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In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the Problems of Neurosurgery named after N.N. Burdenko was included in the List of Leading Peer-Reviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.
Stereotactic Radiotherapy for Spinal Meningiomas and Neurinomas


Burdenko Neurosurgical Institute, Moscow, Russia

**Introduction.** Over the past decades, stereotactic conformal radiotherapy of intracranial meningiomas and schwannomas has been recognized as an effective and safe procedure. The positive experience of widespread use of the CyberKnife system and implementation of extracranial stereotactic radiotherapy and radiosurgery can be extended to treat spinal tumors. This study assessed the effectiveness of stereotactic radiotherapy of spinal meningiomas and neurinomas using the CyberKnife system.

**Material and Methods.** 46 patients (34 women and 12 men) received treatment between November 2009 and December 2013 (63 tumor nodules). The median age of patients receiving radiotherapy was 49 years (range: 20 to 82 years). Twenty neoplasms were subjected to surgical treatment. In 11 patients, formation of the recurrent tumor foci following treatment was observed along with the systemic disease, neurofibromatosis. Six patients had multiple meningiomas. The median total dose for neurinomas was 13.6 Gy (12.1—14.1 Gy) per fraction, up to 18.2 Gy (16.0—21.1 Gy) in three fractions, and up to 25.6 Gy (24.8—27.6 Gy) in five fractions. Higher doses were used for meningiomas: 15.9 Gy (14.1—16.2 Gy) per fraction, 20.9 Gy (19.5—21.1 Gy) in three fractions, and 27.5 Gy (25.0—29.9 Gy) in five fractions. The load to 0.15 cm² of the spinal cord did not exceed the maximum permissible load of 12 Gy per fraction. The mean duration of catamnestic follow-up was 18.1 (4—52) months; 21.9 (4—52) months for neurinomas and 18 (4—31) months for meningiomas. We have not observed complete tumor elimination (i.e., complete response to radiation therapy) in our series. Partial response was observed in 9 (13.8%) cases, stabilization was achieved in 54 (83.1%) cases, and tumor continued to grow in 2 (3.1%) cases. The patients' status was evaluated using the Frankel, the Karnofsky, and the VAS scales.

**Conclusions.** Our findings clearly demonstrate the short-term benefits of using CyberKnife radiotherapy for benign spinal cord tumors. The catamnestic follow-up period needs to be extended to elaborate recommendations for radiation. The progress in this therapy type will considerably improve the quality of medical care provided to this cohort of patients.

**Keywords:** extramedullary spinal cord tumor, CyberKnife, stereotactic radiation therapy, stereotactic radiosurgery.

In the past decades rapid development of surgery and radiation therapy has improved the treatment outcomes in patients with central nervous system pathologies. Interdisciplinary cooperation between neurosurgeons and radiologists allowed expansion of the range of indications for treatment, including in patients with spinal disorders. The success of radiological therapy methods is largely associated with increased precision and conformity of irradiation. The emergence of IGRT, image-guided radiation therapy based on the images obtained during the treatment, can be considered an important stage in the development of modern methods of radiotherapy.

Extramedullary intradural tumors amount to up to 70% of all neoplasms of the spinal cord and its membranes. Among them, meningiomas and neurinomas constitute 25%.

The number of patients who seek treatment for this pathology increases every year. Improvements in microsurgical techniques increase the proportion of radical removal of extramedullary tumors and reduce the number of complications caused by onset of neurological disorders in the postoperative period. Over the past 10 years more than 700 patients with extramedullary spinal cord pathologies have undergone surgery in the spinal department of the Burdenko Neurosurgical Institute. Despite the generally positive outcomes of surgical treatment, in some cases surgical intervention is considered to be inadvisable. In particular, stereotactic radiotherapy is the method of choice in case of recurrent or continued tumor growth after a surgery, multifocal lesions (neurofibromatosis), as well as in case of severe somatic condition of the patient. In some cases, all other things being equal, the patient makes a decision about the choice of treatment himself [2]. The high efficiency of stereotactic radiotherapy for intracranial tumors has been convincingly demonstrated by now [3—6].

We assessed treatment outcomes in patients with extramedullary tumors of the spinal cord, such as meningiomas and neurinomas. We evaluated effectiveness (control of tumor growth, regression/stabilization of symptoms) and safety (incidence of complications, functional outcomes) of radiotherapy and analyzed the particular features of patients' condition and irradiation parameters that define treatment outcome.

**Patients' characteristics**

We present outcomes of treatment of patients with benign extramedullary spinal neoplasms (meningiomas and neurinomas), who underwent radiotherapy using the CyberKnife system at the Burdenko Neurosurgical Institute between November 2009 and December 2013.

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The study included 46 patients (34 women and 12 men). The median age at the time of treatment was 49 years (range: 20 to 82 years).

Indications for radiotherapy using the CyberKnife system were as follows:

— minimal stable neurological symptoms associated with tumor, or lack thereof, in the preceding months;
— remnant/recurrent tumor or continued tumor growth after surgery;
— contraindications for surgery.

A total of 65 tumor nodules requiring radiotherapy were identified in 46 patients included in this study. Twenty neoplasms (10 neurinomas and 10 meningiomas) were verified during the previous surgery. The remaining 45 cases (28 neurinomas and 17 meningiomas) were diagnosed based on past medical history and characteristic neuroimaging findings. A total of 38 neurinomas and 27 meningiomas were treated by stereotactic radiotherapy. Notably, in 11 patients (10 patients with neurinomas and 1 patient with meningioma) the formation of recurrent tumor foci following the treatment was observed along with the systemic disease, neurofibromatosis. Six patients had multiple meningiomas.

A total of 65 targets of different localization were subjected to radiotherapy: 35 (54%) of the targets were located in the cervical spine (19 [50%] neurinomas and 16 [59.25%] meningiomas); 18 (27.7%), in the thoracic spine (7 [18.42%] neurinomas and 11 [40.75%] meningiomas); and 12, in the lumbar/sacral spine (12 [31.58%] neurinomas). It should be noted that meningiomas were located only in the cervical and thoracic spine.

Most of the targets, 42 (64.6%), were located intradurally, and 23 (35.4%) had intradural growth pattern with paravertebral spread.

Clinical manifestations of tumors were not specific and depended on localization. The main reasons for seeking medical care were movement disorders, such as weakness in legs or arms, sensory disorders and dysfunction of the pelvic organs.

Seven patients with neurinomas had minimal neurological symptoms; in three cases a tumor was an incidental finding during MRI examination of the spine for degenerative disc disease.

Patients’ characteristics are shown in Table 1.

**Stereotactic irradiation technique**

Radiotherapy was performed using the CyberKnife system at the Department of Radiology and Radiosurgery of the Burdenko Neurosurgery Institute. Patients were prepared according to standard protocols. An immobilization device was manufactured at the first stage. Standard head restraints and individual thermoplastic masks were used for irradiating the targets in the upper cervical area. The patients with lower spine pathology were immobilized using a vacuum mattress, which becomes rigid as air is removed from it and retains the shape of the patient’s body during the treatment; the next step was CT scanning of the area of interest. All topometric neuroimaging data (CT and MRI) were recorded with 1–2 mm depth and transferred to a planning station. The volume to be scanned was determined based on the requirements of the planning and navigation system and included the affected area and the adjacent body parts, three vertebrae above and below the localization site. MultiPlan software (version 3.5.4) was used to overlay the images, to determine the contours of the targets and critical structures, and to perform direct dosimetric planning and evaluation of the developed plan. After the irradiation plan was prepared and checked for compliance with safety and effectiveness criteria, the plan was transmitted to the instrument for the treatment procedure. During the irradiation of spinal pathologies, navigation was based on the bone structures in XSightSpine mode, which takes into account non-linear spinal deformities. The duration of a session ranged from 30 min to 1.5 h. 4–8 mg of dexamethasone was usually administered as an intramuscular injection after a session.

**Irradiation parameters**

All patients included in the study were treated by irradiation using the CyberKnife system in either radiosurgery (1 fraction, 25 targets) or hypofractionation (3—5 fractions, 40 targets) mode. The average volume of irradiated neurinomas was 6.96 cm$^3$ (0.04—46.9 cm$^3$); for meningiomas the value was 4.5 cm$^3$ (0.124—4.5 cm$^3$) (Fig. 1).

The irradiation was performed according to the schemes adopted in the Department of Radiology and Radiosurgery of the Burdenko Neurosurgical Institute. Normalization and prescription were based on the mean dose. Neurinomas were irradiated up to a mean dose of 13.6 Gy (12.1—14.1 Gy) per fraction, 18.2 Gy (16.0—21.1 Gy) in 3 fractions, and 25.6 Gy (24.8—27.6 Gy) in 5 fractions. Higher doses were used for meningiomas: 15.9 Gy (14.1—16.2 Gy) per fraction, 20.9 Gy (19.5—21.1 Gy) in 3 fractions, and 27.5 Gy (25.0—29.9 Gy) in 5 fractions. The load to 0.15 cm$^3$ of the spinal cord did not exceed the maximum permissible load of 12 Gy per fraction. The distribution of patients according to the fractionation regime is shown in Table 2.

**Follow-up procedure and data processing**

The patients underwent control MRI examination and regular check-ups by neurologists and radiologists. Tumor response to treatment was assessed using neuroimaging by visual comparison of the images and linear dimensions of the targets. Treatment outcomes were evaluated using the Frankel neurological status scale, the Karnofsky quality of life assessment scale, and the Visual Analogue Scale for pain syndrome intensity (VAS).
Microsoft Excel was used for data analysis.

Results

All 46 patients were available for the follow-up examinations. The median follow-up period was 18.1 months (range: 4 to 52 months): 21.9 months (range: 4 to 52 months) for patients with neurinomas, and 18 months (range: 4 to 31 months) for those with meningiomas.

Neuroimaging assessment of tumor response was performed by comparing the results of MRI studies over time and visual comparison of images and linear dimensions of the targets. The following standard options were identified for tumor response to treatment in order to evaluate the outcomes: “complete response” (disappearance of a contrast focus), “partial response” (decreased tumor size), “stabilization” (stabilization of the target size), “continued growth” (increased tumor size).

We have not observed complete tumor elimination (i.e., complete response to radiation therapy) in our series. A partial response was achieved in 9 (13.8%) cases: for 7 (18.5%) neurinomas and 2 (7.5%) meningiomas; stabilization, in 54 (83.1%) cases: for 29 (76.5%) neurinomas and 25 (92.5%) meningiomas; continued growth, in 2 (3.1%) cases: 2 (5%) neurinomas. In two cases where neurinoma size increased, a possibility of “pseudoprogression”, i.e. temporary reversible increase in size in response to exposure to radiation, has been considered (Table 3). However, in both cases this possibility was ruled out based on time criteria and MRI data over time; both situations were classified as true continued growth.

Therefore, control over tumor growth was achieved in 97% of patients with the median follow-up period of 16 months: 94.7% for neurinomas with the median follow-up of 40 months and 100% for meningiomas with the median follow-up of 17 months.

In most cases, assessment of the dynamics of the patients’ neurological status using the Frankel scale revealed no significant changes after the exposure to radiation (Table 4). Improvement was reported in 2 patients with neurinomas (7%): they were moved from group D to group E. Among patients with meningiomas, one (5.5%) patient displayed positive dynamics of neurological symptoms, as evidenced by his move from group D to group E. No negative dynamics of the neurological status was observed.

Assessment using the Karnofsky scale demonstrated improvement for 14 (50%) patients with neurinomas and 3 (16%) patients with meningiomas (Table 5). No cases of patients’ deterioration according to the Karnofsky scale were observed.

Regression of the previously existing pain syndrome was reported in 60% of patients. In patients with

<table>
<thead>
<tr>
<th>Table 1. Patients' characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Including:</td>
</tr>
<tr>
<td>men, abs. (%)</td>
</tr>
<tr>
<td>women, abs. (%)</td>
</tr>
<tr>
<td>Patient age, years</td>
</tr>
<tr>
<td>Duration of observation, months</td>
</tr>
<tr>
<td>average</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td>Targets and localization:</td>
</tr>
<tr>
<td>cervical, abs. (%)</td>
</tr>
<tr>
<td>thoracic, abs. (%)</td>
</tr>
<tr>
<td>lumbosacral, abs. (%)</td>
</tr>
<tr>
<td>Phacomatosis, or multiple nodules, abs. (%)</td>
</tr>
<tr>
<td>(1 — neurofibromatosis)</td>
</tr>
<tr>
<td>Intra-, extradural tumor growth, abs. (%)</td>
</tr>
<tr>
<td>Biopsy, history of surgeries, abs. (%)</td>
</tr>
<tr>
<td>X-ray verification, abs. (%)</td>
</tr>
</tbody>
</table>
neurinomas, significant regression of pain syndrome (by more than 3 points on the VAS scale) was reported by 15 (83.3%) of 18 patients. For three (16%) patients, pain syndrome remained unchanged or decreased by 1—2 points on the VAS scale. For patients with meningiomas, the improvement, i.e. regression of pain syndrome by more than 3 points on the VAS scale, was achieved in two (28.5%) patients (Fig. 2).

No permanent complications were reported in our series. In one case (Fig. 3), a transient increase in pain syndrome was observed after the radiosurgical treatment (13.5 Gy) of the intradural neurinoma near the roots of

Table 2. Distribution of patients with meningiomas and neurinomas according to the fractionation regime

<table>
<thead>
<tr>
<th>Regime</th>
<th>Patients with neurinomas</th>
<th>Patients with meningiomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dave</td>
<td>dave</td>
</tr>
<tr>
<td>1 fraction</td>
<td>13.63</td>
<td>13.63</td>
</tr>
<tr>
<td>3 fractions</td>
<td>18.22</td>
<td>6.07</td>
</tr>
<tr>
<td>5 fractions</td>
<td>25.61</td>
<td>5.12</td>
</tr>
</tbody>
</table>

Fig. 1. Plan of hypofractionated radiotherapy of a ventral meningioma at the C1—C2 level (3 fractions of 7 Gy, 21 Gy in total).
Table 3. Neuroimaging assessment of tumor response to radiation, abs. (%)

<table>
<thead>
<tr>
<th>Neurinomas</th>
<th>Meningiomas</th>
<th>All the histological variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stabilization of the tumor growth</td>
<td>29 (76.5)</td>
<td>25 (92.5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (18.5)</td>
<td>2 (7.5)</td>
</tr>
<tr>
<td>Continued growth</td>
<td>2 (5.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4. Assessment of the neurological status in patients with neurinomas and meningiomas using the Frankel scale (Groups A—E) before and after radiation therapy, abs. (%)

<table>
<thead>
<tr>
<th>Before radiotherapy</th>
<th>After radiotherapy</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>Neurinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1 (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>13 (47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>11 (40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>1 (3)</td>
<td>3 (10)</td>
<td>11 (40)</td>
<td>13 (47)</td>
</tr>
<tr>
<td>Meningiomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2 (11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>10 (55.5)</td>
<td></td>
<td>9 (50)</td>
<td>1 (5.5)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>6 (33.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>2 (11)</td>
<td>9 (50)</td>
<td>7 (39)</td>
<td></td>
</tr>
</tbody>
</table>

the cauda equina. The deterioration was managed by a course of dexamethasone and NSAIDs.

Discussion

Meningiomas and neurinomas are characterized by limited non-infiltrating growth, which makes it possible to safely and effectively use microsurgery to remove these neoplasms. The total removal of tumors minimizes the risk of disease recurrence and the need for repeated surgical intervention [7—11]. Nevertheless, many neurosurgeons have recently been consciously choosing subtotal removal of the tumor. In doing so they adhere to the principle of maximizing the totality, while minimizing the risk of worsening neurological symptoms, in order to preserve functionality and prevent neurological complications. In those cases it is necessary to use stereotactic radiotherapy as a part of combination therapy to irradiate tumor remnants [12].

Control over tumor growth

The high efficiency of radiotherapies — radiosurgery and hypofractionation — to treat intracranial neurinomas and meningiomas has been demonstrated in numerous studies with long follow-up period. Control over tumor growth was achieved within 7 years after the radiosurgery in 92% of patients with intracranial meningiomas [13]. Control over tumor growth was achieved for 93% of patients with intracranial neurinomas with the median follow-up period of 7—8 years or more [14].

Spinal targets are usually adjacent to the spinal cord, which has low radiation tolerance. It is possible to lower the dose applied to small tumor fragments adjacent to the
spinal cord; however, in theory, it can affect the efficacy of the treatment.

Almost all published papers and the present study demonstrate high efficiency of radiation treatment of spinal neurinomas and meningiomas, which is comparable to that for radiotherapy of intracranial targets. In the study by P. Gerszten et al. [15] featuring 73 patients with benign extramedullary spinal cord neoplasms (35 schwannomas, 13 meningiomas and 25 neurofibromas) control over tumor growth after the radiosurgery (except for one case where irradiation was performed in 3 fractions) was achieved in 98.6% of cases with the mean follow-up period of 37 months. R. Dodd et al. [16] presented the results of the radiotherapy of 55 benign extramedullary neoplasms (30 schwannomas, 9 neurofibromas, and 16 meningiomas) in 51 patients. Irradiation of the targets in 1—5 fractions with doses of 16—30 Gy allowed one to achieve the 100% control over tumor growth in 28 patients with follow-up longer than 24 months.

However, it should be noted that all articles on spinal radiosurgery and hypofractionation have one thing in common: the relatively short follow-up periods (compared to the published data on radiotherapy of intracranial targets) [15, 16].

In our series we got different tumor responses to radiotherapy: partial response was observed in 18.5% of neurinoma cases and only in 7.5% of meningioma cases. This can be explained, on the one hand, by shorter follow-up periods in the meningiomas subgroup (it is well known that the proportion of responding foci increases with the length of the follow-up period). On the other hand it can be attributed to the fact that neurinoma size is generally more likely to reduce after the exposure [14, 17].

Clinical effect

In many published studies on radiosurgery and hypofractionated radiotherapy of benign spinal neoplasms, the authors noticed that radiation therapy results in condition stabilization in most cases [15, 16]. It can be mostly attributed to the fact that the goal of radiation treatment is to stabilize benign tumors rather than to drastically reduce their size (which happens very rarely). It is due to the radiobiological features of neurinomas and meningiomas. This aspect must be taken into consideration when choosing the treatment method:

Table 5. Assessment of the severity of condition in patients with neurinomas and meningiomas using the Karnofsky scale (activity, points) before and after radiotherapy (%)

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Neurinomas</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
</tbody>
</table>

| Meningiomas      |     |     |     |     |     |       |
| 60               | 3   | 3   |     |     |     | 6     |
| 70               | 10  | 8   | 2   |     |     | 20    |
| 80               | 0   |     | 0   |     |     | 0     |
| 90               | 3   |     | 2   | 1   |     | 6     |
| 100              | 2   |     |     | 2   | 3   | 10    |
| Total            | 18  | 3   | 8   | 2   | 3   | 30    |

Fig. 2. Evaluation of the efficacy of stereotactic radiotherapy in reducing pain syndrome in patients.

a — patients with pain syndrome prior to the treatment; b — patients whose pain syndrome intensity remained the same or decreased by less than 3 VAS scale points after radiotherapy.
the major neurological disruption is an indication for surgical treatment, which includes decompression of neural structures and leads to regression of symptoms.

In the series by G. Gagnon et al. [18], overall improvement was observed in 44 (22%) of 200 patients; in our study it was reported for 3 (6.5%) out of 46 patients. Other studies mention low improvement rates without giving the exact values [15, 16]. These differences may be associated with different methods for assessing the changes in neurological status (various scales). Furthermore, we must bear in mind that evaluation of neurological outcomes is a challenging task. For example, a significant portion of the patients who have undergone a surgery prior to radiotherapy, which makes it difficult to distinguish between progression of disease-related symptoms, complications after the surgery and radiation treatment.

Significant rates (25—73%) of complete or partial regression of pain syndrome were reported in virtually all studies [15, 16, 18]. In our study, regression of pain syndrome was observed in most patients with neurinomas (83.3%) and in some patients with meningiomas (28.5%). More frequent reduction in the severity of pain syndrome for neurinomas may be associated with their more pronounced response to irradiation.

Most of the examined studies did not include assessment of changes in the patients’ status using the Karnofsky scale. Our study demonstrated that patients’ condition according to the Karnofsky scale improved in 39% of cases (50% for neurinomas and 16% for meningiomas). This improvement may largely be attributed to the regression of pain syndrome rather than to actual recovery of neurological function.

Complications

Literature review shows that the use of stereotactic conformal radiotherapy using the CyberKnife system to irradiate vertebral neoplasms in radiosurgery and hypofractionation modes is associated with very low incidence of complications.

In the study by R. Gerszten et al. [15], 3 (4.1%) patients developed radiation-induced myelopathy within 5—13 months after the treatment. The complications were reversible in all cases. The higher rate of complications reported in this work compared to other studies may be associated with the use of radiosurgery in all cases except one. In the study by R. Dodd et al. [16], one (2%) patient developed radiation-induced myelopathy 8 months after the irradiation of a meningioma in 3 fractions. The authors believe that deterioration in this case was caused by exceeding the tolerance threshold: 1.7 cm³ of the spinal cord received 8 Gy per fraction. I. Gibbs et al. [19] reports myelopathy for 6 out of 1075 patients at, on average, 6.3 months after various spinal cord tumors were irradiated using the CyberKnife system.

Fig. 3. Neurinoma at the L4—L5 level, volume of 2.52 cm³, 13.5 Gy on average (prescribed dose of 12.2 Gy based on the 80% isodose curve).
In our study we did not observe cases of radiation-induced myelopathy. This may be due to the restrictions on dose load to the spinal cord adopted in the department.

Uncertainty of prescribed doses and safe radiation dose

There is one important issue that must be taken into account when irradiating benign spinal lesions. It is uncertainty surrounding exposure modes, therapeutic doses, and safe loads.

R. Dodd et al. [16] irradiated meningiomas, neurinomas, and neurofibromas 0.136—24.6 cm³ in size in 1—5 fractions with a total dose of up to 16—30 Gy. The authors limited the maximum dose for radiosurgical treatment to 10 Gy per 0.2 cm³ of the spinal cord volume. Wherever it was impossible to comply with this dose limit, the authors switched to the hypofractionation mode and limited the exposure of the spinal cord to 8 Gy per fraction. In the study by P. Gerszten et al. [15], all subjects underwent radiotherapy in the radiosurgery mode, except for one patient who received treatment in 3 fractions. The average prescribed dose was 17.3 Gy; the target sizes ranged from 0.3 to 93.4 cm³. The authors limited the maximum dose to the spinal cord to 8 Gy. The study by J. Kirkpatrick et al. [20] indicates that the risk of damage is less than 1% when the maximum dose to the spinal cord is limited to 13 Gy (per fraction) or 20 Gy (in 3 fractions). I. Gibbs et al. [19] reported 6 cases of radiation-induced spinal cord injury among more than 1000 cases of radiosurgery and hypofractionation. However, re-calculation of the equivalent doses revealed that the maximum dose of 8 Gy to the spinal cord per session was exceeded in 3 out of 6 cases. The authors also noted the increased risk of complications with repeated exposure.

One can hope that accumulation and analysis of a sufficient quantity of data will result in the development of the more stringent criteria and recommendations.

Conclusions

Over the past two or three decades stereotactic conformal radiotherapy of intracranial meningiomas and schwannomas has been recognized as an effective and safe procedure. Widespread use of modern irradiation techniques, development and implementation of extracranial stereotactic radiotherapy and radiosurgery allowed extending this positive experience to targets located in the spine. This approach has also allowed one to enhance the conventional schemes — radiosurgery and standard fractionation — with a hypofractionation technique that significantly broadened our therapeutic options.

The present study demonstrates the high rate of control over growth of spinal meningiomas (100%) and neurinomas (94.7%) in case of stereotactic radiotherapy after radiosurgical treatment. The outcomes are comparable to those for intracranial targets, despite the currently limited duration of follow-up period. We will undoubtedly continue this study and monitoring of these patients in order to assess the long-term effectiveness of the treatment.

Even though radiation therapy does not physically remove a tumor, it can have a positive clinical effect. In our series, the regression of pain syndrome after the exposure was reported in substantial portion of cases (60%), leading to improved quality of life and positive dynamics of the patients according to the Karnofsky scale in 39% of cases.

Strict adherence to safe radiation dose load on the spinal cord prevented development of myelopathy.

The results clearly demonstrate the short-term advantages of using the CyberKnife system radiotherapy to treat benign spinal lesions. To elucidate better recommendations for the exposure, the pilot project needs to be extended, including continued follow-up of the patients and enrollment of new ones.

The development in this field of medicine will significantly improve the quality of medical care provided to this cohort of patients.

REFERENCES


Vertebral meningiomas and neurinomas are benign tumors that can cause compression of the spinal cord and nerve roots. Surgical treatment is usually prescribed to resolve neurological symptoms associated with these neoplasms. However, surgery is associated with a high risk of complications in a substantial portion of cases, which can reduce patients’ quality of life after the surgery. The development of radiological methods, such as emergence of high-precision radiotherapy with neuronavigation (including CyberKnife), has recently made it possible to carry out effective and safe radiotherapy of targets located in the spine.

This work is devoted to evaluation of exposure outcomes, and complications among 190 consecutive patients stereotactic radiosurgery of large lesions of the spinal cord (including CyberKnife), has recently made it possible to carry out effective and safe radiotherapy of targets located in the spine

According to the follow-up results, control over tumor growth was achieved in 97% of patients for the median follow-up period of 18 months: 94.7% for neurinomas with the median follow-up of 21 months and 100% for meningiomas with the median follow-up of 18 months. Taking into account the limited follow-up period, the results are in accordance with those for intracranial neoplasms. Unfortunately, due to the short follow-up period (18 months on average), the data on tumor growth control should be considered to be preliminary.

The condition of all patients was either improved or stabilized. Pain was reduced in the majority of patients with neurinomas (83.3%) and in some patients with meningiomas (28.5%). The positive dynamics according to the Karnofsky scale was reported in 39% of cases (50% for neurinomas and 16% for meningiomas). There was one case of a transient increase in pain syndrome. No other complications were observed.

This work may be of interest to various specialists: neurosurgeons, radiologists, and oncologists. It contains important information on the new effective and highly demanded treatment method, which had previously been available primarily for intracranial targets. Transfer of vast experience accumulated in treatment of brain pathologies will considerably improve the quality of medical care provided to patients with tumors of vertebral localization.

E.L. Razumova (Moscow, Russia)
Introduction. Cerebral arteriovenous malformations (AVMs) are congenital anomalies of the cerebral vessel development during the embryonic period. Currently, the conventional therapy for AVMs includes endovascular management, microneurosurgical resection, and stereotactic irradiation. Material and methods. A total of 315 patients with cerebral AVMs were subjected to stereotactic radiotherapy in 2005—2011. 238 (76%) patients had subarachnoid hemorrhage (SAH) at different times (6 months to 5 years) before the therapy; 214 (68%) patients had headaches; 113 (36%) patients had focal neurological symptoms due to the localization; 82 (26%) patients had seizures. Twenty-three of 315 patients were subjected to surgical resection of an intracerebral hematoma prior to radiotherapy, and 119 (36%) patients received endovascular treatment, including partial embolization of the stroma of AVM. Seven (2%) patients received both types of treatment. 267 patients underwent single fraction radiosurgery. In patients with large AVMs, we used hypofractionation including irradiation of the target in several (typically 2—7) fractions, with the radiation dose per fraction exceeding 2 Gy. Forty-six patients were irradiated in the hypofractionation regimen; two patients had a course of stereotactic radiotherapy in the standard fractionation regimen. The marginal dose of radiosurgical irradiation was 13—30 Gy (the mean dose was 24 Gy). The main group of patients (38 individuals) with large AVMs was treated using hypofractionation of up to 35 Gy in 5 fractions. Results. Control angiography (or SCT-angiography) of 225 patients who were followed up for at least 2 years after therapy, showed that complete obliteration was achieved in 83% of cases. The rate of symptomatic radiation reactions was less than 10%. A higher obliteration rate was observed for AVMs of less than 2 cm in size and at marginal doses of more than 24 Gy. After hypofractionation, obliteration was observed in 10 (37%) of 27 patients with a complete follow up rate. The rate of symptomatic radiation reactions was less than 35%. Conclusion. Radiosurgery is a minimally invasive treatment option for patients with cerebral AVMs that provides a sufficiently high degree of obliteration with the minimum complication rate. The hypofractionation procedure is the method of choice for treating large AVMs. Stereotactic irradiation using a Novalis linear accelerator makes it possible to treat patients with AVMs of virtually any generalization, location, and volume.

Keywords: arteriovenous malformation, radiosurgery, obliteration, radiation reactions, hypofractionation.
included paroxysmal symptoms in the form of full-scale and local convulsive seizures.

267 patients received single fraction radiosurgical irradiation. Hypofractionation was used in the case of large AVMs and included irradiation of the target in several (typically 2—7) fractions; the radiation dose per fraction exceeded 2 Gy. Forty-six patients were treated in the hypofractionation regime; two patients had a course of stereotactic radiotherapy in the standard fractionation regime.

