on regression rate of inflammatory CSF changes, reduction of systemic inflammation markers and lasted for approximately 10—14 days for gram-positive pathogens of drainage-associated meningitis and 14—21 days for gram-negative bacteria.

Conclusion

External ventricular drainage is a well-recognized risk factor for infections. In our study, the incidence of drainage-associated meningitis in the population of complicated neurocritical care patients was 19.8 per 100 patients and 18.3 per 1000 catheter-days, being consistent with other published data.

The risk factors that significantly increase the rate of drainage-associated meningitis include the factors directly related to insertion and use of an EVD (duration of drainage, association with liquorhea) and those that indicate overall condition of patients (requirement for ALV, vasopressors, invasive monitoring of systemic BP). The analysis of our cases showed that most patients (57.6%) developed drainage-associated meningitis in the first week of drainage. In our study, meningitis did not cause a significant increase in mortality among neurocritical care patients with an EVD. This indicates the presence of other non-meningitis risk factors of mortality in a population of complicated neurocritical care patients.

Authors declare no conflict of interest.

REFERENCES


24. Kurdyumov a NV, Danilov GV, Ershova ON, Savin IA, Sokolova EYu, Alek...


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Commentary

A significant evidence for increased risk of CSF infection associated with external ventricular drainage (EVD) led to separation of drainage-associated meningitis (DAM) in an individual group of diseases. Meanwhile, wide heterogeneity in occurrence of DAM along with diagnostic challenges requires a thorough analysis of available data from large neurosurgical clinics, since comprehensive research on this issue is missing. This is especially relevant to the Russian neurosurgical departments. This paper presents interesting results of a five-year prospective study of EVD-related nosocomial CNS infectious complications obtained by one of the most respected neurosurgical institutions. This original evidence-based and relevant prospective research paper carries scientific and practical value for health care professionals.

V.A. Rudnov (Ekaterinburg)
Blood D-dimer levels are most often elevated in patients with vein thrombosis and hence D-dimer has been used as a diagnostic indicator of this condition. D-dimer is a degradation fragment of cross-linked fibrin. Cross-linked fibrin, which occurs at later stage of the formation of fibrin from fibrinogen, is produced by the action of thrombin on soluble fibrin polymers. D-dimer is subsequently produced from degradation of cross-linked fibrin by plasmin [1].

Elevated blood D-dimer levels are often revealed in cancer patients [2], including after surgery [3, 4] or chemotherapy [5] of malignant brain glioma (MBG), with 24% of these patients being detected with deep vein thrombosis of the leg or rare cases of pulmonary embolism (PE) [6]. The cause of an elevated blood D-dimer level in most other cases remains unclear.

The occurrence of PE secondary to deep vein thrombosis of the leg is a frequent cause of death among patients with MBG. Therefore, a search for approaches to prevent this complication is highly important and assay for blood D-dimer can be significant. Some authors [7] regard an elevated level of blood D-dimer as a marker of PE risk. For example, these authors believe that a four-time elevation of a D-dimer level is most often observed only in peripheral vein thrombosis and a 20-time increase or higher can indicate a possible development of PE.

Clinical indicators such as age, hemiparesis and male gender are unfavorable predictors for an increase in the blood D-dimer level in patients with MBG [6].

The same factors are also associated with poor survival after combined treatment in patients with MBG. For example, elevated blood D-dimer levels higher than 1.0 μg/mL were associated with a shorter recurrence-free survival [5] and shorter 2-year survival of patients with glioblastoma (GB) [8]. Therefore, the causes of elevated blood D-dimer levels in patients with malignant gliomas and without vein thrombosis, a mechanism of such elevation, and an effect of these factors on the efficacy of treatment, including adjuvant radiation therapy (ART) remain unclear.

The purpose of this study is to identify the features associated with an elevated blood D-dimer level in patients after resection of MBG, which may be used to improve the efficacy of adjuvant radiation therapy.
Radiology Department for ART, in the period from 2014 to 2016. The normal D-dimer level is $<$0.25 μg/mL.

In statistics, quantitative variables were described using number of patients ($n$) and median ($Me$). The results were estimated using χ² Pearson’s test, Fisher’s exact test, and Mann—Whitney U-test. The differences were significant at $p<0.05$.

Results

Blood D-dimer levels exceeded the upper reference cutoff values in 39 (78%) of the 50 patients included in this study. There was a 20-time increase or higher in the D-dimer levels in only 3 (7.7%) of these patients. Eleven (22%) patients had D-dimer level within the reference values (Table).

Blood D-dimer levels were compared between groups in relation to gender.

An increased blood D-dimer level was less frequent in patients with MBG at the age of before 60 years compared to patients with MBG at the age of 60 years and older. In the first group, D-dimer elevation was detected in 20 (71.4%) of 28 patients and in the second group — in 19 (86.4%) of 22 patients. However, further statistical analysis of the data showed that the differences in these indicators were insignificant ($p=0.3$). The median blood D-dimer value in 20 patients from the first group was 0.6 (0.3—3.0) μg/mL and was significantly ($p=0.049$) lower than the median value for 19 patients of the second group — 1.24 (0.3—5.0) μg/mL (Fig.).

In addition, blood D-dimer levels were compared between patients with gliomas of different grades of malignancy. Elevated blood D-dimer levels were detected at a similar rate in both groups, in 36 (77.8%) of 36 patients with GB and 14 (78.6%) of 18 patients with AG ($p>0.05$). The median elevated blood D-dimer level in 28 patients with GB was 0.74 (0.3—4.9) μg/mL and did not differ significantly from the median level of this indicator in blood in 11 patients with AG, which was 1.08 (0.3—5.0) μg/mL ($p>0.05$).

Discussion

The occurrence of a solid tumor substantially raises the risk of thrombosis, limiting the extent of anti-cancer measures with refusal from radiation therapy and frequent mortality. Approximately 20% of cancer patients are diagnosed with deep vein thrombosis of the leg and/or PE. More frequently, vein thrombosis is diagnosed at autopsy in 30—50% of cancer patients. A blood D-dimer level is a marker of thrombosis, including in oncology [8]. Several studies [9—11] found that a disseminated tumorous process (metastasis to the brain) and age of a patient with cancer are associated with an elevated blood D-dimer level.

A blood D-dimer level often increases in patients with brain tumors immediately after craniotomy [12], but vein thrombosis and/or PE was diagnosed in only 1/3 of them [5, 13]. Several authors [14] reported intraoperative brain tissue injury associated with thromboplastin release as a cause for elevated blood D-dimer level in patients without clinical signs of vein thrombosis.

Blood D-dimer level is believed to be a criteria when selecting a particular type of treatment in patients with MBG. Thus, chemotherapy in patients with hemiparesis and an increased D-dimer level of $>$8.6 µg/mL is not recommended due to the high risk of PE [15]. Although the risk of GB progression in earlier periods after combined treatment was significantly higher in patients with an elevated blood D-dimer level [5, 8], in available Russian and foreign literature we failed to find any information on the possibility of using this indicator to optimize ART in such patients.

In our study, a blood D-dimer level was increased in 78% of patients with MBG at the time of ART initiation, i.e., 3—4 weeks after surgery. In addition, a high level of D-dimer was not associated with clinical picture of vein thrombosis in most cases (98%) and only 7.7% of cases made us beware of possible PE occurrence (D-dimer level exceeded the normal value by 20 times or higher). Hence, an elevated blood D-dimer level was not associated with a high probability of vein thrombosis in the overwhelming majority of the patients under study.

An effect of patient age on an elevated blood D-dimer level ($>$0.25 µg/ml) in 3—4 weeks after resection of a malignant brain glioma.

The first group — 20 patients younger than 60 years; the second group — 19 patients at the age of 60 years or older.
Our data do not answer the question what causes an elevation of blood D-dimer level at the time of ART initiation in patients with MBG and without symptoms of vein thrombosis or PE. However, evidences on adverse effect of high blood D-dimer on treatment outcomes of cancer patients [16] demand more attention to changes in this indicator in patients with MBG during ART. Thrombosis of small vessels, which is difficult to diagnose, can cause an increase in the blood D-dimer level in such patients. Pulmonary tumor thrombotic microangiopathy (PTTM) is such an example. PTTM is believed to be caused by hyperepression of the VEGF factor in metastatic cells. VEGF is carried to small pulmonary arterioles with blood flow and causes thickening of their walls and narrowing of their lumen with subsequent formation of a blood clot that causes an elevated D-dimer level, according to many researchers [17]. In patients with MBG, a similar mechanism of thrombosis can be present in tumor vessels or in brain matter areas adjacent to GB, which highly expresses VEGF [18]. An occlusion of tumor vessels with clot can lead to occurrence of hypoxic regions within the bed of resected GB resulting in radiation resistance in residual GB tissue and impaired microcirculation in the peritumoral region, with inevitably poor quality of life and decreased survival in these patients. Such a suggestion is supported by the fact that an elderly age (>60 years) of patients with malignant gliomas and their general performance on Karnofsky scale are unfavorable factors for occurrence of vein thrombosis and/or PE associated with an elevated blood D-dimer level and decrease survival after combined treatment, including ART. The above data dictate the need to develop an algorithm of anticoagulant therapy after craniotomy in such patients. The use of anticoagulants in patients with brain tumors has been noted to have a rare association with appearance of subdural or intra-tumor hematomas [9] but several authors report that anticoagulants can significantly reduce the risk of PE [19] and substantially enlarge patient survival [9].

We believe that lack of significant differences in the frequency and level of the blood D-dimer elevation in the postoperative period in patients with GB and AG can only indicate that surgery itself can be a leading factor contributing to the blood D-dimer level elevation, as mentioned above. This is confirmed by a growth of D-dimer level in blood following resection of a meningioma, which most frequently has benign morphology [12, 14], or after cholecystectomy [20].

**Conclusion**

Our data indicate that an increase in blood D-dimer level in patients without symptoms of vein thrombosis in 3—4 weeks after craniotomy for MBG is insignificantly more evident in the age group older than 60 years. A grade of glioma does not influence significantly an elevation of D-dimer level in these periods. Subsequent research into the causes of an increased blood D-dimer level and medical therapy of the detected changes will improve survival and quality of life in patients with GB.

Authors declare no conflict of interest.

**REFERENCES**


This study is focused on important issue — improvement of treatment outcomes in patients with malignant gliomas after neurosurgery and adjuvant radiation therapy. Quite many papers on this topic have been published but this article demonstrates a unique methodology to study the issue, i.e., by assessing the level of D-dimer, a fibrin degradation product, in blood in such patients. A D-dimer level was measured in 3—4 weeks after a neurosurgical manipulation. There are no other studies based on such methodological approach.

D-dimer is a fibrin degradation product derived during clot lysis. A lysed blood clot can be located in any part of the vascular system. Therefore, D-dimer is generally recognized as a highly sensitive indicator of thrombotic events.

A blood D-dimer level assay is performed for different purposes. For example, we use this indicator in our study and now in routine practice for preoperative screening of neurosurgical patients to identify patients at risk for routine surgery. An elevated D-dimer level is an indication for ultrasound of the leg veins that commonly detects thrombosis in the deep veins of the leg [1]. However, the authors with an elevated D-dimer values in 78% of 50 patients tried to take a broader look at the issue: they related high D-dimer levels to both vein thrombosis and reparative processes in brain tissue after surgery; the authors made conclusions on the prognosis of treatment of such patients. This is an intriguing thought and an interesting direction based on proved phenomenon of PTTP, which the authors mention in the discussion section. This phenomenon is now recognized to be also responsible for high values of PE in cancer patients.

Hence, this paper contains interesting facts that can be important for neurooncologists, radiologists and chemotherapists.

A.Yu. Lubnin (Moscow, Russia)

REFERENCES

Results of Surgical Treatment for Segmental Instability of the Lumbar Spine

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Aim. To perform a comparative analysis of outcomes in patients with lumbar spine segmental instability who underwent surgical treatment using transforaminal lumbar interbody fusion (TLIF) and direct lateral interbody fusion (DLIF) techniques. Material and methods. The multicenter study involved 209 patients who underwent surgery for lumbar spine segmental instability. Long-term outcomes (up to 2 years) were studied in 134 patients: patients of the first group (98 patients) underwent traditional transforaminal lumbar interbody fusion (TLIF) and transpedicular stabilization of vertebral segments; patients of the second group (36 patients) underwent direct lateral interbody fusion (DLIF) in combination with transpedicular stabilization of the lumbar vertebral segments. We used standard checkpoints for monitoring the patients’ condition: before surgery, at discharge, at 3, 6 and, 9 months, and at 1 and 2 years after surgery. To follow-up the patients, we used the Visual Analogue Scale, Oswestry Disability Index, and Goal Attainment Scaling. Results. A comparative analysis of the two interbody fusion techniques was enabled by the developed Vertebrologic Registry profile (http://spineregistry.ru/Register_treatment.php) that was designed for entering data of Russian and foreign neurosurgeons. A comparative analysis of outcomes (up to 2 years) were evaluated in 134 patients. All the subjects were divided into two groups: group 1 patients (n=98) underwent the conventional transforaminal lumbar interbody fusion (TLIF) and group 2 patients (n=36) underwent direct lateral interbody fusion (DLIF) in combination with transpedicular stabilization. The comparison of the two techniques was based on the data of the Vertebrologic Registry. Conclusion. 1. An analysis of the outcomes in the first group of patients who underwent traditional transforaminal lumbar interbody fusion (TLIF) and direct lateral interbody fusion (DLIF) reveals that the DLIF technique is associated with some advantages in the quality of surgical treatment when compared to the TLIF technique. Keywords: direct lateral interbody fusion, transforaminal interbody fusion, spine segmental instability, intraoperative computed tomography scanner, navigation system.

Materials and methods

The multicenter longitudinal study involved 209 patients operated on for segmental instability of the lumbar spine at the Department of Spinal Neurosurgery of the N.N. Burdenko National Scientific and Practical Center for Neurosurgery (Ministry of Health of the Russian Federation), at the Neurosurgical Department of the District Clinical Hospital "Traumatology Center" (Surgut, Russia), and at the Neurosurgery Department of Central Military Hospital (Ružomberok, Slovakia). The use of data for several study sites made it possible to increase the sample size, to compare treatment outcomes, and to objectify the resulting data. A profile for the online version of the Russian Spine Registry designed at the N.N. Burdenko National Scientific and Practical Center for Neurosurgery was created during this study; Russian and foreign neurosurgeons can enter their data to this registry. This international collaboration will allow one to analyze the outcomes of surgical treatment of degenerative spine disorders in different countries.

In terms of its design, this study was a controlled, prospective study. The long-term outcomes (up to 2 years long) were evaluated in 134 patients. All the subjects were divided into two groups: group 1 patients (n=98) underwent the conventional transforaminal lumbar interbody fusion (TLIF) and direct lateral interbody fusion (DLIF) techniques.
fusion (TLIF) and transpedicular stabilization of vertebral segments; patients in group 2 (n=36) were subjected to direct lateral interbody fusion (DLIF) in combination with transpedicular stabilization of the lumbar vertebral segments.

The main inclusion/exclusion criteria of the study are listed in Table 1.

The data for all the patients (key characteristics and clinical data) were entered to the profile of the patients with segmental instability of the lumbar spine on the Spine Registry website (http://www.spineregistry.ru/). The mean age in both groups was 59±11.9 years. The study included 55 (41%) males and 79 (59%) females. There were no intergroup differences in key parameters. An analysis of patient distribution with respect to the level of surgical intervention showed no significant discrepancy between the patients in both groups; the L3—L4 and L4—L5 levels were typically most affected.

The standard criteria were used to determine indications for surgery: long-lasting symptoms before surgery and conservative treatment failure (6—8 weeks). Prior to surgery, all patients underwent routine examination that included neurological examination, functional spondylography, helical CT and MRI of the lumbosacral spine.

We used the standard periods to follow up patients’ condition: preoperatively, at discharge, 3, 6, 9 months and 1, 2 years after surgery. The following scales were employed for longitudinal follow-up in this study:

— the Visual Analogue Scale;
— the Oswestry disability index; and
— the Goal Attainment Scaling.

The long-term outcome of surgical treatment in patients with segmental instability of the lumbar spine (12 and 24 months after surgery) was formulated in accordance with the modified criteria proposed by Kawabata et al. (1973):

— class 1 (good) outcome: no complaints or pathological symptoms; normal results shown by objective examination; significant improvement; no disabling dysfunction (mild sensory impairment and grade IV—V paresis with improvement by at least one grade;
— class 2 (poor outcome): no positive dynamics (persistent complaints, profound neurological deficit and atrophy) or worsening of the condition.

The modified criteria for outcome assessment proposed by Kawabata et al. allow one to evaluate the neurological symptoms and disease severity.

Statistical analysis was performed using Microsoft Excel and Statistica 8.0 software. The p-value<0.05 was considered sufficient to regard the differences as significant; at p>0.05, the difference was regarded as having lack of statistical significance.

The 360-degree segmental fusion, including interbody and transpedicular fusion combined with placement of various implants is the international “gold standard” for surgical treatment of segmental instability of the lumbar spine. Positioning of these devices in the spine undoubtedly dictates certain requirements to surgical instruments. First of all, they need to be equipped with an intraoperative neuroimaging system. An electron-optical converter (EOC) is the most common one.

An intraoperative cone-beam computed tomography scanner and a navigation system are used for intraoperative imaging at the N.N. Burdenko National Scientific and Practical Center for Neurosurgery to increase patient safety and quality of surgical aid.

In group 1 patients, interbody fusion was performed through the transformaminal approach. Before the surgical intervention, a patient lying prone on an operating table under endotracheal anesthesia underwent intraoperative 2D CT (iCT) to identify the zone of surgical intervention. Next, the surgical approach to the spine was made through a 3—4 cm long parasagittal skin incision earlier described by Wiltse. Once the surgical approach had been performed, a navigation frame was inserted into the iliac crest and 3D CT was carried out (Fig. 1).