Prior to radiotherapy, twenty-three of 315 patients were subjected to surgical resection of an intracerebral hematoma and an attempt of AVM excision after hemorrhage; 119 (36%) patients received endovascular treatment, including partial embolization of the stroma of AVM. 7 (2%) patients received both treatments. Six patients underwent previous irradiation treatment: 3 patients underwent treatment using a proton accelerator, 2 patients underwent conventional radiotherapy (58 Gy), and 1 patient was treated using a cobalt machine. In all the cases, control angiograms did not reveal AVM obliteration within 4 years after the exposure.

The distributions of patients according to the AVM localization and Spetzler—Martin grading scale are shown in Tables 1 and 2.

Radiosurgery planning and execution

The accelerator is equipped with a micro-multileaf collimator. The collimator has 52 leaves. Each leaf is a thin moving plate, with the plate thickness being different at the center and margins of irradiation coverage and amounting to 3 and 5 mm, respectively. The accuracy of leaf positioning is 0.1 mm. The maximum coverage size is 10×10 cm. The field penumbra width, defined as the distance between the 20 and 80% dose levels, is 2.5 mm. The machine is shown in Fig. 1.

The static and dynamic arc radiation techniques (Fig. 2a, b) were used for treatment of patients with AVMs. In the first method, the target is irradiated from several preselected directions. Collimator leaves form the field covering the target and remain immobile during irradiation from this direction. The dynamic arc approach refers to an irradiation technique when the accelerator head rotates, and, at the same time, the position of collimator leaves changes according to a program developed at the radiotherapy planning stage. The required conformity is achieved through the field shape that is generated by collimator leaves and follows the target contours.

In all the cases, the cerebral angiography data aligned with the MRI data were used. The arteriovenous nidus (AV nidus) to be irradiated (Fig. 2c) was identified based on the angiography data.

Direct angiography and contrast-enhanced MRI in T1- and T2-weighted modes were used at the planning stage in all the cases. The images were aligned by performing CT and angiography in a localizer.

Radiosurgical treatment was performed in the case of relatively small AVMs of up to 10 cm in size. The mean radiation dose for radiosurgery ranged from 22 to 32 Gy. The prescribed isodose was 66—94%.

AVMs larger than 10 cm or smaller AVMs located in functionally critical areas of the brain were the indications for fractionated irradiation in 90% of cases. Two of 48 patients were treated by conventional teletherapy with the total boost dose (TBD) of up to 60 Gy in 30 fractions. The remaining 46 patients were treated using hypofractionation:

— 5 patients received TBD of 20—24 Gy in 2 fractions;
— 3 patients received TBD of 35 Gy in 5 fractions of 7 Gy.
— 38 patients received TBD of 35 Gy in 7 fractions of 5 Gy.

Dosimetric parameters of the performed irradiation are shown in Table 3.

Out of 48 patients who underwent fractionated irradiation, 42 patients were irradiated using the dynamic arc technique, and 6 patients were treated using static beams. Out of 225 radiosurgery patients (single session irradiation), 192 patients were irradiated using arches, and 33 patients were irradiated using static beams.

Clinical outcomes

The follow-up data covering more than 3 years after the exposure were obtained for 225 out of 267 patients who received radiosurgical treatment. Out of 48 patients who received fractionated treatment, the follow-up data covering more than 3 years were obtained for 39 patients.

Analysis of the treatment outcomes was based on assessment of obliteration, the repeated hemorrhage rate, radiation toxicity (analysis of edemas, symptomatic edemas, and radiation necroses), and long-term changes including cases of the cyst development.

Clinical outcomes of radiosurgical treatment of patients with cerebral AVMs

After a radiosurgical procedure, 83 (37%) out of 225 patients demonstrated objective signs of an improved condition in the form of regression of the cerebral and focal neurological symptoms. These patients had a higher Karnofsky score compared to the pre-irradiation indicators. Epileptic seizures observed in 61 patients prior to irradiation either stopped or became less frequent in 21 patients. Twenty-nine (13%) patients developed a worsening or onset of the neurological symptoms within 18 months after the exposure.

After the treatment, all patients we enrolled in the dynamic follow-up, with neurological status assessment every 6—12 months. MRI of the brain, including angiography, was performed annually. In the case of AVM obliteration signs (typically after 2 years), the patients were advised to undergo digital cerebral angiography.

Assessment of the treatment outcomes was based on the following parameters:

— obliteration;
— repeated hemorrhages;
— post-irradiation changes in the form of:
  — edema (based on the T2-weighted MRI data) over time;
  — symptomatic edema;
  — radiation necrosis (morphological damage to the brain matter that is characterized by damage to the endothelium and oligodendroglia, which is visualized by contrast in contrast-enhanced MRI).

Assessment of obliteration

187 (83%) out of 225 patients developed complete obliteration after radiosurgical irradiation (Fig. 3).

Based on the data of control examinations, 20 (9%) patients had partial AVM obliteration (Fig. 4). Eighteen (8%) patients demonstrated no changes in the size, volume, and structure of AVM. An example of an AVM volume reduction after radiosurgical treatment is presented in Fig. 5.

Comparative analysis of the obliteration and post-irradiation complication rates depending on various irradiation parameters (marginal dose, irradiated volume, mean dose) was performed.
The histograms presented in Fig. 6 show that post-radiation obliteration was more often observed for the mean doses of 24 and 27 Gy and the marginal doses of 24 and 26 Gy. In 57% of the cases, obliteration was identified for AVMs of <2.0 cm³ (Fig. 7).

Analysis of the obliteration rate depending on the marginal dose and malformation volume revealed that more than 90% of the obliteration cases were observed for the marginal dose of >23 Gy and for the AVM volume of <2.0 cm³ (Fig. 8).

Repeated hemorrhage

Ten (4%) patients experienced repeated hemorrhage within 16 to 12 months after radiosurgical treatment. In all the cases, repeated hemorrhage was not related to the volume of healthy tissues irradiated with a dose of 12 Gy.

Six patients died: the cause of death in 3 patients was repeated hemorrhage, and the remaining deaths were not related to the underlying disease.

Radiation reactions (post-radiation changes)

1. Post-radiation edema development

Based on the data of T2-weighted MRI, the development of (symptomatic or asymptomatic) edema was observed in 32% of 225 patients. This group included all cases of perifocal edema aggravation detected by T2-weighted MRI. Edema was most often observed in groups of patients with the marginal dose of >25 Gy and the mean dose of 28 Gy (Fig. 9). The period of edema development ranged from 6 to 15 months after the exposure.

Twenty-eight (13%) patients developed edema with aggravation of the neurological symptoms, usually in the form of worsening of headache, within 6 to 18 months after therapy. In 80% of the cases, the development of edema accompanied by the neurological symptoms was associated with the AVM localization within functional areas. Assessment of the edema development depending on radiation exposure of healthy tissues revealed that edema with clinical presentations developed most often if the volume of healthy tissues with the received dose of 12 Gy was more than 15 cm³.

2. Post-radiation necrosis development

In our series, the development of radiation necrosis (local radiation injury) was observed in 12 (5%) patients within 5 to 15 months after the exposure (Fig. 10).

Radiation necrosis occurred in 10% of the cases at the marginal dose of 22 to 29.7 Gy. Necrosis developed most often when the volume of healthy tissues with the received dose of 12 Gy was more than 20 cm³.

In 6 (3%) cases, the development of cysts was observed in the later follow up periods (Fig. 11). The cyst development was asymptomatic.

Based on cerebral angiography, AVM obliteration was observed, while the emergence of a cerebrospinal fluid cyst in the deep-seated parts of the left frontal lobe was also noted.

Outcomes of hypofractionation in patients with AVMs

Assessment of the treatment outcomes was based on analysis of the data from 38 patients who underwent radiosurgery in the hypofractionation regimen (7 fractions of 5 Gy each). Complete follow up data were obtained for 27 patients. Objective signs of improvement, including regression of the paroxysmal symptoms or disappearance of headache, compared to the clinical condition prior to the treatment were achieved in 10 out of 27 patients. The Karnofsky index in these patients was higher than the pre-radiation indicators. According to control angiography, all cases of the improved Karnofsky index were accompanied by complete or partial obliteration of the AVM stroma after the exposure.

Assessment of obliteration after hypofractionation

After hypofractionation radiosurgery (7 fractions of 5 Gy each), 10 (37%) out of 27 patients with follow up of more than 3 years achieved complete obliteration (Fig. 12 and 13).

A partial reduction in the AVM size was observed in eight (30%) patients. Nine (33%) patients had no changes in the size, volume, and structure of AVM.

Analysis of the obliteration rate depending on the AVM volume, marginal dose, and mean dose per fraction was performed. 90% of the cases of complete obliteration were observed for the AVM volume of <11 cm³. Obliteration was

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**Table 1. Distribution of patients with cerebral AVMs according to the localization**

<table>
<thead>
<tr>
<th>Localization</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemispheres</td>
<td>189</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>46</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>51</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>69</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>25</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>14</td>
</tr>
<tr>
<td>Thalamus/basal ganglia</td>
<td>70</td>
</tr>
<tr>
<td>Pineal region</td>
<td>8</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>12</td>
</tr>
<tr>
<td>Cerebellum and brain stem</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 2. Distribution of patients with AVMs according to the Spetzler—Martin scale**

<table>
<thead>
<tr>
<th>Spetzler—Martin grade</th>
<th>Number of patients, abs. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>44 (14)</td>
</tr>
<tr>
<td>III</td>
<td>150 (48)</td>
</tr>
<tr>
<td>IV</td>
<td>72 (23)</td>
</tr>
<tr>
<td>V</td>
<td>49 (15)</td>
</tr>
</tbody>
</table>

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Fig. 1. A machine for stereotactic radiotherapy and radiosurgery.
**Fig. 2.** AVM irradiation plans using “conformal beam” (a) and “dynamic arc” (b) techniques; c — overlay of angiography and MRI data. Identification of an AV-nidus.

**Table 3.** Physical parameters of stereotactic irradiation upon radiosurgery and fractionated radiation therapy in patients with AVMs

<table>
<thead>
<tr>
<th>Irradiation parameter</th>
<th>Radiosurgery</th>
<th>Hypofractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose covering 95% of the target, Gy</td>
<td>13—30</td>
<td>3—9</td>
</tr>
<tr>
<td>Marginal coverage, mm</td>
<td>0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Volume (V), cm³</td>
<td>0.07—16.683</td>
<td>10.04—100.0</td>
</tr>
<tr>
<td>Mean dose, Gy</td>
<td>22—32</td>
<td>3—7</td>
</tr>
<tr>
<td>Volume of healthy tissues with the received dose of more than 10 Gy, cm³/Dose</td>
<td>1.289—62.65</td>
<td>1.88—9.00</td>
</tr>
<tr>
<td>Volume of healthy tissues with the received dose of more than 12 Gy, cm³/Dose</td>
<td>0.08—42.62</td>
<td>1.82—8.40</td>
</tr>
<tr>
<td>Isodose, %</td>
<td>66—95</td>
<td>83—94</td>
</tr>
<tr>
<td>Number of arches in the dynamic arc technique</td>
<td>4—10</td>
<td>3—5</td>
</tr>
<tr>
<td>Number of beams in the conformal beam technique</td>
<td>6—15</td>
<td>6—10</td>
</tr>
</tbody>
</table>
observed in 83% of the cases for the AVM volume of less than 12 cm$^3$. In 37% of cases, obliteration turned out to be possible upon hypofractionation at the marginal dose per fraction of 4.10 to 6.30 Gy.

In the case of previous incomplete AVM embolization, complete obliteration was observed only in 14% of the cases, whereas it was 62% in the group without embolization.

Radiation reactions

**Post-radiation edema development after hypofractionation**

Perifocal edema developed in 71% of cases upon the hypofractionation regimen with TBD of 35 Gy in 7 fractions, if the AVM volume was between 17 and 24 cm$^3$ (Fig. 14).

The occurrence of edema increased at doses of ≥4 Gy per fraction per 10 cm$^3$ of healthy tissues (Fig. 16). In 27% of the cases, edema developed at a dose of ≥3 Gy per 10 cm$^3$ of healthy tissues (see Fig. 16).

In 17% of the cases, edema developed at the dose of ≥3 Gy as well as ≥4 Gy per 15 cm$^3$ of healthy tissues (Fig. 17).

**Post-radiation necrosis development after hypofractionation**

Radiation damage (necrosis) was detected in 3 patients. The necrosis rate was 23% for the AVM volume of 18 to 47 cm$^3$. Necrosis developed at the marginal dose of ≥4.5 Gy per fraction. Analysis of the necrosis rate and the dose per 10 and 15 cm$^3$ of healthy tissues revealed the necrosis development in 11% of all 27 patients, with the dose per fraction being ≥4.5 Gy. Marginal coverage to compensate geometric and dosimetric errors was additionally used in first patients who underwent the treatment. The correlation between necrosis and marginal coverage is shown in Table 4.

Increasing marginal coverage to 1 mm or more increased the occurrence of radiation necrosis.

**Discussion**

Intracranial AVMs are relatively rare congenital vascular anomalies (malformations) of the brain [1]. They are comprised of a snarled tangle of arteries and veins interconnected by shunts that leads to shunting of arterial blood into veins, bypassing capillaries [3].

A treatment approach depends on the AVM volume and localization, features of blood supply, and neurological symptoms. Currently, the main treatments for AVM are surgical approaches (excision and embolization of AVM) and stereotactic radiotherapy.

Endovascular embolization can be used as a supplement prior to surgical resection of AVM, as an independent treatment method, or as a stage before stereotactic radiosurgery. In some cases, embolization preceding radiosurgery can lead to less reliable obliteration of the AVM target volume, which is observed in radiosurgical treatment. Upon endovascular treatment, high obliteration rates are observed for small AVMs with well-developed afferents. Recanalization of vessels after AVM embolization may require additional treatment of some AVM portions that were previously successfully embolized. According to many authors [12, 16, 36], the efficacy of endovascular treatment is estimated at 35—40%.
The efficacy of surgical treatment of AVM is 95% for Spetzler-Martin grade 1—2 AVMs [6, 23, 26]. Grade 4—5 malformations are considered to be inoperable. One should also keep in mind anesthetic risks that are involved in surgery and are virtually absent in the case of radiosurgery.

Stereotactic radiosurgery is indicated for AVM patients who are not eligible for surgical resection or embolization with a good occlusion effect without or with the minimal risk for the development or aggravation of the neurological symptoms. Radiosurgical irradiation can be performed using many machines for radiation therapy and radiosurgery, including cobalt machines, cyclotron, and (proton) linear accelerators. The disadvantage of irradiation is a long period (up to 3 years) when changes occur that are accompanied by progressive intimal thickening caused by a rapid increase of smooth muscle cells, which leads to a narrowing or disappearance of the vascular lumen [31, 37].

Currently, representative experience in treatment of AVM patients using a Gamma Knife device has been gained worldwide. However, there are almost no examples of large scale series of observations with long-term follow up for the use of linear accelerators in treatment of AVM patients. The linear accelerator technology was pioneered by Betti in Paris, Barcia-Salorio in Spain, and Columbo in Italy. High precision irradiation techniques have been improved in the United States by researchers working at the United Center in Boston and in Gainesville in Florida. They have fundamentally modified the principle of accelerator operation to perform irradiation in a single session [2, 4, 6, 9, 18, 22, 27, 29]. This approach has been appreciated and considered as an alternative to microsurgical resection of AVMs in functionally important areas of the brain.

Fig. 4. AVM of the fronto-parietal region.

a — cerebral angiography prior to radiosurgery; b — control cerebral angiography 24 months after stereotactic radiosurgery (AVM obliteration is observed).
Fig. 5. AVM of the right occipital region. Blood supply occurs from the carotid and vertebral arteries (volume: 9.88 cm³, prescribed dose: 22 Gy, isodose: 80%).
Cerebral angiography before (a–c) and 4 years after radiosurgery (d–f), a decrease in the AVM volume to 6.65 cm³.

Fig. 6. The obliteration rate depending on the mean and marginal doses.
AVM obliteration

According to various authors [2, 5, 7, 14, 24, 40], the obliteration probability is 50—95% five years after a single session radiosurgical procedure.

The long-term (5—14 years) follow up outcomes after radiosurgical treatment using a Gamma Knife machine demonstrate that 73% of patients, on average, after radiosurgery have all chances to avoid repeated hemorrhage and continue normal activities.

One of the most representative series featuring more than 1,000 patients after radiosurgery using a Gamma Knife device was presented by D. Kondziolka and L. Lunsford [15]. According to them, the obliteration rate based on the results of control angiography 2.5—3 years after the exposure is 73%, while that based on the results of MRI angiography is 86%. The MRI accuracy in assessing AVM obliteration is 96%, on average, whereas the angiography accuracy is 79%.

In this study, the obliteration rate after radiosurgery was 83%.

According to D. Koziolka and L. Lunsford [15], the success of obliteration depends on the AVM volume and the absence of previous embolization. These indicators are the only significant factors associated with the marginal dose. Similar results were obtained in the present study: obliteration was more often observed for the mean doses of 24 and 27 Gy and the marginal doses of 24 and 26 Gy. In 57% of the cases, obliteration was observed for AVMs of <2.0 cm³.

Poorer data on obliteration were observed in treatment of large AVMs. There are several classifications of large cerebral AVMs. In radiosurgical practice, we rely on the concept by B. Pollock et al. [25] who proposed to consider AVM to be large if its volume is more than 10 cm³. There are certain difficulties in treatment of large AVMs (larger than 10 cm³) that are associated with generalization and blood supply. Most of these malformations are considered to be untreatable [11, 21]. Endovascular embolization of AVM prior to radiosurgical treatment is often used in patients with large malformations. Thrombosis of an AV-nidus is observed only in 14—15% of cases [12]. Radiosurgical irradiation (delivery of a dose in a single fraction) is associated with a high risk of complications due to a high level of exposure of surrounding healthy tissues.

S. Sirin et al. [32] proposed a technique of staged radiosurgery for treatment of patients with large AVMs, in

Fig. 7. The obliteration rate depending on the AVM volume.

Fig. 8. The obliteration rate depending on the marginal dose and AVM volume.
which a malformation is irradiated in parts. This radiosurgical irradiation technique is usually used when the irradiated target volume exceeds 15 mL. After selection of the total volume of an AV-nidus, the irradiated volume is divided into several parts (median or lateral, upper and lower parts of the whole volume) based on cerebral angiography and MRI data. Certain landmarks, such as large vascular reservoirs, the ventricles, or other anatomical structures, e.g., the inner capsule, are used. The AVM volume is divided into approximately equal parts using a computer system for planning. Radiosurgical irradiation of a preselected AVM fragment, which is demarcated using anatomical landmarks, is performed. Doses per session are varied from 12 to 20 Gy based on the 50% isodose, or the marginal dose at the minimum should be at least 16 Gy.

The second stage of radiosurgical treatment is performed 3—6 months after the first procedure. A group of authors from Pittsburgh [15] reported the obliteration rate of 50% (7 out of 14 patients) after 36 months without development of neurological deficits; complete obliteration was achieved in 29% of the cases. Other papers also report on a potentially significant role of staged radiosurgery in the treatment of large AVMs [8, 24, 34]. The disadvantage of this technique is the difficulty of aligning the two irradiation plans; therefore, the second stage must be completed within 6 months after the first one.

According to J. Jones et al. [11], the staged approach to treatment allows healthy tissues to recover after irradiation of an AVM fragment, using a break between treatment stages. The authors’ conclusions are based on the data of a series of 28 AVM patients who underwent staged radiosurgery. As a result of staged treatment, the AVM volume decreased by 27% for the dose of 12 Gy. The authors believe that this approach to treatment is associated with lesser adverse radiological effects on the surrounding structures. The AVM obliteration rate after fractionated radiotherapy (2—4 Gy per fraction and TBD of up to 50 Gy) is relatively low. R. Kjellberg et al. [14] present data

**Table 4. The necrosis incidence rate depending on the margin**

<table>
<thead>
<tr>
<th>Marginal coverage, mm</th>
<th>Nocrosis</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

**Fig. 9. The edema incidence rate depending on the marginal and mean doses.**
Fig. 10. MRI of the female patient S.
a — before radiosurgery; b — exposure plan (volume: 0.5 cm$^3$; 23.4 Gy delivered based on 90% of isodose); c, d — 14 months after stereotactic radiosurgery (radiation necrosis in the form of accumulation of a contrast and perifocal edema of the brain matter are observed).

on the use of stereotactic proton radiotherapy in treatment of large AVMs. According to them, the efficacy of thrombosing is 19% within 3—5 years after the exposure. Despite a relatively low obliteration rate, the risk of repeated hemorrhage is reduced. According to another study [22], the 25% embolization rate was achieved in 48 patients with AVMs of $\geq 15$ cm$^3$ within 40 months after the exposure. The mean marginal radiation doses were 17.7 and 16.5 Gy for the AVM volume of 10—20 cm$^3$ and $>20$ cm$^3$, respectively. During follow up, 37% of patients with AVMs of $>10$ cm$^3$ had moderate, and 12% had serious complications that were associated with the post-radiation changes in surrounding tissues.

L. Miyawaki et al. [18] showed that the obliteration rate in patients with AVMs of $>14$ cm$^3$ after linear accelerator radiosurgery was 22%. G. Nagy et al. [21] reported the obliteration rate of 36.4% and the hemorrhage rate of 35.7% for a group of patients with AVMs of $>10$ cm$^3$ after radiosurgical treatment. In a group of patients with the mean volume of an AV-nidus of 30 cm$^3$, the obliteration rate was 33.3% after a single session of radiosurgical treatment. However, a correlation between the radiation dose and development of complications was noted. High doses required to achieve obliteration are clearly associated with the development of complications [18, 19].

In our series, patients who underwent hypofractionation (7 fractions until TBD of 35 Gy) developed obliteration in 37% of cases at a marginal dose per fraction from 4.1 to 6.3 Gy. In more than 90% of cases, obliteration was detected for AVMs of $<11$ cm$^3$.

Complications

Clinical presentations after radiosurgical treatment include short-term headaches from the frame, nausea, and, possibly, a slight increase in the risk of symptomatic epilepsy in patients with cortical AVMs, especially if symptomatic epilepsy was already reported previously [30, 40]. For this reason, many authors recommend the use of anticonvulsants during treatment of patients with cortical AVMs. In our practice, we prescribed steroid therapy in all cases of edema, and all patients who experienced convulsive seizures prior to treatment received anticonvulsants.

The likelihood of the development of post-radiosurgical changes depends on the dose and volume of the irradiated target. The volume of tissue irradiated by a dose of 12 Gy or
Fig. 11. AVM of the left frontal lobe before (a) and 34 months after (b) radiosurgical irradiation.

Fig. 12. MRI angiography before (a) and after (b) radiosurgical treatment (AVM volume: 4.27 cm$^3$; 7 fractions of 5 Gy each).
AVM obliteration in the right cerebellar hemisphere is seen.
Fig. 13. Cerebral angiography before (a) and 3 years after (b) fractionated stereotactic radiotherapy. AVM obliteration is observed. AVM volume prior to irradiation was 33 cm$^3$.

Fig. 14. The edema incidence rate depending on the AVM volume.

Fig. 15. The edema incidence rate depending on the marginal dose per fraction.
Fig. 16. The edema incidence rate depending on a dose per 10 cm$^3$ of healthy tissues.

Fig. 17. The edema incidence rate depending on a dose per 15 cm$^3$ of healthy tissues.

more is a factor correlating with a probability of the development of local changes [40] (Fig. 18).

Symptomatic deterioration is associated with the AVM localization, even though the localization is not important for the development of certain post-radiation changes. Post-radiosurgical changes in the form of edema (regions of a high T2-weighted MRI signal in the brain matter surrounding the irradiated AV-nidus) develop in approximately 30% of patients within 1—24 months after radiosurgery.

Post-radiation changes are asymptomatic in 70% of patients. Approximately 9—10% of patients experience symptomatic post-radiosurgical changes. A multicenter study was performed in 1,255 AVM patients who developed neurological complications after radiosurgical treatment using a Gamma Knife machine [8]. The mean marginal dose was 19 Gy (10—35 Gy), and the mean volume of the irradiated target was 5.7 cm$^3$ (0.26—14.3 cm$^3$). The mean period for developing any complications was 34 months (9—140 months). 80 patients had post-radiation changes in the brain parenchyma in the form of edema. In our study, edema was detected in 32% of 225 patients within 6 to 18 months. The conducted analysis revealed that edema with clinical presentations most commonly developed when the volume of healthy tissues with the received dose of 12 Gy exceeded 15 cm$^3$.

Twelve patients were detected with radiation necrosis within 5 to 15 months after the exposure. If the volume of healthy tissues with the received dose of 12 Gy exceeded 20 cm$^3$, the development of edema was observed in all cases.

Another post-radiation complication is repeated hemorrhages. According to various authors, the repeated hemorrhage rate in AVM patients prior to irradiation is 56—78% [10, 35]; after irradiation, the repeated hemorrhage rate does not exceed 5% within 3 years after treatment. In our series, 10 (4%) patients had repeated hemorrhage within 16 to 12 months.
after radiosurgical treatment. In all cases, repeated hemorrhage was not related to the volume of healthy tissues received the dose of 12 Gy.

All cases of repeated hemorrhage occurred within 1.5 years after the exposure. In the cases of incomplete AVM obliteration, no repeated hemorrhage episodes were observed in the long-term period.

**Late complications after radiosurgical treatment**

Delayed complications after radiosurgical irradiation of AVM include: temporary or permanent radiation damage to the brain in the form of persistent edema and post-radiation necrosis as well as the development of radiation-induced tumors and the formation of cysts. According to L. Steiner et al. [35], post-radiation cysts are observed in 4.7% of cases. Japanese researchers [4] were the first to report the formation of cysts after radiosurgical treatment of AVMs, they analyzed long-term outcomes in patients initially treated in Sweden using a Gamma Knife machine. Many authors report on the delayed formation of cysts [7, 8, 24]. According to D. Kondziolka et al. [15], previous hemorrhage is not associated with the greater cyst formation rate after therapy.

In our series, the development of cysts was detected in 6 patients within more than 3 years after the exposure. Only one case of a patient with the cyst formation in the long-term period after the exposure required surgical assistance.

In the case of clinical presentations, various surgical approaches to treatment of these cysts can be used, ranging from surgical fenestration of the cyst walls to cyst shunting. Patients with a changed signal of control T2-weighted MRI who lack neurological manifestations do not require any active intervention. In discussing the formation of cysts, one should take notice of a paper by S. Chang et al. [4] who believe that hypofractionation may be associated with a lower rate of cysts compared to that upon stereotactic radiosurgery. In our series, only one case of cyst formation in the long-term period was detected in patients treated in the hypofractionation regimen.

Also, one has to keep in mind a risk for developing radio-induced tumors after radiosurgery. There are single cases of malignant tumors developed within 5—10 years after radiosurgical treatment. It is impossible to estimate the actual formation rate of radio-induced tumors, since the exact number of patients who underwent radiosurgical irradiation is unknown. Some authors [15, 37] inform their patients that the risk for the radio-induced tumor development is 1 per 10,000, even though these figures are not supported by the data of experts from Pittsburgh or Sheffield.

According to J. Rowe et al. [28] who examined the follow up data of 1,200 irradiated patients over the period of 10 years, the occurrence rate of radiation-induced tumors was lower than that in a general population.

In our series, no cases of radio-induced neoplasms were detected.

The hypofractionation technique has been used for treatment of large and giant AVMs for over 20 years. Fractionation is carried out on the daily basis at a dose of 2—7 Gy for 5—7 days. The full dose upon hypofractionation exceeds the dose that is delivered in a single session of radiosurgical treatment. Hypofractionation may provide an earlier radiation response and is characterized by fewer complications (ca. 5—7% within 3 years after the exposure) [17, 33, 38, 39].

**Fig. 18. Relationship among the AVM volume, dose, and rate of various complications.**
Despite the range of doses used in hypofractionation, there is the minimum dose per fraction that is required to achieve high degrees of obliteration. Various studies have shown that AVM obliteration amounts to 8—22% for the dose of <7 Gy per fraction compared to 50—85% for the single dose of 7 Gy or higher. The authors report that the data on obliteration varied in all cases of irradiation of large AVMs, with later obliteration occurring after 5 years. In the cases where a single dose did not exceed 7 Gy, earlier thrombosing was observed within 3—5 years. If the used dose per fraction was 7 Gy or more, the full dose was in the range of 30—50 Gy, although the difference in the obliteration degree in groups between <7 Gy and ≥7 Gy was not statistically significant. In our series, post-radiation changes in the form of edema were observed in 71% of cases when the AVM volume was 17—24 cm³. Edema was accompanied by clinical manifestations in 35% of cases. Evaluation of the edema development depending on the marginal dose per fraction revealed edema in 44% of cases at a dose of 4—6 Gy per fraction.

Hypofractionation allows thrombosing of large AVMs within 24 months or more after irradiation [38, 39]. Thrombosing of large AVMs within 5 years after irradiation amounts 20—27%. In 2003, P. Lindvall et al. [17] demonstrated that the use of hypofractionation for treatment of AVMs led to complete obliteration in 56% of cases for the AVM volume of 4 to 10 cm³ and in 50% of cases for the AVM volume of 10 cm³ after 2 years; the authors also noted that the obliteration rate increases with time elapsed since the exposure. For example, obliteration was observed in 81% of cases for the AVM volume of 4 to 10 cm³ and in 70% of cases for the AVM volume of above 10 cm³ 5 years after treatment.

Therefore, hypofractionation allows irradiation of AVMs of virtually any size. It is the method of choice for extensive AVMs. Increasing the number of fractions slightly reduces the efficacy of obliteration.

The principles of successful obliteration and the factors contributing to its implementation established in this work are similar to the data of the most representative world series of observations with the minimum amount of complications (Table 5).

**Table 5. The obliteration rate and occurrence of radiation changes in a patient with cerebral AVM after stereotactic irradiation using a Novalis machine, abs. (%)**

<table>
<thead>
<tr>
<th>Irradiation technique</th>
<th>Partial Obliteration</th>
<th>Complete Obliteration</th>
<th>Based on T2 MRI</th>
<th>with clinical presentations</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiosurgery (187 patients)</td>
<td>20 (9)</td>
<td>187 (83)</td>
<td>60 (32)</td>
<td>28 (13)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Hypofractionation (27)</td>
<td>8 (30)</td>
<td>10 (37)</td>
<td>19 (71)</td>
<td>9 (35)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

The conclusions are as follows:

**Conclusion**

Radiosurgical irradiation of patients with cerebral AVMs of different localization is a sufficiently effective technique with the high (up to 82%) rate of obliteration of the malformation stroma and a relatively small number of complications. A higher obliteration rate is observed for small AVMs (< 3 cm³) and for the higher mean radiation dose (>27 Gy) and the marginal dose of >26 Gy. The rate of repeated hemorrhages is less than 3%. The rate of symptomatic radiation reactions is less than 13%.

The rate of radiation complications depends on the AVM volume, marginal dose, and volume of healthy tissues with the received dose of 12 Gy.

If AVM obliteration is not achieved, in particular within less than 3 years after the treatment, a tendency to decreasing the hemorrhage rate after irradiation is noted. All repeated hemorrhages occurred within 2 years after stereotactic radiosurgery.

Hypofractionation is the method of choice for large AVMs (>10 cm³) or AVMs located in functional areas.

The efficacy of obliteration upon hypofractionation (TBD of 35 Gy for 7 fractions) is 37%. In 71% of cases, edema developed when the AVM volume was 17—24 cm³. The rate of symptomatic edema did not exceed 35%, and the necrosis rate was 10% (n=3).

Stereotactic irradiation by means of a linear accelerator makes it possible to treat patients with AVMs of almost any generalization, localization, and volume.

**REFERENCES**

Treatment of cerebral arteriovenous malformations (AVMs) remains a challenge. On the one hand, these are congenital malformations of cerebral vessels, and the indications for surgical treatment of AVM patients are complex. On the other hand, the rapid development of modern neurosurgical technologies (endovascular neurosurgery, microneurosurgery with neuronavigation and intraoperative mapping of functional areas and pathways, radiosurgery) makes it possible to perform minimally invasive brain surgeries. However, even with these capabilities, neurosurgeons still have difficulties in providing assistance or have to exclude a rather large group of patients with AVMs of a large size and deep-seated localization. This group of authors has already published their data on application of radiosurgery for AVM with extended indications for radiosurgery. The work is undoubtedly innovative. It provides in-depth coverage of the issue, including a detailed description of the technique and the analysis of clinical outcomes and complications. Similar studies have not been performed in Russia, especially regarding the use of the hypofractionation technique that allows treatment of patients with AVMs of any generalization, localization, and volume.

The article should undoubtedly be published in specialized journals, since this problem is of great interest to doctors of various specializations.

V.A. Lazarev (Moscow, Russia)
Successful surgical treatment of intracranial vascular aneurysms requires complete aneurysm exclusion, with the patency of the blood carrying arteries and their branches preserved. According to M. Sindou et al. [7, 15], incomplete aneurysm clipping even in specialized neurosurgery clinics accounts for 4—8% of all clipping cases, while the risk of repeated hemorrhage in this situation is estimated as being 4%. Although the neurosurgeons’ inventory of methods has recently been enriched with new intraoperative techniques of blood flow assessment, such as contact Doppler ultrasonography and flowmetry, contrast-enhanced angiography continues to be the gold standard of the quality of aneurysm exclusion. In its turn, intraoperative angiography is expensive for being used in routine practice; it requires a specially equipped operating room and is used only in large clinics abroad.

The neurosurgical technique of intraoperative visualization of cerebral blood vessels with a fluorescent contrast agent, an external camera and color filters was first demonstrated by W. Feindel et al. [6] in 1967. In 1994, C. Wrobel et al. [18] described the first case of using indocyanine green videoangiography in surgery of aneurysms. Zeiss became the first company to manufacture a neurosurgical microscope with an integrated near-infrared radiation lamp (800 nm), allowing indocyanine green-contrasted visualization of blood vessels. In 2003, the study by A. Raabe et al. [12], which included 14 patients with aneurysms and fistules, on whom the technique of intraoperative indocyanine green fluorescence angiography (IFA) was performed, opened up a series of publications investigating the capacity of the new technique.

In 2014, after the contrast agent had been certified in Russia, the IFA technique became available for Russian neurosurgeons. This study describes the starting experience of using this technique in the Vascular Department of the Burdenko Neurosurgical Institute.

**Material and methods**

Indocyanine green (ICG) is a iodine-containing water-soluble fluorescence dye absorbing infrared radiation in the spectral range of 750—950 nm with the peak value of 800 nm. After intravenous injection, 98% of the contrast agent gets bound to the blood plasma proteins without being metabolized and practically not leaving the capillaries. The dye is fully eliminated by the liver, ejected as it is with bile. Adverse effects are rare (0.1—0.2%) and include anaphylactic shock, hypotension, tachycardia, and urticarial rash reported as individual responses [3]. Indocyanine green has been widely used in surgical practice for over 40 years to evaluate the liver function, blood supply of intestinal anastomoses, vascular bypass grafts, transplants, etc. The technique plays an important role in ophthalmology in diagnosing choroid processes in the eye.

For neurosurgical diagnostics, the contrast agent is supplied to the Russian market as “Indocyanine green-pulsion” by Pulsion Medical Systems, in flasks containing 25 mg of lyophilisate. The agent is diluted with 5 ml water to be injected immediately before intravenous injection (saline solutions may trigger
The IFA results and the actions performed by the operating surgeon are summarized in Table 2. In two cases of aneurysms in the region of ACeA—ACoA, videoangiography did not allow the remnant of the aneurysmal neck to be detected. In the first case (#2), the remaining part was detected by selective angiography following the surgery. In the second case, the remnant was detected by IFA. In the first case, the near-neck remnant was revealed by post operative angiography.

### Table 1. Characteristics of the group of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group under study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients/aneurysms</td>
<td>15/21</td>
</tr>
<tr>
<td>Men/women</td>
<td>9/6</td>
</tr>
<tr>
<td>Age (average, min—max + σ), years</td>
<td>43.2±9.6 (17—56)</td>
</tr>
<tr>
<td>Aneurysm localization:</td>
<td></td>
</tr>
<tr>
<td>the paraclinoid segment of ICA</td>
<td>1</td>
</tr>
<tr>
<td>the supraclinoid segment of ICA</td>
<td>9</td>
</tr>
<tr>
<td>ACeA—ACoA</td>
<td>6</td>
</tr>
<tr>
<td>MCA</td>
<td>3</td>
</tr>
<tr>
<td>PA</td>
<td>2</td>
</tr>
<tr>
<td>Giant aneurysm, number of patients</td>
<td>1</td>
</tr>
<tr>
<td>Large aneurysm, number of patients</td>
<td>2</td>
</tr>
<tr>
<td>Multiple aneurysms, number of patients</td>
<td>5</td>
</tr>
</tbody>
</table>

*Footnote. Here and in Table 2 the abbreviations used indicate the following: ICA — internal carotid artery; ACeA—ACoA — ACeA—ACoA — anterior cerebral artery—anterior communicating artery; MCA — medial cerebral artery; PA — pericalcull artery.*

precipitate formation). The half-life time depends on the liver function and is on average 3—4 min [3].

On May 2014, 15 patients were operated on for aneurysms in the surgical department using the IFA technique, which was duplicated by evaluating the blood flow with contact Doppler ultrasonography (DUS). The group under study consisted of nine men and six women aged from 17 to 56 (the mean age was 43.2 years). One patient was operated on in the acute period (the hemorrhage severity according to the Hunt and Hess scale was grade 2); three patients had unruptured aneurysms clipped. Five (33.3%) patients had multiple aneurysms; one patient had a giant paraclinoid aneurysm, while two had large aneurysms. All the aneurysms were successfully excluded. To assess the surgery outcomes, control angiography was performed in seven patients (46.7%), and SCT angiography was conducted for two patients (13.3%). A more detailed characteristic of the group is shown in Table 1.

### Table 2. IFA results for the group under study

<table>
<thead>
<tr>
<th>Patient’s number</th>
<th>Aneurysm</th>
<th>Surgery</th>
<th>IFA results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ophthalmic segment of ICA, bifurcation of ICA and MCA</td>
<td>All clipped</td>
<td>Complete exclusion, all blood vessels patent</td>
</tr>
<tr>
<td>2</td>
<td>ACeA—ACoA, left</td>
<td>Clipping</td>
<td>IFA did not reveal near-neck remnant, which was detected by postoperative angiography</td>
</tr>
<tr>
<td>3</td>
<td>ICA, right</td>
<td>Clipping</td>
<td>Complete exclusion, ICA and frontal choroidal artery patent</td>
</tr>
<tr>
<td>4</td>
<td>ACeA—ACoA, left</td>
<td>Clipping</td>
<td>Complete exclusion, near-neck remnant not visible, detected by revision</td>
</tr>
<tr>
<td>5</td>
<td>MCA, right</td>
<td>Clipping</td>
<td>Complete exclusion, MCA branches patent</td>
</tr>
<tr>
<td>6</td>
<td>Two ICA aneurysms, right</td>
<td>Clipping</td>
<td>Complete exclusion, ICA and frontal choroidal artery patent</td>
</tr>
<tr>
<td>7</td>
<td>PA, left</td>
<td>Clipping</td>
<td>Artery stenosis detected, clip reposition performed</td>
</tr>
<tr>
<td>8</td>
<td>MCA, right</td>
<td>Clipping</td>
<td>Artery stenosis detected, clip reposition performed</td>
</tr>
<tr>
<td>9</td>
<td>ICA, right</td>
<td>Clipping</td>
<td>Complete exclusion, ICA and frontal choroidal artery patent</td>
</tr>
<tr>
<td>10</td>
<td>ACeA—ACoA, right</td>
<td>Clipping</td>
<td>Complete exclusion, light ICA stenosis, IFA and DUS revealed good blood flow, clip reposition not performed</td>
</tr>
<tr>
<td>11</td>
<td>PA, left</td>
<td>Clipping</td>
<td>Complete exclusion, PA patent. IFA allowed anatomy clarification and exclusion of PA branch without adverse effects</td>
</tr>
<tr>
<td>12</td>
<td>ACoA, bifurcation of ICA, right</td>
<td>Clipping</td>
<td>Complete exclusion, branches patent</td>
</tr>
<tr>
<td>13</td>
<td>ACaA, left</td>
<td>Clipping</td>
<td>Complete exclusion, all blood vessels were patent. IFA allowed visualization of the artery of Heubner, which is hardly accessible for DUS</td>
</tr>
<tr>
<td>14</td>
<td>Bifurcation of ICA, MCA, left</td>
<td>Clipping</td>
<td>Complete exclusion, branches patent</td>
</tr>
<tr>
<td>15</td>
<td>ACeA—ACoA, right</td>
<td>Clipping</td>
<td>Complete exclusion, all blood vessels patent</td>
</tr>
</tbody>
</table>
case, after the final review of the clip following the IFA, the surgeons were able to clarify the aneurysm anatomy, to reveal incomplete clipping, and to exclude the aneurysm using another clip.

The IFA did not reveal any cases of incomplete aneurysm clipping. Control angiography showed aneurysm exclusion in all ten cases. As mentioned above, in the first case a small cervical region was detected; another patient (#10) was found to have mild stenosis of the ICA after two supraclinoid aneurysms had been clipped.

In our opinion, the IFA was essentially beneficial in three cases. It allowed stenosis of the PA and of the branch of the MCA, not visible during DUS, to be revealed in cases #7 and 8. In case #13, blood flow in the contralateral recurrent artery of Heubner, the patency of which could not be assessed otherwise, no cases of disagreement between the results and the DUS data were found.

**Clinical cases**

Case 1 (Fig. 1). Patient V., 52 years old (#9). Diagnosis: a giant partially clotted aneurysm of the posterior communicating artery (PCA) on the right side. Surgery: aneurysm clipping, IFA confirmed blood flow in the anterior choroidal artery (shown with an arrow); no aneurysm was detected by contrast-enhanced angiography.

Case 2 (Fig. 2). Patient E., 26 years old (#11). Diagnosis: a large aneurysm of the PA on the left side. The interhemispheric approach revealed an artery crossing the aneurysm body and impeding the access to the aneurysmal neck (shown with an arrow) (Fig. 2b). IFA demonstrated retrograde-filled artery that was not an immediate branch of the PA. The branch was coagulated and the aneurysm was successfully clipped, which was confirmed by control angiography (Fig. 2d). The neurological status of the patient after the surgery remained unchanged.

*Fig. 1. SCT angiography of patient V. (#9), in which a giant partially clotted aneurysm of the PCA on the right side is visualized (a); b — selective carotid angiography allows contrasting of only a part of the aneurysm; c — an intraoperative image after clipping; d — IFA confirmed blood flow in the anterior choroidal artery (indicated with an arrow), the aneurysm is not contrasted.*
Table 3. Clip reposition and incomplete aneurysm exclusion rate according to IFA

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of patients</th>
<th>Clip reposition rate, %</th>
<th>Aneurysm remnant, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Raabe et al., 2005 [13]</td>
<td>114</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>R. Dashti et al., 2009 [5]</td>
<td>190</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>C. Washington et al., 2013 [17]</td>
<td>49</td>
<td>4.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Our study</td>
<td>16</td>
<td>12.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Case 3 (Fig. 3). Patient М., 44 years old (#13). Diagnosis: a small aneurysm of the left ACeA—ACoA. After aneurysm clipping, IFA confirmed functioning of the right recurrent artery of Heubner (Fig. 3c, d, shown with an arrow), which could be compressed with a clip. It was not possible to assess the blood flow in the recurrent artery of Heubner by contact-enhanced DUS.

Case 4 (Fig. 4). Patient E., 39 years old (#2). Diagnosis: a large aneurysm of the left ACeA—ACoA, excluded with two clips during surgery. Blood flow in both A2 segments (Fig. 4b, c) was confirmed by IFA, which, however, did not allow one to visualize the functioning part of the aneurysmal neck during selective angiography (Fig. 4d).

Discussion

Visual assessment of the patency of arteries after clipping the aneurysmal neck does not always provide...
reliable evaluation of the situation. Aneurysm centesis (perforation) allows one to assess completeness of aneurysm exclusion farther from the clip but does not provide information on the functioning part of the aneurysm closer to the branches or on the blood flow in the branches. It is currently believed that an operating surgeon should assess the blood flow in an aneurysm and in the adjacent branches using objective intraoperative techniques, without relying on the visual approach only.

IFA is a simple and reproducible method of real-time blood flow assessment, which allows the surgeon to assess the situation within 3—5 min, to detect the vascular conflict, and to take the required actions. It is interesting that, according to the IFA provided by different authors [14], the rate of clip reposition significantly varies: from 2 to 38%. The causes of such variation include the different number of patients covered by the studies, inconsistent use of the technique, the heterogeneous character of the patient groups’ composition and limited experience of the surgeons. Notwithstanding the small number of the patients, our results are aligned with the large foreign studies (Table 3).

Ultrasound diagnostics, contact Doppler ultrasonography and blood flowmetry have long been used in intraoperative assessment of blood flow in cerebral arteries. While the latter method has not become widespread due to the large size of the sensors, which have limited mobility in the narrow wound, contact Doppler ultrasonography is the most common method for evaluating the quality of aneurysm clipping. In the studies by J. Gilsbach and W. Hassler, R. Stendel et al. [8, 16], the possibility of using intraoperative DUS was demonstrated, with surgically significant complications recorded in 10—18.9% cases. J. Bailes et

![Fig. 3. SCT angiography of patient M. (#13).](image)

- a — a small aneurysm is visualized in the region of ACeA—ACoA on the left side; b — an intraoperative image showing the aneurysm closely seated near the artery of Heubner; c, d — after clipping the artery of Heubner is patent both visually and in IFA.
al. and J. Gilsbach and W. Hassler [4, 8] later conducted comparative studies, where they reported 100% agreement between the results of contact DUS and control angiography. An analysis of our data has shown that in 23% aneurysm operations, the results of contact DUS were grounds for further active measures to be taken by the operating surgeon, such as repositioning or using another clip, changing the clipping scenario, etc.

It is to be noted that contact Doppler ultrasonography is the most accessible, affordable and easily reproducible method of blood flow assessment. Meanwhile, it does not allow one to evaluate the patency of small perforating arteries, the good condition of which determines a positive neurological outcome. In addition, as many years’ experience of using sensors has shown, the sensors require careful handling and cannot be sterilized often.

Contact Doppler ultrasonography is the method of manual diagnostics lacking complete precision. Its results depend on the angle of insonation of a blood vessel, the investigation point, thickness of the vessel wall, and other variables, which characterize the technique as a qualitative rather than a quantitative one. The essential advantage of ultrasound flowmetry is that it measures the volume velocity of the blood flow, as opposed to the linear velocity shown by Doppler ultrasonography. This feature makes flowmetry an indispensable method of blood flow assessment in anastomoses in excluding a large blood vessel to trap an aneurysm, which is especially essential for large and giant aneurysms [2].

In this regard, the emergence of IFA, a new technically simple and non-invasive technique of blood vessel visualization, evoked wide interest among vascular neurosurgeons. In fact, conducting IFA requires only a modern microscope equipped with an infrared module, which is now offered by all the leading manufacturers of microscopes (e.g., Zeiss Pentero, Leica FL800, Fig. 4. SCT angiography of patient E. (#2).

A large aneurysm is visualized in the region of ACeA—ACoA on the left side (a); an intraoperative photo after clipping (b); both A2 segments (the right segment is indicated by an arrow) are well-contrasted by IFA (c); the functioning near-neck part of the aneurysm was detected by selective carotid angiography (d).
However, IFA has a number of disadvantages, related to the fact that the surgeon can trace down the fluorescent blood flow only within the limits of direct visibility, while it often happens that the zone of interest is concealed by a vessel branch, a clip, an aneurysm, etc. In the opinion of K. Roessler et al. [14], who analyzed the outcomes of surgical treatment of 246 patients, IFA is more informative, as all the patients for whom clip reposition was required according to IFA, had normal DUS results. Yet, comparison of the efficiency of contrast-enhanced angiography and IFA, as shown by C. Washington et al. [17], did not favor IFA. When the results of 49 aneurysm patients, for whom both angiographies were performed, were compared, the authors discovered disagreement between the conclusions in 14.3% cases, mainly because IFA allowed visualization of only those blood vessels that were directly accessible to the eye. A similar drawback was indicated by K. Roessler et al. [14]: in 9.1% cases selective angiography allowed identification of small near-neck aneurysm remnants, not visible during IFA. In 2 (0.8%) patients, opening the aneurysm demonstrated its incomplete exclusion, despite normal IFA visualization. D. Hardesty et al. [9] compared the results of using intraoperative angiography (100 patients) and IFA (100 patients) and demonstrated that the risk of postoperative ischemia, false-negative results and clip reposition rate did not reliably differ in the study groups.

During the operation, the difficult-to-see areas of interest can be best seen using an endoscopic IFA, a new technique whose capabilities have recently been demonstrated by D. Mielke et al. [10]. The authors indicated that the endoscope has become a more informative tool of blood flow control with 11 (42.3%) patients, which allowed one to perform better visualization of small and occult blood vessels. In addition, they noted the duration of the fluorescence effect to be several times longer for endoscopic IFA.

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Test cost estimate</th>
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<tr>
<td>Selective angiography</td>
<td>The gold standard in vascular surgery: the test is indispensable for operating on complicated, giant, and fusiform aneurysms</td>
<td>An invasive technique (complication rate, 1.7—2.9%)</td>
<td>14,000 rubles (one arterial basin)</td>
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<td></td>
<td>A high probability of identifying blood vessel stenosis/aneurysm exclusion</td>
<td>The long preparation period (20—30 min)</td>
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<tr>
<td>IFA</td>
<td>A simple, fast and reproducible method</td>
<td>Only the directly visible blood vessels are contrasted.</td>
<td>5,500 rubles</td>
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<td></td>
<td>Safe</td>
<td>False-positive results in retrograde artery filling</td>
<td></td>
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<tr>
<td></td>
<td>Almost as precise as angiography</td>
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<td></td>
<td>Allows visualization of small blood vessels (arteriae perforantes)</td>
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<td>Does not limit the surgeon during the procedure</td>
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<tr>
<td>Contact DUS</td>
<td>A simple, fast and easily reproducible method</td>
<td>Less precise than angiography</td>
<td>650 rubles per operation</td>
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<td></td>
<td>Harmless</td>
<td>A local test</td>
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<td></td>
<td>Cost-efficient</td>
<td>Assessment bias</td>
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<td></td>
<td>Convenient in everyday work</td>
<td>Determines the linear velocity of blood flow</td>
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<tr>
<td>Flowmetry</td>
<td>An accessible and safe method</td>
<td>Blood flow assessment is possible only for large arteries.</td>
<td>1,200 rubles per operation</td>
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<td></td>
<td>Cost-efficient</td>
<td>A large sensor size</td>
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<td></td>
<td>Indispensable in shunts, trapping or proximal exclusion of an aneurysm</td>
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<tr>
<td>SCT/MR angiography</td>
<td>A perspective neuro visualization method</td>
<td>A very high equipment cost</td>
<td>12,000—14,000 rubles per operation</td>
</tr>
<tr>
<td></td>
<td>Visualization of both blood vessels and brain structures</td>
<td>The experience of application has not been accumulated yet.</td>
<td></td>
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Speaking about the modern techniques of intraoperative blood flow assessment, MR and spiral CT angiography should be mentioned. These are the techniques that make up an indispensable part of the state-of-the-art operating theaters VISIUS, AMIGO, etc. The patient’s preparation time and the test time are evaluated by min. However, despite the fact that multimodal operating rooms have been opened in some foreign clinics, consistent results of aneurysm surgery under such conditions have not been reported yet.

Affordability plays a significant role in comparing the techniques of intraoperative blood flow control. Calculation of the cost of technique application is rather tentative and does not include the costs of basic equipment, such as a microscope, a DUS apparatus, etc. and its amortization. The cost of ultrasound control was calculated, assuming that the sensor is used five times per an operating week and considering the subsequent gas sterilization and 3-month service life. The price of indocyanine green and SCT/MR angiography is shown in accordance with the costs of the services at the time when this paper was written (June 2014). Table 4 summarizes approximate costs of the control tests and the key advantages and disadvantages of each technique.

Conclusions

Intraoperative indocyanine green fluorescence videoangiography is an affordable, safe and reproducible method for assessing local blood flow, which is comparable to selective angiography. Performing IFA does not require any additional skills, presence of technicians, or availability of sophisticated equipment. The possibility of visualizing arteriae perforantes and small arteries during IFA makes it a preferred technique compared to the available alternatives. The short test duration gives a surgeon time to quickly correct an error made and to reposition a clip.

The main disadvantage of the method is that visualization can be performed only for the directly accessible blood vessels, which reduces its sensitivity and brings about false results. Atherosclerotic plaques or thickened or calcined aneurysm walls are the factors essentially limiting the fluorescence effect, which makes the method hardly useful in such situations. Our initial experience has shown that the IFA technique definitely enables an operating neurosurgeon to adequately evaluate the local blood flow in most routine cases. The method is less informative for operations on large aneurysms and aneurysms with complicated anatomy, where some regions of interest remain concealed. Such cases require the use of contact Doppler ultrasonography and other alternatives.

REFERENCES

It is beyond any doubt that control of blood flow in blood vessels directly adjoining an aneurysm after its exclusion is a required and a standard part of surgery. The arsenal of methods used by vascular neurosurgeons having Doppler ultrasonography and flowmetry at their disposal is now enriched with the technique of intraoperative fluorescence videoangiography, a technique quite well-known abroad. The technique proved to be useful as a simple and non-invasive method of blood flow assessment. In 2014, after the contrast agent had been certified to be used in Russia, the Russian neurosurgeons became able to employ fluorescence videoangiography in aneurysm surgery.

Prof. Eliava et al. described the features of using IFA in 15 patients with different intracranial aneurysms. The authors demonstrated the strengths and weaknesses of the technique by describing the clinical cases and showed the outlook for its application compared to the alternative methods of blood flow control. Videoangiography is a simple, easily accessible and affordable method of local blood flow assessment. The study is definitely of interest for neurosurgeons working in vascular clinics. Unfortunately, the small size of the patients’ group does not allow statistical analysis to be made and the impact of the technique on the general treatment outcomes to be reliably evaluated. The study included only patients with aneurysms. Yet, IFA is clearly promising in placing vascular shunts, in surgery of brachiocephalic vessels and in removing arteriovenous malformations.

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Intraoperative Indocyanine Green Video Angiography in Cerebrovascular Surgery

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Keywords: video angiography, indocyanine green, cerebrovascular surgery.

Field of Application

Cerebrovascular interventions belong to one of the most technically complex fields of modern neurosurgery. When clipping cerebral aneurysms, it is extremely important to close completely the aneurysm neck, with patency of the feeding vessel and perforating veins and branches extending from it being preserved. This is strict adherence to these technical details that enables achieving good treatment outcomes. In surgery of cerebral arteriovenous malformations (AVMs), determination of residual angles (in the case of the diffuse structure) and evaluation of afferents and efferents of a malformation are of considerable importance. Gaining the information on bypass functioning is necessary to prevent early bypass closure when placing extracranial-intracranial anastomosis. In carotid endarterectomy, gaining of intraoperative data on the stenosis elimination and absence of early vessel thrombosis is of a key value.

Neuronavigation technologies, microvascular Doppler sonography, and intraoperative digital subtraction angiography are widely used to improve the quality of microsurgical manipulations. However, all these methods have significant limitations and shortcomings. In recent years, indocyanine green video angiography (ICG VA) has been widely used in intraoperative cerebrovascular surgery.

Principles of intraoperative indocyanine green video angiography (ICG VA)

ICG VA is fluorescent angiography that uses a special dye, indocyanine green (ICG), injected intravenously during intervention conducted using a surgical microscope. Absorbing light of a defined wavelength, the dye begins to luminesce. A near-infrared light source is used to excite luminescence. The use of this technology in neurosurgery became possible after the development of a special unit (FLOW 800) and its integration into a surgical microscope (Carl Zeiss Surgical GmbH, Oberkochen, Germany).

The special unit enables video image analysis. The unit emits excitation light in the wavelength range between 700 and 850 nm; for the purpose of visualization, fluorescence is detected in the range of 780—950 nm. The surgeon observes an image that is transmitted from a video camera to a video monitor coming with the microscope.

History of the method development

Fluorescent angiography was first used by ophthalmologists to study the retinal blood flow; fluorescein was used as a dye. In 1967, fluorescent angiography was used to visualize the cerebral microcirculation [1]. Later, another dye, indocyanine green, turned out to produce brighter and sharper fluorescence and to have a very low complication rate compared to fluorescein. ICG was approved by the US Food and Drug Administration (FDA). Since 1975, the dye has been widely used in cardiology, ophthalmology, and hepatology. In the early 2000s, the results of the use of ICG VA in cerebrovascular pathology were published [2, 3]. Since May 2010, analysis of images with creation of a color map and construction of graphical intensity diagrams has become available.

ICG VA technique

The recommended dye dose for the procedure is 0.2—0.5 mg/kg of patient’s body weight, with the maximum daily dose of 5 mg/kg. The standard 12.5 mg dose of the dye dissolved in 2.5 mL of injection water per injection has been used by several authors [4]. No saline solutions can be used for dissolution of the dye; only non-ionic solvents are approved. A microscope is adjusted to the center of the area of interest, with the working distance being less than 300 mm. The fluorescence option is activated with a button located on the microscope handle. After switching on the unit, the dye is intravenously administered as a bolus by the anesthesiologist at the surgeon command. At this very moment, a real-time video image of the arterial, capillary and venous phases of angiography is viewed on the microscope monitor. The resulting images can be visually evaluated by the surgeon as well as processed to produce...
intensity diagrams and color maps. These options enable in-depth analysis of the obtained data.

The intravenously injected dye tightly binds to plasma proteins and circulates in the bloodstream. The dye half-life is 3—4 min. ICG is eliminated only by the liver into the biliary tracts. Given the fact, another ICG VA should be performed after 15 min. However, when clipping cerebral aneurysms, several authors allow for repetitive angiography after 10 or even 5 min because of the risk of ischemic attacks, even being aware of the possibility of false-positive results [5].