After the approach to the interbody space had been performed, transformaminal placement of interbody implant was conducted. First, a test template was inserted into the interbody space and the cage size was determined using the navigation system. Since navigation tools were used at the interbody fusion stage, no additional fluoroscopic imaging was required. Next, the cage was placed into the interbody space under microscopic control and its position was controlled by navigation (Fig. 2).

After interbody fusion, stagewise 3D scanning was performed to control the cage position and ensure proper placement of transpedicular screws.

Transpedicular screw fixation was carried out using the minimally invasive procedure with neither additional muscle skeletonization nor using the percutaneous technique. Ipsilateral to the interbody fusion cage, transpedicular screws were inserted through the same approach under control of a navigation system. Contralaterally, a similar paravertebral incision of skin, subcutaneous fat, and aponeurosis was made and the entry points for screw placement were identified. Control CT scanning and 3D reconstruction were performed after transpedicular stabilization.

In group 2 patients, the anterior and middle vertebral columns were surgically accessed via the iliacus. Direct lateral interbody fusion was carried out for patients lying on their either side; L1—L5 were the levels allowed for implantation. This limitation is because there is costal margin in the cranial direction and the iliac crest, in the caudal direction. Selection of the side for placing the interbody fusion cage usually depends on surgeon’s preference. Nevertheless, it is technically simpler to perform the surgery on the side of the interbody space that is more “opened”: in case of degenerative scoliotic deformity, it is the convex side of the arch, higher interbody space and larger distance between the iliac crest and the ribs. The same correction procedures will be employed via the ap-
proach through any side, but it is technically simpler to access the site from the convex side. This can be assessed using preoperative spondylograms during the operative planning stage and intraoperatively, after the patient was positioned on the operating table and fluoroscopic imaging was performed (either by 2D iCT scanning or by using an EOC) (Fig. 3).

When passing the intervertebral fusion cage through the iliacus to the anterior and middle vertebral columns, one should remember about the surrounding anatomical structures that can potentially be damaged. This primarily refers to the lumbar plexus schematically shown in Fig. 4.

One should use intraoperative neuromonitoring (IONM) to avoid damaging the branches of the lumbar plexus, and primarily the genitofemoral nerve that is formed of the plexus of superior lumbar spinal nerves and runs along the anterior surface and deep in the psoas muscle. Stimulating electroneuromyography is the principal method used when performing direct lateral interbody fusion (DLIF).

After the patient had been positioned on the operating table and IONM electrodes had been inserted by intraoperative 2D CT scanning or using an EOC, the accurate entry point to the interbody space is identified when performing mapping directly in the projection of the vertebral disc (Fig. 5).

The surgical access to the spine was performed through three layers of the muscles of the anterior abdominal wall and the retroperitoneal space by bluntly delineating the psoas muscle (Fig. 6).

Once the channel had been formed in the psoas muscle, a needle electrode was placed there and the presence of neural structures was assessed by neurophysiological monitoring. If there was no signal from the branches of the lumbar plexus, dilators—smaller to larger—were sequentially inserted in a twisting manner to ensure access to the interbody space and a retractor was applied. The free end of the retractor was rigidly attached to the operating table. The dilators were then removed and discectomy was performed. After the discectomy, an interbody fusion cage matching with the size of the interbody space was selected using the test template and the navigation system (Fig. 7).

After finishing the interbody fusion stage under control of the navigation system (at the Department of Spinal Neurosurgery of the N.N. Burdenko National Scientific and Practical Center for Neurosurgery) or the EOC (at the Neurosurgical Department of the District Clinical Hospital "Traumatology Center" (Surgut) and at the Neurosurgery Department of the Central Military Hospital (Ružomberok, Slovakia)), percutaneous transpedicular stabilization using the minimally invasive technique was carried out identically to how it was performed in group 1 patients.

### Results

We analyzed the key advantages and the potential of using iCT along with the navigation system for surgical treatment of degenerative spine disorders. Surgery duration was monitored. The first surgical interventions conducted using iCT and the navigation system lasted longer because it took some time to learn how to use the system. However, surgery duration tended to decrease as the personnel was acquiring these skills. It is important to mention that when iCT and the navigation system were used at the stage of interbody and transpedicular fusion, the surgical team was not exposed to radiation, since the medical personnel, except for the anesthetist, was not present in the operating room during 3D scanning that lasted 13—23 s, while subsequent implant placement was conducted under control of the navigation system. The accuracy of implant placement was evaluated by analyzing the intraoperative iCT scans with 3D reconstruction.

When performing the stabilization stage of the surgery, which requires placement of interbody implants and transpedicular screws (including the cases when the per-

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<table>
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<tr>
<th>Table 1. The key inclusion/exclusion criteria</th>
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<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>The L2—L5 vertebral level is affected</td>
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<tr>
<td>Patients 20—75 years old</td>
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<td>Lumbodynia with any combination of compressive radiculopathy and neurogenic intermittent claudication that developed after the orthopedic provocation</td>
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<td>Long-lasting symptoms before the surgery and conservative treatment failure (6—8 weeks)</td>
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<td>Functional spondylograms showed signs of moderate segmental instability (vertebral displacement relative to each other by 4—10 mm)</td>
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<td>Instability accompanied by possible combination of grade 1 spondylolysis + spondylolisthesis, degenerative spondylololisthesis, and spinal stenosis</td>
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<tr>
<td>The clinical symptoms are caused by one or two lumbar functional spinal units affected</td>
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cutaneous procedures were used), the intraoperative computed tomography scanner and the navigation system were employed to identify the intervention zone, to intraoperatively monitor implant placement accuracy, and to control the restoration of disc height and diameter of the intervertebral foramina. The surgery was followed by 3D scanning and 3D reconstruction. We believe that it is most reasonable to use the intraoperative computed tomography scanner with a navigation system when surgical treatment is performed under extremely challenging anatomical conditions (e.g., thin pedicle, scoliotic or post-traumatic spinal deformity) and proper imaging of the surgical site cannot be achieved by 2D scanning. Furthermore, application of iCT and the navigation system is useful for neurosurgeons in clinics where stabilization surgeries and the percutaneous techniques are employed rarely or only start to be launched into practice.

We have encountered a number of difficulties when performing a comparative analysis of the two interbody fusion procedures. The reason is that transforaminal lumbar interbody fusion (TLIF) has been widely used over the past few decades and over 1,000 TLIF surgeries are annually performed in Russia. In its turn, direct lateral interbody fusion was first employed in Russia as recently as 2014, making the sample size of patients operated on using this technique rather small. In this connection, we analyzed the data obtained by our European colleagues and found that neurosurgeons at the Central Military Hospital in Ružomberok (Slovakia) can boast a significant experience in using the DLIF technique. Owing to establishment of an international profile of the Russian Spine Registry, it is now possible to enter the data for patients from foreign clinics, while adhering to the main principles of information personalization. Among Russian neurosurgeons, the ones from the Dis-

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**Fig. 1.** Stages of mapping of the segment being operated on and navigation frame placement.

a — future incision is mapped in the patient lying prone after 2D scanning; b — the navigation frame (shown with an arrow) is placed into the iliac crest; intraoperative CT monitoring (3D mode) is performed; the gantry is left in the parking position.

**Fig. 2.** Transforaminal placement of an interbody implant.

a — a fusion cage is inserted into the interbody space using the navigation tools; b — intraoperative monitoring of the cage position and size using the navigation system.
strict Clinical Hospital "Traumatology Center" (Surgut, Russia) have participated in database merging. The designed Spine Registry profile (http://spineregistry.ru/Register_treatment.php) is intended for data entry by Russian and foreign neurosurgeons to analyze clinical characteristics, to evaluate the outcomes, and to perform longitudinal follow-up of patients with lumbosacral degenerative disorders (Fig. 8).

Pain intensity in the lumbar spine and lower extremities assessed using the VAS scale was significantly decreased in both patient groups in the early follow-up period (at discharge). This decrease was also observed during the long-term follow-up. In the early postoperative period, most patients (81% of patients in group 1 and 95% of patients in group 2) showed either complete or partial regression of radicular pain the next day after the surgery. Assessment of the postoperative dynamics of the pain syndrome showed that pain intensity in lower extremities steadily decreased 3, 6, 9 months, 1 and 2 years after the surgery in both patient groups. However, the VAS score for spine and leg pain intensity in group 2 in the long-term follow-up period (>1 year after the surgery) was almost twice as low ($p<0.05$) (Table 2).

The indicator for disability level, the Oswestry Disability Index, was assessed prior to surgery: 79.63±3.75 in group 1 patients and 73.45±4.2 in group 2 patients, being indicative of significant preoperative disability. In both groups, the operated patients showed significant reduction in the Oswestry Disability Index in the early postoperative period (at discharge): 33.19±2.4 in group 1 patients and 27.89±2.9 in group 2 patients. The disability level was gradually decreasing during the long-term follow-up period. No differences in the Oswestry Disability Index were observed in both patient groups ($p<0.05$).

In both groups, we analyzed the level of treatment goal attainment one year after the surgery. The best results were observed in group 2 patients who had undergone interbody fusion using DLIF. In both groups, the treatment goal was not achieved in some patients: in 11 (11.2) group 1 patients and in 2 (5.6%) group 2 patients.

Assessment of surgery duration showed that surgical interventions using DLIF lasted longer as it took some time for the personnel to master the new method. How-

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**Fig. 3.** Positioning the patient on the operating table when performing direct lateral interbody fusion.

a — the operating table is flexed at a certain angle to increase the distance between the wing of the ilium and the ribs; b — mapping of the incision by intraoperative CT scanning.

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**Fig. 4.** Arrangement of the lumbar plexus and vertebrae with respect to the interbody spaces.
ever, surgery duration tended to decrease over the training period (6 months). No statistically significant difference in duration of TLIF and DLIF was detected.

An analysis of intraoperative blood loss showed significant intergroup difference. In group 1, the volume of intraoperative blood loss during single-cage interbody fusion was 33% greater than that in group 2. None of patients required substitution blood transfusion during DLIF or TLIF.

In both groups, the mean length of stay was 7±4 days; no significant intergroup differences were detected.

Radiological examination, helical CT, and MRI performed 3, 6, 12 months, 1 and 2 years after the surgery revealed neither implant degradation nor implant incor-

**Fig. 5. Stages of mapping the segment being operated on.**

a — identifying the projection of the operated segment and the entry point to the interbody space; b — intraoperative 2D CT examination; the pointer is projected onto the entry point to the interbody space; c — mapping of the incision.
poration into the vertebral bodies in all patients. Signs of bone tissue resorption around the interbody implants were detected in 9 patients in group 1, which was regarded as failure of interbody block formation. No changes of this kind were revealed in group 2 patients. Hence, direct lateral interbody fusion (DLIF) in combination with transpedicular fixation results in interbody block formation.

An analysis of the results demonstrated that good (class 1) outcomes were achieved in 79 (81%) patients in group 1 (patients operated on using the TLIF procedure) and in 32 (89%) patients in group 2 (those operated on using the DLIF procedure).

In both study groups, postoperative complications were typical of surgeries of this kind. Neither infectious nor implant-related complications (improper position or migration of implants) were observed.

Dura mater injury in one group 1 patient was managed by meticulous suturing and sealing the dura mater at the final surgical stage.

Postoperative aggravation of neurological deficit presenting as worsening leg paresis and hyperesthesia as a result of postoperative swelling of spinal nerve root was revealed in 12 (12%) group 1 patients and 4 (11%) group 2 patients. The comprehensive conservative treatment for almost 2 months restored the lost functions, either partially or completely.

Slow healing of the postoperative wound was observed in 5 (5%) group 1 and in 2 (5.6%) group 2 patients. This required delayed wound suturing in the early postoperative period; the sutures were removed once a firm cicatrix had been formed (on postoperative day 10—12).

Discussion

The key objective of surgical treatment of patients with segmental instability of the lumbar spine is to restore stability of the spinal segment and to eliminate compression of the neural structures. The challenge related to decision making regarding selection of the optimal surgical treatment for segmental instability of the lumbar spine is that one needs to take into account various factors, including the degree of instability, whether or not a patient has spondylolisthesis and stenosis, clinical manifestations, the imaging data, treatment goals, concomitant diseases, patient’s age, etc. The most effective and safe method for treating segmental instability of the lumbar spine must be chosen after comprehensive analysis of each individual case with allowance for the outcome prediction data.

Transforaminal lumbar interbody fusion (TLIF) and direct lateral interbody fusion (DLIF) are the most common minimally invasive techniques used to place an interbody implant [3, 4]; these techniques were employed in patients in this study.

DLIF has proved to be a high-efficiency procedure for correcting the segmental sagittal and frontal balance, as well as laterolisation [3, 5]. A cage inserted using DLIF has a larger size and larger contact area compared to other implants. It rests upon the marginal dense portion of a vertebral endplate, thus ensuring good support to the anterior column and maintaining the middle and posterior columns of the spine. Hence, direct lateral interbody fusion does not require resection of bone structures, making it possible to avoid injury to the neural structures [6]. Meanwhile, it allows one to perform indirect decompression without opening the spinal canal and to restore the height of the interbody space and the diameter of intervertebral foramina [7].

Preservation of the anterior and posterior longitudinal ligaments when using DLIF plays a crucial role in preventing posteriad or anteriad cage migration and increasing the dynamic stability as a result of ligamentotaxis [8]. In our case series, we observed no complications related to migration of interbody implant, which confirms the aforementioned hypothesis.

The complication rate for DLIF varies within the range between 0.7 and 62.7% [9—11]. The most common complications include damaging the branches of the lumbar plexus, resulting in weakness of hip flexors and sensory impairment [12—14]. Therefore, intraoperative neuromonitoring must be used when performing DLIF to prevent the injury to lumbar plexus roots that run deep in the psoas muscle and are difficult to control visually) and also to prevent damaging the roots because of traction during cage placement [12]. The complication rate observed after interbody fusion gradually went down to 20% due to application of IONM [10, 11, 14]. In this study, the complication rate of DLIF was 11% due to the
Fig. 7. Placement of an interbody implant by DLIF.

a — dilator placement; b — cage placement; c — intraoperative monitoring of cage position and size using the navigation system.

Table 2. Dynamics of pain intensity score assessed using the VAS, M±SD

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Follow-up period</th>
<th>Back pain intensity</th>
<th>Leg pain intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>preoperatively</td>
<td>at discharge</td>
<td>after 3 months</td>
</tr>
<tr>
<td>1</td>
<td>7.8±2.19</td>
<td>4.26±1.17*</td>
<td>3.12±1.7*</td>
</tr>
<tr>
<td>2</td>
<td>8.06±1.87</td>
<td>3.21±1.56*</td>
<td>2.78±1.95*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5.67±1.84</td>
<td>2.3±1.8*</td>
<td>2.0±1.17*</td>
</tr>
<tr>
<td>2</td>
<td>6.14±2.32</td>
<td>1.8±1.14*</td>
<td>1.47±0.7*</td>
</tr>
</tbody>
</table>

Footnote. * — the difference with the postoperative value is significant; p<0.05.
additional advantage of using the intraoperative computed tomography scanner and navigation system.

**Conclusions**

Indirect decompression using direct lateral interbody fusion (DLIF) minimizes the risks of intraoperative damage to the dura mater and the neural structures. The class 1 (good) outcomes according to the Kawabata’s classification were achieved in 89% of patients who had undergone direct lateral interbody fusion (DLIF) and in 81% of patients subjected to transforminal lumbar interbody fusion in combination with transpedicular fixation. Under international collaboration, the profile of Spine Registry enabling data entry in Russian and English languages allows one to accumulate data about patients operated on using direct lateral interbody fusion (DLIF). The use of intraoperative computed tomography along with the navigation system increases safety, ensures high-accuracy implant placement, and reduces the duration of the stabilization stage and the radiation dose absorbed by the surgical team and the patient.

Authors declare no conflict of interest.
REFERENCES


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Commentary

This article focuses on the topical problem of selecting the method for surgical treatment of lumbar spine instability using the transforaminal (TLIF) and direct lateral (DLIF) interbody fusion. Intraoperative fluoroscopic imaging and neurophysiological imaging have broadened the scope of application of minimally invasive techniques in spine surgery. Both placement of percutaneous implants and transcutaneous placement of transpedicular screws are now the routine procedures. The authors have conducted a comparative study of the transforaminal and direct lateral interbody fusion in terms of compliance with the principles of minimal invasiveness (MISS criteria, 2012). They compared the results of using these techniques in terms of effectiveness (surgery duration, length of stay), the outcome (ODI, VAS), and postoperative complication rate. The findings showed that the results obtained for the study and control groups were comparable in terms of all these parameters. Technical considerations of performing DLIF and the need for neurophysiological imaging of branches of the lumbar plexus are described.

However, taking into account the technical nuances it is important to refine the indications for direct lateral interbody fusion.

Since early manifestations of scoliotic deformity can be corrected by DLIF as reported by A. Cappuccino and G. Cornwall, it would be reasonable to elaborate specific indications for this method and to discuss them in further studies. Furthermore, the technical features of this type of interventions and features of the approach suggest that the technique used to perform the interventions of this type should be widely discussed in the specialized literature.

A.O. Gushcha (Moscow, Russia)
Correlation of Intracranial Pressure and Diameter of the Sheath of the Optic Nerve by Computed Tomography in Severe Traumatic Brain Injury

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Background. Noninvasive techniques to evaluate intracranial pressure (ICP) are important for everyday practice in intensive care and neurosurgery departments. CT data can be used to evaluate the optic nerve sheath diameter (ONSD) and, indirectly, the ICP value. The ONSD value is an additional criterion in deciding on invasive monitoring of ICP.

Objective. To analyze a correlation between CT-based ONSD and the results of invasive measurements of ICP in patients with severe traumatic brain injury.