**General contraindications for the use of ICG-PULSION** (Pulsion Medical Systems AG) include: hypersensitivity to ICG; hypersensitivity to iodine; Graves’ disease and endemic goiter; premature newborns and infants who need blood transfusion due to hyperbilirubinemia; re-injection due to poor dye tolerance upon previous administration.

**Advantages of ICG VA**

ICG VA is a low-cost, practical, and easy to use technique involved in routine neurosurgery. Upon microsurgical clipping of arterial aneurysms and bypass surgery, agreement between the ICG VA data and the results of more expensive and labor-consuming analysis methods amounts to 90—100% [6—8]. Implementation of digital subtraction angiography takes at least 20 min, even for an experienced team. This exceeds the cerebral ischemia development time limit. Therefore, the re-clipping in digital subtraction angiography is associated with the 33% risk of stroke [5]. The use of ICG VA avoids interrupting surgery and adjusting a microscope. As soon as 2 min after dye injection, the surgeon can see a sharp image of vessels and make a decision about replacing a clip on the aneurysm neck.

According to the literature [9—11], the rate of incomplete clipping of the aneurysm neck amounted to 4—19% in the recent past, and the rate of unintentional exclusion of the feeding vessel and perforating vessels was 0.3—12%. ICG VA enables timely detection and correction of this technique complication [3, 7].

ICG VA reliably confirms the accuracy of the clip placement on the aneurysm neck and complete exclusion of the aneurysm (Fig. 1, 2). Our own experience and literature data suggest that ICG VA allows the surgeon to see only objects within the microscope field of view during clipping an aneurysm. The aneurysm neck closed by a blood clot, cotton pad, or brain tissue, can not be distinguished. The thick aneurysm wall may cause a decrease in the fluorescence signal that complicates identification of residual filling of the aneurysmal sac [3, 12]. Repeated injections of the dye within a short time may lead to false-positive results. One should be aware of the possibility of retrograde filling of the branches distal to the aneurysm [8]. Our own experience shows that at least 5 min should pass after ICG VA before clipping of the aneurysm neck and performing the control ICG VA.

This time is required for complete elimination of the dye from the aneurysmal sac into the bloodstream. Thereby, false filling of the aneurysmal sac is avoided during control ICG VA after clipping of the aneurysm neck.

During ICG VA, post-processing of images in the microscope to produce color maps (see Fig. 1b) and to...
Fig. 2. Clipping of a middle cerebral artery aneurysm. ICG angiograms.

a — preoperative; b — before clipping; c — after the placement of clips on the aneurysm necks.

Construct intensity plots (see Fig. 1c) significantly facilitates assessing the completeness of clipping of the aneurysm neck. Color maps visualize the time of the maximum of the relative indocyanine concentration in each vessel segment. The intensity plot shows a time-dependent change in the dye concentration along with a pulse wave in the area of interest. The fluorescence intensity curve for the aneurysm before its occlusion has a similar form as that for the feeding vessel. Less than 5 min after clipping and re-injection of the dye, the color map can visualize fluorescence within the aneurysm, since clipping was performed before ICG elimination from the body (see Fig. 1b). However, the intensity plot shows that the aneurysm-related fluorescence peak disappears, and the curve is flattened. This proves complete aneurysm obliteration (see Fig. 1b, red plot). In the case of incomplete aneurysm occlusion and residual blood flow through it, the peak fluorescence in the aneurysm decreases, but does not disappear completely.

**Capabilities and limitations of ICG VA**

In AVM surgery, ICG VA provides good visualization of an arteriovenous shunt, feeding arteries and draining veins on the brain surface, and even deep-seated malformations in the case of the widely open Sylvian fissure (Fig. 3). It should be emphasized that this technology enables rather reliable identification of the remnants of malformation nidi [8, 13]. In our opinion, this becomes particularly important in removing malformations after their embolization with adhesive or nonadhesive materials (Fig. 4). However, there are limitations to visualization upon removing of deep-seated malformations in the narrow wound gap [14]. Creation of a color map allows the surgeon to identify the feeding vessels and to facilitate AVM removal. Construction of graphical intensity charts enables differentiation between the feeding arteries and arterialized veins. This option can provide additional important information upon clipping of the arterial aneurysm neck (see Fig. 1).

Upon application of extracranial-intracranial anastomosis (Fig. 5), ICG VA allows one to clearly visualize patency of the prepared bypass [8, 15]. The rate of microanastomosis patency often was less than 90%; the use of ICG VA raised it to 100% [16, 17]. However, direct viewing the video image after ICG injection does not provide information on the blood flow direction. For this purpose, Doppler sonography is additionally required [8].

Application of the technique for endarterectomy may provide reliable data on postoperative patency of the internal carotid artery [18]. However, identification of stenosis before arteriotomy is unreliable due to intense luminescence of the calcified tissue and the vascular wall thickness.
Fig. 3. Clipping of a posterior communicating artery aneurysm.
a — preoperative multislice CT angiography (3D reconstruction); b — ICG VA before clipping of an aneurysm; c — ICG VA after the clip was placed on the aneurysm neck; residual filling of the aneurysm cavity is observed; d — ICG VA after repeated clipping, no aneurysm filling is observed; e — postoperative multislice CT angiography (3D reconstruction).
Fig. 4. ICG VA during resection of a partially embolized AVM.

a — preoperative angiogram; b — view of the surgical field after extirpation of AVM; c — ICG VA after resection of AVM.

Fig. 5. ICG VA during application of extracranial-intracranial anastomosis.

a — view of the surgical field after application of extracranial-intracranial anastomosis; b — ICG VA after application of extracranial-intracranial anastomosis.
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The Use of Transcallosal Ventriculostomy to Treat Complicated Aneurysmal Intracranial Hemorrhages

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The present paper reports two cases of successful use of the anterior interhemispheric transcallosal approach during ultra-early surgery in patients in decompensated condition with severe intraventricular hemorrhage caused by rupture of cerebral aneurysms.

**Keywords:** anterior interhemispheric transcallosal approach, cerebral aneurysms, early surgery, patients in critical condition.

Ultra-early surgical interventions in the acute period of aneurysmal intracranial hemorrhage (AIH) are traditionally viewed as high-risk operations.

The technical complexity of such surgery significantly increases if a patient has complicated forms of AIH: extensive clots in the basal cisterns or massive intracranial and/or intraventricular hemorrhage [4]. In such patients, an operating surgeon often faces a situation when the measures taken by an anesthesiologist to enable the “soft brain” [15] prove to be insufficient, and tension in the brain substance remains significant. In such cases, in order to complete the main operation phase successfully, the surgeon is to ensure relaxation of the brain substance by surgical methods [6].

Brain relaxation implies the possibility of carrying out “internal brain decompression” by aspiration of CSF and blood clots from intracranial reserve space [2].

Transcallosal ventriculostomy is one of the most effective, although technically complicated, brain relaxation methods [5]. The method consists in performing frontal parasagittal craniotomy followed by interhemispheric transcallosal approach to the contralateral lateral ventricle to treat it. The surgeon then approaches the ipsilateral lateral ventricle via the interventricular foramen and the third ventricle through the interventricular foramen. Aspiration of the CSF and blood clots from the ventricular system causes significant retraction of the medullary substance, allowing one to non-traumatically reach the source of AIH through the subfrontal (or another required) microsurgical approach [5].

Below we report our experience of surgical treatment in patients with complicated forms of AIH.

**Clinical case 1**

The 36-year-old patient S. had an acute onset of condition on March 2, 2013, when, after severe headache, he experienced mental confusion. The ambulance team did not suspect any cerebral pathology and decided not to hospitalize the patient. He stayed at home for two days. During this time, the patient’s conscience regained clarity; however, due to persistent headache, another ambulance team was called, which hospitalized the patient to one of the Krasnodar city hospitals. As the patient was admitted to a primary care department, the on-duty neurologist evaluated his condition as “a medium severity case”. The patient’s somatic status did not show any significant abnormalities. His neurological status was as follows: clear consciousness and the severe meningeal syndrome. No focal neurological signs were revealed. CT of the brain showed a basal subarachnoid hemorrhage characteristic of aneurysmal rupture of the anterior cerebral artery (ACA) (Fig. 1). The patient was urgently transported to the Regional clinical hospital no. 1 to be surgically treated. He endured transportation sufficiently well; however, at the moment of his repositioning from a transport stretcher onto a hospital stretcher his condition aggravated and an episode of psychomotor excitation developed, followed by fast depression of consciousness, first to the soporific state and then to superficial coma. Urgent CT of the brain was performed after the resuscitation measures, which verified an aneurysmal rerupture (Fig. 2). Cerebral angiography revealed an aneurysm of the right pericallosal artery (PA) (Fig. 3).

After brief pre-surgical preparation, the patient was delivered to the operating room and subjected to right monofrontal parasagittal craniotomy. The patient's brain was very tense, despite accurate adherence to the anesthesiological protocol of enabling “the soft brain”. After ventricular puncture of the anterior horn of the right lateral ventricle by the anterior intracranial transcallosal approach, the left lateral ventricle and subsequently the right lateral ventricle were approached, with blood clots and CSF were removed by aspiration. The cavity of the third ventricle was cleaned through the interventricular foramen. After the medullary substance had relaxed, we continued dissecting the frontal departments of the interhemispheric fissure. After
fixing the aneurysmal neck, the aneurysm was clipped, and the intracerebral hematoma of the corpus callosum was extracted.

In the early postoperative period, the patient’s consciousness improved to the level of deep stupor. Symptoms of the damage to the brain stem structures could be seen: bilateral miosis, horizontal and vertical gaze palsy, and bilateral pyramidal insufficiency. The control CT of the brain showed significant reduction in the volume of the intracranial and intraventricular hemorrhages. The hemorrhage volume in the fourth ventricle remained the same (Fig. 4).

Due to incomplete recovery of the consciousness level and inadequate respiratory function, a decision was taken to provide continuous respiratory support to the patient. On March 6, 2013, dilational tracheostoma was performed.

Further on, the patient’s condition was complicated by bilateral pneumonia accompanied by the negative trends in the patient’s neurological status: depression of the level of consciousness to the soporific state and aggravated focal symptoms. The patient’s neurological disorders and pneumonia regressed due to long-term conservative treatment in the intensive care unit; his postoperative wound healed by primary intention. On March 28, 2013, the patient was switched over to spontaneous respiration. On April 2, 2013, the patient was transferred to the neurology department of the local hospital, where he underwent deccannulation and later was discharged from the hospital in a satisfactory condition.

Follow-up examination was conducted three months after. The patient’s general condition was satisfactory. His neurological status was determined as follows: clear consciousness, correct orientation in time, space, and one’s own personality. The cognitive function score measured with MMSE was 30. Speech fluency was impaired, while conceptualization, selection response and dynamic praxis in the right hand preserved when exposed to the frontal assessment battery. Examination of the cranial nerves revealed no pathology. Deep reflexes were normal, without asymmetry. Abdominal reflexes were missing. The muscle strength score was 5 points for all muscle groups. The muscle tone remained unchanged. Pathological reflexes were not induced. No sensitivity impairments were found. The patient performed coordination tests by his left extremities with intention. The patient was stable in Romberg position and had no gait changes. The patient was able to control the functions of his pelvic organs. Intermanual conflict was noted, with the alien hand syndrome for the left hand. The left hand interfered with the actions of the right hand: it grasped objects and did not let them go when attempts were made to take them both by the neurologist and by the patient’s right hand.

MRI of the head showed cicatrices and atrophic changes in the surgical intervention area; no signs of hydrocephalus were seen. Contrast-enhanced MRI angiography detected no aneurysm.
Clinical case 2

Patient N., 48 years old, had an acute onset of the disease on June 18, 2013, when he felt acute headache and became unconscious during a hypertension episode.

The ambulance team delivered him to one of the Krasnodar city hospitals. As the patient was admitted to the primary care institution, the neurologist on duty considered his condition as severe. Somatically, the patient was diagnosed as having high blood pressure; otherwise no essential deviations from the norm were found. Neurologically, his status was as follows: deep depression of consciousness and severe meningeal syndrome. No focal symptoms were revealed. CT of the head revealed basal subarachnoid-parenchymatous-ventricular hemorrhage characteristic of aneurysmal rupture of the anterior communicating artery (ACoA) (Fig. 5).

The patient was urgently transported to the Regional city hospital no. 1 to be surgically treated. Patient’s condition deteriorated during transportation: consciousness depression to the soporific state was
After the resuscitation measures had been taken in the intensive care unit, another urgent CT of the brain was performed, showing no essential changes. The CT of the lungs showed bilateral signs of aspiration in the lower lobes of the lung (Fig. 6). Cerebral angiography revealed an ACoA aneurysm with its dome directed upward and supplied by the left ACA (Fig. 7).

After brief presurgical preparation, the patient was admitted to the operating room, where the combined right two-flap anterior intracerebral pterional approach was performed. The patient's brain was very tense, despite accurate adherence to the anesthesiological protocol of ensuring the "soft brain". After the ventriculopuncture of the anterior horn of the right lateral ventricle through the anterior interhemispheric transcallosal approach, the left and right lateral ventricles were approached with blood clots and CSF being aspirated from both ventricles. The cavity of the third ventricle was cleaned through the interventricular foramen. Significant retraction of the medullary substance was detected after the first phase.

During the second phase, the ACA was accessed using the right-sided transsylvian approach. A large partially clotted aneurysm of the ACA was found with its dome oriented upwards and posteriorly and supplied by the dominant left ACA. After intermittent temporary clipping of the anterior cerebral arteries, the aneurysmal neck was isolated and clipped.

The patient remained in severe stupor in the early postoperative period. Symptoms of the damage to the brain stem structures could be seen, including bilateral miosis, horizontal and vertical gaze palsy, and bilateral pyramidal insufficiency. Control CT of the brain (Fig. 8) revealed considerable reduction in the volumes of intracerebral and intraventricular hemorrhages and regression of occlusive hydrocephalus. The hemorrhage volume in the fourth ventricle remained unchanged.

Because of the incomplete recovery of the level of consciousness and aspiration pneumonia, a decision was taken to provide long-term respiratory support to the patient; so dilational tracheostomy was performed.

Fig. 4. CT scans of the brain of patient S. recorded on the first day of the postoperative period.
Fig. 5. CT scans of the brain of patient N. recorded after his admittance to the Regional clinical hospital no. 1.

Fig. 6. CT scan of the lungs of patient N. recorded after his admittance to the Regional clinical hospital no. 1.

on June 19, 2013. In the intensive care unit, the patient’s neurological disorders and manifestations of pneumonia regressed and the postoperative wound healed by primary intention. On July 2, 2013, the patient was transferred to the intensive care unit of the local hospital from where he was discharged in a satisfactory condition 1.5 months after disease onset.

Control examination seven months after the discharge showed that the patient was in satisfactory condition. His neurological status was as follows: clear consciousness, correct orientation in time, space, and one’s own personality. The cognitive functions were described as slightly impaired: the MMSE score being 26. The patient was found to be normal when exposed to the frontal assessment battery. Examination of the cranial nerves revealed no pathology. The patient’s reflexes were normal. The muscle strength score was 5 points for all muscle groups. The muscle tone remained unchanged. No sensitivity impairments were found. The patient performed coordination tests satisfactorily. The patient was stable in Romberg position and had no gait changes. The patient was able to control the functions of his pelvic organs. No clinical signs of corpus callosum abnormalities were detected.

CT of the brain showed cicatrices and atrophic changes in the surgical intervention area (Fig. 8). Cerebral angiography did contrast any aneurysm (Fig. 9).
Discussion

The issue of reasonability and the amount of surgical intervention in patients with complicated forms of AIH admitted to the hospital in decompensated condition remains a matter of debate. Meanwhile, improvement in the outcomes of treating patients admitted after aneurysmal rupture in Hunt and Hess (H—H) condition IV—V remains an important issue of modern neurosurgery because of the large number of such patients and the high rate of adverse functional outcomes in this type of patients.

Three strategic approaches can be used to treat patients with AIH:

1. The strategy of "deliberately delayed treatment". According to this concept, surgeons deliberately refrain from early surgery in patients with AIH. Patients are treated conservatively and are operated on 2—3 weeks after the hemorrhage.

This treatment strategy currently has a limited number of supporters, as its use inevitably results in losses among patients who were admitted in decompensated...
Fig. 8. (continued).

Fig. 9. Control cerebral angiogram of patient N. recorded after microsurgical treatment. Contrast-enhanced left carotid angiography in the orthogonal projection shows no ACA aneurysm.
condition, yet either died or became disabled as a result of repeated hemorrhages from the aneurysm, which developed as they were waiting for delayed surgery.

II. The strategy of early "differentiated treatment". According to this concept, patients with AIH are subject to early surgical treatment on a selective basis, depending on the individual characteristics of the patient’s general and neurological condition and test data [1, 4]. In a simplified way, this approach divided AIH patients into three groups:

Group 1: compensated patients (H—H grades I and II) are operated urgently, irrespective of the time passed since the last AIH;

Group 2: decompensated patients (H—H grades IV and V) are operated on early only if a large intracerebral hematoma, determining the severity of patient’s condition, is detected. The other patients of this group are operated on for an aneurysm only after their condition improves;

Group 3: subcompensated patients (H—H grade III) are divided into two subgroups. Subgroup 1 consists of patients with condition severity determined by the anatomical shape of the intracranial hemorrhage. Such patients are operated on urgently, irrespective of the time passed since the last AIH. Subgroup 2 consists of patients with the risk of developing symptomatic vasospasm in the postoperative period. Aneurysm exclusion is performed in this subgroup of patients after the arterial spasm is eliminated.

Although this strategy is now dominating, it is inconsistent in some aspects.

Numerous studies conducted by Russian and foreign researchers [4, 7, 18] have proven that patients admitted in a decompensated condition have a higher risk of repeated hemorrhage from the aneurysm compared to compensated patients. However, early exclusion of a ruptured aneurysm from blood circulation is not performed in this group of patients.

It has been found that cerebral vasospasm in a patient does not diminish the risk of repeated hemorrhage from a ruptured aneurysm; yet, according to some authors, the rate of repeated hemorrhages rises in patients with vasospasm [3, 4, 7]. However, the wait-and-see surgical strategy is proposed for this category of patients.

In addition, it must be admitted that, in refraining from early surgery in patients with the risk of developing symptomatic vasospasm, hemodynamic (triple-H) therapy administered to compensate for the developing cerebral ischemia will not be conducted in full volume due to the increased risk of fatal hemorrhage from a functioning aneurysm [14]. Prolonged use of antifibrinolytic agents to reduce the risk of repeated hemorrhage may reduce the efficacy of medical treatment of cerebral ischemia even further [8].

III. The strategy of "early undifferentiated treatment", in accordance with which all the patients with AIH, irrespective of the severity of their condition, are subject to early surgical treatment as soon as possible after the hemorrhage source is verified.

Although this strategy reasonably resolves the inconsistencies of “early undifferentiated treatment”, there are few advocates of this approach to treating patients with central aneurysms.

This is explained by the fact that application of such surgical tactics is accompanied by a significant increase in the load on all the medical and diagnostic services of a hospital participating in provision of urgent medical care for the patients. The use of such tactics undoubtedly decreases the rate of adverse functional outcomes due to repeated hemorrhages from aneurysms in patients who were not operated on [9, 12, 13, 16, 19—21].

Meanwhile, the reverse side of the medal is that the number of urgent non-stop surgeries performed (including those on patients in decompensated condition) increases, which is inevitably accompanied by higher mortality rate among the operated patients.

Since no large-scale studies on this subject matter have been conducted, it is not clear now whether the use of the “early undifferentiated treatment” strategy significantly improves the characteristics of the general mortality rate and functional outcomes compared to the results of using the “early undifferentiated treatment” concept.

Yet, over the recent twenty-five years that have passed since the International Cooperative Study on the Timing of Aneurysm Surgery was completed, the most active surgical centers have accumulated vast experience in treating patients with AIH in different time intervals of the acute period, including those admitted in decompensated condition [9, 12, 13, 16, 19—21].

The results obtained by the medical researchers testify to the fact that the functional outcomes in patients with the severity of their condition graded I—III according to the H—H scale, operated on in different time intervals of the acute AIH period, do not reliably differ [12, 16]. That means that this category of patients may be operated on immediately after the hemorrhage source had been verified, irrespective of the time of establishing a correct diagnosis and admission to a specialized hospital [12, 16].

Studies [9, 12, 13, 19—21] and other publications have demonstrated that early surgical treatment of patients admitted in decompensated condition (H—H grade IV—V) allows one to achieve much better statistics of general and post-operative mortality compared to the results of the previously conducted cooperative studies. Thus, there is a clear trend towards extending the list of indications for early surgical treatment in patients with complicated forms of AIH, which was stated in the recommendations of the American Stroke Association (2012) on treatment of patients with subarachnoid hemorrhages [10].

In this regard, we believe that further improvement of the system of providing medical care to patients
with AIH, the available anesthesia and resuscitation measures and the microsurgical and endovascular technologies will in the foreseeable future essentially increase the surgical activity for patients with complicated forms of AIH in the decompensated condition.

The reported clinical cases demonstrate that favorable results of treating patients with the severe clinical course of the aneurysmal disease of the brain can be achieved in regional healthcare hospitals and illustrate one of the possible technical ways to solve the problem of surgical treatment in patients with complicated forms of AIH [11, 17].

REFERENCES


The paper focuses on a very important and complicated issue: early surgical interventions in patients with aneurysmal intracranial hemorrhages.

As it is correctly indicated in the paper, the edematous brain, which cannot be sufficiently relaxed by neither osmodiuretics, nor lumbar drainage, nor hyperventilation, is a significant problem for managing patients in the acute hemorrhage period.

Meanwhile, before the arachnoid cisterns are opened, the absence of tension in the medullary substance is extremely important for enhancing the visual field angle and mitigating the traction injury. The authors discuss two cases of massive ventricular hemorrhages and severe intraoperative brain edema for which they used the method of direct extraction of blood clots from the lateral and the third ventricles of the brain though the interhemispheric transcallosal approach. In both cases, this surgical technique proved to be effective, which allowed the surgeons to relax the medullary substance, clip the aneurysms, and achieve satisfactory neurological outcomes.

It is to be noted that elimination of hematoma before aneurysm exclusion is always associated with the risk of its intraoperative rupture; therefore, the technique described by the authors should be used only in exceptional cases of untreatable edema rather than being a routine procedure.

Direct evacuation of blood clots from the ventricular system via a hematoma or by encephalotomy may also be carried out after aneurysmal exclusion. This phase may also include installation of external drainage under immediate visual control to clean out the remaining part of the intraventricular hemorrhage and to monitor intracranial pressure in the postoperative period.

The question dealing with time and amount of surgical treatment for patients in severe condition (Hunt and Hess grades 4 or 5) after aneurysmal intracranial hemorrhage is still under discussion. This group of patients is rather heterogeneous in terms of the risks of surgical treatment. The prognosis for postoperative outcomes in patients with isolated intracranial and intraventricular hemorrhages (Fisher grade IV), provided their timely surgical extraction, always seems to be more favorable compared to that of patients having massive subarachnoid hemorrhages (Fisher grade III) and profound diffuse edema.

To sum up, the clinical cases described by the authors and demonstrating the possibilities of transcallosal ventriculostomy in early surgical management of patients with intraventricular aneurysmal hemorrhages, as well as substantiation of their view of the problem, deserve attention of the neurosurgeons’ community.

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The Outcomes of Treatment of Cauda Equina Ependymomas in Adults


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Ependymoma is a rare tumor that accounts for about 4% of all central nervous system tumors. Ependymomas typically have the intramedullary localization; however, the tumor is sometimes localized outside of the spinal cord, in the cauda equina root region. **Objective.** The objective of the study was to analyze the outcomes of treatment in patients diagnosed with extramedullary ependymoma. **Material and Methods.** Fifty patients (23 males and 27 females aged 18—76 years, mean age of 38.7 years) with ependymoma of the cauda equina region were operated on at the 10th Department of the Burdenko Neurosurgical Institute between January 2009 and December 2013. Thirty-six patients were newly diagnosed with tumors. Fourteen patients were admitted to the Burdenko Neurosurgical Institute with recurrent tumor or continued tumor growth. The patients were subdivided into two groups according to this criterion. The outcomes of treatment were evaluated using the Frankel, Karnofsky, and VAS scales. Criteria (scale) proposed by Kawabata et al. were used to assess the long-term outcomes of surgical treatment. Tumor growth was monitored by contrast-enhanced MRI. **Results.** Tumors were divided into two subtypes: encapsulated and infiltrative. Subtotal resection of ependymomas was performed in 5 patients; continued growth of ependymoma was observed in 3 patients. According to the evaluation performed using the scales, positive outcomes were achieved in both groups. According to the criteria of Kawabata et al., the patients were distributed as follows: in group 1, good outcome (class 1) was observed in 26 (72%) patients, satisfactory outcome (class 2) in 8 (22.5%) patients, and equivocal outcome (class 3) in 2 (5.5%) patients. A number of patients received radiotherapy as a component of combination treatment. Tumor growth stabilization was achieved. **Conclusions.** Microsurgical intervention is obligatory, since it has a positive effect on outcomes of surgical treatment of intradural extramedullary tumors, in particular ependymomas of the cauda equina region. The treatment efficacy decreases for the infiltrative pattern of tumor growth. Radiation therapy should be used in the case of continued tumor growth or intentionally subtotal tumor resection.

**Keywords:** intradural extramedullary tumor, cauda equina tumor, myxopapillary ependymoma, Frankel, Karnofsky, VAS.

According to the 2007 WHO Classification of Tumors of the Central Nervous System [1], ependymal tumors include the following types: cellular, papillary, clear cell, tanyctic and anaplastic ependymomas, subependymoma, and myxopapillary ependymoma. The latter is the most common histological type (Fig. 1).

From the topographic anatomy standpoint, ependymomas of the terminal filament are intradural extramedullary spinal tumors of the neuroectodermal origin. Currently, with the advent of the microsurgical technique, resection of extramedullary tumors is not a problem for the neurosurgeon. However, according to the experience of the Spinal Department of the Burdenko Neurosurgical Institute, application of patients with relapses and continued tumor growth creates a complex situation in choosing the tactics of treatment and in understanding disease diagnosis. The purpose of this study was to investigate the early and long-term outcomes of treatment of patients diagnosed with extramedullary ependymoma localized in the cauda equina region.

**Material and Methods**

A total of 197 patients with the histologically verified diagnosis of spinal cord ependymoma underwent surgical treatment at the Spinal Department of the Burdenko Neurosurgical Institute from January 2009 to December 2013. Of them, an intradural extramedullary tumor was diagnosed in 50 patients. Our observation group included 23 males and 27 females aged 18—76 years (mean age of 38.7 years) with terminal filament ependymomas localized in the cauda equina roots. Despite the fact that the study included patients who underwent treatment during 2009—2013, the follow-up period ranged from 6 months to 25 years (mean of 52.2 months), because this period was calculated since the first surgery listed in the past medical history. All patients were divided into two groups. Group 1 included 36 patients with newly diagnosed ependymomas of the cauda equina. Group 2 was comprised of 14 patients who were previously operated on for ependymoma of the cauda equina and had either recurrent tumor or continued tumor growth. 4 patients had repetitive surgeries; 3 patients underwent subtotal resection at the place of residence; and 2 patients underwent an open biopsy of the tumor.

In 26 cases, ependymomas had the expansive growth pattern and macroscopically appeared as a round or elongated node coated with a dense sac (Fig. 2).

In 24 cases, the tumor had the infiltrative growth pattern, had no sac, and was tightly adjoining to the cauda equina roots (Fig. 3) and to the medullary cone (9 cases).
For simplicity, the term “infiltrative” tumor was used with respect to ependymomas without sac and tightly adjoining to the cauda equina roots.

The mean length of tumors in spinal segments was 2 segments (1 to 5) in group 1 and 4.85 segments in group 2. Ependymomas were typically localized at the L2—L3 level. The disease duration from the onset of symptoms till reference to the neurosurgeon ranged from several months to 14 years, with 31 months, on average, being spent before surgical intervention.

Among the main symptoms, local pain syndrome was observed in all patients and was the chief complaint. Sensory disorders of varying intensity were detected in 16 patients. Paraparesis was observed in 12 patients only. Pelvic dysfunctions were observed in 18 patients. Of them, 12 patients had ischuria, and 6 patients suffered stool retention and enuresis. Ischuria was caused by compression of the medullary cone in 4 cases and by compression of the cauda equina roots in the other cases. Along with pain syndrome, erectile dysfunction was the chief complaint and disease presentation in 5 male patients. The tumor had the infiltrative growth pattern in 13 patients with pelvic dysfunction.

Presurgical examination of the patient included evaluation by a departmental neurosurgeon and neurologist and contrast-enhanced MRI (see Fig. 2 and 3). Patients with newly diagnosed tumors underwent surgery using either laminectomy or hemilaminectomy, which were sufficient to visualize the tumor poles, followed by microsurgical resection. Given the two different patterns of tumor growth (encapsulated and infiltrative), various resection techniques were applied. En block resection was used for encapsulated tumors (Fig. 4).