Material and methods. The study evaluated 41 patients with severe traumatic brain injury within the first 48 h after injury. Invasive monitoring of ICP (Codman & Shurtlett, MA, USA) was performed during 7±1.7 days. ONSD was measured using axial CT scans (CereTom, Neurologica Danvers, MA, USA) with a slice thickness of 2.5 mm. The ONSD value was measured at a distance of 3 mm from the posterior eyeball contour. The patients were allocated in a group with normal ICP (10 patients) and a group with high ICP (31 patients). ONSD served as an ICP classifier. The data were processed using ROC analysis.

Results. According to the CT data, the optimal threshold ONSD value was 6.35 mm in patients in the acute TBI period. The sensitivity was 0.93 (95% CI 0.84―1.00), the specificity was 0.80 (95% CI 0.50―1.00), and AUC was 0.87 (95% CI 0.69―1.00).

Conclusion. We found a correlation between the CT-based ONSD and the median ICP (R=0.32, p<0.05). An ONSD value of 6.35 mm and more is one of the signs of previous or existing ICP.

Keywords: optic nerve sheath diameter, computed tomography, traumatic brain injury, intracranial pressure.

Development of intracranial hypertension (ICH), i.e. increase in intracranial pressure (ICP) over 20 mmHg for more than 5 minutes, is the main cause of secondary brain damage and adverse outcomes in patients with severe traumatic brain injury (TBI) [1—3]. Edema of the brain matter that develops as a result of primary traumatic brain damage is one of the leading causes of ICH in patients with TBI, along with such factors as disruption of venous outflow, liquorodynamics, autoregulation of cerebral blood flow, failure of spatial compensation mechanisms, etc. [4—7]. All these mechanisms contribute to the development of secondary ischemic brain damage [4, 7—12].

According to the international recommendations of the Brain Trauma Foundation [3], as well as the recommendations adopted by the Association of Neurosurgeons of the Russian Federation [2], invasive ICP monitoring is indicated only for TBI patients whose condition is assessed as less than 9 points on the Glasgow Coma Scale (GCS) in the presence of pathological changes in the brain based on the computed tomography (CT). In the absence of pathological changes at CT, the ICP sensor is implanted when any two criteria are met: age over 40 years, arterial systolic pressure less than 90 mmHg, presence of poznontic reactions of decortication or decerebration.

Such brain CT data as displacement of the median structures of more than 5 mm, narrowing of the basal cisterns and convexital subarachnoidal fissures, are only indirect criteria of increasing ICP and cannot be used to predict its dynamics. In patients with traumatic brain injury the assessment of changes in ICP is possible only with continuous measurement using an invasive ICP sensor [6].

Modern technological advances led to the development of mobile transport CTs, which greatly facilitates the performance of this diagnostic procedure, making it possible to use it even for non-transportable patients and expanding the options for non-invasive ICP assessment. Along with generally accepted criteria for evaluating the state of the brain matter and intracranial contents, the use of CT in the department of neuroreanimation makes it possible to measure the diameter of the sheath of the intraorbital part of the optic nerve.

Measurement of the optic nerve sheath diameter (ONSD) is a non-invasive method for diagnosis of ICP and can be used as an additional criterion when deciding on the use of the invasive ICP measurement [13, 14]. The term “optic nerve sheath diameter” (ONSD) is commonly accepted and widely used in foreign literature. In this case, the optic nerve sheath is visualized as a cylinder, which can be stretched when the ICP rises, leading to an increase in its diameter. In our work we decided to use the literal Russian translation of the term and the corresponding abbreviation.

Since intraorbital sections of the optic nerves are surrounded by a solid and arachnoid membranes and are communicating with the subarachnoidal space of the brain, the increase in ICP is transmitted to the intrathecal space of the optic nerve through increase in liquor pressure,
causing it to stretch and increasing ONSD. Many experimental and clinical studies [15—17] have demonstrated that ONSD increases in diameter for a few minutes after an increase in ICP and it reaches its maximum value at ICP 35—45 mmHg.

Measurement of ONSD has become a routine practice in intensive therapy of patients with CNS lesions and polytrauma and is performed with the help of ultrasound [18—20]. However, successful implementation of this examination require adherence to a standardized procedure by a highly qualified specialist.

MRI can also be used for these purpose, but it is usually limited by the severity of the patient’s condition, the duration of the examination, the need for anesthesia [7]. It has been shown that the measurements of ONSD using CT and MRI correlate well with each other [21].

The purpose of the study was to calculate the correlation between ONSD and ICP values from invasive monitoring data, and to carry out a statistical analysis of the data obtained.

Materials and Methods

The work is a single center retrospective cohort study. The data of the Burdenko Neurosurgical Institute (FGAU NNPTCN named after NN Burdenko of the Russian Ministry of Health) from a prospectively collected database of patients who sustained severe traumatic brain injury in the period from 2004 to 2013 were used for the analysis.

The inclusion criteria were: the diagnosis of severe TBI at the time of hospitalization (GCS score 8 points or less), age over 16 years, admission to the Institute within the first 2 days after the injury, the availability of CT scan data at the time of admission to the intensive care unit, blood pressure monitoring data, ICP for the duration of stay in the ICU in the specified period of time.

The exclusion criteria were: presence of cranio-orbital trauma, hospitalization after more than 2 days from the moment of the injury, absence of neuromonitoring data, presence of artifacts on CT scan in the projection of the optic nerve, and history of craniotomy and decompressive trepanation, signs of basal liquorrea.

Based on the presented criteria, 41 patients (11 women and 30 men) with a severe TBI (GCS 8 points or less) were enrolled in the study. The mean age was 30±11 years. All patients have indications for invasive measurement of ICP based on the severity of their condition, clinical-neurological picture and CT data.

Distribution of patients by GCS scores is presented in Fig. 1. There were 19 (40%) patients with isolated TBI, and 16 (33%) with closed TBI. All patients underwent CT scan upon admission to ICU (CereTom, Neurologica Danvers MA, USA). Scanning was carried out with a slice thickness of 2.5 mm. All the patients were in the intensive care unit on ALV, intensive therapy was performed in accordance with international recommendations [3].

Parenchymal ICP (“Codman & Shurtleff, MA”, USA) was measured in all patients with the average duration of monitoring of 7±1.7 days.

The ICP sensor was installed in the intensive care unit. The sensor was implanted into the white matter of the brain into the premotor zone according to a conventional technique to a depth of 2 cm from the inner bone plate through the trephination hole in the projection of the Kocher point. The implantation side was selected based on the nature of the injury. In case of a diffuse lesion, the sensor was implanted in the subdominant hemisphere; in case of a focal lesion, it was installed to the side of greater damage to the medulla. The sensor was calibrated according to the manufacturer’s instructions on the surface of the sterile saline solution at the water-air interface. The values of the main parameters (BP, ICP) were recorded using Software ICM + (“Cambridge”, United Kingdom) with a frequency of 100 Hz. The ICP parameters used for further analysis are presented in the Table.

The evaluation of ONSD was performed “blindly” by two radiologists (DAS and TAM). ONSD measurements were carried out on a range of 25—300 units. The ONSD value was measured at a distance of 3 mm from the posterior eyeball contour (Fig. 2). The larger of the two ONSD measurements was chosen for further statistical analysis. Only the data of the first CT scan after the hospitalization were analyzed.

Figure 3 shows the dynamics of ICP in a patient with severe TBI, who underwent CT (see Figure 2), and met the requirements for invasive ICP monitoring based on clinical-neurological and neuroimaging criteria. Despite the fact that at the time of the installation of the sensor the ICP was at the level of 5—6 mmHg, the patient subsequently had repeated and multiple episodes of ICP increase up to the level exceeding 20 mmHg, which required targeted intensive therapy.

The ICP parameters were recorded for each patient using the Software ICM + (“Cambridge”, United Kingdom) and were used for subsequent statistical analysis (see Table) as a mean, median and maximum values, as well as standard deviations, the total duration of ICH (ICP>20 mmHg) over the entire monitoring period. Based on the data obtained, correlation and ROC analysis was performed using the R-project software package (www.r-project.org).

All patients were divided in two groups: the first group included 10 patients with normal ICP, and the second group included 31 patients with the development of ICH. ROC-analysis was performed to assess the possibility of using ONSD as the classifier of ICH. Calculated quantitative characteristics of ROC analysis: Area Under Curve (AUC), optimal threshold value and corresponding values of sensitivity and specificity. 95% confidence intervals for AUC, sensitivity, and specificity were calculated using the bootstrap replication method by generating pseudo-sample sets.
Results

In 31 (76%) out of 41 patients, the total duration of the recorded ICH (ICP>20 mmHg) was more than 1 hour.

Based on the results of the ROC analysis, a threshold value of CT-based ONSD equal to 6.35 mm was established for both groups of patients. This ONSD value corresponds to a point with a maximum total sensitivity of 0.93 (95% CI 0.84—1.00) and specificity of 0.80 (95% CI 0.50—1.00) and AUC of 0.87 (95% CI 0.69—1.00) (Figure 4).

The distribution of the optic nerve sheath diameter was considered normal, as values of $p>0.05$ were obtained in the Shapiro-Wilk tests. The Pearson correlation coefficient between the diameters of the sheath of the left and right optic nerves is 0.78 ($p<0.05$, 95% CI 0.62—0.88) (Fig. 5). Such high correlation indicates narrow spread of the ONSD of the left and right eye in each patient under study.

Discussion

The first studies of ICP dynamics were conducted by Lundberg in 1960. He was the first to perform continuous measurement of cerebrospinal fluid pressure in the ventricles of the brain. Later, various methods of invasive ICP measurement were developed and introduced into practice: in the subarachnoid and subdural spaces, in the parenchyma of the brain. Each of these methods has its own advantages and disadvantages [22, 23].

The installation of an intracranial pressure sensor of any type is a surgical intervention and is associated with the development of hemorrhagic and infectious complications, as well as the problem of the ICP “zero value” drift [24]. There are a number of non-invasive techniques that allow one to indirectly assess the presence of ICH: quantitative papillometry, ophthalmodinamometry, assessment of the swelling of the tympanic membrane, measurement of ONSD (by different methods), transcranial dopplerography, MRI, CT [25].

According to the literature [26], the accurate measurement of ONSD can be performed using ultrasound or MRI, and the values obtained by these methods are in good agreement with each other. The data obtained by MRI and CT are also well correlated [21]. In the case of severe TBI, the primary diagnostic method is CT, which, in contrast to ultrasound, is an operator-independent method of examination.

Examined ICP parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Patients without ICH</th>
<th>Patients with ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (standard deviation)</td>
<td>41</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Number of men, %</td>
<td>32 (12)</td>
<td>32 (16)</td>
<td>32 (11)</td>
</tr>
<tr>
<td>Number of women, %</td>
<td>30 (73)</td>
<td>8 (80)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>GCS, median (25—75 quantiles)</td>
<td>11 (27)</td>
<td>2 (20)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>GOS, median (25—75 quantiles)</td>
<td>6 (4—7)</td>
<td>7 (5—7)</td>
<td>6 (4—7)</td>
</tr>
<tr>
<td>Marshall scale, median (25—75 quantiles)</td>
<td>3 (3—4)</td>
<td>3 (3—4)</td>
<td>3 (3—4)</td>
</tr>
<tr>
<td>Average ONSD on the left, mm (deviation)</td>
<td>6.73 (0.66)</td>
<td>6.08 (0.71)</td>
<td>6.94 (0.49)</td>
</tr>
<tr>
<td>Average ONSD on the right, mm (deviation)</td>
<td>6.52 (0.75)</td>
<td>5.75 (0.62)</td>
<td>6.77 (0.62)</td>
</tr>
<tr>
<td>Average ONSD of the largest optic nerve, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(standard deviation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of lethal outcomes, %</td>
<td>6 (15)</td>
<td>0 (0)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Number of adverse outcomes, %</td>
<td>22 (54)</td>
<td>5 (50)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Median ICP (standard deviation)</td>
<td>16.45 (6.11)</td>
<td>10.95 (4.18)</td>
<td>18.22 (5.59)</td>
</tr>
<tr>
<td>Mean ICP (standard deviation)</td>
<td>12.26 (4.86)</td>
<td>8.1 (5.00)</td>
<td>13.61 (4.03)</td>
</tr>
<tr>
<td>Duration of ICP &gt;20 mmHg (standard deviation)</td>
<td>16.84 (32.93)</td>
<td>3.02 (6.37)</td>
<td>21.30 (36.73)</td>
</tr>
</tbody>
</table>
The increase in ONSD with an increase in ICP is associated with the peculiarities of the optic nerve structure. An increase in ICP alongside with the depletion of the mechanisms of spatial compensation, causes redistribution of CSF from the intracranial to extracranial spaces, which is accompanied by an expansion of the optic nerve sheaths and an increase in ONSD. These changes are most pronounced in the distal third of the optic nerve, closer to the eyeball [15]. It has been shown experimentally that the most pliant part of the optic nerve sheath is located in the region of its ampullar part, therefore it is generally accepted practice to evaluate ONSD at a distance of 3 mm from the posterior wall of the eyeball [16]. Normal CT-based values of ONSD in this area were calculated in a study of 300 patients without clinical and radiological signs of ICH. According to the results of the study, ONSD values were in the range from 4.94±1.51 to 5.17±1.34 mm [27].

Measurements of ONSD using of MRI showed that at a diameter of less than 5.3 mm the development of ICH is unlikely, whereas with a ONSD of more than 5.82 mm, the probability of ICH development is 90% [20].

M. Sekhon et al. [14] identified a strong correlation between the ONSD and ICP values in severe acute TBI. Using the threshold value of 6 mm, the authors obtained an area under the curve AUC=0.83 (95% CI 0.73-0.94) with a true positive value in 67% of cases, false-positive in 92%. The authors concluded that the CT-based measurement of ONSD is more accurate criterion for development of ICH (R²=0.56) compared to such CT signs (R²=0.21) as compression of the lateral ventricles, smoothing of the border of white and gray matter, lateral displacement of more than 5 mm, and compression of basal cisterns. They also showed that nosocomial mortality doubles with an increase in ONSD of 1 mm (ratio of probability of occurrence and non-occurrence of the event, odds ratio (OR) 2.0, 95% CI 1.2—3.2, p=0.007).

Our results on the correlation between ONSD and ICP are fairly close to the data of M. Sekhon et al. [14], since the studies were conducted on similar groups of patients in an early period after the injury and were compared with the analysis of invasive ICP measurement.

Despite the results obtained, which are consistent with the data of other authors, we want to emphasize a

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![Fig. 2. CT of the patient with severe TBI and intracranial hypertension. ONSD on the left, 7.48 mm, on the right, 7.15 mm. Intracerebral hematoma in the basal parts of the right temporal lobe.](image2)

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![Fig. 3. Dynamics of ICP in the patient after a CT scan (see Figure 2) and deciding on invasive monitoring of ICP (data for the first 24 hours are presented).](image3)

ICP at the moment of the sensor installation was 5—6 mmHg.
number of important points that should be taken into account in clinical practice.

First of all, CT is a screening diagnostic method that provides information on the state of the injured brain and adjacent tissues at a particular time point.

Secondly, we analyzed a limited number of patients (41 patients) who were admitted to the Institute within the first 48 hours from the moment of the injury. According to the literature [28], this period is associated with the maximum risk of ICH development due to traumatic brain damage and formation of cerebral edema. Therefore, we did not rule out a possibility that some of the patients could have undergone ICH prior to hospitalization and the beginning of invasive ICP monitoring. We would like to remind that all patients had severe TBI and were in coma, which indicates the severity of the primary brain damage and, accordingly, the high probability of ICH. Therefore, some patients could have had overextended sheath of optic nerves with corresponding high ONSD values already at the time of hospitalization. This fact can explain rather low, but reliable correlation of ICP and ONSD, which was lower than in the studies by Sekhon et al. ($r=0.7$).

According to literature data [15, 16], ONSD is a fairly dynamic parameter which can rapidly increase after the increase in ICP. Long exposure to ICP over 35—55 mmHg can promote overextension of the sheaths, which can persist in the future even at normalization of ICP. In our work, we compared only ONSD at the time of hospitalization with parameters of invasive measurement of ICP (maximal, mean, median). Preliminary analysis showed that ONSD values were significantly correlated with median and mean ICP values, but since most patients had abnormal ICP distribution, we chose median values for the analysis. In our opinion, the low correlation coefficient between ONSD and the median ICP can also be attributed to the "noisiness" of the ICP (Figure 3).

Thirdly, the objective of our retrospective study was to evaluate the correlation between ONSD and ICP and we have achieved this objective. In addition, we estimated the threshold value for ONSD, which can, potentially,
allow a clinician to identify a group of patients which has already experienced ICH, with ICH that developed at the time of CT examination, or, which is of the highest particular importance, with a high probability of ICH development in the short term after the CT. We would like to note that ONSD values in the group of patients with ICH (Table 1) significantly exceeded those in the group with normal ICP. According to our data, 76% of the subjects developed ICH with a total duration of more than 1 hour, despite the full range of preventive and curative measures in accordance with accepted guidelines. In our opinion, higher than the threshold ONSD value at the time of the primary examination of patients with severe TBI may be an additional indication for invasive ICP monitoring, as it can reveal both the likelihood of the previous ICH and the likelihood of ICH development in the future. However, it should be noted that the interpretation of ONSD values may be difficult in case of liquorreha, cranio-orbit-facial trauma, after craniotomy, and drainage of the ventricular system.

Conclusions

A correlation between the CT-parameter ONSD and the median ICP in patients with severe TBI was identified with a correlation coefficient of 0.32 (p<0.05). The threshold ONSD value was 6.35 mm, with sensitivity of 0.93 (95% CI 0.84—1.00), specificity of 0.80 (95% CI 0.50—1.00), and AUC of 0.87 (95% CI 0.69—1.00).

Authors declare no conflict of interest.
Intracranial hypertension is one of the most important problems in neurosurgery and neuroreanimatology, which arises in treatment of patients with severe traumatic brain injury (TBI) associated with both primary traumatic brain injuries and secondary changes and subsequent edema of the brain, disruption of perfusion parameters and liquorodynamic disturbances, and it requires a complex of individualized medical interventions.

This work reflects the constant drive in medicine to reduce the invasiveness in both medical and diagnostic practice at any stage of the patient’s management. Computed tomography has long gone beyond the stationary diagnostic units, and mobile and compact CT machines are widely used in operating and resuscitation rooms.

The article analyses retrospective data of the measurement of the CT-cased optic nerve sheaths diameter (ONSD) in 41 patients in the acute period of TBI (within 2 days after the injury) and evaluates a correlation between them and the results of the invasive measurement of intracranial pressure (ICP) by the parenchymal sensor.

This method is highly relevant since CT-based ONSD measurement make it possible to indirectly assess the presence of intracranial hypertension without resorting to the invasive ICP monitoring, which naturally reduces the number of complications. There are quite a few publications devoted to this topic in foreign literature, but the number of Russian articles is quite low. The low prevalence of this technique is due, among other things, to the fact that intracranial pressure is a very labile indicator.

The authors rightly note that in the acute period of TBI ICP can vary a lot, whereas the diameter of the optic nerve sheath appears to be a more inert indicator of intracranial hypertension. There are may be cases when the patient already had a history of low intracranial pressure, and the ONSD remains elevated.

In the article, the authors consider cases in which the patients with certain to anatomical features or racial origins who had no history of TBI, have enlarged optic nerves with wide perineural spaces. Although this does not concern the topic of this paper, it would be interesting to investigate the dynamics of the restoration of the optic nerve sheaths after the normalization of intracranial pressure.

Overall, the work is interesting and relevant, well-presented and contains the results of the correlation analysis. The article can be useful to neuroradiologists, neurosurgeons and, of course, resuscitators. Resuscitators who have only just started their career can learn important information about various forms of non-invasive control of changes in intracranial pressure. It will also be of interest to neurophysiologists studying the features of liquorodynamics in patients with intracranial lesions.

M.B. Dolgushin (Moscow, Russia)
Over the past two decades, improvements in surgical tools, navigation systems, and endoscopic techniques have resulted in the widespread use of keyhole surgery for a wide range of skull base tumors. Currently, the trans-eyebrow supraorbital approach is being increasingly used in surgery for anterior cranial fossa and parasellar tumors [1—20]. The advantages of supraorbital craniotomy are reduced brain traction and wide access to the anterior cranial fossa and suprasellar region [3, 4, 8, 11, 12, 17—20]. A small skin incision and minimum soft tissue dissection result in absence of severe pain syndrome in the postoperative period compared to standard craniotomies [3, 17—20].

**Material and methods.** The study included 7 patients (5 females and 2 males) who underwent surgery for meningioma using the trans-eyebrow supraorbital approach at the Burdenko Neurosurgical Institute in the period between 2013 and 2017. The age of patients ranged from 51 to 75 years (median, 60 years). The maximum size of resected tumors ranged from 20 to 60 mm (median, 40 mm).

**Results.** Total tumor resection was achieved in all 7 cases, which was confirmed by postoperative MRI control. All 7 patients had a good cosmetic result. In 1 case, there was postoperative cerebrospinal fluid rhinorrhea due to incomplete closure of the frontal sinus, which required reoperation. None of 7 cases was complicated by injury to the main vessels or cavernous sinus.

**Conclusion.** Supraorbital trans-eyebrow craniotomy provides a minimally invasive approach for removing most anterior cranial fossa base and suprasellar tumors. The advantages of keyhole surgery, in comparison with traditional craniotomies, are minimal complications associated with the approach.

*Keywords: meningioma, keyhole surgery, surgical approach.*

**Patient’s position on the operating table**

The patient is positioned supine with the head fixed with the Mayfield frame (Fig. 1).

The head is rotated by 30° in case of the suprasellar meningiomas. The head is rotated by 45—60° to the contralateral side of the approach in case of olfactory fossa meningiomas. The degree of the head rotation depends on tumor location and projection: large tumors located in the anterior parts of the anterior cranial fossa require the greatest rotation of the head to approach the tumor margin opposite to the trephination. The head should be slightly bent for eminence of the zygomatic bone to be the most elevated point. When frontal sinus repair is needed, a small area of the anterior abdominal wall is prepared for collection of subcutaneous adipose tissue.

**Surgical approach**

The eyebrow is shaved off and borders of an incision are marked for skin incision. The supraorbital foramen is a landmark point for the medial border of an incision. The preoperative clinical symptoms were cephalic syndrome in 4 and decreased visual acuity in 3 cases. The choice of surgical approach depended on abundance of the eyebrow hair, size of the frontal sinus, anatomical and topographic features of the tumor and the patient’s agreement. The maximum diameter of the resected tumors ranged from 20 to 60 mm (median 40 mm). All operations were performed using the Mari precision control system in conjunction with a surgical microscope, without the use of retractors.
temporal muscle is also pulled by hooks to expose the “key point” posteriorly to the frontal-zygomatic process of the zygomatic bone (Fig. 3a). A single burr hole is made posteriorly to the “key point” and downward from the superior temporal line using a high-speed drill. Afterwards, approximately 15—20 × 20—25 mm osteoplastic craniotomy without involvement of the orbital roof is performed (Fig. 3b).

After performing craniotomy, to improve view and reduce brain traction, it is very important to remove the inner bone plate along craniotomy margins using a drill but the outer bone plate should remain intact (Fig. 4). Also, it is necessary to remove large bone protrusions on the anterior cranial fossa base using a drill, if they prevent optimal view and approach to the tumor. When the frontal sinus is opened, it must be closed by an autograft.

Suture

After tumor removal, the dura mater is closed with a continuous suture. TachoComb was placed on top of the suture for sealing. It is necessary to examine the anteromedial wall of the trephination for the presence of a defect in the frontal sinus. In the absence of defects, a bone flap is put in place and fixed with 3—4 titanium plates. The site of the burr hole is covered with the superior temporal muscle and fascia. To achieve a good cosmetic effect, the bone flap is placed at an equal distance from the trephination margins. Next, the subcutaneous adipose tissue and skin are sutured; the skin is sutured with an intradermal absorbable suture. When a defect is present in the frontal sinus, adipose tissue is placed in the frontal sinus, which was previously taken from the paraumbilical region. Adipose tissue is additionally fixed with fibrin-thrombin glue.

Results

Total resection of the tumor was achieved in all seven patients that was confirmed by postoperative MRI scans. The dynamics of visual impairment was evaluated 2, 6 and 12 months after surgery. On examination by a neuroophthalmologist, 2 patients out of 3 with reduced visual acuity had a positive dynamics yet in the early postoperative period by the time of discharge. In 1 patient, visual impairment completely regressed by the end of the first year after surgery. Negative dynamics of visual function after surgery was observed in 1 patient: occurrence of chiasmatic syndrome, which completely regressed 4 months after surgery. Bilateral anosmia was revealed in 3 patients in the postoperative period. This complication occurred due to the significant size of the tumor and because that the olfactory tracts were difficult to identify intraoperatively. Periorbital edema was observed in 5 cases and regressed on the 7th day after surgery. The frontal branch of the facial nerve was not injured in any of the 7 cases. In 1 case, the supraorbital nerve was injured resulting in the loss of surface sensitivity of the skin in the frontal region above the incision. Two patients had a temporary decrease in sensitivity. In 1 case, there was postoperative cerebrospinal fluid rhinorrhea because of incomplete closure of the frontal sinus and required re-operation.
None of the 7 cases was associated with injury to the main vessels or cavernous sinus. All 7 patients achieved a good cosmetic effect (Figs. 5, 6).

Case report No. 1
A female patient, 55 years old. The patient started to notice an aggravation of headaches over a year. The patient noticed a decrease in visual acuity 4 years ago and a narrowing of visual field on the right eye 1.5 years ago. MRI of the brain revealed a meningioma of the tuberculum sellae (Fig. 5a, b). Preoperative ophthalmological examination revealed an asymmetric chiasmal syndrome with a significant compression on the right optic nerve, visual acuity OD=0.1, OS=1.0. The patient was operated on through the right supraorbital trans-eyebrow approach. In the early postoperative period, acuity on the right eye improved to 0.4. The patient was discharged on the 7th day in a satisfactory condition (Fig. 5c, d). One neuro-ophthalmologic examination 2 years after surgery, a positive dynamics with improvement of visual acuity to 0.7 on the right eye and vision field expansion on the right eye were noted. Control MRI did not reveal any signs of the tumor (Fig. 5e, f).

Case report No. 2
A female patient, 61. The patient noted severe headaches over 2 years, with increased frequency of headaches over the past year. She underwent MRI on her own and a large meningioma of the anterior cranial fossa base was revealed (Fig. 6a, b). Preoperative ophthalmologic examination revealed no abnormalities, acuity OD=1.0, OS=1.0. The patient was operated on through the left supraorbital trans-eyebrow approach. Preliminary, lumbar drainage was inserted to the patient in the operating room. The operation proceeded normally. The wound healed by primary intention. The patient was discharged on the 5th day after surgery (Fig. 6c). In the postoperative period, there was hypesthesia in the frontal region at the side of the approach that regressed completely in 3 months. Control MRI did not reveal any signs of the tumor (Fig. 6d, e).

Discussion

Minimally invasive keyhole approaches
The advancement of navigation systems, endoscopes, microsurgical instruments and aspirators has resulted in widespread use of a keyhole surgery for resection of a wide range of tumors, including meningiomas [21, 22]. In a keyhole surgery principle, a significant depth of a surgical wound permits an optimal view even with a small craniotomy (Fig. 7). With its improvement, a keyhole-microsurgery has become increasingly popular among neurosurgeons and its application is gradually increasing compared to traditional approaches to the anterior and anterolateral skull base parts.

Supraorbital trans-eyebrow approach
Classic neurosurgical approaches to the skull base, such as Dandy’s frontotemporal macrosurgical approach and Yasargil’s microsurgical pterional approach, are well described in the literature. Their safety and efficacy are widely known from research papers and routine clinical practice [23, 24]. However, these approaches require extensive manipulations with tissues and bone structures, which can lead to the formation of rough scars, bone defects, temporal muscle atrophy and cause pain when chewing [25]. Therefore, the supraorbital trans-eyebrow approach was developed allowing one to access intracranial lesions through a minimum skin incision, minimal injury to soft tissues and minimal impact on bone structures. Although the surgical corridor with the supraorbital trans-eyebrow approach is narrow in vertical and horizontal directions, most tumors of the anterior cranial fossa and parasellar region can be easily resected through this approach [3, 4, 18, 26]. In addition, in experienced hands, this approach increases the efficiency of the operation reducing intraoperative blood loss and operative time [27].

The technique of supraorbital trans-eyebrow approach has been improved over the last 20 years. Its safe-
ty and efficacy in adults [28] and children [29] have been shown. The approach is used in a wide range of pathologies, including aneurysms, cavernomas, meningiomas and optic nerve compression.

A review of the literature [18, 27, 30—35] on the supraorbital trans-eyebrow approach over the last 20 years revealed 8 papers that included large series of publications (a total of 2783 patients, 2508 aneurysms and 577 [19%] tumors).

The main types of tumors were meningiomas, gliomas, and metastases. The main locations of tumors were the anterior cranial fossa, suprasellar region, interpeduncular cistern, anterior and medial parts of the temporal lobe.

Data on extent of resection were presented in 238 (41%) cases of 577 resected tumors; total removal was achieved in 215 (90%) cases, subtotal — in 17 (7%), and partial — in 6 (3%).

The most frequent location of aneurysms clipped through this approach was aneurysms of the anterior cerebral — anterior connective artery (31%). In other cases, middle cerebral artery bifurcation (26%), the internal carotid artery (20%), the basilar artery and the superior cerebellar artery (23%) aneurysms were found. Despite cases of intraoperative rupture, there were no difficulties over control of bleeding associated with the approach; 97% of patients achieved complete exclusion of aneurysm from the circulation [18, 27, 32—35].

The literature reports that complications occurred when the approach was performed improperly. The most frequent complications included temporary accumulation of CSF under the skin flap and decreased sensitivity in the frontal area on the approach side — temporary in 1.6% of cases and permanent — 4.3%. These complications occur in approximately 1 of 20 patients. More serious of the described complications was injury to the frontal branch of the facial nerve resulting in inability to raise the eyebrow. This complication was revealed in almost 3% of cases (Table).

Wound revisions were performed in 52 (2.5%) cases. The exact relationship of the revision and the selected approach could not be assessed due to insufficient information on revision.

The cosmetic effect is difficult to evaluate objectively because of the subjective perception by the patients, similar to aesthetic effect evaluated by some independent person. However, in 89.3% of cases, aesthetic effect was considered as excellent; headache and pain in the postoperative wound area were absent or minimal [36], more than 90% of patients were satisfied [37]. 92.8—96.9% of patients considered the cosmetic result to be “quite pleasant” and “excellent” [36]. The aesthetic advantage of this approach is most evident in patients with high growth of hair, in whom a common incision of the skin would result in a noticeable scar on the scalp. The most common complaint was on “depression” at the burr hole site [36].

**Limitations of the approach**

Investigations on cadavers have greatly expanded the understanding of limitations in the supraorbital approach. The research showed that the anterior cranial landmarks for safe skin incision differ significantly (for example, the position of the supraorbital foramen in relation to the lateral frontal sinus) [38, 39]. In addition, a large frontal sinus limits trephination size and forces the surgeon for more lateral trephination and to change an approach trajectory [40]. Cadaveric studies have also shown that supraorbital approach mostly provides a good view of the anterior cranial fossa structures while view of the middle cranial fossa structures and cavernous sinus is partially closed by the lesser sphenoid wing. The orbital bar can also restrict the view of deep structures. Orbital bar removal provides more maneuverability in angles of attack but does not improve view of the structures [41]. In addition, view of the anterior cranial fossa is limited by the orbital roof making impossible to resect midline lesions of anterior parts of the anterior cranial fossa. The results of cadaveric investigations showed that the supraorbital approach offers the same working area as the pterional and orbitozygomatic approaches but with much smaller angles of attack compared to standard approaches [42].

At first, this approach appears sophisticated and there seems to be a gradual acquisition of experience in operating through this approach. Inadequate approach to tumors with substantial spread can provide partial resection of the tumor and reoperations through another approach may be needed subsequently. Practicing to use the approach on cadavers is often necessary for a surgeon to become acquainted with anatomical landmarks and viewing angles, which are very different from traditional craniotomies. In addition, anatomical features, such as the superior bony margin of the orbital rim or a large frontal sinus, can significantly complicate an approach to complex or giant aneurysms [43].

Frequent movement of a microscope for an optimal view of the operating field is a disadvantage of a keyhole surgery. Frequent movement of the surgical microscope

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**Fig. 4. The dura mater is moved downwards by vacuum aspirator (1) paralleled by inner bone plate removal at the edges of trephination by a pneumatic drill (3). The outer bone plate remains intact (2).**
and adjustment of focus and zoom during manipulations in deep skull base structures, especially in the absence of a retractor system, is physically demanding for the surgeon and limits the surgeon’s work under high zoom. Therefore, all operations were performed using the Mari control system of the surgical microscope [44].

**Supraorbital trans-eyebrow approach for resection of meningiomas**

Meningiomas of the anterior cranial fossa constitute approximately 12—22% of all intracranial meningiomas [45—47]. Following pioneering publications by Durante (1884), Cushing and Eisenhardt (1938), various
A series of research papers on the removal of olfactory and suprasellar meningiomas were published. According to the published data [46—64], over the last two decades, olfactory and suprasellar meningiomas were operated using various approaches, including bifrontal, unilateral subfrontal, pterional and fronto-pterional approaches. The most radical removal of olfactory meningiomas (85—100%) was achieved using pterional and bifrontal approaches.

Fig. 6. A female patient with a large meningioma of the anterior cranial fossa base, more on the left.

a, b — T1-weighted contrast-enhanced MRI scans; c — the patient 1 year after surgery; d — postoperative T1-weighted contrast-enhanced MRI scan, no signs of the tumor; e — T2-weighted MRI scan, no signs of brain injury.
approaches and resulted in a low rate of complications [48—50]. The probability of tumor recurrence varied from 5 to 41% within 10 years and was mainly associated with incomplete removal. Residual tumor fragments were mostly located on the anterior cranial fossa base and base of labyrinth of ethmoid or sphenoid sinus [49, 50, 57, 61, 65, 66].

Total resection of suprasellar meningiomas often seems more difficult, as these tumors can spread along the optic nerves, the hypothalamic-pituitary region, the anterior portions of the circle of Willis and cavernous sinus [51—54]. In recent papers [46, 47, 51—54, 58—60, 62, 63], radical removal of suprasellar meningiomas ranged from 67 to 100%, visual deficits occurred at a rate of 20% and mortality ranged from 0 to 8.7%.

A comparative analysis of the supraorbital and traditional transcranial approaches for anterior cranial fossa and parasellar tumors is presented in several references. The extent of radical tumor resection through these approaches was approximately similar and reached 86—100% for olfactory meningiomas and 40—100% for suprasellar meningiomas [4, 11, 17, 19]. Subtotal removal occurred largely because of non-optimal approach and invasive growth of tumors [4, 11, 17, 19]. When deciding to use this approach for the removal of suprasellar and anterior cranial fossa meningiomas it is recommended to take into account topographic and anatomical features of the tumor, experience of the surgeon and availability of necessary neurosurgical tools. Absence of meningioma invasion to the anterior cranial fossa, particularly on the opposite side of the approach, and tumor sizes not exceeding 60 mm are optimal for surgery through the supraorbital approach [3, 4, 8, 18, 50]. Larger tumors can also be removed through the supraorbital approach as long as major tumor volume is located within the surgical corridor (Fig. 7) [4].