Ependymomas with the infiltrating growth pattern and without a sac were resected by intratumoral decompression and morcellation, i.e. by reducing the tumor volume using an ultrasonic aspirator and microsurgical instruments, followed by resecting the tumor in several fragments (Fig. 5).

In 11 cases, the dura mater was thinned and had a defect. After tumor resection, there arose the need for enthesis using synthetic glue materials (Gore Preclude, TachoComb, Tissucol, or Resodura). The enthesis efficacy was achieved in 10 cases. In one case, there was the necessity in revision of a surgical wound to remove a cerebrospinal fluid (CSF) cyst and to close a CSF fistula of the dura mater. In the second case, liquorrhea was resolved by draining the cerebrospinal fluid via a lumbar drainage and repeated wound punctures.

In 6 cases of subtotal tumor removal, radiation therapy was used; 3 patients underwent a course of conventional radiation therapy at the place of residence. The mean exposure dose for the longitudinal axis of the spinal canal was 50.4 Gy. Three patients underwent stereotactic radiotherapy in the hypofractionation regimen using the CyberKnife system at the Burdenko Neurosurgical Institute. The hypofractionation regimen involved 14—16 Gy delivered in 3—5 fractions (Fig. 6).

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**Fig. 1.** Histologic specimen of myxopapillary ependymoma. × 200.

**Fig. 2.** MRI of encapsulated ependymoma of the terminal filament at the L2—L3 level before and after surgery.
Results

A postoperative examination of the patient included evaluation by a departmental neurosurgeon and neurologist as well as contrast-enhanced MRI 3 months and 1 and 3 years after surgery. In the long-term postoperative period, an analysis was conducted based on the data of outpatient observation; MRI was performed when needed.

Only 1 (2.7%) ependymoma relapse with infiltrative growth was detected in group 1. The relapse was detected due to the clinical presentation 5 years after surgery.

In group 2, subtotal resection of ependymomas was performed in 5 (35.7%) cases. Continued tumor growth was observed in 2 (14%) patients during follow-up. According to the MRI data, no dynamics of tumor growth was detected in 3 patients. Neurological symptoms emerged and progressed in 2 (14%) cases (complaints appeared 12 months after reoperation in the first case and after 36 months in the second case).

Radiation therapy provided a positive outcome in 5 patients in the form of tumor growth stabilization and pain reduction by more than 3 points on the VAS scale during a follow-up period of 12 to 28 months. According to the literature [2, 3, 5, 6, 8], conventional therapy has been widely used for ependymoma treatment. Radiation therapy in the postoperative period significantly reduces the tumor growth rate [7]. No stabilization of tumor growth after radiation therapy was observed in 1 case.

Fig. 3. MRI of anaplastic ependymoma of the cauda equina at the T12—L5 level before and after surgery.

Fig. 4. Intraoperative images of encapsulated ependymoma.
1 — cauda equina roots; 2 — tumor; 3 — terminal filament.
Treatment outcomes were determined using the Frankel classification for assessment of the neurological status, Karnofsky scale of the life quality, and visual analogue scale of the pain syndrome intensity. Also, tumor growth or tumor relapse was controlled using the MRI data.

In group 1, the following grades were obtained according to the Frankel classification (Table 1): grade C (2 patients), grade D (26 patients), and grade E (8 patients). According to the Frankel grading system, the following grades were detected in group 2: grade C (4 patients) and grade D (10 patients). According to the Karnofsky scale, the distribution of patients in group 1 was as follows: 4 patients had a score of 60, 30 patients had a score of 70, and 2 patients had a score of 90. In group 2, the results were as follows: 9 patients had a score of 60, and 5 patients had a score of 70.

The assessment of pain syndrome on the VAS pain scale was performed before surgery and in the long-term postoperative period (Fig. 7). Clear predominance of severe pain syndrome was observed in group 1 where 29 (80%) patients had more than 7 points.

In the long-term follow-up period, the following outcomes were achieved in group 1: on the Frankel scale (see Table 1), 18 (50%) patients were upgraded; 8 (22.5%) patients had the same grade E; 8 (22.5%) patients had the same grade D and C (7 and 1 patients, respectively); and 2 (5.5%) patients were downgraded.

In group 2 of patients who underwent reoperation, the following results were achieved (see Table 1): 3 (21.4%) patients were upgraded, of whom 2 patients were upgraded from C to D and 1 patient was upgraded from D to E; 10 (64.2%) patients had the same grade, namely 2 patients with grade C and 8 patients with grade D; and only 1 (7%) patient from D was downgraded.

In the long-term follow-up period, the assessment of patients in group 1 according to the Karnofsky scale showed that an improvement in the quality of life (increasing the score) was observed in 32 (89%) patients; no change in the score was in 2 patients (5.5%); and the score was decreased in 2 patients (5.5%).

In group 2, the quality of life was improved in 8 (57%) patients, remained the same in 4 (28.5%) patients, and worsened in 2 (14.5%) patients only.

According to the VAS scale (see Fig. 7), regression of pain syndrome by more than 3 points on the analogue scale was considered as a positive outcome. In group 1, complete regression of pain syndrome was observed in 26 (72%) patients; a decrease in pain was noted in 6 (16.6%) patients. Three (8.3%) patients had a decrease in the pain

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Fig. 5. Intraoperative images of the tumor with infiltrative growth pattern.
1 — medullary cone; 2 — tumor; 3 — cauda equina roots; 4 — terminal filament.
syndrome intensity, but by less than 3 points. Pain aggravated in 1 patient. In group 2, regression of pain syndrome occurred in 10 (72%) patients, and poor outcomes were observed in 4 (28%) patients: 2 (14%) had complains of aggravated pain, and the pain reduced only by 2 points in the other 2 (14%) patients.

The long-term outcomes were evaluated using three classes of the Kawabata et al. scale (criteria). According to the criteria of Kawabata et al., patients were distributed as follows: group 1, good outcome (class 1) was observed in 26 (72%) patients, satisfactory outcome (class 2) in 8 (22.5%), and equivocal outcome (class 3) in 2 (5.5%) patients only. In the postoperative period, the equivocal outcome in one of the two patients resulted from aggravated local pain in the lumbar spine. These complaints were associated with a concomitant degenerative spine disease. After surgery, the second patient with the infiltrative growth pattern of ependymoma adjoining to the medullary cone developed sensory disorders and pelvic dysfunctions. Both these patients received conventional radiation therapy that improved their condition. In the first case, the pain syndrome regressed. Unfortunately, in the second patient, no sensory disorder regression was observed on the background of recovery of pelvic organ functions.

In group 2, the results were as follows: good outcome was observed in 3 (21.4%) patients, satisfactory outcome in 9 (64.4%) patients, and equivocal in 2 (14.2%) patients. In 1 patient, worsening of the neurological symptoms occurred after removal of large recurrent ependymoma with a sacral ulcer due to the tumor. Also, the equivocal outcome in 2 patients was associated with continued

Fig. 6. Plan of stereotactic radiotherapy for a patient with recurrent ependymoma of the cauda equina using the CyberKnife system.

Fig. 7. VAS pain scale, after surgery.
tumor growth after subtotal resection. These patients have been planned for stereotactic radiotherapy of tumor nodes based on the control MRI data.

### Discussion

Tumors of the cauda equina occur very rarely compared to other neurosurgical pathologies. Ependymomas of this localization are much less common. The series of examined patients that is described in this article is the largest one in the CIS countries and is one of the largest series in the world. For example, 62 patients were operated on at the Romodanov Institute of Neurosurgery (Kiev, Ukraine) for 20 years (from 1988 to 2007) [3].

In most cases, extramedullary ependymoma do not cause motor deficits in the absence of medullary cone compression. Based on analysis of a group of patients with ependymomas of the cauda equina, L. Meneses et al. [4] divided the symptoms into local pain (31.25%), radicular pain (56.25%), and paraparesis (12.5%). A decrease in the motor function was observed only in every 10th—12th patient in the series and was accompanied by urination and defecation disorders and sexual dysfunction. In this case, severe local and radicular pain syndromes as well as sensory disorders caused intense discomfort and were the main cause of disability and reference to a doctor.

The precursor symptoms of the disease usually include unilateral sensory disorders in certain sensory areas. While progressively spreading from the tumor localization level down to the feet, the sensory disorders become bilateral. This phenomenon progresses along with an increase in the tumor size.

Urination disorder, like sexual dysfunction, develops in a small number of patients. The development of these symptoms is associated with medullary cone compression. The medullary cone includes sacral plexus segments that are responsible for the pelvic organ function. In our series of observations, only 4 of 18 patients with the pelvic organ dysfunction had tumors at the medullary cone level. The remaining 14 patients with the pelvic organ dysfunction had the tumor localized distal to the cone and had, to our opinion, more pronounced symptoms. For example, the dysfunction was accompanied by enuresis and stool retention in 6 cases. Unfortunately, no regression of this disease manifestation occurred during the postoperative follow-up after tumor resection, even on the background of specific therapy. This is likely related to microcirculation failure in the cauda equina roots that resulted from long-lasting compression by the tumor; however, we could not find confirmation of this fact in the literature. Remarkably, the tumor had the

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### Table 1. Assessment of patients’ neurological status on the Frankel scale

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Footnote. A—E are the types of neurological spinal disorders.

### Table 2. Criteria for assessment of treatment outcomes (Kawabata et al.)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Criterion</th>
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<tbody>
<tr>
<td>Good (class 1)</td>
<td>No complaints and pathological symptoms, normal results of objective examination, significant improvement, no disabling dysfunction</td>
</tr>
<tr>
<td>Satisfactory (class 2)</td>
<td>Minor complaints, some residual symptoms, and minimal objective signs</td>
</tr>
<tr>
<td>Equivocal (class 3)</td>
<td>Retained complaints, no positive dynamics, or worsening</td>
</tr>
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</table>

Criterion

- Minor sensory disorders and grade IV—V paresis with improvement by, at least, one grade
- Minor sensory disorders, mild atrophy, grade III—V or grade IV—V paresis with improvement by, at least, one grade
- Severe sensory deficit and atrophy
infiltrative growth pattern in most cases (13 patients) of pelvic organ dysfunction.

P. Sonneland et al. [2] and E.I. Slyn'ko and A.G. Karleychuk [3] in their series divided tumors into two patterns of growth (infiltrative and encapsulated) affecting treatment outcomes. Certainly, this was not true infiltrative growth but exophytic one, since ependymomas of the cauda equina do not grow into adjacent structures. In our own practice, we have often observed the inclusion of the cauda equina roots in the tumor sac. Frequently, these ependymomas can reach a giant size. Two patients in our series were detected with giant ependymomas. The tumors of the cauda equina were large in size and extended over more than 7 spinal segments (T10—S3). These tumors compressed the medullary cone and occupied the whole space inside the sac ending in the sacrum region. In these cases, destruction of the bone tissue was observed; the tumor stretched the presacral fascia and penetrated to the pelvic region (Fig. 8).

We analyzed the treatment outcomes of large international series of patients. For example, complete resection of ependymomas was achieved in 80% of cases in a series presented by E. Kucia [5] and in 73.4% of cases in a series presented by M. Nakamura [6]. According to P. Sonneland et al. [2], radical resection was achieved only in 59% of patients. In a series of patients operated on at the Burdenko Neurosurgical Institute, total tumor resection was achieved in 33 (91%) cases in group 1 and in 9 (64%) cases in group 2. Undoubtedly, these data indicate that there are a large number of unsatisfactory outcomes in reoperated patients.

Resection of the tumor with the infiltrating growth pattern that was tightly adherent to the cauda equina roots was a complex problem. Total resection of ependymoma of this type was performed with extreme caution. The basic principle of surgery was the maximal safe resection [2, 5, 9]. During surgery, it was necessary to correlate the radicalness of tumor resection and the risk of neurological deficit in the postoperative period. We used neurophysiological monitoring with analysis of evoked motor and sensory potentials in order to prevent neurological complications. M. Meneses et al. in their study also emphasized the need for neurophysiological monitoring.

Recurrence tumors were observed in 19% of cases, according to P. Sonneland et al. [2]; in 10% of cases, according to E. Kucia et al. [5]; and in 7.4% of cases, according to E.I. Slyn'ko and A.G. Karleychuk [3]. No relapse was revealed by M. Meneses et al. [4] in a series of 16 patients with a follow-up period ranging from 2 to 84 months.

According to the 2013 National Comprehensive Cancer Network (NCCN) guideline for the management of patients with primary tumors of the spinal cord [9], which was developed in the USA, it is recommended to perform the maximal safe resection with subsequent follow-up and regular MRI. Repeated surgical
intervention or radiation therapy is recommended if continued tumor growth or relapse is detected. The tactics for treatment and follow-up of patients with extramedullary tumors of the spinal cord was developed at the Spinal Department of the Burdenko Neurosurgical Institute based on the acquired experience (see Diagram).

The patient is subjected to surgical intervention (tumor resection) when a radiographically verified intradural tumor, ependymoma of the cauda equina, is detected by contrast-enhanced MRI. Depending on the radicalness of surgery and histological diagnosis, further treatment tactics for the patient is planned. In the case of total tumor resection, the patient is recommended to have contrast-enhanced MRI 3, 12, 36, and 60 months after surgery (regardless of the tumor growth pattern) with subsequent evaluation by the neurosurgeon. In the case of subtotal tumor resection or a high risk for relapse, the patient consults the radiologist and, if necessary, undergoes radiation therapy. Patients who are detected with a recurrent tumor during follow-up and lack progression of neurological symptoms are recommended to have stereotactic radiotherapy for the tumor. Reoperation is performed in the case of aggravation of the neurological symptoms associated with motor or sensory deficit; radiation therapy is not the method of choice in this case.

Neither chemotherapy nor targeted therapy was used for treatment of patients in our series. However, chemotherapy for treatment of ependymomas in adult patients is limited and is used if radiotherapy is not effective. Forty-four patients out of 127 patients with anaplastic ependymoma received cisplatin, lomustine, and vincristine in a study by A. Korshunov et al. [10]. According to this study, patients who underwent chemotherapy had better outcomes (extended relapse-free period and stabilization of tumor growth) compared to patients who did not receive chemotherapy (78% vs 48%; \( p=0.01 \)).

Several authors have also noted the efficacy of chemotherapy or targeted therapy in patients with continued growth of grade III ependymoma. For example, N. Fakharai et al. [11] reported a clinical case of the use of imatinib in treatment of a female patient with continued growth of a cauda equina tumor (grade II ependymoma); the patient was followed up for 11 months. A regression of the neurological symptoms and positive dynamics, according to MRI, in the form of a tumor volume reduction were observed. Good outcomes in the form of stabilization of ependymoma growth were achieved by oncologists from the USC Norris Comprehensive Cancer Center (Los Angeles, California, United States) [12]. Ten patients diagnosed with grade III anaplastic ependymoma were involved in the study. They received etoposide therapy (50 mg/m² a day) in 2 cycles of 21 days each with a 14-day interval. Stable, good outcome (stabilization of tumor growth) was achieved in 5 (50%) patients. However, most patients of the study group (9 (90%)) had gastrointestinal and hematopoietic complications.
Conclusion

The use of the microsurgical technique in modern neurosurgical practice has resulted in a significant improvement in outcomes of surgical treatment for intradural extramedullary tumors, particularly tumors of the cauda equina. This is largely related to the radicalness of resection of ependymomas in the cauda equina region, with the risk for injury of surrounding structures being relatively low. The maximal radical resection should be followed during tumor resection. If necessary, tumor parts tightly adherent to the cone and cauda equina roots should be left to preserve the nervous tissue function. The use of an ultrasonic aspirator can not ensure radical resection in this situation. At present, with the availability of modern neuroimaging techniques enabling sufficiently correct differential diagnosis, there is no reason for a tumor biopsy. It should be noted that the pattern of tumor spreading or tumor growth largely affects the rate of tumor relapses and the radicalness of their resection. Therefore, the quality of life of patients in the postoperative period is affected as well. Most patients are of working age, but they can not fulfill their duties due to severe pain. Surgical treatment of ependymomas is highly effective in reducing pain after surgery and increasing patients’ quality of life. As the experience has proven, great attention should be paid to control and follow-up of patients in the postoperative period, even after total tumor resection. Timely detection of a recurrent tumor could help to avoid repeated surgical intervention and apply an alternative method of treatment, e.g., radiation therapy. Analysis of the literature demonstrated ambiguous evaluation of the efficacy of radiation therapy for treatment of cauda equina ependymomas. Despite this fact, radiation therapy is the method of choice, and importance of stereotactic radiotherapy is growing.

Given the lack of consensus on the role of chemotherapeutic drugs in treatment of ependymomas in adult patients, we are not in the position to recommend this method. However, this method of treatment is promising for patients with repeatedly occurring recurrent tumors resistant to radiation therapy. Therefore, it is necessary to continue studying biology of ependymoma cells and methods of their drug treatment.

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Ependymomas of the cauda equina of the spinal cord belong to the group of extramedullary tumors. They comprise a separate pathomorphological subgroup of the so-called myxopapillary ependymomas. Interestingly, according to the classification of central nervous system tumors, myxopapillary ependymomas are absolutely benign tumors (grade I), and should have theoretically a better prognosis than intramedullary ependymomas (grade II) in adults. The clinical series of 197 patients presented in the study demonstrates all the difficulties and problems in treatment of invasive ependymomas of the cauda equina. Indeed, for some reason, a number of myxopapillary ependymomas are aggressive. They infiltrate surrounding structures, recur, and form drop metastases. Unfortunately, the authors did not analyze the factors that may affect the “biological behavior” of myxopapillary ependymoma. My own experience shows that the tumor size at the time of surgery is one of these factors, which indirectly reflects the timeliness of diagnosis. For example, the signs of arachnoid infiltration are hardly ever seen for tumors of up to 5 cm in length. Long-term, chronic compression of surrounding neural structures by a tumor leads, for unclear reasons, to infiltration of these structures. The radicalness of the first surgery is another factor. Many times, I have operated patients with a so-called “relapse” that is, in fact, a progression of the residual tumor. In these situations, even repeated surgery may be radical and result in recovery. A more significant and, in fact, unsolvable problem is giant ependymomas (5—7 grades) causing destruction of the dura mater and vertebral bodies. These tumors always infiltrate both the roots, cone, and arachnoid and the dura mater, even destroying the latter and spreading into soft tissues. All patients whom I operated on for these giant tumors had been followed up for a long time by various specialists, sometimes having the MRI proven diagnosis, and had “drifted” to surgery for years (or even decades). These cases are a vivid example of the importance of timely diagnosis and early surgical treatment of ependymomas of the cauda equina. A trivial delay in surgery for a few years transforms a potentially curable condition to incurable one. The role of radiation therapy in the treatment of infiltrative tumors is correctly highlighted by the authors. Meanwhile, I strongly believe that the way to improve outcomes of treatment of myxopapillary ependymomas is timely diagnosis and high quality surgery, but not adjuvant therapy.

Yu.V. Kushel’ (Moscow, Russia)
The Outcomes of Arthroplasty of Degenerative Lumbar Lesions

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District Clinical Hospital “Center of Traumatology”, Surgut, Tyumen Region, Russia

Aim. The aim of the study was to investigate the safety and efficacy of total intervertebral disc replacement with a Maverick prosthesis in patients with discogenic pain in the lower lumbar spine and to review the reference data. Lumbar disc arthroplasty has been developed as an alternative to rigid interbody fusion for patients with pathology of the lower lumbar discs. According to the developers, preservation of motion in the operated segment should prevent secondary pathology of the adjacent segments.

Material and methods. 41 patients were operated on and 42 disc prostheses were placed by a particular surgeon at a particular hospital between November 2007 and March 2013. The clinical and radiological results of treatment of 35 patients were analyzed. The patients were examined before surgery, immediately after surgery, and then within the intervals of 3—6, 6—12, 12—24, and 36—48 months. The maximum follow-up was 61 months. The mean follow-up was 30 months. Results. Patients who were operated on using total intervertebral disc prosthesis demonstrated a significant improvement compared to their preoperative status. A significant reduction in the back and leg pain intensity was observed. The quality of life was significantly improved. The intervertebral disc space height, segmental sagittal balance, and balance in the adjacent levels were restored and preserved in the corrected state. Movements of the implanted segment were retained. Conclusions. Total lumbar disc replacement with the Maverick prosthesis has been proved to be an effective and safe technique. Clinical and radiological analyses revealed a significant improvement in the patient’s status.

Keywords: discogenic pain in the lumbar spine, discopathy, total intervertebral disc prosthesis, Maverick, adjacent segment degeneration.

Based on studies of lumbar pain causes, many foreign and Russian vertebrologists have recognized that pathological processes in the very disc can be one of the causes of the pain. Pathogenesis of discogenic pain syndrome has a certain specificity. The pain syndrome initially develops as a reflex syndrome [2, 3] associated with minor morphological changes; subsequent degenerative, inflammatory changes result in functional failure, which makes painless maintaining of human body weight impossible. Similar anatomical and radiological changes occur in a significant portion of an adult population, however, most of them remain asymptomatic [2, 3, 5, 6, 9, 11, 15, 16, 27]. In the presence of clinical manifestations, debilitating lumbar pains usually dominate leg pains. These pains are often nocturnal and not “orthopedically provoked”; the recumbent position does not provide any relief. The radiological signs of the pathology are the so-called “black disc” and degenerative inflammatory changes in the vertebral endplates referred to as Modic changes [25] on MRI scans. In this case, most authors believe that the changes classified as Modic-1 are directly correlated to lumbar pain in 60—85% of cases [20, 26] at a high specificity (96—96.8%) of positive discography [10]. The condition of most patients with low back pain can be alleviated by conservative measures, but patients with degenerative lumbar disc lesions who do not respond to conservative therapy for a long period (according to experts, at least 6 months) can be successfully treated by one of several surgical techniques [2, 3, 7, 12, 17, 19, 21, 28], including total disc replacement (TDR) with a prosthesis. Total intervertebral disc prosthesis stabilizes the affected segment, preserving its motion, and restores and preserves normal biomechanics of the lumbar spine. TDR has been developed and proposed as an alternative to rigid interbody fusion primarily to prevent progression of adjacent segment degeneration [8, 15, 29]. Analysis of the treatment outcomes in our group of patients was undertaken to assess the efficacy and safety of the technique. The indications for surgery are listed in Table.

Material and methods

Since November 2007, 41 patients (19 females and 22 males aged between 24 and 55 years, with a mean age of 39.2 years) have been operated on by a particular surgeon at a particular hospital. A total of 42 prosthetic discs have been placed.

All patients underwent total discectomy through a ventral approach, followed by implantation of the Maverick lumbar prosthesis (Medtronic Sofamor Danek Inc, Memphis, TN).

Treatment outcomes were assessed in 35 patients who had at least 2 control examinations. The longest follow-up period was 61 months; the mean follow-up period was 30 months. The data on 6 patients who failed to attend a control examination were excluded from the analysis.

The clinical outcomes were assessed based on the dynamics of back and leg pain intensity using the Visual Analogue Scale (VAS McDowell) [21] and the Oswestry Disability Index (ODI) questionnaire [20].
before surgery, immediately after surgery, and also 3, 6, 9, 12, 24, 36, and 48 months later. The patients subjectively evaluated the overall treatment outcome with a 4-score scale as excellent, good, fair, and poor. According to the ODI criteria, an index change by more than 15 points or 30% of the initial value is believed to be successful.

The intervertebral disc space height was measured using a lateral X-ray image in the neutral position; the negative evaluation criterion was subsidence or displacement of the prosthesis by more than 2 mm. Movements at the levels of the operated segment and adjacent segments were determined by summing up the disc wedge angle at the maximum flexion and extension.

The sagittal balance in the operated segment and adjacent segments was evaluated with the patient in the upright position using the Cobb and posterior tangent methods. The lumbar lordosis was measured between the cranial L1 and S1 endplates.

Heterotopic ossification was evaluated based on the CT and spine radiography data according to the procedure by P. McAfee et al. [23] on a scale from 0 to 4, where 0 means the lack of ossification, and 4 refers to its maximum severity with bridging of adjacent vertebrae.

Degeneration of adjacent segments was assessed based on spondylograms and CT and MRI images at the time of control examinations, using the same criteria: intervertebral disc space height, osteophytes, changes in the endplate and subchondral layer of vertebral bodies, and disc hydration.

The safety criteria for the technique and device were as follows:
— a neurological status of the patient at each re-examination compared to the preoperative status;
— the nature and frequency of minor and major complications that were classified as “not serious” (grades 1 or 2) or “serious” (grades 3 and 4) according to the World Health Organization (WHO) recommendations;
— the need for repeated surgeries, such as additional fixation, revision, removal of a prosthesis, or reoperation.

The overall result was evaluated based on the criteria recommended by the US Food and Drug Administration (FDA). Regression of pain, improvement in the quality of life, good radiological outcome, and the absence of both intraoperative and postoperative complications were considered as a successful outcome.

The disability index was evaluated according to the standard criteria: return to the previous work, transfer to light work, or incapacitation.

**Surgical technique**

Patients were operated on at the LIII—LIV (1 patient), LIV—LV (26 patients) and LV—SI (14 patients) levels. The patient’s position was as follows: a neutral supine position with the abducted lower limbs (Da Vinci position) and slightly bent knees to create a more physiological lumbar lordosis. Under X-ray control, the most flattened position was achieved for subsequent proper prosthesis placement whose criteria include the midline position of the spinous process in the frontal plane and parallel alignment of the endplates in the sagittal plane.

A left pararectal retroperitoneal mini-approach (transverse skin incision of 5—7 cm) using a universal SynFrame retractor was used in all cases. Stepwise dissection of the fibrous ring and removal of the nucleus pulposus were performed; the endplate cartilage was removed with the maximum preservation of the osseous part. The posterior longitudinal ligament was dissected only if there was a chance of leaving a herniated sequestrum in the spinal canal.

After full decompression, the intervertebral disc space was measured in the anteroposterior and transverse directions in order to select an appropriate size prosthesis that should provide the maximum coverage of the endplates. The prosthesis height was adjusted after placement of a special tool into the intervertebral disc space and trial expansion of the disc; the height of adjacent intervertebral disc spaces served the tentative criterion. After control midline positioning in the frontal plane, the deviation from which may lead to a change in the frontal balance during prosthesis placement, special tools were used to cut a slit for the prosthesis keel. Then,

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<th>Indications and contraindications for surgery</th>
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<td><strong>Indications for surgery</strong></td>
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<td>Age of 18—60 years</td>
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<td>Intense back pain</td>
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<td>Significant deterioration of the life quality (ODI &gt; 30—40)</td>
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<td>Ineffective conservative therapy for more than 6 months</td>
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the appropriate size prosthesis was placed into the prepared intervertebral disc space under X-ray control. The rear edge of the prosthesis should be 1—1.5 mm away from the posterior edge of the vertebral body. Incomplete insertion of the prosthesis can change the rotation point located between the joints and the posterior third of the lumbar vertebral bodies.

Results
The mean duration of pain syndrome prior to surgery was 5.16 months. The mean duration of surgery was 120.2 min (70—220 min); the mean intraoperative blood loss was 169.44 mL (50—900 mL).

The most indicative change was observed for the pain syndrome severity that decreased from 6.57 points before surgery to 0.7 points (according to VAS) by the end of follow-up (change by 89.3%) for back pain and from 6.44 to 0.7 points (change by 89.1%) for leg pain.

The ODI value of 56.32% at the beginning was reduced to 9.27% by the end of follow-up (change by 47.05%) (Fig. 1), which is well above the recommended value of 15 points or 30% for the “effective change”.

Prior to surgery, 23 (65.71%) out of 35 patients had radicular syndrome in the form of either hypoesthesia or hyporeflexia or hypotonia. On control examination, complete regression of neurological disorders was observed in 13 (37.14%) patients, partial regression was observed in 2 (5.71%) patients, and retention of the neurological status at the preoperative level was observed in 2 (5.71%) patients. Also, the development of previously absent hypotonia and hypoesthesia were detected in 2 (5.71%) cases (in both cases, patients had a vertebral body fracture).

10 (28.57%) patients subjectively rated the treatment result as excellent, 21 (60%) as good, 3 (8.57%) as fair, and 1 (2.86%) as poor, which required additional fixation.

By the time of the last examination, 32 (91.43%) out of 35 examined patients (the maximum follow-up was 61 months after surgery) returned to their previous work, 1 (2.86%) was transferred to light work (from a head nurse to a station nurse), 1 (2.86%) female patient had to leave work due to a chronic pain syndrome, and 1 (2.86%) patient was unemployed throughout the entire follow-up.

Radiographic data
Postoperatively, the loss of intervertebral disc space height (subsidence) was observed in 7 (20%) out of 35 examined patients.

The range of movements in the operated segment was 8.6° before surgery. A certain reduction in the range of movements immediately after surgery (down to 6.8°) is obviously explained by pain syndrome and stiffness of the muscle corset. The range of movements in the prosthetic segment increased to 13.9° for the period of up to 61 months (Fig. 2—4).

Sagittal balance: the segmental lumbar lordosis increased from 16.8° before surgery to 24.2° within 61 months after the surgery; the total lumbar lordosis increased from 39.1 to 44.2°, respectively.

In 1 (2.86%) case, slight progression of pre-existing degeneration at the adjacent level in the form of a decrease in the intervertebral disc space height and an increase in osteophyte growth was observed.

Type 1 heterotopic ossification (growth of the bone tissue over the top or bottom prosthetic plates, without bone penetration into the prosthesis lumen and without

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*Fig. 1. Changes in the disability index (ODI) and back and leg pains (VAS).*
limitation to movements in the prosthesis) was noted in 6 (17.14%) cases. There was 1 (2.86%) case of bone ingrowth into the prosthesis lumen, with to-and fro-movements being retained.

Adverse events and complications: there were no serious complications resulting in fatal outcomes or significant deterioration of patient’s health. There was 1 case of surgical injury to the iliac vein, which led to blood loss (900 mL). The vein was sutured, and the bleeding was stopped through a standard incision without transformation into major vascular surgery. There was no injury to other adjacent anatomic structures.

There were 3 cases of a marginal fracture of the vertebral body with insertion of a bone fragment into the intervertebral foramen that led to the development of radicular compression syndrome that required surgical reintervention: transforaminal removal of bone fragments in 2 cases was performed through a posterior tubular mini-approach. During follow-up, grade 3 heterotopic ossification and prosthesis failure were found in 1 of these patients by the 39th months. In one more case, stabilizing surgery was required (transpedicular fixation) after decompression in connection with developed segment instability that led to actual failure of the prosthesis and its conversion to an expensive interbody implant.

Prosthesis subsidence with insertion (2—4 mm) of the upper or lower parts of the prosthesis into the vertebral body occurred in 7 cases.

No late vascular disorders of the lower extremities and no case of retrograde ejaculation were observed.

According to the FDA methodology, the overall success of treatment amounted to 80%.

Discussion

The obtained clinical and radiological results are identical to the results of meta-analysis published by a number of experts [19, 21, 22]: a condition was significantly improved in most patients, the radicular syndrome regressed, lower back pain and leg pain were significantly reduced, the quality of life was substantially improved, and most (91.43%) of patients retained the ability to work at the previous position.

An analysis of the radiological data demonstrated preservation of the prosthesis function, minimal degeneration of adjacent segments, and retention of the segmental and total lumbar balances. The author’s own

Fig. 2. Spine radiography. A 36-year-old male patient A. 53 months after the surgery.
1 — segmental sagittal balance; 2 — total lumbar balance. The difference between extension and flexion angulations is equal to the range of prosthesis movements.
data on certain intraoperative and postoperative adverse effects are also comparable with the published results. Based on meta-analysis of 405 arthroplasties, M. Gornet et al. [22] reported 23 (5.7%) reoperations and 60% of mistakes that were made in the first series of arthroplasty and required reoperation. Accumulation of practical experience led to a significant decrease in the number of mistakes made by surgeons who had performed a large number of lumbar arthroplasties; complications became rarer; surgery duration and hospital stay shortened [28]. I. Punt et al. point out the necessity to place the widest possible prosthesis, thereby reducing the load on the vertebral endplates and preventing subsidence [13]. In a 10-year follow-up of 75 patients who, for various reasons, underwent reoperations after lumbar arthroplasty, 24 out of 39 cases of prosthesis subsidence were due to an unreasonably small prosthesis size.

A tendency to place the tallest possible prosthesis is also unsubstantiated, as it leads to marginal fractures of the vertebral bodies [22].

The community of vertebrologists is highly concerned with the long-term outcomes of lumbar arthroplasty. Prosthesis durability, reactions of periprosthetic tissues, late complications, as well as the possibility and need for revision surgery remain the topical issues [1, 4, 8, 18].

**Conclusion**

The conducted retrospective study of the clinical and radiographic outcomes of treatment demonstrated the efficacy and safety of total intervertebral disc replacement...
with the Maverick prosthesis. The results presented in the article support the use of this technique and give hope that total lumbar disc replacement with the prosthesis could take its rightful place among vertebrogenic surgery techniques and may, at least in part, replace rigid interbody fusion.

REFERENCES


Treatment of degenerative diseases of the lumbar spine is one of the most urgent challenges and objectives in modern medicine. In the recent years, the number of surgeries for this disease has been steadily increasing due to the improved diagnosis and development of new technologies. New surgical techniques ranging from minimally invasive outpatient procedures to major reconstructive surgeries are introduced into routine practice. Restoration of the sagittal balance, prevention of the degenerative cascade, preservation of vertebral segment mobility remain the topical issues. Total intervertebral disc replacement can solve these problems. This paper is dedicated to this technology.

The author operated on 41 patients and placed 42 prostheses for 4 years. The treatment outcomes were examined in 35 patients who had at least 2 control examinations. The maximum follow-up was 61 months. According to the author, patients operated on using total intervertebral disc prosthesis demonstrated a significant reduction in the intensity of back and leg pains in the postoperative period. The quality of life was significantly improved. The intervertebral disc space height, sagittal balance, and balance in the adjacent levels were restored and preserved in the corrected state. Movements of the implanted segment were preserved. These clinical and radiological outcomes were identical to the results of meta-analyses published by a number of experts.

The conclusions state that total lumbar disc replacement has turned out to be the effective and safe technique. The clinical and radiological methods of analysis demonstrated a significant improvement in the patient status.

It should be noted that the technique is recommended for spinal surgeons who are familiar with the minimally invasive retroperitoneal approach. One of the serious complications of this surgical intervention can be damage to the major vessels located in the operative field that should be significantly shifted at the LIV—LV and LV—SI level to place a prosthesis strictly at the midline. Undoubtedly, it is safer to perform this surgery in multipurpose hospitals.

In general, the technique is acceptable as long as the exact indications for its use are complied with. Undoubtedly, further technical improvement will lead to the development of new disc prostheses to maximally reproduce the natural biomechanics of a vertebral segment.

N.A. Konovalov (Moscow, Russia)
A clinical case of a 12-year-old female patient with hydrocephalus complicated by a rare disease, diverticulum of the lateral ventricle, is reported. Progression of the diverticulum was followed up by MRI. The diverticulum of the lateral ventricular wall developed within a year (within 14 months between two MRI examinations) and extended towards the quadrigeminal cistern. In addition, compression of the cerebellum, Sylvian aqueduct, and fourth cerebral ventricle developed. Surgery was suggested after an initial diagnosis of hydrocephalus (while the diverticulum was not formed yet); however, the child’s parents refused the treatment. One year later, a series of epileptic seizures emerged suddenly, and MRI revealed a cyst in the postcranial fossa, above the cerebellum. The genesis of the cyst and its nature were unclear, therefore, additional invasive analysis methods were required. MSCT ventriculography diagnosed a diverticulum of the right lateral ventricle towards the quadrigeminal cistern.

Keywords: ventricular diverticulum, arachnoid cyst, porencephaly, CT ventriculography.

"Science never solves a problem without creating ten more".
George Bernard Shaw (British playwright) [11]
tumors, vascular malformations, and congenital obstruction of the ipsilateral foramen of Monro.

A lateral ventricular diverticulum may often present in the form of other nosologies (hydrocephalus, arachnoid cyst, tumor, etc) [31, 32]. The pathognomonic clinical signs of a ventricular diverticulum are most likely lacked or hidden by symptoms of the underlying disease. A ventricular diverticulum presented as cerebellar ataxia was reported [38]. However, the neurological symptoms are always nonspecific and often minimal, which necessitates purposeful examination.

Diagnosis of a cerebral ventricular diverticulum using introsopic methods involves the use of both noninvasive (percutaneous sonography, magnetic resonance imaging (MRI), cardiac-gated phase-contrast MRI, and computed tomography (CT) in various modes) and invasive (CT ventriculography, 3D MSCT angiography, and cerebral angiography) techniques [2, 10, 29, 35, 37]. The cumulative information provided by noninvasive methods in most cases replaces the need for contrast enhancement. T. Naidich et al. [32] identified 10 computed tomography features of a cerebral ventricular diverticulum. On a MRI scan, a diverticulum looks like a clearly defined region of a modified signal that has the equal intensity to the CSF signal in all sequences. At the same time, a diverticulum is not clearly delineated from the walls of adjacent lateral ventricles [37]. Therefore, a certain combination of intrososcopic examinations may sufficiently objectively characterize the morphological features of a cerebral ventricular diverticulum. Objectivization of involvement of a diverticulum in the overall CSF circulation is also a significant aspect of the morphological and functional characterization of the pathological process.

Differential diagnosis of a ventricular diverticulum has been performed with an arachnoid cyst of the area of the tentorial notch (extending from the quadrigeminal or ambient cistern), a neuroepithelial cyst of the posterior cranial fossa, a cystic tumor of the pineal body, etc [2, 4, 10, 16, 38]. Detection of the diverticulum opening (ostium) or a communication between the cyst and ventricular system is important for diagnosis [18, 30].

Regarding treatment of a ventricular diverticulum, this disease is believed to occur asymptptomatically and rarely requires surgical treatment [17]. Most clinicians prefer surgical treatment in the case of symptomatic progression of the disease [18, 34]. A diverticulum regression may occur after placement of a CSF shunt, neuroendoscopy, or tumor resection [25, 27, 30].

In the case of a lateral ventricular diverticulum, certain difficulties in the interpretation of diagnostic indicators may be related to the lack of sufficient theoretical and summarising studies in the special neurosurgical and radiological literature. The reason for this probably is that a diverticulum is not an object of direct treatment. In addition, there is no unified etiologic concept, but there are numerous hypotheses of the pathogenic mechanism. All the above mentioned was the basis for presenting this case report.

A 12-year-old female patient was admitted to the somatic department of a regional multipurpose center of emergency medicine, complaining of convulsive seizures and dizziness.

The past medical history revealed that the patient was detected with an increased head circumference at the age of 1 year. However, adequate attention was not paid to the fact. At the age of 9 years, limb trembling and poor scholarship developed after the emotional stress (due to a hyperactive bladder during a school class). The patient underwent MRI at the age of 11, since the administered treatment had no effect. Based on detected hydrocephalus with the Evans’ index of 0.61 (Fig. 1), a local neurosurgeon suggested surgery for hydrocephalus, but the child’s parents refused the treatment. About a year later, tonic convulsions suddenly developed at night. She was admitted to the pediatric department, but then was transferred to the intensive care unit because of an increased frequency of multiple convulsive attacks. Multiple convulsions were reversed.

Life history: the patient was the child of the first pregnancy. Her mother was treated at a hospital during the fourth month of pregnancy due to threatened miscarriage. No complications at delivery. The girl started walking at the age of 1.5 years; she started school at the age of 7 years. The girl had good scholarship at elementary school.

Objective evaluation of the patient was as follows: the general condition was very poor; impaired consciousness (deep stupor); poorly communicating. Instructions were carried out partially, after a pause. Slight exotropia. Sideward glance was limited. The abdominal reflexes were depressed. The tendon reflexes were brisk, D>S. Muscle tone was spastic. Tetraparesis (muscle grade of 1 or 2). Poor response to painful stimuli. Stiff neck, Kernig’s symptoms. Locally: a hydrocephalic head shape with the head circumference of 59 cm (+4.5 cm).

Electroencephalographic examination (EEG) revealed a decrease in the convulsion threshold and the foci of pathological activity of subcortical structures. Ophthalmoscopy revealed angiopathy of retinal vessels and mild venous stasis. MRI detected a fluid intensity mass lesion above the cerebellum associated with triventricular hydrocephalus (Fig. 2).

Differential diagnosis was performed to differentiate among three nosologies: an arachnoid cyst of the quadrigeminal cistern, a cystic tumor of the pineal region, and a diverticulum of the third or lateral ventricle [6, 10].

 multislice computed tomography (MSCT) with intravenous contrast revealed no tumor mass (Fig. 3). Contrast-enhanced MRI was not conducted due to patient intolerance to a paramagnetic contrast agent.

For the purpose of differential diagnosis of an arachnoid cyst, the patient underwent MSCT.
ventriculography through the anterior horn of the right lateral ventricle. MSCT ventriculography confirmed the diverticulum of the lateral ventricle (Fig. 4). CSF pressure measured in the course of ventricular puncture was 240 mm w.g. Laboratory CSF parameters were as follows: cytosis was 5/3 (under the equal neutrophil-lymphocyte ratio); the protein content was 0. Removal of a certain amount of CSF for the “relief” purpose during ventriculography had an effect—the patient consciousness level improved to moderate stupor.

The patient was prepared for CSF shunt surgery, but unfortunately, the plan was never implemented. The patient died due to an idiopathic acute intestinal disease accompanied by severe diarrhea and complicated by a hypovolemic shock. No autopsy study was carried out. It is likely that hydrocephalus complicated by the diverticulum, as a competitive disease, also played a role in the lethal outcome.

Case features:
1. The diverticulum was an acquired disease.
2. The diverticulum development rate, i.e. the time during which the diverticulum grew up to a giant size and contributed to decompensation, was approximately 14 months.
3. The development of a lateral ventricular diverticulum in symmetric hydrocephalus.

The poor clinical and past medical history data (due to a decompensated patient condition at admission) confine the objective evaluation of the pathological process progression. However, it may be assumed that an outpouching of the ventricular wall in one of the morphologically complex regions near the choroid glomus (glomus chorioideum) occurred due to progressive CSF hypertension in the cerebral ventricular system [1, 14]. In this region, CSF “found” a weak spot by stretching and pulling out tissues along the pathway of least resistance towards the supracerebellar cistern [28]. It was most likely the pulsion diverticulum (diverticulum pulsione verum) [15, 31] formed due to pressure from within a hollow organ on its altered wall.

A detailed retrospective study of initial MRI images (of 2012, when the diverticulum had no obvious outpouching) revealed tomographic signs of a developing diverticulum (Fig. 5). The typical tomographic features of a diverticulum were also detected by repeated MRI.
(of 2013) on the background of a pronounced cystic outpouching (Fig. 6). The firm knowledge of reference tomographic signs of a ventricular diverticulum would probably enable prognosing for diverticulum progression [32].

Taking into account all the above mentioned, certain questions and suggestions arise. Answering these questions could reveal the morphological and functional structure of cerebral ventricular diverticula:

1. The association of a ventricular diverticulum with hydrocephalus. Is a diverticulum always associated with hydrocephalus or it may be an independent disease?

2. Is a ventricular diverticulum a definite sign of occlusive hydrocephalus, or it may also develop in the association with communicating hydrocephalus? [22]

3. Is a ventricular diverticulum a sign of liquor hypertension, or it may occur under normal CSF pressure?

4. Is the persistent diverticulum localization in certain anatomical parts of cerebral ventricles due to the structural features of the liquor system of the brain or due to other causes?

5. What exactly a ventricular diverticulum is? Is it a compensatory mechanism for tension hydrocephalus (similar to spontaneous ventriculocisternostomy [13, 20, and 28]), a genetically determined process [23], or a combination of these phenomena?

6. How much stable is compensation of hydrocephalus in the case of diverticulum formation (by analogy with the Bechtereva’s mechanism of steady compensation states)?

7. Which intervention is effective in the case of a ventricular diverticulum (CSF shunt surgery, internal cyst-cisternal shunt, endoscopic surgery, or their combination) [16, 38]?

8. What are the duration and degree of regression for a lateral ventricular diverticulum after surgery [38]?

9. What is the probability of diverticulum recurrence after surgery?

10. How much is it clinically and practically reasonable to distinguish a cerebral ventricular diverticulum upon hydrocephalus (the impact of diverticulum detection on the treatment tactics?)
**Fig. 4.** MSCT ventriculography. The cavity of diverticulum and the ventricular system are filling with contrast agent simultaneously.

a – axial sections; b – sagittal sections; c – frontal sections; the opening (ostium) of diverticulum is visualized (*).
According to the described case, it is clear that a lateral ventricular diverticulum is a disease that, under a particular clinical situation, requires a neurosurgical set of diagnostic (for indications) and invasive measures for the purpose of differential diagnosis [39]. It may be assumed that the use of an extensive complex of introscopic and neurophysiological examinations for each particular case will make possible to gain the morphological and functional characteristics and pathophysiological aspects of a cerebral ventricular diverticulum in detail. This, in turn, will facilitate systematization and classification of diverticula and, most importantly, will determine the right choice of the disease management. According to the literature [38], there have been attempts to classify ventricular diverticula by size, relationship with the tentorial notch, and relation to the superior cerebellar cistern.

The purpose of this report was not so much to describe a particular case of a cerebral ventricular diverticulum as to demonstrate and set out, if possible, promising directions in systematization of information on this phenomenon. The issues related to the features of surgical treatment of diseases associated with a diverticulum may help outline and correct possible directions of further research.
Cerebral diverticula, arachnoid cysts, and porencephaly; cerebral diverticula in children documented; the disease development is followed up over time.


**REFERENCES**


**Commentary**

The article describes a rare case of a 12-year-old child with hydrocephalus complicated by the development of a diverticulum of the lateral ventricle. The article is well documented; the disease development is followed up over time clinically and by MRI data.

A very detailed analysis of the literature data is conducted that is dedicated to the anatomical features and pathogenesis of cerebral diverticula in children.

The article points out the difference in the origins of cerebral diverticula, arachnoid cysts, and porencephaly; differential diagnosis of these lesions is discussed, which is very important for the practitioner. Diverticula of the cerebral ventricular system are a rare and still underexplored phenomenon. The article not so much solves the specified problem as brings up the right questions and makes one think about the principles of diagnosis and treatment of the disease.

S.K. Gorelyshev (Moscow, Russia)
2. Diagnostics of a spinal injury

2.1 Diagnosing a spinal injury

In each particular case, a patient with an injury delivered to the intensive care unit should be viewed as one potentially having a spinal injury and be respectively treated until the absence of the spinal injury has been evidenced at all levels. The diagnostic algorithm consists of the following steps:

a) Talking to the patient or a witness of the accident;

b) Examining and palpating the patient;

c) Determining the patient’s neurological status;

d) Using instrumental examination methods (spondylography of the spine, lumbar puncture with cerebrospinal fluid circulation assays, CT (and/or MRI), myelography, CT myelography, and vertebral angiography).

To ensure full-scale diagnostics, a hospital should be equipped with a spiral CT scanner operated on a 24-hour basis and a high-field magnetic resonance imaging scanner.

2.1.1 Collecting past medical history

When collecting past medical history of the injury, one needs to identify injury mechanism and time, pain localization, motor and sensory disorders, and the time of their emergence.

2.1.2 Examination and palpation

Examination allows the doctor to locate the injury traces and visible deformities, as well as to determine the level of mandatory X-ray examination to rule out combined lesions. The spine should be palpated with extreme caution in order not to inflict another injury to the patient. The doctor should examine and palpate the entire body, not only the “suspected organs”, which will minimize diagnostic errors. In patients with severe combined injury or cervical spine injuries, examination should be conducted simultaneously with treatment in the intensive care unit.

2.1.3 Neurological examination

In evaluating the neurological status of spinal patients, it is reasonable to use the ASIA scale (ASIA/ISCSCI — American Spine Injury Association/International Standards for Neurological and Functional Classification of Spinal Cord Injury, the international standard of neurological and functional classification of spinal cord injuries), which has a digital form for evaluating neurological lesions (optional). Muscle strength, touch and pain sensitivity, and reflex activity in the anogenital zone were chosen to be criteria for assessing the condition of the spinal cord. Motor functions were assessed by checking the strength of 10 control groups of muscles associated with spinal segments. Five segments were selected for upper extremities (C5—T1) and 5 segments for lower extremities (L2—S1) (Appendix 4 — the examination map).

Muscle strength is evaluated as follows: 0 — plegia, 1 — palpable or visible contractions of individual muscle groups; 2 — active movements in the assisted position; 3 — active movements in common position (overcoming gravitation); 4 — active movements overcoming certain resistance; 5 — active movements against high resistance.

The muscle strength is evaluated on both sides, and the scores for each segment are summed up. The results are entered into the examination map. If for some reasons it is impossible to check the muscle strength (for example, the extremity is in a cast), the mark NT (not tested) is made. The maximum score for 10 segments on each side equals 50.
The absence or presence of voluntary external anal sphincter contraction, checked by digital rectal examination, is recorded in the examination map. Spinal lesion is considered to be incomplete if there is voluntary sphincter contraction, even in the absence of active movements in the extremities.

Sensitivity is checked in 28 segments on both sides. In order to determine sensitivity in the entire segment, it is sufficient to inspect it in the control point referenced to a specific anatomic benchmark: C2, the occipital protuberance; C3, the supraclavicular fossa; C4, the apex of the acromioclavicular joint; C5, the lateral portion of the cubital fossa; C6, the big toe; C7, the middle finger; and C8, the minimus; T1, the medial side of the cubital fossa; T2, the apex of the axilla; T3, the third intercostal space; T4, the level of the nipples; T6—T9, corresponding intercostal spaces; T10, the level of the navel; T11, the eleventh intercostal space; T12, the inguinal fold, L1, half the distance between T12 and L2; L2, the middle of the frontal hip surface; L3, the medial condyle of the hip; L4, the medial portion of the ankle; L5, the back surface of the foot at the level of the third metatarsophalangeal joint; S1, the lateral surface of the heel; S2, the poples in the median line; S3, the ischial tuberosity; and S4—S5, the perianal zone.

Sensitivity is evaluated using the following scale: 0 — no sensitivity; 1 — impaired sensitivity; 2 — normal sensitivity. If sensitivity was not tested, the corresponding box of the examination map should be marked as NT.

The impossibility to distinguish between a sharp prick and a prick caused by blunt touch is evaluated as the absence of sensitivity to pain. Touch sensitivity is determined by touching with a cotton stab or Frey h’s stiff hairs.

The test results are recorded on the map. When sensitivity is tested in 28 segments on both sides, the maximum score will be 56. Anal sensitivity is additionally tested to determine the degree of lesion (either complete or not).

When evaluating sensitivity, the position of the extremities is to be assessed, as well as the sensations of deep pressure. Those are evaluated as absent, impaired, or normal. To evaluate the muscle-joint feeling, it is suggested that passive movements in the index fingers and in the big toes should be tested. These data are not recorded in the map but provide additional information on the degree of damage.

All patients are divided into five types according to the degree of spinal injury: type A — complete injury: neither motor nor sensitive functions are manifested. Signs of anal sensitivity are missing in S4—S5 segments. Type C — incomplete injury: motor functions are missing below the injury level but the elements of sensitivity in the S4—S5 segments are retained. Type C — incomplete injury: motor functions are retained below the injury level, and the strength is below 3 points in most control groups. Type D — incomplete injury: motor functions are retained below the injury level, and the strength equals to 3 and more points in most control groups. Type F — the norm: neither motor nor sensitive functions are impaired.

The following definitions are used in the classification:

- Tetraplegia — complete loss of functions (tetraparesis — partial impairment of functions) of the arms, legs, body, and pelvic organs as a result of lesion of the cervical spine.
- Paraplegia — complete loss of functions (paraparesis — partial impairment of functions) of the body, legs, and pelvic organs as a result of lesion of the thoracic, lumbar, or sacral segments of the spine, of the cone or roots of the cauda equina.

The classification presented allows the bias in the evaluation of the patient’s neurological status to be diminished and makes the examination results more reliable. The control groups of muscles and the sensitivity testing points were selected in such a way so that examination could be conducted in the supine position.

A digital characteristic of motor and sensitivity impairments allows clear identification of the level and degree of the spinal lesion, which is decisive for determining the treatment tactics and evaluating the treatment efficacy in its development.

Spinal injury may either complete (anatomic or functional due to spinal shock) or incomplete (concussion and contusion of the spine). Concussion of the spine is manifested by slight neurological disorders, which typically regress within the first 3—7 days and are not accompanied by morphological changes in the spine and its roots. Contusion of the spine is a spinal lesion occurring at the moment of injury and accompanied by complete or partial anatomic destruction of its substance with hemorrhages, areas of ischemia, necrosis, and regional edemas. It is manifested by neurological disorders lasting more than 7 days. Spinal shock: the absence of the spinal function in the area of the injury during 3—30 days as a result of its edema, contusion, and, possibly, extreme defensive inhibition of the nerve cells activity. It is accompanied by micro- and macro-injuries of the spine with non-fixed unstable spinal fractures and/or with continuing spinal compression.

Incomplete injuries of the spine are classified according to the following clinical syndromes: the central medullary syndrome — the lesion occurs only in the cervical spine and is characterized by preserved sensitivity in the sacral segments and by prevailing weakness of the upper extremities over the lower extremities; the frontal medullary syndrome — impairment of the motor functions and of the pain and temperature sensitivity with preserved proprioceptive sensitivity; the Brown-Séquard syndrome — impairment of motor functions and proprioceptive sensitivity on the lesion side and loss of pain and temperature sensitivity on the opposite side (half lesion of the spine, more characteristic of knife wounds and tumors); the syndrome of the lesion of the cone...
and cauda equina — flaccid paralysis of the legs, areflexic urinary bladder and rectal sphincter.

2.2 The instrumental methods for diagnosing spinal and cerebrospinal injuries in the acute period

Doctor’s main objective is to distinguish between compression of the spine, compression of its great vessels and roots and other kinds of lesions, which are treated conservatively. Therefore, compression of the spine should be suspected in each patient having a spinal and cerebrospinal injury until it is ruled out by special diagnostic actions.

Before surgery, one needs to collect information as precise as possible not only on the level and character of spinal cord lesions but also on the character of the vertebral lesion. This may be achieved only by comprehensive examination of a patient, which establishes the following facts:

I. The level of the spinal and cerebrospinal lesion.
II. The character of vertebral lesion:
   a) the number of the impaired vertebrae;
   b) the presence and the degree of impairment of the vertebral body;
   c) fractures of the vertebral arcs, articular and/or transverse processes, localization of the displaced fragments;
   d) fracture type (stable or unstable);
   e) disk impairment and the direction of its (their) displacement;
   f) presence of hematomas in the spinal cord, the character of changes in the spinal cord and its roots.
III. The condition of the spinal cord:
   a) the degree and type of spinal deformity (kyphotic, scoliotic);
   b) the presence and the character of the dislocation (bilateral, unilateral, interlocked, “apical”, etc.);
   c) the presence of rotational, transverse or axial displacement of the spine;
   d) the condition of the ligament apparatus.

Based on the data obtained, the following is determined:

1. Indications for surgical or conservative treatment.
2. The time of surgery depending on patient’s condition and the sequence of surgical intervention (in combined spinal injury).
3. The amount of surgery, its strategy and tactics (one-stage or two-stage treatment, the contents of each stage, the time of performing stage surgeries; the most convenient approach for this kind of surgery ensuring the minimum traumatization of surgical intervention and its maximum radical efficacy).

It is impossible to solve these tasks by conducting only clinical or neurological examination of the patient, even when a well-tested algorithm is used, since spinal shock, slow increase in spinal compression with a hematoma or its expanding edema prevent a surgeon from seeing the true picture of the lesion. One needs to use all the available modern instrumental diagnostic methods (in addition to clinical examination) to answer the questions posed.

The diagnostic algorithm of the set of instrumental examinations in the acute period of a spinal-cerebrospinal injury needs to include the following sequence of actions:

a) spine spondylography in the anterodorsal projections for the thoracic and lumbar spinal segments and additionally orally for the cervical segment;

b) spine spondylography in special positions (the oblique projection to examine the articulationes zygapophysiales and intervertebral foramina);

c) SCT (standard);

d) lumbar puncture with cerebrospinal fluid circulation assays;

e) ascending or descending myelography;

f) CT myelography;

g) MRI (optional);

h) somatosensory evoked potentials;

i) vertebral angiography (when the cervical spine is injured).

In some cases, solution of diagnostic tasks does not require implementation of all the above procedures. SCT and MRI are the optimal tests allowing correct diagnosis of 95—98% patients. In the intensive care units, radiographic examination of the spine is not informative for 80—90% patients, so it is reasonable to carry out spiral CT (SCT) immediately for all the spinal segments, and patients suspected of a combined injury require SCT scanning of the entire body.

2.2.1 Radiographic diagnosis of spinal injuries

Spondylography is a mandatory and affordable examination method in diagnosis of spinal injuries when SCT cannot be conducted.

Radiography allows one to see changes in the spinal axis, contour changes and deformities on the vertebral bodies and in the other vertebral elements, vertebral displacements and dislocations, pathologies of the craniovertebral transition and of the C2 vertebra, and, in some cases, changes in the paravertebral soft tissue shadow.

Conventional radiograms make it possible to measure the distances between different osseous structures of the spine and thus to get a more precise impression of the character of the trauma.

However, in a number of cases radiography is unable to provide all the necessary information about spinal cord compression, about the fracture of a vertebra or vertebral arch and it typically does not allow the optimal treatment tactics to be selected. Therefore, in all cases of spinal injury (with the clinical data on spinal cord injury or the injury of the spinal cord roots available and in patients with an expressed pain syndrome), the spinal injuries need to be scanned using CT (standard) or MRI (optional), even in the absence of vertebral injury signs on spondylograms. CT scanning (without additional
complex positions) allows complete clarification of the scope and character of osseous injury, with the scanning time being just few minutes.