A contraindication to the supraorbital approach is invasive tumor growth to labyrinth of ethmoid and the sphenoid sinus because small size craniotomy restricts the surgeon’s work when repair of the base of the anterior cranial fossa and removal of tumors from these areas are needed. Tumors with bilateral spread to the anterior parts of the anterior cranial fossa and paranasal sinuses are more suitable for removal through bifrontal, pterional and other traditional approaches to the anterior cranial fossa base [48, 50, 56].

### Conclusion

Supraorbital trans-eyebrow craniotomy offers minimally invasive approach for the treatment of a wide range of pathology in the anterior cranial fossa base and suprasellar region. An advantage of a keyhole surgery compared to traditional craniotomies is minimum complications. Key factors in the choice of the approach are location and spread of the tumor, anatomical features of the patient and experience of the surgeon. Tumor spread to the anterior cranial fossa contralaterally to the approach and tumor spread to paranasal sinuses are contraindication to the removal of olfactory meningiomas through the supraorbital approach. Simplified closure of the surgical

### Table: Number and types of complications associated with the supraorbital trans-eyebrow approach, according to published data

<table>
<thead>
<tr>
<th>Author</th>
<th>Number and types of complications (T — temporary, P — permanent), abs. (%)</th>
<th>Number of revisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. Thaher et al., 2015 [30]</td>
<td>0 8 (2.3)</td>
<td>0 8 (2.3)</td>
</tr>
<tr>
<td>R. Reisch et al., 2014 [31]</td>
<td>13 T; 18 T; 13 P (4.4; 3.2)</td>
<td>23 (5.6)</td>
</tr>
<tr>
<td>G. Fischer et al., 2011 [32]</td>
<td>0</td>
<td>9 (1.1)</td>
</tr>
<tr>
<td>W. Warren et al., 2011 [33]</td>
<td>2 P (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>R. Reisch et al., 2005 [18]</td>
<td>25 P (5.6)</td>
<td>34 P (7.6)</td>
</tr>
<tr>
<td>J. Paladino et al., 2005 [34]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S. Czirjak et al., 2002 [35]</td>
<td>1 P (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>E. van Lindert et al., 1998 [27]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number, %</td>
<td>13 P (1), 36 T (2.9)</td>
<td>18 T (1.6), 49 P (4.3)</td>
</tr>
</tbody>
</table>

**Fig. 7.** Schematic representation of the trajectory in the supraorbital trans-eyebrow approach (indicated by arrows) and the corresponding areas within the approach (marked in yellow). The anterior parts of the anterior cranial fossa on the contralateral side of the approach are the “blind spot”.
wound and minimal risk of postoperative CSF leak and the possibility of safe manipulation near the vessels of the anterior portion of the Willis circle and the optic nerves are advantages of the supraorbital trans-eyebrow approach.

Authors declare no conflict of interest.
This paper by authors from the Burdenko Neurosurgical Institute is relevant and valuable in modern medicine. The authors are recognized leaders in skull base tumor surgery; they have extensive experience acquired on a wide base of the Burdenko Neurosurgical Institute clinics, one of the leading centers for the treatment of neuro-oncologic diseases. The authors used their clinical material to tackle a particular clinical issue and successfully used a sophisticated but the optimal method for resection of complicated tumors.

The use of these keyhole-approaches can reduce surgical trauma and offers the most favorable outcomes. Currently, supraorbital trans-eyebrow approach has its advantages and drawbacks and is actively used in many clinics, along with lateral supraorbital approach and transphenoidal endoscopic access for the same group of patients. Surely, this approach should be used for a certain category of patients. Choice of an approach is mostly individual for each patient based on features of tumor growth, the patient’s desire, and sometimes capacities of the surgeon.

In addition to the personal experience of the authors, this paper contains a literature review, which gives insight into opportunities of this approach.
CASE REPORTS

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Surgery for Intractable Epilepsy in a Patient with Encephalocele of the Temporal Lobe: a Case Report

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We describe a case of surgical treatment of intractable temporal epilepsy in a female patient with congenital middle cranial fossa encephalocele. We analyze outcomes of surgery for this pathology, which have been reported in the literature. To date, there have been a few articles on this subject in the domestic literature. The development of neuroimaging techniques and a growing number of verified encephalocele cases promote the widespread use of surgery for treatment of intractable epilepsy. Congenital encephalocele should be considered in the differential diagnosis of intractable temporal epilepsy, and, if verified, surgical treatment is the method of choice in most cases.

Keywords: temporal epilepsy, epilepsy surgery, encephalocele.

The presence of encephalocele was verified prior to surgery using neuroimaging. Magnetic resonance imaging (MRI) of the brain involved epileptologic scanning with a focus on the cortex and the medial temporal lobe. Bulging of the meninges and brain matter with a size of 15x21x21 mm was revealed along the anterior contour of the left temporal lobe (Fig. 1). Helical computed tomography revealed a defect of the sphenoid wing at site of encephalocele location (Fig. 2).

Since traumatic brain injuries, surgical interventions, inflammatory diseases of the craniocerebral system were not indicated in anamnesis, encephalocele was regarded as congenital.

Fig. 1. A female patient K. Meningoencephalocele of the left temporal lobe pole. Magnetic-resonance tomography in axial view.

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Preoperatively, the patient had a consultation with a neuropsychologist. Neuro-psychologic tests did not reveal any signs of functional deficit in the left temporal lobe.

Meningoencephalocele and the anterior portions of the middle and inferior temporal gyri in the region of the sphenoid wing on the left side were resected on February 22, 2017 through a standard pterional approach to the left frontal-temporal area. Bone formations of the MCF and the sphenoid wing with thinning of bone tissue and a bone defect covered with the dura mater were resected. Afterwards, an approach along the base of the left temporal lobe was made; medial dissection of the Sylvian fissure, resection of the anterior parts of the middle and inferior temporal gyri (less than 3 cm from the temporal fossa pole) were performed. Encephalocele in the basal parts of the MCF was resected (Fig. 3). The defect after
the excision of meningocele was plugged with autologous muscle tissue and covered with Evisel glue.

A defect in the MCF base and encephalocele were visualized. During the entire operation, electrical cortical activity of the brain was recorded using scalp electrodes; patterns of seizures during monitoring were not observed.

Postoperatively, epileptic seizures were not recorded. Anticonvulsant therapy was continued in the same regimen and was adjusted in 6 months after surgery. The patient’s condition was satisfactory. Follow-up and neuropsychological testing are planned. The pathomorphological study of resected tissues showed that the material is represented by brain tissue (cortex and white matter with impaired architectonics and irregular glial hyperplasia); there were sites of sclerotic pia mater and single siderophages. An assembly of thin-walled vessels was revealed (Fig. 4).

Discussion

Encephalocele is a rare possible cause of intractable epilepsy. The literature describes about 45 such cases [3—5, 8—11]; surgical treatment was effective in the vast majority of these cases.

The extent of brain tissue resection is debated; however, many authors agree that resection of the encephalocele with adjacent 1—1.5 cm² of brain tissue is sufficient [3—5, 12]. It is suggested that the resection extent can be increased according to neuroimaging data pointing to morphological changes of the amygdala and hippocampal complex or rapid spread of epileptiform activity to this region on EEG [7, 13]. Determination of the extent of surgical resection is very important due to possible development of neuropsychological defect during lobectomy, particularly when encephalocele is located in the dominant hemisphere, as in the described case report. We have chosen the tactics of minimal resection that allowed us to prevent occurrence of postoperative neurological deficit. The literature reports that outcome also depends on duration of preoperative epilepsy [13].

We believe that growing awareness of radiologists, epileptologists, neurosurgeons in terms of encephalocele and use of more precise neuroimaging techniques will result in more frequent detection of this pathology. Therefore, some patients with MRI-negative pharmacoresistant epilepsy may need surgical treatment.

Authors declare no conflict of interest.

REFERENCES


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This paper is focused on a rather rare condition — symptomatic focal epilepsy due to meningoencephalocele of the middle cranial fossa and glial-cicatricial changes in the temporal lobe neocortex at the site of its prolapse into skull base defect.

The authors present their own case of a young woman who had a 4-year history of frequent temporal lobe seizures that were resistant to main antiepileptic drugs. Resection of pathological cortical regions stopped epileptic seizures. Meanwhile, the authors initially refused not only to resect the medial structures (amygdala, hippocampus, entorhinal cortex), but also, unlike to conventional practice, did not use invasive EEG study (extra— or intraoperative) to confirm or exclude the involvement of these structures in epileptogenesis. Apparently, we can agree with the authors because the defect in their patient was located on the side of the dominant hemisphere and preoperative neuropsychological testing did not reveal any decrease in the patient’s verbal memory.

Case description shows that the true cause of the disease was revealed mainly due to careful neuroimaging, first according to epilepsy tailored MRI protocol involving ultra-thin sequential sections in the area of interest and only then by visualization with helical computed tomography in the “bone” mode to identify topography and size of the skull base defect. The epileptologists are energetic and dedicated and persistently sought for structural-anatomical cause of focal seizures. The authors conclude on the need for correct and complete examination of patients with unique focal forms of epilepsy and advise not to be satisfied with superficial routine visualization and do not regard these patients as having a disease with a cryptogenic origin. This is the main point of this study, which should be taken into account by practicing epileptologists.

A.G. Melikyan (Moscow, Russia)
The accessory middle cerebral artery (aMCA) is a rather rare congenital vascular anomaly. In 1962, M. Crompton [1] described the accessory MCA as an abnormal artery arising from the distal A1 ACA segment, which, passing along the segment, run parallel to the main MCA trunk. J. Teal et al. [2] identified two types of additional MCA: an accessory artery (when the artery originates from the distal A1 segment, in the region of transition from the A1 to A2 segment) and artery duplication where the anomalous vessel branches from the ICA in an interval between the anterior choroidal artery trunk and the ICA bifurcation. The occurrence rate of anomaly varies from 0.3 to 4% [3]. A combination of the accessory MCA with cerebral aneurysms is a frequent phenomenon [4—6]. The formation of associated aneurysms is most likely associated with hemodynamic features of cerebral blood supply in the presence of an additional artery [7, 8].

The article describes a case of a ruptured giant partially thrombosed aneurysm of the accessory MCA. The case is of great interest due to rarity of the pathology and associated diagnostic errors.

Clinical case
A 37-year-old female patient E. had subarachnoid parenchymal hemorrhage with the formation of an intracerebral hematoma of the right temporal lobe. She was hospitalized to a local district hospital. Cerebral angiography revealed changes that were regarded as an aneurysm of the right MCA (Fig. 1). The aneurysm was clipped, and the intracerebral hematoma of the right temporal lobe was removed. The patient was discharged with improvement one month after surgery. A month after discharge, the patient had repeated hemorrhage. Repeated SCT-AG revealed signs of functioning and an increase in size of the right MCA aneurysm. The clip occurred in the projection of the anterior Sylvian fissure (Fig. 2). The patient was referred to the Burdenko Neurosurgical Institute. At admission, the patient’s condition was relatively satisfactory. She presented with complaints of headache and limited lateral vision. On examination, left upper quadrant homonymous hemianopia was detected. There were no other focal neurological symptoms. CT revealed signs of a giant (2.5 cm in diameter) partially thrombosed aneurysm in the projection of the right MCA and signs of previous hemorrhage (Fig. 2c). Angiography demonstrated that the aneurysm formed on the accessory MCA (Fig. 3). The accessory MCA originated from the distal A1 segment, initially following the course of the recurrent artery, then bending several times, and running laterally towards the Sylvian fissure, locating along the main MCA trunk. There were signs of thrombosis of the M1 MCA segment. The M2 MCA segment was filled through an anastomosis with the distal accessory artery (Figs. 3, 4).

The patient underwent surgery. During surgery, the M1 MCA segment was found to be thrombosed throughout its entire course. The clip placed during the previous operation was situated along the M1 segment and was tightly adherent to it. The accessory MCA trunk branched from the distal A1 segment. The trunk run laterally along the A1 segment and then turned around it backward, forming a loop. Small perforating arteries branched from the loop. Further, the trunk run along the thrombosed
M1 segment, following the course of the lateral fissure, with 2nd order branches (M2) arising from the trunk. A narrow neck of the giant partially thrombosed aneurysm arose from the posterior wall of the distal loop segment. The aneurysm was clipped (Fig. 5).

Control angiography revealed complete exclusion of the aneurysm. The accessory MCA and M2 MCA segment were enhanced (Fig. 6). The patient was discharged home in satisfactory condition, without worsening of focal neurological symptoms.
Discussion

Three accessory MCA types have been described in the literature: type I — an additional trunk originates between the ostia of the anterior choroidal artery and the main MCA; type II — an artery arises from the proximal A1 ACA segment; type III — an additional artery branches from the distal A1 segment. The first type is considered as a MCA duplication variant, and types II and III are considered as the true accessory MCA [9]. In the presented case, the accessory MCA was of type III.

Some authors [10, 11] have believed that the accessory MCA is a variant of the recurrent artery (artery of Heubner). In our opinion and according to other authors [6, 12], this theory is not completely correct. First, the recurrent artery trunk is known to penetrate through the anterior perforated substance, going to the subcortex. In the presented case, the abnormal artery, as seen during both angiography and surgery, followed the course of the main MCA trunk in the lateral fissure (Figs. 3—5). It passed laterally to the anterior perforated substance, not penetrating through it. Second, perforating arteries do not always branch from the accessory MCA. Third, the recurrent artery may occur simultaneously with the accessory MCA.

Most often, the accessory MCA diameter is smaller than that of the main MCA trunk [13], but the accessory MCA is an important source of collateral blood supply to the frontal lobe and basal nuclei if the main MCA trunk is occluded [6, 13].

Some authors [14] have believed that the accessory MCA is a true anomaly. The genesis of this anomaly is not clear. Phylogenetically, the MCA trunk has developed later than the ACA, with the latter being an extension of the primitive ICA, and can be considered as an ACA branch. This circumstance suggests that the accessory MCA may be a persistent embryonic anastomosis between the ACA and the main MCA trunk [6].

According to the literature [3], aneurysms most often form in proximal segments of the accessory artery (in the ostium). Several cases have been reported where the aneurysm, as in the presented case, arises distal to the ostium — from the accessory artery trunk [5, 15].

Analyzing the data of cerebral angiograms of the patient after the first hemorrhage, we will dwell on the main aspects.

1. The angiographic picture (Fig. 1) is, to a certain extent, similar to the changes associated with moyamoya
syndrome. A stump of the M1 segment of the main trunk is seen, and tortuosity of the accessory trunk looks like a network of anastomoses. However, comparison of angiograms in the acute and cold periods of hemorrhage reveals signs of angiospasm in the acute period (Figs. 1, 3).

2. The accessory artery trunk, in contrast to cases reported in the literature, has a tortuous course.

3. Despite the massive hemorrhage, angiospasm, and thrombosis of the main trunk of the M1 segment, the patient had no ischemic foci, which was associated with the collateral blood flow through the accessory branch. Thrombosis of the M1 segment of the main MCA trunk most likely developed due to angiospasm after severe subarachnoid parenchymal hemorrhage.

4. The aneurysm originated from the distal accessory artery and was projected onto the lateral fissure, which complicated diagnosis interpretation at primary hospitalization.

According to the literature [16], rare anatomical features are the cause of approximately 10% of medical errors. Knowledge of anatomical variants and structural anomalies of the cerebral vessels helps to avoid diagnostic errors, as evidenced by the presented case.

Conclusion

The accessory MCA is a rare congenital vascular anomaly. The prevalence of this anomaly in the population is not exactly known. The accessory MCA may be an important source of collateral blood supply in cases when the main MCA trunk is occluded; but in some cases, it may be associated with the formation of aneurysms. Awareness of the existence of this anomaly helps to avoid diagnostic errors and treatment complications.

Authors declare no conflict of interest.

REFERENCES


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Developmental anomalies of carotid territory vessels have been in detail described in the literature. And the structural anomalies of the “youngest” artery — the middle cerebral artery — are represented by several variants that are briefly discussed in the article, with reference to the available sources. On the basis of analysis of publications devoted to the MCA anatomy, K. Cillers and B. Page demonstrated that the occurrence of the accessory MCA varies from 0.1 to 9.1%. Although the accessory MCA usually branches from the A1 segment near the anterior communicating artery, five different types of the accessory MCA location may be distinguished. The accessory MCA types differ by the point of branching from the anterior cerebral artery: from the A1 ACA segment (proximal, middle, or distal portions), at the anterior communicating artery level, or from the A2 segment.

The authors describe a rare clinical case of a giant accessory MCA aneurysm and discuss in detail the angiographic and surgical findings. In the presented case, the accessory MCA originated from the distal A1 ACA segment, was characterized by double looping, and was located in the Sylvian fissure, continuing to the M2 segment. The article emphasizes importance of timely diagnosis of the anomaly because correct preoperative assessment of the angiographic findings would have led to the use of an adequate technique of aneurysm clipping during the first microsurgical intervention conducted at the patient’s local hospital.

The accessory artery usually has a slightly smaller caliber compared to that of the main MCA trunk, but may be characterized by reciprocal relationships with the anterior choroidal artery. Preservation of blood flow through the accessory MCA during isolation and clipping of aneurysms is very important because this artery in many cases provides blood supply to functionally important brain areas. In the presented case, the main MCA trunk and accessory artery had approximately the same diameter, which provided preservation of the patient’s neurological functions after the first intervention that led to thrombosis/occlusion of the main MCA trunk. Successful clipping of the aneurysm emphasizes the importance of preoperative adequate evaluation of angiographic findings. It is necessary to emphasize the perfection of authors’ microsurgical skills who, in very difficult conditions (giant size and partial thrombosis of the aneurysm, two previous hemorrhages, main MCA trunk occlusion, and previous surgery), could successfully clip the accessory MCA aneurysm with preservation of blood flow in the parent vessel, which prevented massive ischemic brain injury.

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REFERENCES

A Modern Strategy of Combined Surgical and Radiation Treatment in Patients with Brain Metastases

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The treatment standards for patients with brain metastases have been developed for several decades. An important element in the evolution of approaches to the treatment of these patients is the development of microsurgery, stereotactic radiotherapy, and targeted therapy and introduction of these techniques into clinical practice. Surgery is an effective treatment option in patients having single brain metastases and/or occurring in life-threatening clinical situations. Irradiation of the whole brain after surgical treatment is a necessary step in achieving satisfactory local control of intracranial metastatic foci, but the development of neurocognitive disorders and deteriorations of life quality after this irradiation necessitates the search for alternative radiotherapy techniques in this clinical situation. Currently, an alternative to postoperative irradiation of the whole brain is stereotactic radiotherapy, which is used before or after surgical treatment. Stereotactic radiotherapy improves local control of intracranial metastatic foci and reduces the risk of neurotoxicity. In this review, we analyze the literature data on outcomes of stereotactic irradiation as a component of combined treatment of patients with metastatic brain lesions.

Keywords: brain metastases, radiosurgery, hypofractionation, whole brain irradiation, surgical treatment, radionecrosis.

According to [1], 9—26% of patients with malignant tumors develop brain metastases, which is the main cause of neurologic complications and death in this group of patients.

Improvement of surgical and neuroimaging techniques, as well as radiotherapy and systemic therapy improved the overall survival in this group of patients. All this changed the paradigm of treatment of patients with brain metastases (BMs), especially in patients with a localized (4 or less foci) metastatic brain lesions [2, 3].

Surgery is a primary therapeutic option for patients with single BM in the multidisciplinary approach system. R. Patchell et al. [4] have shown that surgical treatment improves the survival and results in maintenance of high functional status. Whole-brain radiation therapy (WBRT) after surgery with the incidence of local recurrence of 46—59% reduces this value to 28% [4—6].

Neurotoxicity and decreased quality of life after WBRT becomes increasingly important, since increase in life expectancy and preservation of the quality of life in these patients is an important clinical problem. In connection with problems related to the potential toxicity of WBRT, many researchers [7] use radiosurgery to irradiate the bed of resected metastasis in order to improve local control, while avoiding WBRT and reducing the risk of cognitive impairment.

The use of radiosurgery of resected metastasis bed is a relatively new method of radiation treatment of patients with BM. However, the use of radiosurgery in this clinical situation is associated with high risk of post-radiation complications, because the radiation dose is usually quite high. This dictates the need to reduce the dose, which in turn leads to increased risk of local recurrence. In this regard, stereotactic radiotherapy in the hypofractionation mode is used for irradiation of the bed of resected BM in some centers, which enables escalation of ionizing radiation dose and reduces radiation-related complications [8—11].

Stereotactic radiotherapy of the bed of resected BM is associated with technical problems of radiotherapy target contouring due to postoperative changes and possible presence of implantation micrometastases around the postoperative cavity. This raises a topical and debated issue of adding boundary offset to the target, which is not applicable in the case of the BM radiosurgery [12].

In recent years, there is a new possibility of stereotactic radiosurgery, preoperative radiosurgery followed by removal of metastatic lesions within 48 hours. The available data of small retrospective studies [13, 14] have shown the advantage of preoperative radiosurgery in terms of lower neurotoxicity, reduced risk of leptomeningeal progression, and preserved high-level local control comparable to postoperative stereotactic radiotherapy.

Postoperative stereotactic radiosurgery

Postoperative WBRT reduces the risk of local recurrence and distant metastases. However, 52% of patients develop neurocognitive disorders after WBRT compared to 24% of patients in the group without WBRT [15].

The results of retrospective studies demonstrate that the use of radiosurgery of the bed of resected metastatic lesion provides good local control and reduces the number of patients who require WBRT [8, 16, 17].

The results of M. Amsbaugh et al. [18] demonstrate that stereotactic radiotherapy of the bed of resected metastatic lesion and postoperative WBRT result in equivalent local control of BMs.

C. Brennan et al. [16] reported the results of a prospective phase II study evaluating the outcomes of radiosurgery of the bed of resected BMs in 49 patients. Recur...
rence rate of local and distant BMs during 12 month-long follow up was 22 and 42%, respectively. Patients with large (3 cm or more in diameter) metastatic lesions or those located close to the meninx had higher risk of local recurrence. No recurrence was observed within 12 months in the cases where metastatic foci were located in the subcortical brain structures and lesions were less than 3 cm in diameter. The incidence of radionecrosis was quite high and amounted to 17.5%. The authors found no significant clinical and dosimetric factors associated with the development of this complication.

G. Rao et al. [19] published the study of the effectiveness of treatment of 215 patients with localized metastatic brain lesions, who were randomized to the group of postoperative radiosurgery of resected BMs and the group of postoperative follow-up. Local control was 83 and 57% in the group of postoperative radiosurgery of resected lesion bed and in the follow-up group, respectively, in 6 months and 72 and 45%, respectively, in 12 months. There were no significant complications in the group of postoperative radiosurgery of resected BM bed. The incidence of distant BMs in 12 months was 33% in the group of radiosurgery of resected lesion bed and 43% in the follow-up group ($p=0.29$). The median of the overall survival was 17 months in both groups ($p=0.37$). Multivariate analysis shows that histology, BM number, and systemic or GPA-status of the disease did not affect local recurrence rate. Radiosurgery of resected lesion bed resulted in 2.5-fold lower risk of local recurrence, while the presence of a large lesion before the surgery was associated with higher risk of local recurrence.

**Irradiation target volume**

Radiosurgery of large metastatic foci requires lower dose of ionizing radiation (according to the study RTOG 9005), which leads to increased local recurrence rate.

A. Hartford et al. [8] studies a series of 47 patients and showed that the presence of large lesions is associated with early local recurrence, which determined the use of WBRT in this group of patients. Similar results were shown in the study of C. Jensen et al. [20], where the risk of local recurrence was 13.6 times higher ($p=0.01$) in patients with major BMs than in patients with smaller lesions. N. Luther et al. [21] also reported a correlation between irradiation target volume and probability of local control.

Since irradiation target volume depends on the size of postoperative cavity, the dynamics of its size after surgery is of great importance. B. Atalar et al. [22] evaluated the dynamics of postoperative cavity volume based on MRI in 63 patients. It was found that most of postoperative cavities were smaller than preoperative tumor size. Postoperative cavities after removal of large BMs regressed faster and maximum volume reduction occurred in the first 3 days after surgery. Further, there were almost no changes in cavity volume for 33 days ($p=0.75$). The authors concluded that the optimal time for initiation of postoperative radiotherapy is 1—2 weeks after surgery, when decrease in the postoperative cavity size is considerably slowed down.

J. Shah et al. [23] published different results on the dynamics of the postoperative cavity volume based on MRI data in 21 patients. The average volume of the postoperative cavity decreased by 43% in 41 days compared to the postoperative cavity size 24 hours after surgery. Patients who underwent MRI within one month after surgery demonstrated decrease in postoperative cavity by 13% compared to reduction by 61% in patients who underwent MRI in more than one month ($p=0.0003$). The volume of post-resection edema was not associated with decrease in cavity volume ($p=0.59$). Repeated MRI showed tumor progression signs in the postoperative cavity wall in 52% of patients. There was no significant difference in the local recurrence rate in the case of the interval between surgery and radiosurgery of less than a month and more than a month ($p=0.46$). These are the only studies where the terms of the beginning of postoperative radiation therapy depending on the postoperative cavity size were discussed. When considering regression of perifocal edema, changes in hematoma volume, which in most cases hides the remaining metastatic lesion, and hypoxia in the surgical margins, which may reduce the effectiveness of stereotactic radiotherapy, the time of postoperative radiotherapy ranges from 2 to 6 weeks. However, the optimal timing of initiation of postoperative radiotherapy is not defined at the moment.

**Boundary offset**

Boundary offset size is another important issue, when planning radiotherapy of resected BM bed. Irradiation target is determined based on the results of postoperative high-resolution MRI and CT and includes the entire postoperative cyst volume including the residual volume of metastatic lesion. Boundary offset is added to the postoperative cavity volume, which determines the target volume. The need for boundary offset is determined by the complexity of cavity margin contouring due to the uncertainty of postoperative changes or the presence of residual tumor based on MRI data, as well as due to possible micrometastases in the tissue surrounding the postoperative cavity [24].

The significance of micrometastases in the development of local recurrence is shown in the study of L. Rogers et al. [25], who reported the results of intraoperative irradiation of resected BM bed using GliaSite apparatus. Despite the dose of more than 300 Gy on the intrastat surface, local recurrence rate was higher than 15%.

S. Soltys et al. [26] published treatment outcomes of 76 patients who underwent radiosurgery of the resected metastatic lesion bed. The authors emphasized that less conformal radiation plan resulted in better local control values and boundary offset of 2 mm from the postoperative cavity margin is a standard of bed irradiation.
Some authors include the boundary offset in radiation target volume only in patients with large lesions, who have higher risk of relapse. J. Kirkpatrick et al. [12] evaluated the optimal dimensions of the boundary offset when planning radiotherapy: 1, 2, or 3 mm. The study showed no correlation between local control and increase in boundary offset; at the same time, there was higher level of radionecrosis in patients with boundary offset of 3 mm. It is currently believed that boundary offset from the margin of resected BM should be 2 mm when forming a stereotactic radiotherapy target [9, 16].

Postoperative stereotactic radiotherapy in the hypofractionation mode

Apart from formation of the irradiated target volume, improvement of stereotactic radiotherapy technology opens an important question of fractionation conditions. The doses for radiosurgery of resected BM bed are selected according to the research RTOG 90-05. It is based on the assessment of tolerance of normal brain tissue and enables selecting the maximum possible radiation dose during radiosurgery with an acceptable level of post-radiation toxicity according to irradiated target volume [27].

Taking into account large volume of irradiated targets, lower radiation doses (20—30% lower than the doses recommended by RTOG 90-05) were typically used in the studies evaluating the efficacy of postoperative stereotactic radiosurgery of resected BM bed. Despite this fact, the local control in the study was satisfactory, supporting the idea that application of low radiation doses is sufficient to control possible perifocal micrometastases. Further increase in the local control and decrease in neurotoxicity are possible when applying hypofractionation technique, when increase in the total radiation dose does not exceed the tolerance of brain tissues surrounding the postoperative cavity [11, 28].

G. Minniti et al. [9] used postoperative stereotactic radiotherapy with 3 fractions of 9 Gy in a series of 101 patients. In all patients, postoperative cavity diameter was larger than 3 cm and boundary offset was 2 mm. Local control was 93 and 84% in 12 and 24 months, respectively. Radionecrosis developed in 9 patients.

The prospective study of B. Eaton et al. [29] demonstrated the advantage of hypofractionation irradiation mode versus radiosurgery in 75 patients with a postoperative cavity sized 3 cm. Radiosurgery of resected BM bed (1 fraction, 15 Gy) was carried out in 40 patients and 36 patients received stereotactic radiotherapy in hypofractionation mode (5 fractions of 6 Gy, 4 fractions of 6 Gy, 3 fractions of 7—8 Gy). The patients who received stereotactic radiotherapy in hypofractionation mode had larger postoperative cavity volume (median of 24.0 and 13.3 cm³, respectively) compared to the radiosurgery group (p<0.001); boundary offset was 2 was 1.5 mm and planned irradiation target volume was 37.7 and 20.5 cm³, respectively.

Local recurrence rate was 18.9% in hypofractionation group vs 15.9% in the radiosurgery group in 6 months and 25.6% vs 27.2% in 12 months (p=0.80). There was higher risk of radionecrosis in the group of radiosurgical treatment (risk ratio 3.81, p=0.043).

A. Bilger et al. [30] reported the results of stereotactic radiotherapy of the bed of resected metastatic lesion in the hypofractionation mode. Fractionation regimen included 5 fractions of 6 Gy or 5 fractions of 7 Gy in the case of residual tumor tissue in the postoperative cavity. Boundary offset was 3 mm from the cavity margin. The median overall survival was 15 months. Local recurrence was detected in 6 (11.5%) patients during the follow-up period, 12-month local control was achieved in 81.5% of patients. The results show that the hypofractionation modes are the preferred option in the case of postoperative cavity size of 3 cm or more (Table).

Postoperative stereotactic radiotherapy in hypofractionation mode provides potential advantage over radiosurgery in the case of irradiation target located near functionally important brain structures, residual tumor tissue in the bed of resected lesion, as well as in the case of large lesion resection, when added boundary offset results in exponential increase in the volume of normal brain tissue included in the irradiation target, which increases the risk of radionecrosis.

Complications

Acceptable neurotoxicity level and preserved quality of life are the most important aspects of radiotherapy of patients with BMs. Brain metastases often cause neuropsychological disorders and worsen patient’s quality of life. In this case, it is quite difficult to assess the impact of radiation therapy on the further cognitive impairment, because different dynamics of cognitive and neurological functions is possible after removal of symptomatic metastases.

Phase III clinical study carried out by the EORTC showed higher quality of life in the group of patients who were followed after surgical resection or radiosurgery compared to the patients who additionally underwent WBRT. Therefore, exclusion of WBRT from the treatment regimen prevents a number of complications, including cognitive disorders, alopecia, fatigue, and associated psychological stress, reduction of role functioning, as well as systemic therapy delay [34].

The development of radionecrosis is another most common complication of stereotactic radiotherapy, which is usually accompanied by edema of the surrounding tissue and local neurological symptoms. The incidence of symptomatic necrosis depends on the location, irradiation target volume, and radiation dose. M. Shehata [34] demonstrated that increase in the risk of radionecrosis associated with increase in the dose and volume of irradiated normal brain tissue correlated with increase in metastatic lesion size.
Apart from the known “dose/volume” limitations during radiosurgery, it was found that BM location near to critical brain structures is predictive of post-radiation complications. Cerebral and cerebellar hemispheres have the highest tolerance to radiation followed by diencephalon structures, while the highest risk of radiation injury was observed when irradiated target was located in the brainstem. According to most published studies, optic nerves and chiasm are tolerant to radiosurgery doses up to 8—10 Gy, while the risk of post-radiation complications dramatically increases, when the dose increases to 12 Gy.

Phase II prospective study of C. Brennan et al. [16] demonstrated the development of radionecrosis in 17.5% after radiosurgery of resected BM bed. Decrease in post-radiation toxicity is possibly associated with change in the fractionation mode.

B. Eaton et al. [29, 35] reported the advantages of postoperative cavity irradiation in hypofractionation mode compared to radiosurgery. The incidence of radionecrosis in 6 and 12 months was 3.3 and 10.7% in the hypofractionation group and 10.3 and 19.2% in the radiosurgery group. The risk of radionecrosis in radiosurgery group was 3.8-fold (p = 0.043) higher compared to that in hypofractionation group. Therefore, stereotactic radiotherapy in the hypofractionation mode should be considered as an optimal therapeutic option, when lesions larger than 3 cm in diameter were detected.

Stereotactic irradiation of resected metastasis bed is well tolerated by most patients with neurotoxicity level of 0—26.6% [9, 10, 36].

Postoperative leptomeningeal progression

Increased risk of leptomeningeal progression is one of the most serious complications of surgical resection of BMs.

J. Ahn et al. [36] carried out a retrospective analysis of treatment outcomes of 242 patients who underwent only surgery. It was shown that 39 (16%) patients developed leptomeningeal progression within 6 months. En-bloc removal of the lesion is the main factor that reduces the risk of leptomeningeal progression.

M. Johnson et al. [38] evaluated the incidence of leptomeningeal progression in 330 patients who underwent stereotactic radiosurgery. Of these, surgical resection of at least one of detected BMs was carried out in 112 patients, and 218 patients underwent radiosurgical treatment. Within the follow-up period (median 9 months), 39 (12%) patients had leptomeningeal progression on the average 6 months after treatment. The incidence of leptomeningeal progression with fatal outcome was observed in 5.2% of cases in the radiosurgery group vs 16.9% in the surgery group (p < 0.01). Previous surgery (p < 0.01) and the presence of breast cancer as a brain metastasis source (p = 0.03) were the significant factors for leptomeningeal progression in the multifactorial analysis.

Preoperative radiosurgery

The results of published studies show that patients who underwent radiosurgery of the postoperative cavity with boundary offset to improve the local control have higher risk of post-radiation toxicity [38].

In this clinical situation, stereotactic radiotherapy in hypofractionation mode is associated with lower risk of post-radiation complications. However, increase in radiation doses during hypofractionation and increase in irradiation target volume due to formation of boundary offset do not always improve local control and potentially increase neurotoxicity.

The use of radiosurgery followed by surgical treatment within 12—24 hours is one of the methods aimed at reducing post-radiation toxicity and improving local control. There are several advantages of this approach compared to stereotactic radiotherapy of resected BM bed.

First, when planning radiotherapy of intact metastatic lesion, more accurate evaluation of irradiation target volume without additional boundary offset is possible.

Second, the probability of a good response of the lesion to radiotherapy may be higher due to intact blood flow in the lesion and no postoperative hypoxic cavity.

Third, since the tumor will be subsequently removed, the maximum possible escalation of radiation dose does not increase the risk of post-radiation toxicity.

Further, preoperative radiosurgery theoretically reduces the risk of tumor dissemination, which is possible during surgery.

A. Asher et al. [13] were the first who reported the results of retrospective analysis of safety and efficacy of preoperative radiosurgery in 47 patients with BMs. In this study, local control of metastatic foci was up to 97.8, 85.6,
and 71.8% in 6, 12, and 24 months, respectively. Radiotherapy planning was considerably simplified compared to the postoperative treatment protocols and conformal plans could be created in most patients. Furthermore, preoperative radiosurgery significantly reduces treatment time because there is no need for radiotherapy course 3—6 weeks after surgery, and, as a result, drug treatment is carried out immediately in most cases.