Radiographic examination of the cervical spine is not obligatory in patients who have clear consciousness, are not intoxicated, have no neck pain, no tension in the paravertebral muscles or a combined injury (standard). It is possible to stop immobilizing the cervical spine in patients with clear consciousness who have neck pain or whose cervical muscles are tense if, according to radiographic examination and CT, a) functional radiograms show no pathology or b) no injuries are seen in MRI scans taken within 48 h after the injury (optional).

It is possible to stop immobilizing the cervical spine in unconscious patients who have no spinal injuries according to radiography and CT if: a) after recording adequate functional radiograms using an electron-optical image intensifier, or b) MRI scan recorded within 48 h after the injury shows no pathology, or c) at the physician’s discretion (optional).

2.2.2 Myelography

Myelography is a supplementary examination method, allowing impairments in the patency of the subarachnoid space to be determined and the degree of deformity of the spinal canal, cerebrospinal compression, and ruptures in the dura mater to be revealed. Neurological symptoms in the absence of radiological and CT data on lesions of the osseous spine structures, when CT scanning is impossible, are an indication for myelography. Ascending myelography is conducted to determine the lower limit of the subarachnoid space blocking (Omnipaque solution at concentration of 300 mg/ml is injected between the L4—L5 or L5—S1 vertebrae) with the head end of the radiological table tilted down. Descending myelography is performed to determine the lower limit of blocking (a contrast agent is injected into the occipital cisterna magna or cisterna lateralis) with the head end of the radiological table tilted up. In cervical spine injury at the C3—C7 levels, descending myelography is to be conducted by puncturing the lateral cistern, since it is allowed neither to turn the patient over nor to tilt his or her head. Conducting myelography is not reasonable for the injury of the C1—C2 vertebrae, since the subarachnoid space is rather large at this level and there should be no blocking even for the significant displacement of the C1, C2 vertebrae or their fragments.

2.2.3 CT in diagnosis of spine injuries

Spiral computer tomography (standard) and CT myelography (recommended) are the methods of choice in diagnosing spine and spinal cord injuries. SCT of all the spine segments is recommended for patients with combined injuries (optional). CT allows a fracture to be characterized with greater accuracy than by spondylography (spinal radiography): its level, the number of injured vertebrae, arch fractures, fractures of articular processes, different parts of vertebral bodies, the length of fracture lines and diastasis between the osseous fragments of broken vertebrae can be determined. It is important that the method makes it possible to see the displaced osseous fragments in the spinal cord lumen, which cannot be seen in the radiograms, since they are hidden by vertebral arches.

CT myelography allows one to see the location and extension of spinal cord compression, patency of the subdural space, and the size of the spinal cord and spinal canal.

In cases when there are doubts as to how to interpret the resulting scans, when the clinical picture does not comply with the available radiological and CT image, it is reasonable to conduct MRI to visualize the spinal cord.

2.2.4 MRI in diagnosing spine injuries

MRI allows one to see soft tissue spine structures: ligaments, intervertebral discs, spinal cord membranes and the spinal cord itself with the corresponding changes (ischemia, edema, hemorrhage, a cyst, extra- and intradural hemorrhages), as well as changes in the vertebral bodies.

MRI holds a leading position in diagnosis of post-traumatic disc herniation. If a patient has symptoms of radicular or myeloradicular compression and the X-ray images do not show any odious pathology, MRI scans can demonstrate post-traumatic disc herniation.

Some patients in the acute period of spine injury show no radiological signs of the lesion. However, 3—6—8 months later, a patient suddenly feels sharp pain in the back at the site of the previous injury or after slight physical overload. The X-ray of the spine shows a compression fracture of a vertebra (Kümmel’s or Verneuil’s disease, post-traumatic spondylitis). This is explained by the fact that hemorrhage occurs in the vertebral body at the moment of injury; its blood supply is disturbed and aseptic inflammation arises, turning into aseptic necrosis of bone trabecula, and finally resulting in “sagging” of the vertebra under axial loading. MRI allows one to detect these hemorrhages in the vertebral bodies (vertebral contusion) in the acute period of spinal injury. It is important to diagnose such intervertebral hemorrhages not only for making injury prognosis and determining the scope of surgery or duration of conservative treatment but also for developing the tactics of early rehabilitation of patients.

2.2.5 Electrophysiological diagnosis

Registration of somatosensory evoked potentials and determining the induced motor response during transcranial magnet stimulation in the acute and subacute periods of spine injury may allow one to determine the level of the lesion and may also testify that the conductive function of the spinal cord is preserved, given the clinical picture of its functional breakage. However, when the signal in the spinal pathways is missing, we cannot say for sure whether the patient has anatomical or only functional spine breakage.
Appendix 4

The ASIA/ISCSCI scale (American Spine Injury Association/International Standards for Neurological and Functional Classification of Spinal Cord Injury)

**Sensory**

**Motor**

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**KEY MUSCLES**

- Elbow flexors
- Wrist extensors
- Elbow extensors
- Distal phalanx flexors (middle finger)
- Finger abductors (little finger)

**Motor Function Evaluation**

- 0 = total paralysis
- 1 = palpable or visible contraction
- 2 = active movement, gravity eliminated
- 3 = active movement, against gravity
- 4 = active movement, against some resistance
- 5 = active movement, against full resistance
- NT = not testable

**SENSORY**

**Evaluation of pain sensitivity**

- 0 = absent
- 1 = impaired
- 2 = normal
- NT = not testable

**Evaluation of touch sensitivity**

Maximum: 56

**Evaluation of anal sensitivity**

- Yes
- No

**Neurological Level**

- The most caudal segment of the spinal cord with normal function

**Zone of Partial Damage**

- Sensory
- Motor

- Incomplete loss – any motor or sensory functions preserved in S4-S5
- Partially innervated segments
Cellular and Molecular Mechanisms of Radiation-Induced Brain Injury: Can Peripheral Markers Be Detected?

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Investigation of the mechanisms of radiation-induced brain injury is a significant fundamental objective of radiobiology and neuroradiology. Damage to the healthy brain tissue is a key factor limiting the application of radiation therapy in patients with nervous system neoplasms. Furthermore, radiation-induced brain injury can be clinically indistinguishable from continued tumor growth and requires methods of differential diagnosis. Thus, there is a high demand for biomarkers of radiation effects on the brain in neurosurgery and radiobiology. These markers may be used for better understanding and quantifying the effects of ionizing radiation on brain tissue, as well as for elaborating personalized therapy. Despite the high demand, biomarkers of radiation-induced brain injury have not been identified to the present day. The cellular and molecular mechanisms of the effect of ionizing radiation on the brain were analyzed in this review in order to identify potential biomarkers of nervous tissue radiation-induced injury.

Keywords: radiation-induced injury, radiation-induced necrosis, radiotherapy, neuroinflammation, differential diagnosis, biomarkers.

1. Introduction

Recent studies show that the late delayed radiation-induced brain injuries are the main cause of complications caused by radiation therapy. At the histological level, vascular anomalies, demyelination, and irreversible necrosis of the white matter have been described [5]. It is now generally accepted that the brain is the major dose-limiting organ in the clinical radiation therapy [Wong, van der Kogel, 2004]. According to the conventional view, the late radiation-induced brain injuries result from reduction in the proliferative activity of glial cells or endothelioocytes. According to different studies, the incidence of radiation-induced necrosis ranges from 3 to 24% [4]. The lowest incidence was noted in the conventional fractionated radiation therapy (with 60 Gy irradiation dose) [52]; the highest incidence occurred when stereotactic radiosurgery was used [Marks et al., 2010]. Cognitive impairments are typically considered separately as side effects of radiation therapy. Six months after fractionated radiation therapy, cognitive impairments are described in 50—90% of neurooncological patients [41]. According to the results of clinical trials [36], cognitive deficit is the second most significant factor (after survival) affecting the quality of life after radiation therapy. It is particularly remarkable that cognitive deficit can be detected in the absence of any structural changes in the brain tissue [Shai et al., 2006].

Acute radiation syndrome (from several days to several weeks) and early delayed (up to 6 months) injuries are transient and respond to corticosteroid treatment. In contrast, late radiation-induced injuries are irreversible and aggravate over time, which is one of the major problems of clinical radiation therapy. The issue becomes more complicated due to the fact that it is presently quite impossible to predict individual sensitivity of a patient to irradiation, which can vary from hypersensitivity to resistance, and to correct the dose or exposure mode accordingly. Furthermore, radiation-induced necrosis can be clinically indistinguishable from continued tumor growth. Therefore, there is a need for developing differential diagnosis methods.

No noninvasive biochemical markers of the radiation-induced brain injuries currently exist. At the same time, experimental works over the past 20 years have revealed new cellular and molecular mechanisms that are induced in the brain by ionizing radiation exposure. The key molecules of these mechanisms are likely to be detected in the peripheral blood and, thus, become biological markers of ionizing radiation exposure affecting the brain tissue.

2. Molecular mechanisms induced by ionizing radiation

As well as any other medium, the brain absorbs the energy induced by ionizing radiation. As a result of absorption processes, ionization and atomic excitation occur. The effect of ionizing radiation is estimated to be about 105 electrons per Gray per cell [67]. Ionization causes the formation of free radicals — high-reactivity atoms with unpaired electrons. Free radicals react with brain molecules resulting in their damage or structural changes [61]. Signaling pathways initiated by ionizing radiation occur in two separated cell compartments: the nucleus and cytoplasm. Nuclear processes are initiated by DNA lesion that leads to the cell cycle arrest in order to promote the repair of strands; cytoplasmic processes include activation of receptor tyrosine kinases without ligand binding, which is mediated by inhibition of activ-
ity of protein phosphatases under the influence of reactive oxygen species.

2.1. Nuclear processes: repair of DNA double-strand breaks

Events in the cell nucleus induced by ionizing radiation include detection of DNA double-strand breaks, involvement of repair proteins in the area of lesion, and subsequent cell cycle arrest [62]. If DNA lesions are not to be repaired, apoptosis occurs. A key role in this process is played by two members of the phosphoinositol-3-kinase (PI3K) family: ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3 related (ATR) protein kinases [37]. ATM and ATR are activated by the involvement in the area of lesion; they phosphorylate many substrates including cell cycle proteins and DNA repair enzymes [22]. Inherited ATM defect is observed in autosomal recessive ataxia telangiectasia disorder associated with hypersensitivity to ionizing radiation due to inefficient DNA repair. On the other hand, increased activation of phosphorylated ATM can be observed in glioma stem cells, making these cells resistant to ionizing radiation [73, 74].

In the case of glioblastomas, according to some authors [52], the combined use of the alkylating agent temozolomide (TMZ) increases the risk of radiation-induced necrosis development over five times, which increases tissue sensitivity to radiation exposure. The repair enzyme O6-methylguanine DNA methyltransferase (MGMT) in its turn protects DNA against alkylating agents such as TMZ. Promoter methylation inhibits enzyme transcription, which increases tissue sensitivity to the radiation therapy effects [25]. Thus, the determination of the MGMT methylation status may become a method for evaluating radiosensitivity and the risk of radiation-induced necrosis development.

The success of repair of double-strand breaks eventually determines whether a cell will survive or apoptosis will occur. Initiation of apoptosis or necrosis starts not immediately, only after 3 or 4 cycles of cell division during attempts of DNA repair [66]. Pharmacological inhibition of DNA repair is currently regarded as a strategy of tumor cell radiosensitization [62].

2.2. Cytoplasmic processes: activation of receptor tyrosine kinases

Cytoplasmic events caused by radiation are more diverse as compared with processes in the cell nucleus. Formation of oxygen and nitrogen free radicals with the participation of mitochondrion is enhanced at early stages [8]. Free radicals inhibit the protein tyrosine phosphatase activity, resulting in activation of receptor tyrosine kinases (RTKs) regardless of ligand presence [15]. RTKs phosphorylate a number of proteins initiating the great number of intracellular cascades; the best described one is the epidermal growth factor receptor (EGFR) signaling pathway. The activation of this pathway causes the proliferative and anti-inflammatory cell response. It is known that the extracellular part of the receptor can be detected in blood when using available immunoenzyme method [27]. Thus, one can assume that the receptor levels in blood may correlate with radiosensitivity. Little is currently known about the level of EGFR biological variation in the healthy brain tissue. However, it has been shown that the glioma molecular subtypes significantly differ in the expression level of this receptor [30].

2.3. Convergence of nuclear and cytoplasmic signaling pathways

DNA lesion as well as RTK activation result in activation of several transcription factors (TFs), thus initiating gene transcription [11]. NFκB and STAT3 are the best-studied ones among all TFs activated by ionizing radiation [2, 44]. Experimental studies revealed that activation of these TFs is a key factor of neuroinflammation initiation that to a significant extent determines cellular radiosensitivity [1]. Activated TFs are transferred into the nucleus and bind to promoter regions of DNA. This enhances the expression of the cell cycle progression regulatory genes (cyclin D1), the genes of angiogenesis (VEGF) [44], the genes of structural changes in the extracellular matrix and invasion (MMPs), and the genes of enormous number of neuroinflammatory response regulators (TNF alpha, IL-1, IL-6, IL-8, COX2, CXCR4) [6, 40]. Many authors agree that it is neuroinflammation that plays the main role in the mechanisms of ionizing radiation damaging effect on the brain tissue [1].

3. Cellular mechanisms of radiation-induced brain injuries

As described above, the effects of radiation exposure on the brain are mediated by both the formation of reactive oxygen species and apoptosis initiation when double-strand breaks cannot be repaired during several cell cycles. Thus, actively dividing cells and oxygen-rich cells are the most radiosensitive ones. In the CNS they are presented by oligodendrocytes, vascular endothelium, and various precursor cells. Consequently, according to the classical point of view, brain radiation-induced injury is caused by endothelial cell lesions and mitotic cell death of oligodendrocytes. Certain confrontation between advocates of the glial and the vascular theories of the development of delayed radiation-induced brain injuries existed for a long time. Experimental studies revealed that the death of both oligodendrocytes and endothelial cells may lead to the development of radiation-induced necrosis. At present, however, it becomes clear that the development of radiation-induced brain injuries in the actual pathogenetic situation can completely be related neither to mitotic death nor to destruction of certain cell types. It results from complex dynamic interactions between various brain cell subpopulations: microglia, neurons, astrocytes, oligodendrocytes, and endothelial cells. Furthermore, the development of cognitive impairments
may occur irrespective of cytological and morphological damages [61].

3.1. Endothelium

As mentioned above, many authors consider the endothelium damages to be a key factor in the development of radiation-induced brain injuries. The advocates of the vascular theory refer to a great number of experimental studies showing that radiation causes vascular wall thinning of brain blood vessels, structural changes in the capillaries, and reduction in the amount of endothelial cells [4, 50]. It has been shown that clinically relevant doses of ionizing radiation cause changes in the permeability of the blood—brain barrier due to the imbalance between the expression of metalloproteinases and their inhibitors, type IV collagen degradation; changes in VEGF, angiotensin I, and angiotensin II expression [34; Won Hee Lee et al., 2012]. At the same time it is known that radionecrosis may be developed in the brain in the absence of microvascular changes [54]. Furthermore, it has been shown that certain substances (agonists of peroxisome proliferator-activated receptor-gamma, inhibitors of angiotensin-converting enzyme) prevent the development of cognitive impairments in rats after the radiation exposure. However, they do not affect the radiation-induced vascular changes [72]. Thus, the delayed radiation-induced brain injuries cannot only be explained by damage to endothelial cells.

3.2. Oligodendrocytes

It is assumed that damage to oligodendrocyte precursor cells results in inability of the brain tissue to substitute dead oligodendrocytes. Eventually, it causes demyelination and white matter necrosis. Actually, it was shown that single doses of more than 3 Gy or fractionated doses exceeding 4.5 Gy cause a progressive decrease in the number of oligodendrocytes in the rat’s brain within 24 h after exposure [28]. These data correspond to early transient demyelination and acute radiation syndrome that are observed in clinical practice. However, these results do not explain the late development of radiation-induced necrosis occurring some months after the treatment. Moreover, it has been shown that progressive cognitive impairment in old rats caused by the same dose is not accompanied by reduction in the number of oligodendrocytes, myelin fibers thinning, or decrease in the number of fibers [58]. Thus, the correlation between oligodendrocyte damages and the development of radiation-induced brain injuries is not as clear as it was previously thought.

3.3. Astrocytes

About a half of all the glial brain cells are astrocytess, which is four times higher than the number of neurons in the human brain [Hansson, 1988]. It was previously thought that astrocytes perform mainly structural and supporting functions, but it is becoming evident now that these cells are represented by a heterogeneous population that plays an important role in modulation of synaptic transmission, regulation of neurogenesis, and differentiation of various precursor cells [55]. In addition, astrocytes and endothelial cells maintain the brain—blood barrier integrity [21]. Ionizing radiation causes astrocyte activation, which is accompanied by increased secretion of glial fibrillary acidic protein (GFAP), cyclooxygenase, and intercellular adhesion molecule-1 (ICAM-1) providing invasion of foreign immunocompetent cells, such as leukocytes [68, 75]. GFAP secretion is increased both in the acute and chronic phases of radiation-induced brain injury [55]. GFAP is known to be detected in the peripheral blood in a number of CNS pathological states [14], this protein can be considered as one of the potential biomarkers of the effects of ionizing radiation on brain tissue.

3.4. Microglia

About 12% of all the brain cells are microglia [17]. Being a homologue of macrophages, inactivated microglia cells play a role of a monitoring agent of homeostasis [60]. Like any other damaging factor, radiation induces microglia activation, which is followed by significant cell shape changes, proliferation, and becoming of secretory phenotype. Activated microglia is one of the main regulators of neuroinflammatory response when secreting a wide variety of mediators: TNF alpha, IL-1, IL-6, MCP1, and ICAM-1 [20, 33]. Enhanced expression of these mediators occurs at the gene and protein levels [29]. It can be expected that the aforementioned mediators may be detected in blood when permeability of the blood—brain barrier changes, which reflects that neuroinflammation and microglia activation processes occur in response to radiation exposure.

3.5. Neurons

Neurons were previously thought to be resistant to radiation exposure due to their inability to divide. At present, however, it is shown that significant changes in expression of the NMDA-receptor subunits, impairment in glutamatergic transmission and long-term potentiation occur in response to ionizing radiation in neurons [38, 65]. These mechanisms are significant for implementation of the processes of synaptic plasticity and thinking; the disorders occurring in these processes are among the most severe side effects of the influence of radiation exposure on the brain. It is interesting that these neuron activity disorders seem to be related neither to the changes in the number of neurons (including a decrease in their amount) nor to the level of myelination processes in the extensions of nerve cells [58].

3.6. Interaction between cell subpopulations

A very delayed manifestation of the worst side effects of ionizing radiation on the brain (radiation-induced necrosis and cognitive impairment) is one of the most intriguing issues in the field of studies of the radiation effect on the brain. In an effort to settle these questions, series
of long-term studies were performed by different researchers. They assessed the expression of a number of genes and proteins in different periods ranging up to several months after the exposure to ionizing radiation [43, 63]. Moravan et al. [43] estimated the expression of a number of neuroinflammation molecules: ICAM-1, TNF alpha, GFAP, and S100A2. A similar pattern of expression was revealed for most compounds: early enhancement (from several hours to several days), subsequent decline and rise again at the later stages (from 6 months to 1 year). The morphology of cells expressing these molecules in this case significantly changed. In the first few hours after exposure, expression was observed mainly in the minute vessels; at the later stages, it was detected in the cells with a secretory phenotype. GFAP showed the earliest secondary enhancement of gene expression. At the same time, enhanced expression of MHC-II (marker of microglia activation) was first observed 30 days after exposure [43].

Thus, one can assume that the neuroinflammation becoming chronic results from changes in cell populations involved in inflammatory response: from vascular endothelium to astrocytes and microglia at the latest stages. Proteins reflecting activity of these cells may be transferred into the blood during neuroinflammation. Thus, they can be regarded as potential markers of various stages of radiation-induced brain injuries.

4. Complex pathophysiological mechanisms

4.1. Neuroinflammation

A growing number of data points to the fact that it is precisely the neuroinflammation that plays a leading role in the development of radiation-induced damage. As evidenced a few years ago, inflammatory reactions play an important role in the development of radiation-induced necrosis; the studies revealed the efficacy of glucocorticoids [Martins et al., 1979] and COX-2 inhibitors in treatment of radiation-induced brain injuries [Khan et al., 2004]. Later, numerous studies revealed that astrocytes, microglia, endothelium, and immune cells express mediators of inflammation both in acute and in delayed stages of the development of radiation-induced injury. Enhanced expression of cytokine proteins (IL1B, TNF alpha, and IL-6), intercellular adhesion molecules (ICAM-1), and transcription factors contributing in anti-inflammatory processes (Nfkb) was detected in the brain exposed to ionizing radiation [43]. Sustained activation of microglia was maintained in the rodent brains 6 and 9 months after exposure [10]. Recent studies show that inhibition of neuroinflammation prevents the development of delayed radiation-induced cognitive impairment in animals [Jenrow et al., 2013]. The hippocampus is known to be the most sensitive area in the whole-brain radiotherapy [Jenrow et al., 2012] and the area most sensitive to neuroinflammation processes [47]. Many authors directly relate the development of somnolence syndrome to activity of inflammatory mediators [Ballesteros-Zebadúa, 2012]. Moderate doses of radiation can decrease the subsequent cell death of neurons mediated by neuroinflammation in rats [Titova et al., 2010]. Curiously, it was found that the decline in expression of anti-inflammatory mediators in response to radiation exposure occurs with age in the rat brain [34]. Meanwhile, there are data on risk reduction of radiation-induced necrosis in adults compared to children [48]. Thus, a great variety of multi-aspect information points up the prominent role of neuroinflammatory processes in the pathogenesis of various radiation-induced brain injuries, including radiation-induced necrosis and cognitive impairments.

4.2. Neurogenesis

Progenitor cells are hypersensitive to ionizing radiation. Dose-dependent cell death of neural precursor cells, reduced proliferation, and inhibition of cell differentiation into neurons are observed in the hippocampus of rodents exposed to radiation [3, 72]. A dose of 10 Gy does not cause demyelination and development of radiation-induced necrosis in young rats. However, this dose results in only 3% of new neurons being formed in the hippocampus of animals when compared to intact rats [42]. Recent clinical data have confirmed the reduction in the number of progenitor cells, resulting from radiation therapy in neurooncological patients [46].

In young rats, the reduction of neurogenesis induced by clinically relevant radiation doses correlates with the development of delayed cognitive impairments [32, 51]. Meanwhile, it should be noted that no radiation-induced reduction of neurogenesis is observed in old rats in spite of the functional disorders [Greene-Schloesser et al., 2012].

4.3. Endocrine mechanisms

Endocrine mediators play a significant role in maintaining the healthy brain function and in adaptation to damaging factors. Specifically, thyroid hormones and sex steroids play a vital role in neurogenesis; estradiol and progesterone may protect neurons against cell death [53]; glucocorticoids are endogenous key regulators of neuroinflammation [19]. The role of endocrine mechanisms in the development of radiation-induced injuries has not yet been surveyed in detail. However, it has been found recently that radiation therapy results in long-term changes in the function of the endocrine system in 80% of patients [13]. The observed changes appear to be linked to pituitary gland damage and are not associated with the damage to the hypothalamus. Experimental studies performed in the acute phase after radiation exposure revealed coordinated induction of inflammatory responses in the hypothalamus (enhanced expression of IL1B and Nfkb) and an increased blood level of corticosterone, which was followed by enhanced transfer of the glucocorticoid receptor in the nuclear fraction of hypothalamic cells [64]. These responses most likely reflect com-
Pensatory activation of anti-inflammatory endocrine response mechanisms to radiation-induced neuroinflammation. One may assume that the changes induced by radiation therapy in endocrine reactions in patients can play a significant role in controlling the loss of the brain inflammatory response and in the subsequent development of radiation-induced injuries. Thus, the variation in glucocorticoid synthesis assessed by the level of these hormones in the peripheral blood may apparently reflect the risk of developing radiation-induced brain injury.

5. Potential biomarkers of radiation-induced brain injuries

Little is known about biomarkers of radiation-induced brain injuries. However, based on the above noted clinical and experimental studies, one can find appropriate approaches to the risk assessment and radiation-induced brain injury monitoring.

5.1. Inflammatory mediators

Neuroinflammation is apparently a key factor of radiation-induced brain injury development. One can expect that inflammatory mediators are likely to be detected in blood as the brain—blood barrier permeability changes in development of radiation-induced brain injury. Meanwhile, the use of inflammation mediators as diagnostic or prognostic biomarkers of radiation-induced brain injuries may be linked to overcoming certain limitations. Primarily, it comes to lack of specificity and to the dual role of inflammatory responses in nervous tissue injury.

Lack of specificity. Neuroinflammation is a common process in all cerebral pathologies. Therefore, inflammatory mediators are less likely to be used as specific biomarkers of radiation-induced injuries and, for example, in the differential diagnosis of radiation-induced necrosis or gliomas with continued growth. The diagnosis specificity may be improved in this case by simultaneously determining the tumor growth biomarkers. Meanwhile, endothelial cells (some of the major cell types involved in inflammatory response) are damaged as a result of brain exposure to radiation. This leads not only to changes in the brain—blood barrier permeability and causes hypoxia, but also to changes in the contribution of these cells to the inflammatory response regulation. Thus, one can expect that the inflammatory response as a result of radiation exposure possesses specific qualitative or quantitative characteristics.

The dual role of neuroinflammation in brain injury. The inflammatory response of the brain is initially a defensive reaction of the nervous tissue dedicated to the removal of damaged cells and stimulation of regenerative processes. Most likely the cell death is mediated not by inflammation alone, but also by dysregulation of its processes or the inflammatory response becoming chronic. The level of mediators of inflammation would thus be expected to reflect to a greater extent the severity of ionizing radiation exposure on the brain tissue than the likelihood of radiation-induced injury development. Using intracranial injury and other cerebral pathologies with evident component of the neuroinflammation as an example, it is well known that the level of inflammatory mediators may be correlated both with the favorable and unfavorable disease outcomes at several points in time. Apparently, the parallel determination of other markers that might point to adaptive or non-adaptive direction of the inflammatory process, the following brain cell activation or cell death could be the solution to this issue.

5.2. The markers of brain cell activation and damage

Experimental studies suggest that the development of radiation-induced brain injuries and the inflammatory response becoming chronic occurs during sequential activation of various brain cell subpopulations. It is clear from studies of other cerebral pathologies that a number of markers in peripheral blood may reflect the processes of nervous tissue cell activation or cell damage. Specifically, GFAP is regarded as biomarker of astrocyte activation; VEGF, VCAM, and ICAM-1 may reflect the endothelium activation [14] [Patrick et al., 2013].

Determination of molecules that are fragments of radiation-damaged cells in blood may become an approach to molecular diagnosis of radiation-induced injuries as well. Specifically, the test for anti-aquaporin-4 antibodies has already shown to be a reliable diagnostic technique for determining demyelinating diseases of the CNS [16]. The level of these antibodies in blood serum would be expected to correlate with the severity of radiation-induced necrosis.

Ubiquitin C-terminal hydrolase (a neuron-specific enzyme) [6, 35], enzyme-specific products of alpha II-spectrin degradation (reflecting the calpain or caspase-3 activity) [Mondello et al., 2010], the fragment of proteolytic cleavage of NMDA receptor or NMDA receptor antibodies, matrix metalloproteinases and their inhibitors (involved in extracellular matrix remodeling) [68], EMAP II cytokine (involved in microgliosis) [70], nitrotyrosine (involved in oxidative stress) [Ryan et al., 2010] etc. can be regarded as potential markers.

5.3. Markers of processes in the nucleus

Examination of lymphocytes as the only blood cells containing full DNA is used to quantify the effects of radiation in clinical radiology [9]. Varied chromosome aberrations (terminal deletions, translocations, ring chromosomes, and dicentric chromosomes) may result from radiation exposure [Granzotto et al., 2011]. Severity of these changes may reflect the “success” of repair mechanisms at equal doses of radiation exposure. Meanwhile, only a small number of lymphocytes are located in the brain, and it is extremely difficult to discover them in blood. At the same time, as noted above, a great number of repair proteins is concentrated and structurally modified in the area of DNA double-strand breaks. Identify-
ing these proteins by in situ hybridization is one of the most promising methods for quantitative assessment of radiation exposure. One may assume that identification of these proteins in the blood serum may also become an approach to assess the effects of ionizing radiation on the brain. However, these approaches require the labor-intensive development of biochemical methods; in addition, the specificity of these biomarkers may be very rough due to the fact that their levels are determined by the overall instability of the genome as well.

5.4. Endocrine markers

The role of endocrine mediators in pathogenesis of radiation-induced brain injury remains virtually unstudied. However, certain studies and the data derived from allied research areas allow one to suggest that various hormones play a significant role in regulation of the response of nervous tissue to radiation exposure, similar to allied research areas allow one to suggest that various hormones in the blood flow. In addition, most hormones are transferred directly into the blood flow. One can hope therefore that new data on the role of the endocrine system in the response of brain tissue to ionizing radiation will appear in the near future.

Conclusion

Radiation-induced necrosis and cognitive impairments are the most severe complications of radiation therapy. Their development is characterized by asymptomatic disease course, late manifestation, irreversibility, and distinct interindividual variability. This determines an acute need to study the mechanisms regulating these processes and to search for relevant objective diagnostic and prognostic biomarkers. Literature data reveal a great variety of cellular and molecular mechanisms of pathogenesis of the radiation-induced brain injuries. The key processes most likely are not confined to mitotic death of oligodendrocytes and endothelial damage; they also include the initiation of neuroinflammatory response resulting in chronic form and the subsequent activation of different brain cell subpopulations. The mechanisms of systemic physiological control involving the endocrine system are likely to play a significant role. One can hope that the key molecules of these processes may become the first noninvasive biomarkers of the radiation-induced brain injuries.

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The Current State of the Brain—Computer Interface Problem

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It was only 40 years ago that the first PC appeared. Over this period, rather short in historical terms, we have witnessed truly revolutionary changes in lives of individuals and the entire society. It is perhaps impossible to find a field of activities that would not involve computer technologies, either directly or indirectly. Today we can confidently claim that computers are manifold superior to a human mind in a number of parameters; however, machines still lack the key feature, the capability of independent thinking (like a human). However, collaboration between the brain and computer rather than competition is the key to successful development of the whole humankind. Such collaboration, when computer extends, supplements, or replaces some brain functions, is known as the brain—computer interface. Our review focuses on implementation of this cooperation into real life.

Keywords: brain—computer interface, neuroprosthesis, robotics, electroencephalography, high-tech medicine.

1.1 Historical background

With pioneering research of a German neurologist Hans Berger, who first managed to record the electrical activity of the cerebral cortex in 1924, it is possible to “see” how the brain works. The results of his work were published in 1929 [1—4]. In subsequent years, electroencephalography (EEG) continued to extensively develop and became ingrained into a clinician' toolkit. Later on, other authors [5, 6] demonstrated that EEG analysis can provide information about the presence of specific activity patterns of various regions of the cerebral cortex that can be then implemented in operation of an external mechanical system (robotic arm).

Research on developing the interface for communication between the human brain and computer system began in 1970. The University of California in Los Angeles, where these studies were conducted under a grant of the National Science Foundation of the US and a project of the Defense Advanced Research Projects Agency, was the main research center. The term “brain—computer interface” was first mentioned in articles published based on the results of this research [7].

Cochlear implants were the earliest devices that to some extent implemented the brain—computer interface concept. In the early 1970s, in experiments on animals, implantation of sensing electrodes into the cochlear structures of the inner ear was demonstrated not to cause any negative changes [8, 9]. The pioneering work of W. House [10] devoted to cochlear implantation in humans was published a year later. Cochlear implantation was rapidly developed; single-channel electrodes with significant limitations (in signal encoding and speech recognition) gave place to multi-channel electrodes whose efficiency was proven by numerous studies [11—15].

The pioneering work of M. Mahowald [16], who for the first time came up with the idea of a “silicon retina” in the early 1990s, focused on the development of an artificial retina. In subsequent investigations of other authors [17], the possibility of creating hybrid bio-electronic sensor based on bacterial rhodopsin, which could acquire black-and-white moving images and transmit data about the geometry of the visible objects, was proved. In the late 1990s, some authors [18, 19] suggested the two-component artificial retina, consisting of an encoder located outside the eye and implanted stimulator contacting with the retinal ganglion layer. The use of bacterial rhodopsin as a photosensitive element of artificial retina continued in 2000s, when technological capabilities allowed using it to build systems that provided the perception of color images [20—22].

In the paper by A. Chow et al. [23], implantation of an artificial retina in patients with retinitis pigmentosa was reported. A silicon chip of 2 mm in diameter consisting of 5000 photodiodes connected to microelectrodes reaching retinal ganglion layer was used as a sensor. The duration of observation ranged from 6 to 18 months; no side effects or complications associated with the presence of the implant were observed during this period. All patients demonstrated improvement of visual function in the operated eye.

Taking all the aforesaid into consideration, we can conclude that neuroprostheses were the historical predecessors and the first real implementations of the brain—computer interface. However, they are mainly

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“The best way to fully understand something is to teach it to a computer”
Donald Knuth

“If you can turn on the computer, you can speak to the world”
Roy Bakay
associated with the replacement of the analyzer function (visual and auditory). True brain—computer interface is characterized by a direct connection between the brain or spinal cord, the computer system, and the effector part. Evolutionarily, it is the next step in the development of neuroprosthesis at methodological and technological levels.

1.2 Research in laboratory animals

The vast majority of these studies deal with the replacement motor of functions based on the analysis of neuronal activity of the motor areas in rat or monkey brain. Research on the operant conditioning in primates have shown for the first time that monkeys can learn to control the movement of a mechanical arm through the neuronal activity [24]. Later on, it was shown that, in the presence of the appropriate reinforcement, monkeys can readily learn to control the intensity of generated pulses both in groups of neurons of the primary motor cortex and in individual neurons of this brain region [25—30]. Due to the more developed cognitive function, apes that received appropriate training can perform fairly complex play-based tasks by merely thinking about them. For example, they can move the mouse cursor on the screen or move the robotic arm based only on visual feedback [31].

In the study by B. Amirikian and A. Georgopoulos [32], the existence of mathematical correlation between the electrical activity of single motor neurons of the cortex and the direction of movement of the extremity was reported. It was also shown that movements are controlled through the functional interaction between neurons of different brain areas. However, it was possible to record the activity of neurons in only one area due to technical limitations.

The technological leap in the mid-1990s led to rapid increase in the number of publications on the brain—computer interface. Several research teams [5, 30, 33—35] managed to record and decode fairly complex activity of neuronal ensembles, as well as to use these data to control the external devices.

1.3 Brain—computer interface (visual analyzer)

In 1999, at the University of California at Berkeley [36], the first reconstruction of the image seen by a cat was obtained. For this purpose, the electrode array was installed into the lateral geniculate body (a total of 177 neurons encoding the signals from the retina were selected). Several short movies were then shown to the animal with simultaneous recording of neuronal activity. The signals characterizing the films seen by the animal were then encoded, using the mathematical processing. Images and moving objects present in the video were reconstructed based on these signals.

1.4 Brain—computer interface (motor function)

The laboratory of M. Nicolelis [37] at the Duke University in Durham (NC) has studied the problem of movement control using large electrode arrays placed on the brain surface. According to the authors, this enables recording the activity of neuronal ensembles rather than individual cells and improves the accuracy of signal recording.

In earlier studies [38], the control of robotic arm movements was shown to require signals from at least 50—100 neurons.

The complexity of extremity movement kinematics in primates is provided by the simultaneous, dynamically changing activity of neuronal ensembles in various areas of the brain (premotor area, primary motor cortex, posterior parietal area). Analysis of these signals using linear and nonlinear algorithms allowed determining the direction of extremity movements both in two-dimensional and in three-dimensional space in real time. These data facilitated creation of the brain—computer interface where a robotic arm was an end-effector. Due to a very high speed of data processing and transmission, the arm was controlled both locally and remotely (signal transmission via the Internet). In the experiment, an animal operated the robotic arm that repeated the whole set of movements required to control a joystick or capture food [39]. According to the authors, the lack of feedback was the interface disadvantage [40].

The article by J. O’Doherty et al. [41] demonstrated that the use of intracortical microelectrode stimulation of the primary somatosensory cortex area may provide a high-quality tactile feedback that is sufficient for manipulation and object texture recognition both in virtual and in real space.

Studies by other authors [42] have shown a sufficient amount of information can be drawn from small neuronal ensembles (15—30). In particular, M. Serruya et al. [43] showed that well-trained rhesus monkeys can use the brain—computer interface based on the information received from the ensemble of 7—30 neurons to track items and move the cursor on the computer screen. The article by M. Velliste et al. [44] also demonstrated that monkeys can eat without assistance by controlling movements of the robotic arm that holds pieces of fruits.

At the same time, according to D. Taylor et al. [45], there are certain limitations associated with the data transmission speed, when moving the cursor on the screen (the maximum value at the beginning of movement and rapid decrease in speed in the middle), as well as certain inertia of the robotic system (in arm movement).

Apart from the possibility of predicting kinetic and kinematic parameters of extremity movements, is also possible to predict electrical or electromyographic characteristics of movements of the animal’s muscles based on the analysis of information obtained from the electrode array [46]. This allows for the use of brain—computer interface to restore movement in paralyzed extremities by electrical stimulation of the muscles.

The analysis of impulses from large neuronal ensembles may provide important information on the position of
extremity, e.g. hand [39]. This allows creating an interface, in which attempts of extremity movements will be transmitted and implemented by mechanical effector. In the article by J. Carmena et al. [47], such a system allowed the monkeys to capture objects using robotic arm. According to M. Lebedev et al. [40], the formation of new cortical representation for the robotic limb along with the existing centers for animal’s own limbs is entirely possible.

1.5 Using a brain–computer interface in medicine

After a long period of preclinical application of the brain–computer interface for research purposes, in the early 2000s the first papers were published reporting the results of using the system in patients with various nervous system disorders. All the existing types of interface can be conventionally classed into the following groups:

a) Invasive;
b) Semi-invasive;
c) Noninvasive.

1.5.1 Invasive brain—computer interface (visual function)

In 1968, G. Brindley and W. Lewin [48] for the first time implanted electrodes into the occipital lobe cortex of a blind patient. The receiver of the device was equipped with a radio antenna that received signals of a certain frequency. The patient could see single flashes of light, “phosphenes”, in response to stimulation. The authors concluded that further development of the prototype could result in creation of an artificial vision system. Similar results were obtained by W. Dobelle et al. [49, 50] in 1974 upon stimulation of the occipital lobe cortex in neurosurgical patients, with one of the patients being capable of resolving individual letters. Technological complexities associated with the initial stage of microelectronics development and the inability to decode and process large amounts of information in real time were the cause why the first actually functioning device was implanted to a patient only in 2000 [51]. The patient was not congenitally blind and lost his sight in adulthood. Technically, the device comprised an array of 68 electrodes placed to the cortical visual analyzer zone. The sensing component of the system was a camera located on the patient’s spectacle-frame and transmitting the signal through a stationary, high-performance computer to the electrode array. Due to this, the patient could differentiate shades of gray in a very small vision field. However, the information refresh rate was low. Later on, both the device and the guidance computer became more compact, allowing the patient to carry out simple visual tests without assistance.

According to K. Moxon et al. [52], a new version of the interface was developed in 2002, which was implanted to 16 patients. With new algorithms of data processing and encoding, the quality of visual information received based on phosphenes improved. This allowed one of the patients to drive slowly moving car during a test trip. In the future, virtually all patients experienced visual deterioration again. It was most likely due to the phenomenon of “burnout” of neurons in the area of implantation of the electrode array, as well as formation of a glial scar.

1.5.2 Invasive brain—computer interface (motor function)

The systems designed to replace the motor functions use a robotic arm as an effector, which allows patients to perform some movements.

The first such system has was designed by a research team under the supervision of P. Kennedy and R. Bakay at the Emory University [53].

In 1998, a conical electrode was implanted into the motor cortex of a female patient with amyotrophic lateral sclerosis. After the appropriate training, the patient was able to interact with the computer (type and articulate a text, turn on and off lights). Another patient was a young man who suffered a stroke in the brain stem, which led to formation of the locked-in syndrome. Twelve months passed from the time of the stroke until the implantation of the electrode array. The device functioned successfully for 4 years. In particular, through the use of this system, the patient was able to communicate using a computer, write and check the e-mail, play simple games. Unfortunately, later on the patient died of aneurysm rupture [53].

In 2005, the BrainGate system was first used. This system was developed with the participation of Brown University, Massachusetts General Hospital, Stanford University, and Harvard University. It was a new generation interface with significantly improved capability of decoding, analysis and transformation of pulses received from the electrode array. Electrodes were installed at the cortical representation of the hand, and the information obtained after processing allowed the patient with quadriplegia to manipulate a robotic arm, control the cursor of the computer, turn off and turn on the lights and TV [54, 55].

1.5.3 Semi-invasive brain—computer interface

Such systems are installed inside the cranial cavity but outside the brain. They provide a better quality of signal reception from the neurons compared to fully non-invasive systems and are not subject to the problems associated with glial scarring and neuronal death due to excessive stimulation.

This system is based on electrocorticography technique using arrays of flat epidural electrodes placed above the surface of hemispheres. According to D. Moran and E. Leuthardt [6, 56], who recorded the results of electrocorticogram in a patient implanted with electrodes due to pharmacoresistant epilepsy, such a system provided a sufficient signal quality to allow the patient to play a computer game using implant. The authors also mentioned the rapid patient teaching to use...
the system, a good balance between the signal quality and relatively low invasiveness of electrode installation process. Today, distribution of such systems is limited. The existing systems are experimental, as there is no formal permission for their use, and the data can be obtained only in patients with epilepsy implanted with electrode arrays. Electroceutography is basically quite a promising technique for the further development of brain—computer interface due to high spatial resolution, better signal-to-noise ratio, wide frequency range, and shorter term of patient teaching.

1.5.4 Non-invasive brain—computer interface

The first brain—computer interface based on analysis of the P300 component was developed at the beginning of 1988 by Farwell and Donchin [58]. Patients with this device could communicate with a computer by typing letters and words and executing simple instructions. The verbal function was implemented using a voice synthesizer.

Along with the development of invasive principles of information gathering, studies in the field of non-invasive information acquisition have been conducted using electroencephalography (EEG), magnetoencephalography, and functional MRI (fMRI) [59—63].

Electroencephalography still remains the most extensively studied and promising component of the non-invasive interface due to its high spatial resolution, ease of use, portability, and cost efficiency. The complexity, long-term training of the patient, and relatively low interference immunity significantly limit extensive application of EEG [64]. For example, in a study by N. Birbaumer [65] that included a group of patients with severe motor disorders, the voluntary control over slow cortical potentials and, therefore, computer cursor movement could be achieved only after months-long training. However, the speed of execution of assigned tasks was extremely slow (typing of 100 characters took more than 1 h).

Recent studies investigated the possibilities of developing a technology that would allow patients to choose arbitrarily other rhythm ranges enabling easier interaction with the interface [66, 67].

According to J. Bayliss [68], A. Kaplan and I. Ganin [69, 70], the use of the P300 component as a control signal for the brain—computer interface is very promising. This component is characterized by a high stability and, most importantly, does not require pre-training of the patient, since it arises in response to the stimuli that are known and significant for the patient [71].

In the following years, such systems acquired currency in combination with virtual reality systems (based on the analysis of P300 user could interact with the elements of the virtual environment). [72]

Furthermore, a number of studies [69] demonstrated that the control signal can be obtained even when patients, either conscious or being unconscious for a long time, who were however capable of modulating neuronal activity in some brain regions in response to the presented stimuli, were not aware of the fact of the signal registration [73].

In some studies [74, 75], it was shown that the combination of new neuroimaging modalities (fMRI) with EEG allows obtaining the accuracy of signal perception comparable to that of invasive brain—computer interface, and executing very complex tasks (model helicopter flight control in a maze based on thinking of motion).

The studies of B. Sorger et al. [76] and D. Lute et al. [77] demonstrated that, based on the combination of fMRI and EEG data, it is possible to implement both-way contact with patients without visible signs of consciousness.

Further progress in the technological aspect of non-invasive brain—computer interface is associated with the development and application of “dry” electrodes, which require no gel application or special preparation of the skin, and have much smaller sensor size, a high signal-to-noise ratio, and full compatibility with existing systems for EEG recording.

The use of optical technologies to obtain information about the functional state of the brain is another promising direction of development of non-invasive brain—computer interface [78]. It is near infrared spectroscopy (NIR) method, which allows assessing the level of metabolic activity in a specific region of the cerebral cortex based on the levels of oxy- and deoxyhemoglobin during functional load [79]. Good results of application of the interface based on this technology in the rehabilitation of patients with movement disorders were reported in the article by T. Nagaoka et al. [80] (thinking of motion leads to stimulation of the paretic limb muscles). S. Power et al. [81] mentioned that NIR method allows using not only thinking of movement, but also the results of the cognitive tasks (thinking of music and solving arithmetic problems) to run the brain movement disorders computer interface. Furthermore, the use of NIR is a good supplement to EEG, which improves the results of analysis of biopotentials, the predictive accuracy of the models used for information processing and overall performance of the interface [82, 83].

1.6 The control of external devices

Brain—computer interface based on EEG data can beBrain—computer interface based on EEG data can be successfully applied in combination with augmented or virtual reality systems. For example, the patient can move in the space of a virtual city using mental modulation of control signals, as shown in the study by R. Leeb and G. Pfurtscheller [84].

Non-invasive brain—computer interfaces based on EEG and magnetoencephalography are also used to control the prostheses of upper and lower extremities in
functioning of the neurons. A functional incompetence of a single neuron was proved.

A multidisciplinary approach with the active participation of specialists in the field of clinical neurosciences is required for successful practical application of developed technologies in medicine. Clinical studies of individual variability of the functional anatomy of the brain in health and disease and the study of neuroplasticity mechanisms and the potential of spontaneous recovery of disturbed functions of the central and peripheral nervous systems of various origins (neurotrauma, diseases, cancer, and degenerative diseases) should be intensified. The limitations and benefits of invasive and non-invasive techniques, their clinical efficacy, potential complications and side effects, as well as the need to address ethical issues should be born in mind when selecting the optimal clinical models.

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REFERENCES


Commentary

Since 1970s, when first solutions for prosthetic acoustic analyzer in the form of a cochlear implant were suggested, enormous number of scientific fields emerged, developing various bioengineering structures to replace impaired human functions. Developments are mainly related to both the quality of perception and adequate, non-traumatic penetration of connector to the brain. Improvement of the perception system (acoustic, visual) was accompanied by investigation of neural activity of different brain structures aimed at maximum facilitation of neurotransmission. The brain—computer interface actually implies replacement of lost efferent pathways, which would allow for prosthetic repair of voluntary movement system in a patients with disordered motor function. Such an invention would result in a revolution in the field of neurological and many other diseases.

The article analyzes the research dynamics and progress in producing neuroprostheses and effenter neurotransmission. The encouraging results of application of these technologies in animals allowed initiating clinical phase of the research at the beginning of this century. The authors analyze the existing medical indications to neuroprosthetics and cortical implantation of sensing electrodes. Various invasive and non-invasive procedures are described in detail. Undoubtedly relevant and exciting prospects of using non-invasive forms of reading and transmitting neuroinduced information suggest the use of these systems not only in the medical directions. Imagination draws unprecedented human capabilities, such as contactless control of mechanical moving systems (extremities) using neuroinduction, the possibility to “see” an object behind the individual (“eyes on the back of the head”), etc.

Along with questionable commercial projects (for example, NeuroG) related mainly to electroneurographic recognition of mental images, investigation of features of neurotransmission and functional features of brain systems even at study stage allows using obtained information in clinical practice in many ways. The data obtained, for example, by microelectrode registration, provide reliable information about the functioning of both cortical and subcortical structures, including the ability to affect them through the immediate and distant stimulating pulses. This method is widely used in the development of new operations for neuremodulation, which is a novel revolutionary direction in neurosurgery.

In general, the work of the authors, which was performed within the framework of fundamental research in neuroscience, is informative and provocative in terms of discussion of conventional views of neuroscience and social adaptation in general. The emergence of such studies, consolidating the vast literary material, allows inducing new ideas and initiating new revolutionary studies of the human brain.

O.G. Gushcha (Moscow, Russia)
Commentary

Research on the development of neuroelectron conjugation systems continues for more than half a century, but only in the last 10-15 years the amount of scientific and technological achievements in this field has allowed to start adapting these systems for practical application in public health (N. Birbaumer et al., 2014). It is commonly known, that the brain—computer interface (BCI) technology allows a person to control external actuators without intermediary of nerves and muscles, based solely on recording and decoding signals of the brain (J. Wolpaw et al., 2002). This makes neurointerface technologies promising for the use in patients with severe disorders of motor systems. This issue presents the first Russian review of clinical aspects of the development and implementation of BCI, which highlights key milestones in development of BCI-based technologies and key recent achievements in the field of both prosthetics of the sensory organs and compensation for impaired motor functions and speech in patients, who suffer a stroke or traumatic brain injury. It becomes obvious that modern developments of neurointerface demonstrate stable operation not only in healthy volunteers in research laboratories, but also in neurological and neurosurgical clinics. Moreover, along with the initially developed invasive approaches that require implantation of electrode clusters in the brain tissue, reliable operation of non-invasive interfaces, e.g. those based on a routine EEG, has been demonstrated in recent years.

The review states that not only signals of electromagnetic activity of the brain (electro- and magnetoencephalography), but also indicators of its metabolism measured using infrared spectroscopy or functional magnetic resonance imaging can act as biometric communication channel between the activity of the brain and external actuators, such as manipulators, prostheses, control panels, etc. It can also be stated that to date there are first successful attempts of replacing brain structures, such as portions of the hippocampus, with neuroelectron chips. (N. Berger et al., 2011).

Data and recommendations provided by the authors in this review, apparently, outline several directions for further investigations and developments in this area. First of all, it is the development of systems for non-invasive and invasive multi-channel recording and computer analysis of electrical, optical and metabolic activity of the brain for subsequent conversion of these signals into commands of neuroelectronic interface systems. This obviously requires the development of the mathematical background for brain activity modeling to search for EEG correlates of basic cognitive and motor acts, which can serve as command patterns for direct communication with the environment. The development of BCI, including feedback loops based on non-invasive electrical or magnetic stimulation of the brain, is another important direction of clinically oriented neurotechnology. Progress in this direction will allow approaching the solution of the problem of sensitization of prostheses and exo-skeletal structures controlled directly by the brain. Finally, the study of mechanisms of plastic brain reconstructions that are responsible for the development of new skills upon impairment of natural motor systems, but using command signals of electrical, optical, or metabolic activity of the brain in neurointerfaces to compensate for or replace the diminished functions, is crucial for implementation of neurointerface systems into clinical practice.

References


A. Ya. Kaplan (Moscow, Russia)
In 2009, at the discretion of the Director of the Burdenko Neurosurgical Institute, Academician A.N. Konovalov, the Presidium of the Russian Academy of Medical Sciences issued the resolution “On the establishment of a new institution of the Russian Academy of Medical Sciences (RAMS) — the Neurorehabilitation Research Center of the RAMS — and management of its design and construction”. Professor A.V. Grechko, who had extensive experience of administrative and clinical work, was appointed the director of the Center.

The Governmental Commission for Budgetary Allocation supported and approved the proposals by the RAMS, Ministry of Health, Ministry of Economic Development and Trade, and Ministry of Finance of the Russian Federation to allocate budget appropriations for the design, construction, and technological infrastructure of the Center. In 2011, the Government of the Russian Federation issued a resolution on budget investment in the Center.

The Center has been created to meet the growing need for neurorehabilitation care for patients with severe brain injuries caused by traumas, strokes, or brain surgeries. The tight situation is due to the fact that the health system of Russia has lacked institutions providing high-quality, evidence-based rehabilitation for patients with a depressed level of consciousness and long-term artificial lung ventilation (ALV). In this regard, the number of patients staying at critical care units for longer than 30 days, which are specified by the compulsory health insurance standards and regulations, amount to more than 6,000 people per saltum in Moscow region only. Across Russia, this indicator is more than 43,000 people.

Patients with a depressed level of consciousness and long-term ALV need special multidisciplinary treatment approaches, effective implementation of which may provide not only significantly better clinical outcomes but also a substantial economic impact. Critical care units are not designed for long-term patient stay. This leads to a lower turnover rate of critical care beds, cancellation of high-tech operations, higher contamination of the units, and delay in rehabilitation measures (weaning away from mechanical ventilation, recovery of cognitive and motor functions) for an indefinite period.

The project purpose is to create a high-tech medical institution for rehabilitation treatment of patients with
severe organic brain lesions using the latest advances in neuroscience.

A particular objective of the Center is to provide evidence-based and methodically verified medical and rehabilitation care for patients with a depressed level of consciousness and ALV.

The Center is located in a picturesque place near Moscow, in Lytkino village of Solnechnogorsk district, where the health resort of the Soviet Academy of Medical Sciences had been located until 1991.

The Center will include two respiratory rehabilitation departments, a patient monitoring department, a ward for patients in the vegetative state, and a rehabilitation department. All of them will have state-of-art equipment and access to modern rehabilitation technologies and technical means of rehabilitation. Diagnostic facilities of the Center will be provided by departments of electrophysiology, microbiology, radiology, and functional diagnostics as well as clinical, biochemical, biomechanics, and neurophysiology laboratories.

The Center will conduct research on the development of principles and methods for recovery of spontaneous breathing, efficacy of methods of motor and cognitive rehabilitation, and evaluation of the rehabilitation potential.

The development of new rehabilitation techniques, their widespread implementation, and the Center’s unique treatment and rehabilitation activities will decrease the burden on critical care units of leading neurosurgical clinics and arrange high-quality rehabilitation for serious patients.

In accordance with the Regulation of the Government of the Russian Federation, the Center is planned to be put into service in 2015. At the present moment, interior finishing and installation of main equipment are completed, medical equipment is purchased, and technical and medical personnel is gradually recruited.

The Chief Intensivist of the Center
A.L. Parfenov, M.D.
Ivan Nikolaevich Shevelev (on the 75th Anniversary)

On the 2nd of November 2014, Professor Ivan Nikolaevich Shevelev, the outstanding neurosurgeon, Doctor of Medicine, and Honored Science Worker of the Russian Federation, celebrated his 75th anniversary.

Ivan Nikolaevich was born in a working-class family in the village of Nikolaevka of the Slavyansky District of the Altai Territory. Immediately after graduating secondary school in 1958, he was drafted into the Red Army and served in Poland for 4 years. Demobilized in 1962, he entered the medical faculty of the Alma-Ata Medical Institute. After receiving his medical degree in 1968, he chose his specialization in neurosurgery.

At first, I.N. Shevelev worked at the neurosurgical department of the 2nd Alma-Ata City Hospital, and then, in 1972, he entered postgraduate studies at the Burdenko Neurosurgical Institute, where he has worked all his life.

The young researcher was committed to conducting complex research on quantitative characterization of the volumetric blood flow of the peripheral circulation in the acute period of severe traumatic brain injury. I.N. Shevelev successfully met the challenge and triumphantly defended his Ph.D. thesis under the supervision of Academician of the Academy of Medical Sciences of the USSR A. I. Aratyunov and Professor N.Ya. Vasin.

Then, Ivan Nikolaevich switched his research and surgical interests to the peripheral nerve pathology. He implemented innovative methods of internal neurolysis, interfascicular suture and autotransplantation, various types of neurotization, DREZ surgery for post-traumatic pain syndrome, and many others into the clinical practice. Manual skills of I.N. Shevelev allowed him to achieve prominent results in microsurgery for traumatic lesions of the brachial plexus that became the subject for his pioneering doctoral thesis, which he defended in 1990.

The talented neurosurgeon, I.N. Shevelev, has demonstrated great organizational skills. In the 1990s, being a senior researcher, he headed the Department of Functional Neurosurgery.

Upon the completion of construction of the new building of the Institute in 1999, Ivan Nikolaevich established a new clinical Department of Pathology of the Spinal Cord, Spine, and Peripheral Nerves. He laid the foundation for the school of spinal neurosurgeons. He and his followers, including A.O. Gushcha, N.A. Konovalov, A.G. Nazarenko, et al, have developed modern spinal cord and spine neurosurgery based on microsurgery, endoscopy, reconstructive surgery, robotics technology, and other innovations.

For many years, Ivan Nikolaevich was a Visiting Consultant Neurosurgeon of the Ministry of Health of the USSR and operated on in various countries in Europe and Asia. He has often presented domestic neurosurgery at international forums. I.N. Shevelev is a member of the editorial board of the journal “Problems of Neurosurgery named after N.N. Burdenko”.

I.N. Shevelev is the author of five monographs and about three hundred scientific publications. He is the author of 14 inventions in the field of neurosurgery. Seventeen Ph.D. theses were completed under the scientific supervision of Professor I.N. Shevelev. He was the scientific advisor for 3 doctoral dissertations.

His great creative work and invaluable contribution to medical science were highly appreciated by the President of the Russian Federation who awarded Professor I.N. Shevelev the honorary title of the “Honored Worker of Science of the Russian Federation” (2008).

In 2013, Ivan Nikolaevich and co-authors were awarded the Russian Federation Government Prize for the development and implementation of innovative methods of diagnosis and surgical treatment of diseases and injuries of the spinal cord and spine.

However, the recognition and respect of Professor Shevelev by his colleagues are possibly much more important.

We all love and deeply respect Ivan Nikolaevich Shevelev for his kind heartedness, goodwill, decency, and desire always to help his neighbor.

Friends and colleagues of I.N. Shevelev hope that this talented neurosurgeon and wonderful person will serve his Clinics and Institute for many years.

N.A. Konovalov, L.B. Likhterman
Topics to be covered in our next issue:

- Military neurosurgery in the Great Patriotic War
- Life quality of patients with skull base tumors
- Neuroendoscopy in treatment of occlusive hydrocephalus in infants