K. Patel et al. [14] analyzed outcomes in 102 patients who received preoperative radiosurgery (66 patients) and WBRT (36 patients). The overall 12-month survival was 58 and 56%, respectively ($p=0.43$). In the reported analysis, total boost dose of preoperative radiosurgery was reduced by about 20% compared to the recommended doses in the RTOG 90-05 study. In 24 months, local recurrence rate was 24.5% in the group of preoperative radiosurgery and 25% in the group of postoperative WBRT ($p=0.81$). The incidence of distant metastases in the preoperative radiosurgery and WBRT groups was 53.2 and 45% ($p=0.66$), respectively; leptomeningeal progression—3.5 and 9.0% ($p=0.66$), respectively. No analysis of neurocognitive changes after two types of radiation treatment was carried out. The authors concluded that preoperative radiosurgery is an alternative to postoperative WBRT as a part of combination therapy for BMs. Preoperative radiosurgery may replace or limit the use of WBRT. The possibility of simultaneous irradiation of metastatic lesions, which are not scheduled for surgical treatment, is an additional benefit of preoperative radiosurgery. When using this technique, radiation therapy is not delayed by several weeks and all of the detected lesions are irradiated in one treatment session.

**Prospects for further research**

Several studies on the effectiveness of stereotactic radiotherapy of resected BM bed are currently carried out.

The results of a randomized study carried out at the M. Anderson Cancer Center (NCT00950001), comparing postoperative radiosurgery of resected BM bed with postoperative follow-up in patients with localized (1—3 lesions) BMs are forthcoming. The study included patients with postoperative cavity size below 4 cm and the remaining lesions sized up to 3 cm in diameter.

The research was aimed at evaluating the incidence of intracranial recurrence in the studied groups. This study will provide level 1 evidence of the effectiveness of radiosurgery of resected BM bed.

Recruitment of patients to phase I—II study of preoperative radiosurgery (NCT01891318) is carried out. The objective of the study is to specify the maximum permissible dose of radiosurgery, which is determined by dose limiting toxicity according to CTCAE v4.0 criteria (study phase I) and local control in 12 months (study phase II). The results of this study will determine the optimal dose of preoperative radiosurgery.

This research is similar to the study carried out at the University of Alabama at Birmingham (NCT01252797) aimed at determining the maximum tolerated dose of preoperative radiosurgery in terms of acute and delayed post-radiation toxicity. Local control and overall survival are the additional aspects of the research.

The ongoing study of the efficacy of postoperative radiosurgery (NCT01372774) seems to be of great importance. This multicenter randomized phase III study directly compares postoperative irradiation techniques, radiosurgery and WBRT, in patients with localized BMs.

The results of the study NCT02576522 aimed at assessing the local control, overall survival, incidence of distant BMs, neurocognitive disorders, and radionecrosis after stereotactic radiotherapy of resected BM bed in the hypofractionation mode are of undoubted interest in terms of treatment of large BMs.

Despite the fact that most of expected research are phase I—II studies, the results may change the repertoire and order of therapeutic options in patients with BMs in combination with surgery.

**Conclusion**

Surgical treatment of BMs, preoperative radiosurgery, and postoperative stereotactic radiotherapy demonstrated equivalent performance in terms of local control, overall survival, and the development of distant metastases. Preoperative radiosurgery demonstrated lower rates of neurotoxicity and leptomeningeal progression compared to postoperative stereotactic radiotherapy.

Given the high risk of neurocognitive deficits after WBRT, the use of stereotactic radiation therapy before or after surgery is the optimal method for patients with localized metastatic brain lesions.

**Authors declare no conflict of interest.**
REFERENCES


Metastatic brain lesions are a common complication in cancer patients with the incidence of 20—40% of all cancer patients. Certain results in the treatment of metastatic brain lesions can be achieved using modern multi-disciplinary approach. Therefore, the individual characteristics of each patient, such as histological variant of the primary tumor, primary tumor status, functional status as assessed by Karnofsky score, location and size of brain lesions should be taken into account when determining treatment strategy and tactics. Surgery plays an important role in the complex therapy of metastatic brain lesions since it neutralizes intracranial mass effect and improves survival and neurological status. It allows either to establish histological diagnosis or to confirm it. The approach to surgical technique of metastasis resection is essential. For example, removal of fragmented metastasis without excision of perifocal and perivascular areas rather than en-bloc resection is associated with negative local control parameters. The best local control may be achieved in the case of compliance with the principles of ablation, the use of modern preoperative neuroimaging methods and advanced microsurgical equipment followed by adjuvant therapy, such as stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT). The algorithm of brain metastasis treatment varies depending on several factors, such as the primary tumor histology, various clinical characteristics of the patients, and therapeutic options available at the medical facility.

The article provides an overview of the current literature in the context of a comprehensive treatment of brain metastases. SRS became superior to surgery due recent technological advances in this field. SRS is widely used at the initial stage of therapy, in the treatment of relapses, as well as in combination with surgery or WBRT. The use of SRS as the first line treatment can be justified due to its non-invasiveness, single outpatient visit, and high level of local control. This method can be used in patients who are not candidates for surgery, and it is used in patients with multiple cerebral metastases. Nevertheless, there are some limitations and drawbacks of radiosurgery in the treatment of cerebral metastases. The main objective of SRS is to avoid potential long-term neurotoxicity caused by WBRT with high rates of local control. Preoperative SRS of cerebral metastases followed by tumor resection within 48 hours is an interesting option. The article summarized various data and modern approaches to the treatment of metastatic brain lesions and determines the directions of personalized treatment.

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Hypofractionated Radiotherapy for Glioblastoma: Changing the Radiation Treatment Paradigm

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Hypofractionation has the dual advantage of increased cell death with a higher dose per fraction and a reduced effect of accelerated tumor cell repopulation due to a shorter overall treatment time. However, the potential advantage may be offset by increased toxicity in the late-responding neural tissues. Recently, investigators have attempted delivering radical doses of HFRT by escalating the dose in the immediate vicinity of the enhancing tumor and postoperative surgical cavity and reported reasonable outcomes with acceptable toxicity levels. Three different studies of high-dose HFRT have reported on the paradoxical phenomenon of improved survival in patients developing radiation necrosis at the primary tumor site. The toxicity criteria of RTOG and EORTC have defined clinically or radiographically suspected radionecrosis as Grade 4 toxicity. However, most patients diagnosed with radiation necrosis in the above studies remained asymptomatic. Furthermore, the probable association with improved survival would strongly argue against adopting a blind approach for classifying radiation necrosis as Grade 4 toxicity. The data emerging from the above studies is encouraging and strongly argues for further research. However, the majority of these studies are predominantly retrospective or relatively small single-arm prospective series that add little to the overall quality of evidence. Notwithstanding the above limitations, HFRT appears to be a safe and feasible strategy for glioblastoma patients.

Keywords: high-grade gliomas, linear-quadratic model, α/β ratio.

The outcome of glioblastoma’s (GBM) treatment involving long periods of irradiation can be jeopardized by tumor cell repopulation with rapid doubling time [1]. In approximately 12—37.5% of patients the disease may progress clinically by the end of the conventional fractionated course [2]. The regimen with a dose of 60 Gy in 30 fractions, proposed several decades ago, remains the standard of treatment for GBM patients and is a starting point for further studies in this field [3, 4]. Theoretically, hypofractionated radiotherapy (HFRT) has the dual advantage of increased cell death with a higher dose per fraction and a reduced effect of accelerated tumor cell repopulation due to a shorter overall treatment time. The value of the linear-quadratic equivalent dose (LQED2) at 2 Gy per fraction is of particular interest to clinicians. The α and β values are determined by the survival curves of stem cells. It is impossible to estimate these parameters separately for cells in a tissue, but one can estimate their ratio (α/β) for equivalent regimens. The value of α/β is measured in units of the absorbed radiation dose (Gy) and numerically corresponds to the dose at which the linear function characterizing the cell death is equivalent to the quadratic one. LQ made it possible to identify differences for rapidly and slowly proliferating tissues. Early-responding tissues, as well as most malignant tumors, have a α/β value of 7—20 Gy, while for late-responding tissues the value is 1—6 Gy [5].

To assess the radiobiological parameters, we summarized the clinical data of 559 patients with GBM. Optimal values (taking into account 95% confidence intervals) are α=0.12 Gy–1 (0.10—0.14), β=0.015 Gy–2 (0.013—0.020), α/β=8 Gy (5.0—10.8). The analysis confirmed high value of the α/β coefficient. The results of the study indicate an improvement in the effectiveness of treatment by increasing the total dose without increasing the number of fractions [6]. Based on the average α/β values provided in the studies of clonogenic proliferation of cells from different GBM lines, the most commonly used α/β ratio for GBM is 8 Gy [1].

Many authors [7—9] believe that, for the sake of simplicity, a fixed α/β level should be used. It is assumed that α/β is equal to 10 Gy for early-responding tumor tissue, while for late-responding tissues (normal brain) α/β is equal to 3 Gy. Accordingly, the following LQ parameters are proposed: α=0.17; β=0.02 for GBM with mutant p53 (mt-p53) and α=0.6; β=0.06 for GBM with wild-type p53 (wt-p53) with a typical tumor α/β ratio of 10.

Nevertheless, the value of the α/β ratio that should be used in treatment of GBM is still under discussion, the unreliability of the LQ model leads to a variability in radiation doses [10], while the interpretation of the data is ultimately limited by small sample sizes, significant within-group heterogeneity and different methodological approaches to HFRT [11].

Many doctors used the LQ model and Biologically Effective Dose (BED) to compare the different fractionation options. Later it was established that the LQ model should not be used in stereotactic radiotherapy (the course of 1—5 fractions). In general, the LQ model is effective at doses not exceeding 5 Gy and is less reliable at
higher doses [12, 13]. Y. Shibamoto et al. [12] believe that the LQ model can be applied to a fractional dose, which is about 2 times lower than the α/β ratio. It has been demonstrated on cell line models that the LQ model is optimal for 7–20 irradiation fractions, with the dose per fraction not exceeding 2.57 Gy. The LQ model can be applied at a dose range below the α/β coefficient [10].

Taking into account significant achievements in the field of molecular GBM radiobiology, improve survival at higher doses of radiotherapy can be predicted, but the arguments in favor of this hypothesis will be a subject of debate for quite a while [14].

A correct assessment of clinical target volume (CTV) can be problematic, since the degree of microscopic propagation of GBM cannot be fully visualized. There is no consensus as to which imaging method should be used, and whether one should use GTV2 with the inclusion of an edema zone [9]. According to a study by P. Bondiau et al. [15], 2—15% (high proliferation) of tumor cells (depending on the type of GBM) remain outside the irradiation zone even in case of the most significant margins from the CTV (+2.0 cm from the edema zone). These data explain the current inadequacy of treatment methods in preventing local recurrences of GBM.

Most studies used different ranges of dose schedules in case of dose escalation with HFRT. A multi-layered PTV (planning target volume) was created with a dose escalation around the central area of the tumor and the postoperative cavity (GTV +0.5—1 cm) with a dose restriction on the surrounding parenchyma of the brain. Another model of volume determination recommends a margin of 2.5—3.0 cm around the primary tumor and the inclusion of the edema zone identified by MRI in T2 mode [11]. The practice of using large volumes is associated with the presence of viable tumor cells in the edema zone [16].

In a systematic review [11] of the role and development of HFRT as a potential therapeutic strategy in patients with GBM, it was noted that the prognosis remains poor, and the use of hyperfractionation and escalation of the dose beyond 60 Gy did not lead to improved survival rates. Most HFRT studies published since 1990 report no significant increase in early and late toxicity. The most recent studies of HFRT in combination with administration of temozolomide (TMZ) reported a trend toward improved survival compared to the historical control group, and several authors noted an increase in median survival to 20 months. In general, high-dose HFRT using IMRT (Intensity-Modulated Radiation Therapy) seem to be a safe and appropriate method of treatment [11].

R. Thomas et al. [17] reported a retrospective study in Royal Marsden Hospital (UK). A total of 38 patients with unfavorable prognostic signs were treated with a dose of 30 Gy in 6 fractions within 2 weeks. During the planning 2-cm margin from the edge of the tumor was used to determine the volume of PTV. The median survival was 6 months, the one-year survival was 23%, there were no serious manifestations of toxicity. In 2003, the same group of authors reported an extended retrospective study of a group of 92 patients with palliative radiotherapy (the median survival was 5 months, the one-year survival rate was 12%); in patients treated with the classical fractionation regime (60 Gy), the median survival was 2.5—4.5 months higher. Less pronounced radiation-induced side effects (in terms of both intensity and duration) were reported after the hypofractionation course. The authors [18] point to the comparability of the two regimes after correction for the quality of survival.

J. Lutterbach and C. Ostertag [19] reported on a German retrospective study of 96 patients with GBM over the age of 60, in which the patients received 42 Gy in 12 fractions with a dose of 3.5 Gy (n=50) and 60 Gy in 30 fractions (n=46). The median survival was 7.3 months, one and 2-year overall survival was 60 and 26% in the HFRT group compared with 5.6 months, 49 and 18% with conventional fractionation, respectively. Non significant long-term toxicity was observed for HFRT.

K. Sultanem et al. [20] reported the results of a Canadian study of 25 patients from McGill University (Montreal), which assessed the use of HFRT in patients with GBM. The target volume did not exceed 110 cm³, and it was located no closer than 1.5 cm to the critical structures (brain stem or optic chiasma). The volume of PTV was formed with an offset of 1.5 cm from the edge of GTV. A cumulative dose of 60 Gy was delivered in 20 fractions of 95—100% isodose covering GTV. The boundaries of PTV were included in the 65—70% isodose (40 Gy), which resulted in a dose gradient between PTV and GTV. The median survival was 9.5 months (range 2.8—22.9 months), one-year overall survival rate was 40%. There were no reports of significant toxicity. All relapses were central, no patient experienced continued growth outside the irradiated volume.

T. Iuchi et al. [21] reported on a Phase II study of 25 patients with high grade gliomas (GBM — 23) treated with HFRT using IMRT. The tumor volume ranged from 3.9 to 132.5 cm³. The definition of PTV: PTv1 included GTV + 5 mm; PTv2 + 15 mm from PTv1; PTv3 was expanded to include the edema zone. The irradiation was carried out in 8 fractions with a dose escalation for PTv1; for PTv2 the cumulative dose was 40 Gy, and for PTv3, 32 Gy. The dose level for PTv1 was 48 (n=3), 56 (n=2), 60 (n=3), 64 (n=5), and 68 Gy (n=13). The increase in dose was associated with an improvement in overall survival: overall, one and two-year survival rates were 71.4 and 55.4%, respectively, which was higher than in the parallel group of 60 patients with standard radiation therapy (p=0.043). The structure of relapses in the groups with high doses of HFRT and the standard dose (60 Gy) differed. Two thirds (n=43) of patients on conventional radiation therapy experienced a local recurrence, while only 6 patients in the HFRT group had a local growth, in 8 patients the progression was diagnosed
outside the irradiation zone. In 2014, T. Iuchi et al. [22] evaluated the effect of HFRT with IMRT using the same technique with the simultaneous administration of TMZ in 46 patients in Phase II trials. The median overall survival after the treatment was 20.0 months. The most frequent form of failure was a distant lesion.

C. Chen et al. [23] published data on the combination of HFRT with concurrent administration of TMZ (median number of cycles was 7.5) in 19 patients with GBM. PTV1 with an offset of 5 mm around the tumor and PTV2 + 5 mm around the edema zone were used in the study. Four dose levels were studied in the area of the tumor center, starting from 60 Gy at 3 Gy per fraction (level 1) to 60 Gy at a dose of 6 Gy per fraction (level 4). Doses per fraction were increased by 1 Gy in each group. The total number of fractions decreased from 20 to 10. The median survival was 16.2 months. Subsequently, all patients were diagnosed with a local recurrence, with the exception of two patients who had a relapse in the area of the isodose curve of 30 Gy. Out of 16 patients, 4 required repeated neurological intervention after radiological progression according to MRI. Histologically, there was one relapse (level 1) and three necrosis with a minimal residual tumor.

V. Panet-Raymond et al. [24] reported the results of treatment of 35 patients by HFRT with concomitant TMZ therapy. Radiation therapy was performed according to the procedure described by Sultanem, with a prescribed isocenter at a 95—100% isodose covering GTV (60 Gy) in 20 fractions. No early and late toxicity was reported. The median survival was 14.4 months. As in previous studies, in most cases of MRT-confirmed relapses (21/23), the foci of continued growth were central; only 2 patients developed a relapse in an area further than 2 cm from the original GTV.

A. Morganti et al. [25] reported Phase I study with escalation of HFRT dose in 19 GBM patients receiving adjuvant TMZ therapy. PTV1 included GTV (contour of tumor or postoperative cavity) plus a margin of 1.5 cm. PTV2 included GTV with an area of surrounding edema according to MRI-T2 and a margin of 1.5 cm. The treatment was performed in 25 fractions with a dose in PTV1 at three levels (60, 62.5, 65 Gy), while maintaining a constant dose of 45 Gy for PTV2. The study reported no complications, the relapses were predominantly local, and only 2 patients developed tumors outside the PTV1 zone and only 1 in the marginal zone. The median relapse-free survival was 12 months, the overall one was 20 months, with a one- and two-year survival rate of 81.9 and 28.9%, respectively.

Tumor control after the hypofraction regimen, with a dose delivered by IMRT to the central region (GTV) at $\alpha/\beta=10$, is presented in the Table.

In 2000, M. Hulshof et al. [26], reporting on the results of a Dutch randomized trial, argued that the therapeutic efficacy of HFRT may represent a true radiobiological effect. The most promising dose escalation studies for HFRT using IMRT were developed as safety and feasibility studies, but eventually reported a long-term survival. Careful analysis shows some interesting and stable trends. There is a clear relationship between dose and response in regimens using doses of more than 90 Gy on the tumor target at $\alpha/\beta=8$ with local cure and overall survival compared to historical control. For example, Iuchi et al. [21] used extreme levels of HFRT with BED ranging from 80 to 140 Gy at $\alpha/\beta=8$ and showed an improvement in the local effect. A. Monjazeb et al. [27] used BED in the range of 90 to 105 Gy at $\alpha/\beta=8$ with a median survival of 13.6 months, with one- and 2-year survival of 55 and 19%, respectively. The results of combining HFRT with TMZ are equally interesting. Two studies [23, 25] of HFRT dose escalation in combination with concomitant administration of TMZ reported median survival of 20 months.

In recent years, there have been studies using a high single dose. For example, K. Miiwa et al. [28] used a dose of 8.5 Gy in 8 fractions combined with concomitant administration of TMZ per GTV region, taking into account PET data with methionine in 45 patients (68 Gy), CTV (GTV + 5 mm, 56 Gy). The dose to PTV area (GTV + 15 mm, including edema) did not exceed 40 Gy. The median overall survival was 20.0 months, the median progression-free survival was 13.0 months, and the one- and two-year survival rate was 71.2 and 26.3%, respectively. Patients with diagnosed GBM ($n$=24) received postoperative hypo-IMRT up to 60 Gy in 10 fractions with simultaneous administration and subsequent courses of TMZ. Enlarged fractionation with a single dose of 6 Gy has changed the character of recurrence resulting in an increase in cases with distant tumor progression in of 9 (37.5%) of 24 cases and leptomeningeal proliferation in 2 cases.

L. Khan et al. [30] conducted a search in the Cochrane Central Register of Controlled Trials (2015, Issue 9), MEDLINE (from 1977 to October 2015) and Embase (from 1980 to the end of October 2015) of the relevant randomized phase III trials with the inclusion of 11 randomized controlled trials. In high-grade gliomas patients with postoperative radiation therapy, the survival is higher with the risk factor for overall survival of 2.01 (95% CI 1.58—2.55, $p<0.00001$). Overall survival was the same in hypofractionated and traditional radiation therapy groups in 5 studies (943 participants), the risk factor was 0.95 (95% CI 0.78—1.17, $p=0.63$) with a low level of evidence. In two studies that included patients with GBM over 60 years of age, the overall survival rate was 1.16 (95% CI 0.92—1.46, $p=0.21$) with a high level of evidence. The authors noted that HFRT has the same survival efficacy as standard radiation therapy, especially for people aged 60 years and older.

The American Society for Radiation Oncology (ASTRO) has prepared a guideline for GBM radiation therapy, published in 2016. In 2017, the American Society of Clinical Oncology confirmed that fractionated radio-
therapy with simultaneous and adjuvant use of TMZ is the standard for treatment of GBM in patients under the age of 70. Hypofractionated radiation therapy in elderly patients with good functional status is an adequate method, and the addition of concurrent and adjuvant TMZ is a safe and effective method that does not impair the quality of life. Reasonable treatment options for patients with poor functional status are hypofractionated courses, or only TMZ or maintenance therapy [31].

Standard reactions and complications of fractionated radiation therapy with a dose of 2 Gy are well known. Nontraditional regimes of radiotherapy have not been adequately studied. In addition, the consequences of harsher treatment programs are no less important than the survival. Therefore, we included data on the main radiation damage in the “Discussion” section.

The main problem with the use of HFRT is an increased risk of late toxicity from damage to functionally important areas, in particular the optic nerves, chiasma and brainstem. In most HFRT series, the authors note the absence of a significant increase in acute or late toxicity. Nevertheless, the study by C. Chen et al. [23] reported a loss of vision in 1 patient seven months after HFRT. A review of radiotherapy plans revealed that the maximum dose for the left optic nerve should not be higher than 51.6 Gy (3.4 Gy per fraction), for the right optic nerve, than 49.2 Gy (3.3 Gy per fraction) and for the optical chiasm, than 45 Gy (3 Gy per fraction). Late toxicity is a significant, but potentially preventable risk of HFRT. Taking into account devastating consequences of damage to critical brain structures, it is extremely important to ensure that all HFRT protocols include strict dose restrictions. Nevertheless, small fields used to determine PTV1, combined with the use of highly effective conformal radiation technologies (IMRT), should facilitate the use of HFRT in most patients [11].

When preparing patients with malignant gliomas for radiation therapy, it is necessary to take into account the toleratedness of healthy brain tissue. Based on the mathematical model proposed by M. Walker et al. [3] and retrospective analysis of the previous randomized trials it has been demonstrated that in case of fractionated irradiation of a portion of the brain, a dose with a 5% probability of potential complications within 5 years averages at 60±10 Gy [32—34].

Late radiation complications can appear in the form of somnolence and decrease in cognitive functions [33, 34]. According to RTOG (Radiation Therapy Oncology Group) 83-02 protocol, an increase in the dose from 64.8 to 81.6 Gy results in the increase in complication rate from 1.3 to 6.8%. The degree of severity of radiation damage varies from minimal, in the form of moderate cognitive impairment (decrease in attention, level of operative memory and learning ability, especially in young patients), to expressed one, including development of dementia, lethargy and local post-radiation necrosis of brain tissue requiring surgical treatment and leading to deep disability [35]. It is very difficult to evaluate the correlation between local brain irradiation and cognitive function impairment, because it is impossible to determine what is the promoter of this pathology: radiation exposure or continued tumor growth [36].

Despite the fact that an increase in single and total doses, as well as the addition of chemotherapy, increases

<table>
<thead>
<tr>
<th>Author</th>
<th>PTV</th>
<th>CFD</th>
<th>Number of fractions</th>
<th>BED*</th>
<th>Chemotherapy</th>
<th>Median, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Floyd et al. [39]</td>
<td>GTV 5 Gy</td>
<td>10</td>
<td></td>
<td>75 Gy</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>E. Sulman et al. [31]</td>
<td>GTV 3 Gy</td>
<td>20</td>
<td></td>
<td>78 Gy</td>
<td>No</td>
<td>9.5</td>
</tr>
<tr>
<td>A. Monjazeb et al. [27]</td>
<td>GTV + 5 mm 2.5 Gy 28</td>
<td>88 Gy</td>
<td>No</td>
<td>13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GTV + 5 mm 2.5 Gy 30</td>
<td>94 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GTV + 5 mm 2.5 Gy 32</td>
<td>100 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. Panet-Raymond et al. [24]</td>
<td>GTV 3 Gy</td>
<td>20</td>
<td>78 Gy</td>
<td>TMZ</td>
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<tr>
<td>A. Morganti et al. [25]</td>
<td>GTV + 15 mm 2.4 Gy 25</td>
<td>74 Gy</td>
<td>TMZ</td>
<td>20.0</td>
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<td></td>
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<td></td>
<td>GTV + 15 mm 2.5 Gy 25</td>
<td>78 Gy</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>GTV + 15 mm 2.6 Gy 25</td>
<td>82 Gy</td>
<td></td>
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</tr>
<tr>
<td>C. Chen et al. [23]</td>
<td>GTV + 5 mm 3 Gy 20</td>
<td>78 Gy</td>
<td>TMZ</td>
<td>16.2</td>
<td></td>
<td></td>
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<td></td>
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<td>90 Gy</td>
<td></td>
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<tr>
<td></td>
<td>GTV + 5 mm 6 Gy 20</td>
<td>96 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. Iuchi et al. [22]</td>
<td>GTV + 5 mm 8.5 Gy 8</td>
<td>126 Gy</td>
<td>TMZ</td>
<td>20.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. Reddy et al. [29]</td>
<td>GTV + 5 mm 6 Gy 10</td>
<td>96 Gy</td>
<td>TMZ</td>
<td>16.6</td>
<td></td>
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<tr>
<td>Tsien et al.</td>
<td>GTV + 5 mm 2.2 Gy 30</td>
<td>81 Gy</td>
<td>TMZ</td>
<td>20.1</td>
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<td></td>
<td>GTV + 5 mm 2.4 Gy</td>
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<td>89 Gy</td>
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<td></td>
<td>GTV + 5 mm 2.5 Gy</td>
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<td>94 Gy</td>
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<tr>
<td></td>
<td>GTV + 5 mm 2.6 Gy</td>
<td></td>
<td>98 Gy</td>
<td></td>
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<tr>
<td></td>
<td>GTV + 5 mm 2.7 Gy</td>
<td></td>
<td>103 Gy</td>
<td></td>
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</tbody>
</table>

Footnote. * BED is the biological effective dose, which is calculated on the basis of LQ and is usually used to standardize doses.
the risk of brain radiation necrosis, the survival of patients with this menacing complication may be higher [37].

The degree, frequency and severity of post-radiation necrosis and edema are directly related to the dose and volume of irradiation [38]. Studies on tolerance, safety, and survival after HFRT reported a paradox: improved survival in patients with advanced centralized radiation necrosis at high dose levels [21, 23, 39].

A retrospective study from the Anderson Cancer Center (Houston) reported no significant acute toxicity after HFRT; however, the study showed 2 confirmed and 1 possible cases of radiation necrosis [40]. After applying 8.5 Gy in 8 fractions per GTV region, K. Sultanem et al. [20] reported the results of a Canadian study of 25 patients from McGill University (Montreal), which assessed the use of HFRT (BED, 78 Gy) in patients with GBM. Out of 25 patients, five required an increase in the dose of steroids as a result of progressing neurological symptoms associated with increased edema.

T. Iuchi et al. [21] reported Phase I study of 25 patients with high-grade gliomas (GBM=23) treated with HFRT using IMRT (BED, 126 Gy). Radiation necrosis requiring re-operation was reported in 3 patients in the HFRT group; 2 patients were alive after 17 months, the third one died from distant tumor spreading 20 months after the treatment. In 2014, T. Iuchi et al. [22] assessed the toxicity of hypofractionated high-intensity modulated radiotherapy (IMRT) according to the same procedure with simultaneous and adjuvant administration of TMZ in 46 patients. Radiation necrosis was diagnosed in 20 patients and was observed not only in the high dose region, but also in the subventricular zone (SVZ). Necrosis in SVZ was significantly correlated with long-term survival (risk factor 4.08, \(p=0.007\)) and caused worsening of the functional state in the long-livers. The authors concluded that the benefit of radiotherapy for the subventricular region remains controversial.

C. Chen et al. [23] published data on a study of HFRT with simultaneous and adjuvant administration of TMZ (BED: 78—96 Gy) in 19 patients with GBM. In 4 patients, repeated neurosurgical intervention was performed after radiological progression according to MRI data. After the surgery, a total of 3 necrosis with a minimal residual tumor were recorded histologically. Patients with radiation necrosis had a median survival of up to 20.3 months.

After applying 8.5 Gy in 8 fractions per GTV region, K. Miwa et al. [28], reported seven cases of necrosis in 45 patients. Nonetheless, the authors believe that HFRT technique and IMRT, combined with MET—PET, leads to favorable outcomes in terms of survival of patients with GBM. Out of 24 patients, three required repeated surgery after HFRT with IMRT up to 60 Gy in 10 fractions and adjuvant TMZ. All patients had radiation necrosis, the median overall survival of this group was 33.0 months.

A study of the Northern California Oncology Group [41] with an assessment of the role of brachytherapy boost (local irradiation) after standard radiation therapy, reported “advantages” of radiation necrosis and better survival. The authors suggested that focal necrosis is the inevitable result of effective tumor treatment. M. Fitzek et al. [42] showed an increase in median survival due to improved local control in patients with central radiation necrosis.

Most HFRT regimens are aimed at achieving high BED, which will lead to more frequent development of necrosis. The toxicity criteria of RTOG and EORTC (European Organization for Research and Treatment of Cancer) define clinically or radiologically suspected radiation necrosis as Grade 4 toxicity. Nevertheless, in the above studies radiation necrosis remained asymptomatic in most patients. In addition, the reported association with improved survival is a strong argument against the treatment of radiation necrosis as Grade 4 toxicity. Obviously, the classification of radiation necrosis should take into account the severity of symptoms and their effect on the functional state, which may be a more appropriate tool for assessing toxicity [43].

Since the beginning of the 1990s, there have been trials examining the use of anti-angiogenic and targeted drugs, such as bevacizumab (avastin) and imatinib (glivec) during radiotherapy, because their use can reduce the frequency of radiation necrosis of the brain [44].

Numerous studies have shown that bevacizumab, in addition to the antitumor effect, reduces the frequency of radionecrosis of brain tissue by blocking the vascular endothelial growth factor (VEGF). J. Gonzalez et al. [45] emphasized that in all patients who developed radiation necrosis after the treatment with bevacizumab, there was a decrease in edema in MRI-FLAIR mode and pathological accumulation on MRI-T1 images. By affecting the capillaries, bevacizumab reduces the cerebral edema, associated with development of necrosis.

A total of 14 patients underwent a placebo-controlled, randomized trial of bevacizumab for treatment of radiation necrosis. All patients had radiographic or morphological confirmation of necrosis and corresponding clinical symptoms. The patients were randomized to intravenous saline or bevacizumab groups at 3-week intervals. MRI data showed that no patient in the placebo group responded positively (0 of 7) to the treatment, while all bevacizumab patients had a decrease in edema in FLAIR mode and pathological accumulation on T1 images. According to the expert assessment, this treatment option should be considered for people with radionecrosis after treatment of head cancer and brain tumors [46].

Between 2007 and 2012, 24 patients with radiation necrosis were treated with bevacizumab. MRI data showed radiographic improvement in 23 out of 24 patients based on post-contrast T1-weighted and FLAIR images. The average daily decrease in the dose of dexam-
methylazone after the initiation of bevacizumab therapy was noted in patients who received steroids for a long time as a therapy for radiation necrosis. In terms of treatment effectiveness there were no differences between different schedules of bevacizumab administration. This study, like the previous one, demonstrated high efficacy of bevacizumab for treatment of radiation necrosis [47].

U. Patel et al. [48] note that corticosteroids, repeated surgery and bevacizumab are effective options for the treatment of symptomatic radionecrosis. Bevacizumab is effective and safe in the treatment of radionecrosis after stereotactic radiosurgery; it alleviates symptoms and reduces steroid dependence. The radiographic picture is significantly improved after its administration [49, 50].

Conclusion

For glioblastomas, the central zone or region in the immediate vicinity of the mass accumulating the contrast remains the dominant structure. In numerous studies, the vast majority of relapses are reported within 95% of the isodose. It is interesting to note that a number of authors still describe the central structure of tumor recurrence, emphasizing the need to treat the tumor area (GTV) with up to the maximum allowable dose. In principle, all patients with high malignancy gliomas will sooner or later develop continued growth.

The main problem with the use of HFRT is the increased risk of late toxicity due to damage to functionally important brain structures. The toxicity is significant, but potentially preventable risk of HFRT. Taking into account the devastating consequences of damage to vital structures, it is imperative that all HFRT protocols include strict dose limits for risk tissues, which can automatically exclude tumors located in close proximity to these structures. Nevertheless, small fields used to determine PTV, combined with the use of highly effective conformal radiation technologies (IMRT), should facilitate the use of HFRT in most patients.

Despite the above limitations, HFRT appears to be a safe method. In case of glioblastomas with poor prognosis, the use of HFRT is a particularly advantageous option in terms of reducing the total time of treatment, which is very important for a patient.

It should be noted that, according to the data of a number of authors [31], the use of conformal radiotherapy techniques, thanks to three-dimensional planning and stereotactic radiotherapy as a whole, allows to reduce the volume of irradiated normal tissue up to 20% (on 95% isodose) compared with conventional two-dimensional radiation planning. It is this circumstance in combination with availability of modern radiotherapy equipment that makes it possible in some cases to use the non-traditional fractionation regimes.

We believe that the hypofractionation regimes with both average and high level of TFD and stereotactic radiotherapy will be more widely used in applied radiology in the future.

Authors declare no conflict of interest.

REFERENCES


Commentary

Radiation therapy is an important part of the combined approach to treatment of glioblastomas, which significantly increases the overall survival. The current generally accepted standard for safe patients under the age of 70 is radiation therapy with total focal dose up to 60 Gy in a standard fractionation regimen with a single dose of 2 Gy while on temozolomide therapy. Unfortunately, in most cases, even with the most radical possible removal of the tumor, these tumors, which are among the most malignant ones, recur within the first few months after the end of chemoradiotherapy, most often at a distance of no more than 2—3 cm from the site of the initial growth. Different approaches are used for treatment of relapses: repeated surgeries, targeted therapy, use of electrostatic fields (TTF), other options for chemotherapy (except for temozolomide), immunotherapy, etc. One of the most promising approaches is repeated courses of radiotherapy using stereotactic techniques in radiosurgery and hypofractionation formats while on bevacizumab therapy. According to the existing recommendations, in particular those of the American Association of Clinical Oncologists (ASCO) and the American Society of Radiation Oncologists (ASTRO), hypofractionation is also important as a first-line treatment in general and radiation therapy in particular in elderly patients (over 70 years of age) and in case of relatively low quality of a patient's life. Timing and localization of its use, indications for prescribing it, optimal parameters of various hypofractionation schemes, in particular single and total focal doses, continue to be intensively discussed.

In the presented review, the authors provide various data on the use of the fractionation regimen in patients with glioblastomas; consider both theoretical (the value of the $\alpha/\beta$ coefficient) and practical aspects of this approach (tolerance of healthy tissues, efficacy and timing of use of different treatment regimens, toxicity of the schemes used, including cases of various accompanying combination therapies, etc.).

Undoubtedly, the work is of interest for neurooncologists, neurosurgeons, neurologists, radiotherapists and other specialists.

It is advisable to change the name of the manuscript to a more "mundane" one, e.g.: "Hypofractionation in radiation treatment of glioblastomas".

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